Mean Platelet Volumes in Non-Alcoholic Fatty Liver Disease (NAFLD): Relationship to Cardiovascular Events

Abstract

Background: Mean platelet volume (MPV) is a biomarker of platelet activity and elevations in MPV have been observed in the setting of acute cardiovascular events. The role of MPV in nonalcoholic fatty liver disease (NAFLD) is unclear at this time.

Aims: The aim of this study is to assess whether increases in MPV during acute cardiovascular events (CE) are observed in patients with NAFLD.

Methods: A retrospective case control study of 104 NAFLD patients with cardiovascular events (CE) matched to 104 NAFLD patients without cardiovascular events (non-CE) was performed. Demographics, cardiovascular risk factors, types of CE, laboratory data including MPV at the time of NAFLD diagnosis, and at the time of the CE as well as medications were collected.

Results: The mean age was 56 ± 8 years (yr) with a majority of white ethnicity (CE, n= 85 versus non-CE, n=76), an average body mass index (BMI) of 31.8 ± 5.1 and little to no fibrosis as based on the APRI (0.34 ± 0.19 in CE and 0.36 ± 0.17 in non-CE group, p= 0.47). The CE group had higher cardiovascular risk calculated by the Framingham Risk Score (FRS) (24 ± 11.6%) compared to the non-CE group (18 ±12%) (p=0.0002). Importantly, the absolute changes of MPV from the time of NAFLD diagnosis (T_0)to the time of the cardiovascular event (T_{CE}) [(MPV T_{CE} -MPV T_0) were statistically higher in the CE group than in the non-CE group.

Conclusion: The absolute change in the MPV level at the time of the CV event was higher in the CE group compared to the non-CE group.MPV may be a convenient marker of increased cardiovascular risk in the NAFLD population.

Keywords: Mean platelet volumes; Cardiovascular risk; Cardiovascular disease; Nonalcoholic fatty liver disease; Non-alcoholic steatohepatitis; Obesity; Diabetes

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Lisa Alvarez[1], Daisha Cipher[2], Rick Weideman[3] and Geri Brown[1,4]*

[1]*Department of Medicine, University of Texas Southwestern Medical Center, USA*
[2]*Dallas Veterans Affairs Research Corporation, Veterans Affairs North Texas Health Care System, USA*
[3]*Department of Pharmacy, Veterans Affairs North Texas Health Care System, USA*
[4]*Department of Medicine, Veterans Affairs North Texas Health Care System, USA*

***Corresponding author:** Geri Brown MD, Veterans Affairs North Texas Health Care System, 4500 S. Lancaster, Dallas Texas 75216, Telephone 214-857-1603, Fax 214-857-1571; Email: Geri.brown@va.gov

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is commonly associated with obesity, type 2 diabetes and the metabolic syndrome, and is now recognized as the most common cause of chronic liver disease in Western countries [1-3]. NAFLD encompasses a histological spectrum of liver disease from hepatic steatosis to the more advanced necroinflammatory form, nonalcoholic steatohepatitis (NASH), which can then lead to cirrhosis and hepatocellular carcinoma. NAFLD patients have increased morbidity and mortality from cardiovascular (CV) disease with CV disease being the leading cause of death [1,2,4-6]. NAFLD is an independent risk factor despite association with traditional risk factors and the metabolic syndrome [1]. At this time the link between NAFLD and CV disease is not well established.

Mean platelet volume (MPV) has been postulated as a marker of CV disease in the general population [7]. MPV is a measure of platelet size and a marker of platelet activity. Platelets play a pivotal role in the pathophysiology of coronary artery disease and atherothrombosis [8]. Larger platelets indicate increased platelet activity and aggregation and have greater prothrombotic potential [9,10]. In a large epidemiologic study of 326 healthy subjects, the normal MPV levels were 7.2 femtoliters (fL) to 11.7 fL with a mean MPV 8.9fL [11]. Higher MPVs have been found in patients with risk factors for CV disease including those with the metabolic syndrome compared to healthy adults [12,13]. Additionally, in a large meta-analysis including 16 cross sectional studies, higher MPVs were associated with acute cardiovascular infarctions, restenosis after PCI and increased mortality [10]. In a pooled analysis of 3 cohort studies, a total of 3,184 patients with an acute myocardial infarction yielded significant mortality prediction value for those with a high MPV with an OR 1.65 (95%CI 1.12-2.52; p=0.012) [10]. While elevated MPV levels have been shown in the general population to be associated with cardiovascular events, it is unclear if this relationship occurs in NAFLD patients with acute cardiovascular events.

There is a paucity of data about MPV levels in chronic liver diseases. Recent data show that MPV levels are higher in patients with NAFLD [9,13,14]. In a cross-sectional study of biopsy proven NAFLD patients, a stepwise increase in MPV levels is found in patients with normal biopsies compared to those with simple

steatosis and to those with NASH with MPV levels of 9.5, 10.2, and 11.3, respectively ($p<0.005$) [15]. MPV has also been speculated as a marker of CV disease in patients with biopsy proven NAFLD and NASH [14,15]. It is unclear whether higher MPV levels are seen during cardiovascular events in the NAFLD population as has been previously observed in the general population [10].

The aim of this study is to evaluate absolute changes of MPV levels in patients with NAFLD at the time of acute cardiovascular events compared with NAFLD control patients. In the general population increased MPV levels are associated with acute cardiovascular events however there is a paucity of data on MPV in the patients with NAFLD.

Methods

Study design

A retrospective case control study of 104 NAFLD patients with cardiovascular events (CE) and 104 NAFLD patients (matched by age, gender and BMI) without cardiovascular events (non-CE) was performed. Data collection was obtained through CPRS, the national computer database for the Veteran's Affairs (VA) Hospitals at the VA North Texas Health Care System in Dallas, Texas. Patients were between the ages 35-80 years old who had been seen at the VA hospital between the years of January 1, 1997 to July 31st, 2012. The study was approved by the local IRB committee.

Patient population

NAFLD was defined by imaging (CT, ultrasound or magnetic resonance imaging) showing steatosis without evidence of portal hypertension (splenomegaly, ascites, varices) and two abnormal levels of ALT >30 U/L in men or ALT >19 U/L in females more than 6 months apart [17]. The CE patient cohort (n=104) was initially identified from the cardiology division data base of patients with left heart catherization during the years, 2007-2008 (n=615) who had the aforementioned criteria for NAFLD. NAFLD controls were obtained initially by querying the VA CPRS database for the NAFLD ICD-9 code (571.8). Of the 2,156 patients identified, 104 [age, gender and body mass index (BMI) matched] NAFLD control patients were identified sequentially. Other types of chronic liver disease including viral, metabolic, genetic and autoimmune liver disease were excluded by laboratory or liver biopsy data. Patients with alcohol use > 20grams per day were also excluded. Hepatotoxic medication, including medications that can mimic fatty liver disease including methotrexate, amiodarone, steroids, and tamoxifen were excluded. Patients with less than five years of follow up were also excluded. Other exclusion criteria included active malignancy, inflammatory and autoimmune diseases, human immunodeficiency virus and blood disorders including inherited macro-thrombocytosis, myeloproliferative disorders, idiopathic thrombocytopenic purpura and myelodysplastic syndromes. Patients with glomerular filtration rate< 30 ml/ min were also excluded.

Data collection

Demographics included age, gender, ethnicity, body mass index (BMI), past medical history and laboratory data were extracted by chart review. Past medical history included smoking history, type 2 diabetes (insulin dependent and independent) (DM), hypertension (HTN), hyperlipidemia (HL), dyslipidemia (low HDL <40 mg/dL and high triglycerides >150 mg/dL), previous history of coronary artery disease, stroke, congestive heart failure (CHF) and peripheral vascular disease (PVD).

Laboratory data included complete blood cell count with white blood cell count, hemoglobin, hematocrit, platelets, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, LDL, total cholesterol, HDL, triglycerides, international normalized ratio (INR), and albumin were collected at time zero (T_0) defined as time of diagnosis of NAFLD. MPV levels were collected at T_0, at the time of the cardiovascular event (T_{CE}) and at the final time (TF) defined as the last MPV at the end of study or at time of death whichever event occurred first. Timing of the cardiovascular event in the control group was the equivalent time to that of the matched patient in the CE group. To determine liver severity AST-to-platelet ratio index (APRI) was calculated by the defined formula, (AST(IU/L)/(upper limit normal)/platelet count ($x10^9$/litre) X 100)[16]. The Framingham risk score (FRS) was calculated using the following variables: age, blood pressure, total cholesterol, HDL-cholesterol, smoking history and history of diabetes [17].

VA North Texas Health Care System's pharmacy database was queried to assess whether the cases or controls had prescriptions for the following medications, aspirin, non-steroidal anti-inflammatory drugs (NSAID), clopidogrel and warfarin.

Cardiovascular events extracted from the cardiology database included acute myocardial infarction as defined by ESC/ACCF/AHA/WHFT ask Force of the Universal definition of Myocardial infarction [18]. Events were designated as ST elevation MI (STEMI) in patients with chest discomfort (or other ischemic symptoms) that develop ST elevation in two contiguous leads as defined by the task force [18], Non-ST elevation MI (NSTEMI) in patients without ST elevation at presentation, and as unstable angina (UA) in patients without elevated biomarkers. Other cardiovascular events included ischemic stroke defined as CT head imaging with new area of infarct and peripheral vascular disease defined as need for vascular stenting of arteries due to atherosclerosis and/or need for arterial bypass surgery.

Statistical analysis

Continuous parameters were presented as mean ± standard deviation and compared using the independent samples t-test or the Mann-Whitney U test, as appropriate. Nominal parameters were presented as percentages and compared with using the Pearson chi-square or Fisher's exact test, as appropriate. Odds ratios with 95% Wald confidence intervals with normal approximation were computed to examine the associations between pairs of binary variables. The purposeful selection SAS macro was used to identify significant predictors and confounders[19]. Any variable having a significant univariate test at the p-value of <0.25 was selected as a candidate for the multivariate analyses. Variables were considered confounders when resulting in a change in any parameter estimate greater than 15%. Analysis of covariance (ANCOVA) was computed to compare the two groups on MPV change using the propensity score as the covariate. Analyses were performed using SAS 9.2 for Linux and SPSS 21.0 for Windows. A P

value < 0.05 was considered statistically significant. The statistical review of the study was performed by a biomedical statistician. This study was approved by the Institutional Review Board of the VA North Texas Medical Center

Results

Demographics

There were 104 patients in both the CE group and the non CE group with an average follow-up duration of 9.5 ± 2.7 years. The majority of the NAFLD patients were male with a mean age of 57 ± 8 years with the ethnic majority being Caucasian. The population was obese (defined as BMI greater than 30) with an average body mass index (BMI) of 32 ± 5.1 (Table 1).

Table 1: The characteristics of patients with NAFLD and cardiovascular events (CE) compared with NAFLD controls (Non CE) including demographics and clinical parameters.

	CE (n=104)	Non CE (N=104)	P	Odds Ratio (CI)
Age	57 +/- 8.7	55+/-8.4	0.07	
Male	102	102		
BMI	32+/- 4.5	32 +/-5.6	0.44	
Caucasian	85	76		
African American	8	23		
Hispanic	10	5		
DM	44 (42%)	29 (28%)		1.9 (1.06-3.38)
HTN	82 (78%)	78 (75%)		
Hyperlipidemia	79 (76%)	67 (64%)		
Metabolic syndrome	76 (73%)	55 (53%)		2.4 (1.35-4.32)
Framingham Risk Score	23 +/- 12 %	18 +/- 12%	0.001	
Smoking	74 (72%)	58(56%)		2.0 (1.10 – 3.47)
HDL <40	63 (61%)	46 (44%)		1.9 (1.12 – 3.36)
TG>150	86(83%)	68 (65%)		2.5 (1.32 – 4.84)
Prior history of PVD	7 (6.7%)	0		1.1 (1.02 – 1.13)
Prior history of CHF	11 (11%)	0		1.1 (1.05 – 1.20)
Prior history of CVA/TIA	4 (3.8%))	1 (1%)		1.1 (1.05-1.2)
Family history of CAD	44 (42%)	24 (23%)		2.4 (1.34 – 4.45)
Death	15 (14%)	2 (1.9%)	0.001	8.6 (1.91 – 38.62)

There were more patients with DM, metabolic syndrome, smoking history, low HDL, high triglycerides (TG >150), hyperlipidemia, peripheral vascular disease (PVD), congestive heart failure (CHF), history of prior stroke (CVA), transient ischemic attack (TIA) and family history of coronary artery disease (CAD) in the CE group. The number of patients with hypertension did not vary between the groups. The CE group also had a significantly higher FRS (a score for assessing 10 year cardiovascular event risk) (23 ± 11.6%) compared to the non CE group (18 ±12%) (p<.0001) with low risk being <10%, intermediate risk ≥10-20%, and high risk >20% [6].

There was no difference between the groups in baseline (Time 0) platelet level (p=0.66) or AST (p =0.32) (Table 2). The CE group had significantly lower ALT (CE, 38 IU/L vs non-CE 45 IU/L, p=0.013) There was a lower LDL in the non CE group than the CE group (115 mg/dL vs 127 mg/dL, respectively, p=0.045). There was no difference between the groups for INR (CE, 0.95 and non CE 1.0, p = 0.06) or total bilirubin (CE 0.6 mg/dL, non CE 0.6 mg/dL, p=0.06). There was no difference in APRI between the groups (0.34 ± 0.19 in CE and 0.36 ± 0.17 in non-CE group, p=0.28) with APRI <0.5 consistent with NAFLD without fibrosis while APRI > 1.5 consistent with cirrhosis [20]. Evidence of a prescription for the following medications (aspirin, clopidogrel, NSAID, and warfarin) was collected. The percentage of patients in the CE cohort with a prescription for ASA, clopidogrel, NSAID and warfarin was higher than the percentage of patients in the non-CE group (p < 0.0001, p < 0.0001, p < 0.0003 and p <0.001, respectively).There were more deaths in the CE group (n=16) than non-CE group (n=2) (p=0.001), and the cases were 8 times more likely to die than controls (OR = 8.60, 95% CI: 1.91 – 38.62)

Table 2: Laboratory data in both CE group and Non CE group.

Lab	CE Group	Non CE Group	P
AST	29 +/-12	30 +/- 12	0.32
ALT	38+/- 19	45 +/-21	0.01
Platelet	231 +/- 60	224 +/- 44	0.66
Total Bilirubin	0.6 +/- 0.24	0.6 +/- 0.22	0.61
INR	0.95+/- 0.22	1.0 +/- 0.04	0.06
APRI	0.36 +/- 0.17	0.34 +/- 0.19	0.28

Levels of Mean Platelet Volume

The CE group had lower MPV level at baseline (T_0) compared to the non CE group (10 ± 1.1fL vs 10.5 ±1.2fL, p = 0.007) (Table 3). Average time to CE event was 4.9 ± 2.8 years. At the time of the CE event (T_{CE}) there were no differences in MPV levels (CE group, 10.6 ± 1.0 fL; non CE group, 10.7 ± 0.9fL) (p=0.39). At final time of follow up (TF) there were no differences in MPV levels (CE group, 10.7 ± 1.1fL; non CE group 10.8 ±0.95fL) (p=0.44). CE included 81 urgent coronary artery bypass grafts (CABG) for multi vessel coronary artery disease, 20 patients with ACS with 6 NSTEMIs, 2 STEMI and 12 patients with UA. There was one ischemic cerebral vascular infarction (CVA), one acute peripheral vascular disease (PVD) requiring urgent stenting of a peripheral artery, and one patient had a transient ischemic attack (TIA).

The absolute changes of MPV from T_0 to T_{CE} (MPV T_{CE}-MPV T_0) in the CE group (0.54 ± 1.1) was significantly higher than the non-CE group (0.21 ± 0.9, p =0.023) (Table 4). A significant higher change was also seen in the MPV level from T_0 to TF in the CE group (0.63 ±1.2) than in the non CE group (0.26 ± 1.2) (p=0.02).

Table 3: MPV levels at Time 0, the cardiovascular event and at final follow up.

	CE Group	Non CE Group	P
MPV initial	10 (1.1)	10.5 (1.2)	0.007
MPV cardiac event	10.6 (1.0)	10.7 (0.9)	0.39
MPV final	10.7 (1.1)	10.8 (0.95)	0.44

Table 4: The absolute change of MPV at the time of the cardiovascular event in both groups.

	Change in MPV T_{CE}-T_0	Change in MPV T_F-T_0
CE group (n=104)	0.54 (1.1)	0.63 (1.2)
Non-CE group (n=104)	0.21 (0.9)	0.26 (1.2)
P Value	0.02	0.02

In multivariate analysis, when controlling for multiple covariates including triglycerides, BMI, platelets, albumin, presence of metabolic syndrome, APRI, FRS and prescriptions for aspirin, clopidogrel, NSAIDs, and warfarin, the CE group still had a significantly higher change in MPV at the time of the CE event compared to the Non CE group (p=0.03). Importantly, there were no significant changes in BMI or APRI over the 9year period (p = 0.74 and p = 0.83 respectively) indicating that the both cohort's fibrosis scores remained fairly stable over this time frame.

Discussion

A retrospective cohort study was performed at the VA North Texas Health Care System where the absolute changes of MPV levels in patients with NAFLD who had cardiovascular events were compared to NAFLD control patients. Both groups had a majority of Caucasianobese (mean BMI 32) middle-aged (mean age 57yr) males with minimal to no liver fibrosis as indicated by low APRI. The NAFLD patients with CE had a greater rise in MPV at the time of the CE compared to controls. Elevated MPVs have been associated with cardiovascular disease in the general population and this study suggested that MPV may also be an easily assessable marker of cardiovascular risk in patients with NAFLD.

Mean platelet volume is an attractive index due to its widespread availability and it is routinely measured by automated hematology analyzers [7] Elevated MPVs have been associated with DM, HTN, obesity, smoking, the metabolic syndrome as well as atherothrombotic events like acute myocardial infarction and cerebrovascular events [10,14]. Platelets secrete and express crucial mediators of coagulation, inflammation, thrombosis and atherosclerosis [10]. An elevated MPV may be a prognostic indicator to identify patients with higher risk of cardiovascular disease.

This study provided an opportunity to compare MPV in a unique population of NAFLD patients with CV events to those without CV events. Both groups of patients were followed over a mean of 9.5 years with an average time to cardiovascular event being 4.9 years. The majority of patients in the CE group had urgent CABGs (n=81) followed by UA (n=120, NSTEMI (n=6), STEMI (n=2) and CVA/PVD (n=2). At the time of the CE event, the absolute change in MPV from baseline was higher in the CE event group compared to the non-CE group.

At baseline, the CE group evidently had a higher risk for CV disease compared to NAFLD controls. More comorbidities were noted in the CE group including DM, the metabolic syndrome and traditional CV risk factors along with a higher FRS compared to the non CE group (p< 0.0001).Of note, the CE cohort had more exposure to aspirin, clopidogrel, coumadin and NSAIDs compared to the non- CE group (p< 0.05). However, by performing a multivariate analysis, controlling for history of smoking, ALT, DM, triglycerides, BMI, platelets, albumin, presence of metabolic syndrome, APRI, Framingham risk score, this study continued to confirm the increased change in MPV in the CE group versus the non CE group. This was a similar finding to the meta-analysis by Chu et al. where those with acute myocardial infarctions had higher MPVs compared to those without MIs supporting the hypothesis that platelet size may play a pivotal role in both the development and consequence of cardiovascular disease [10].

Upon review, the underlying reason for the lower MPV in the CE at time 0 may have been multifactorial including medication side effects, variables not assessed, as well as lab collection methods. Though aspirin has been shown to have little effect on MPV [21], clopidogrel can increase MPV levels [22]. Conversely, Coumadin has been associated with an inverse relationship with MPV [23]. Another etiology of the inaccurate measurement of platelet indices could be due to inappropriate blood sampling and storing. Platelet indices are sensitive to blood sample anti-coagulation, storage temperature and delays in processing [8]. At this institution EDTA (ethylenediamine tetraacetetic acid) is used and can result in artifactual increase of MPV due to time dependent swelling platelets. Due to the retrospective nature of the study, it is unclear how long it took for the samples to be processed. It is known that rapid processing (within 1 hour) can minimize platelet swelling [8]. A prospective study with strict lab sampling would be required to eliminate this confounder.

A previous study showed that MPV levels in those with acute myocardial infarctions were higher than healthy controls and this increase platelet size remained elevated [24]. It has been suggested that this may indicate that increases in MPV are chronic rather than acute [10], Higher MPVs after CE are associated with higher mortality and possibly chronic changes of MPV may be associated with the higher mortality [10].

This study also found that patients in the CE group had greater mortality over the duration of the study compared to the non CE group (14% vs 1.9% respectively, OR 8.6, 95% CI: 1.91 - 38.62, p=0.001). With the prevalence of NAFLD rising parallel to that of obesity it will be important to realize that these patients are at increased CV risk as well as increased morbidity and mortality. Prognostic indicators in these patients may be useful such as the MPV.

The limitations of the study include the following: the retrospective nature of the study, the sample size as well as other biases/confounders not identified. The study included mainly Caucasians males and the specific findings may not be applicable to other ethnicities or gender. Further studies would be required to assess whether the results from this study hold true in patients with nonalcoholic steatohepatitis. Though data from healthy controls were not included, the review of the literature would support that these cohorts had higher MPV levels than healthy controls. .

Conclusion

NAFLD prevalence is only expected to increase overtime with the growing obesity rates. NAFLD and its role in either directly or indirectly contributing to an increased risk of CV disease will be problematic. In this study, increases in MPV levels were found in patients with NAFLD at the time of the CE event and the overall increase in MPV in the CE cohort appears to be associated with higher mortality compared to NAFLD controls. NAFLD patients with elevated MPV may warrant further evaluation for prognostic indicators of more severe CV disease. MPV may be a convenient marker of increased cardiovascular risk in the NAFLD population.

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