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Original Article

The Relationship of Mean Platelet Volume and Atherogenic Index of Plasma with Atherothrombotic Cardiovascular Disease in Diabetes

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Abstract

Introduction: Atherothrombotic cardiovascular disease is the major cause of disability and death in diabetic patients. Dyslipidemia and inflammation play a major role in the pathogenesis of atherothrombotic cardiovascular disease in diabetic patients. We aimed to assess the association between platelet volume and the atherogenic index of plasma in relation to atherothrombotic cardiovascular disease in diabetes. **Material and Methods:** In 108 diabetic patients, which were divided into two groups according to the atherothrombotic cardiovascular disease, we assessed the mean platelet volume and the atherogenic index of plasma. In diabetic patients without atherothrombotic cardiovascular disease, we calculated the Framingham risk score, which was then correlated with the mean platelet volume and atherogenic index of plasma. **Results:** The mean platelet volume and atherogenic index of plasma were significantly higher in diabetic patients with atherothrombotic cardiovascular disease. Also, both were increased in diabetic patients with a high calculated Framingham risk score compared to other groups. There was a statistically significant positive correlation between atherogenic index of plasma, mean platelet volume, and Framingham risk score (n= 54, r = 0.595, P < 0.0001 and r = 0.473, P = 0.0003). **Conclusions:** This study concluded that the mean platelet volume and the atherogenic index of plasma are increased in diabetic patients with atherothrombotic cardiovascular disease. Also, they were increased in diabetic patients with higher Framingham risk score and this may confer future risk for atherothrombotic cardiovascular events.

Keywords: atherothrombosis, diabetes mellitus, inflammation, platelets.

Introduction

Diabetes mellitus (DM) is considered an atherothrombotic cardiovascular disease (ACVD) – defined as an atherosclerotic lesion disruption with thrombus formation – that remains a major cause of cardiovascular morbidity and death in diabetic patients, particularly long-term type 2 DM (T2DM), with a more complex, serious and worse outcome relative to nondiabetic individuals [1].

Clinically, platelet volume measurement has been of interest to researchers since the mean platelet volume (MPV), which defines the blood platelet average size, correlates with platelet function and activation, including aggregation, synthesis of thromboxane, the release of beta-thromboglobulin, procoagulant activities or expression of adhesion molecules [2]. In dyslipidemia and diabetes mellitus, cardiovascular risk factors, MPV is also increased [3].

DM and dyslipidemia commonly coexist, with lipid abnormalities occurring in about 60% to 70% of patients with T2DM and hyperglycemia, hastening atheroma formation [4]. Hypertriglyceridemia with an increased ratio of low-density lipoprotein-cholesterol (LDL-C) to high-density lipoprotein-cholesterol (HDL-C) characterizes diabetic dyslipidemia that pre-

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disposes diabetic patients to ACVD [5]. Atherogenic index of plasma (AIP) [log triglyceride/HDL-Cholesterol] – in mmol/L – has recently been regarded as a reliable marker for plasma atherogenicity and is positively correlated with the cardiovascular disease risk. The high levels of triglycerides (TG) are known to be an important risk factor for increased LDL-C particles, with small and dense LDL-c, leading to increased cardiovascular risks [6].

Although MPV and AIP are studied in some studies in different populations of patients, few data exist regarding their role as indicators of ACVD in patients with diabetes. Therefore, we have designed this study in this respect.

Material and Methods

Study Population

All the procedures used in this study were consistent with the current revision of the Declaration of Helsinki. Written consent was obtained from participants before enrollment in the study.

This study included one hundred and eight people [45 males (41.7 %) and 63 females (58.3 %)], with type 2 diabetes; diabetes was diagnosed by patient history in conjunction with laboratory investigations, including fasting plasma glucose (FPG) of 126 mg/dL, or 2-hour plasma glucose of 200 mg/dL during the oral glucose tolerance (OGTT), or hemoglobin A1C (HbA1c) of 6.5% or more [7]. As evidenced by history, clinical examination, ECG, echocardiography, neuroradiological investigations, or Doppler ultrasound, we included two groups. Group I included diabetic patients with ACVD and group II included diabetes patients without demonstrated ACVD.

We excluded patients with hematological disorders and neoplastic disorders. None of the study participants had received anticoagulant drugs, non-steroidal anti-inflammatory drugs, lipid-lowering drugs, or oral contraceptive drugs before hospital admission; also, we have excluded patients with hemorrhagic stroke, liver disease, renal failure, or patients with thrombocytopenia due to any cause. Patients that refused to be enrolled in the study were also excluded.
All study participants were subjected to history taking and thorough clinical examination. Laboratory investigations were done according to the clinical pathology laboratories of Zagazig University hospital protocols: complete blood count (CBC), liver function tests, renal function tests, FPG, HbA1c, high-sensitivity C-reactive protein (hsCRP).

All CBC analyses were performed in the hematology laboratory of the Zagazig University Hospital. CBC analyses were performed with the same analyzer within one hour after collecting blood samples using Sysmex XS-500I, Sysmex Europe GmbH automated analyzer (Norderstedt, Germany). Reference values of MPV for the Sysmex XS-500I equipment are 7.1- 11.2 fL at our laboratory. MPV assay was standardized according to the manufacturer's instructions. All measurements with the Sysmex XS-500I device were performed using the flow cytometric technique.

Roche/Hitachi Cobas 8000 (Cobas c702) was used for the lipid profile, including total cholesterol (TC), triglycerides (TG), low-density lipoproteins cholesterol (LDL-C) and high-density lipoproteins cholesterol (HDL-C). Non-HDL-C was calculated as total cholesterol – HDL-C. Calculation of the atherogenic index of plasma (AIP) was done by using the following formula = Log10 (TG/HDL) in mmol/L [6]. Based on AIP, we classified patients into three groups: low risk < 0.11; intermediate risk 0.11 – 0.21; and high risk > 0.21 [6, 8]. For diabetic patients without ACVD, we calculated the risk level of future development of ACVD based on the Framingham risk score (FRS), and then we categorized the risk using FRS; the resulted categories were low risk (< 10%); moderate risk (10 – 20%); and high risk (>20%) [9].

Statistical analysis

Data were analyzed using MedCalc for Windows®, version 18.9.1 (MedCalc Software, Ostend, Belgium). Data were tested for normality using the Shapiro Wilk test, and continuous variables that were found normally distributed were expressed as mean (M) ± standard deviation (SD); for non-normally distributed data, they were expressed as median and (minimum-maximum). For parametric variables, Student's test was used for comparison, while the nonparametric rank-sum test was used for non-normally distributed data. For comparisons of quantitative variables between the three groups, if data were parametric, one-way ANOVA was used, whereas Kruskal-Wallis (KW) was used if data were not parametric. For categorical variables, a number (percentage) was used to express them; they were compared using the Chi-square ($\chi 2$) or Fisher's exact test. Pearson's correlation or Spearman rank correlation was used to evaluate the association between MPV, AIP, and other study parameters. Univariate and multivariate linear regression analysis was used to evaluate the impact of MPV and AIP on FRS (numerical value). Receiver operating characteristic (ROC) curve analysis was used to identify the utility of MPV and AIP for prediction of future ACVD outcomes with maximum sensitivity and specificity of generated cut-off values. A p-value < 0.05 was considered statistically significant.

Results

A total of 108 individuals (45 male and 63 female) were included in this study, with a mean age of 61.02 years. Patients with diabetes and ACVD (group I) had an HbA1c value of 8.92% versus 8.52% in diabetic patients without ACVD (group II). Fasting blood glucose was higher in group I (M=199.68, SD=62.57) compared to group II (M=161.13, SD=58.75); t(106)= -2.09, p=0.043. Other baseline characteristics between the two main groups are summarized in Table 1.

Table 1. Demographic, clinical and laboratory features between the study groups (n=108).

	Group I (Patients with diabetes and CVD) (n=54)	Group II (Patients with diabetes without CVD) (n=54)	Test	P-value
Age (Years)			t	0.094
Mean± SD	61.80 ± 4.33	60.24 ± 5.22	-1.69	(NS)
Sex			χ^2	0.560
Male 'No (%)'	21 (38.9%)	24 (44.4%)		(NS)
Female 'No (%)'	33 (61.1%)	30 (55.6%)	0.340	
Smoking Status			χ^2	
Non-Smoker 'No (%)'	38 (70.4%)	39 (72.2%)		0.832
Smoker 'No (%)'	16 (29.6%)	15 (27.8%)	0.045	(NS)
Hypertension			χ^2	
No 'No (%)'	17 (31.5%)	21 (38.9%)		0.546
Yes 'No (%)'	37 (68.5%)	33 (61.1%)	0.365	(NS)
DM duration (Years)			**MW**	**0.0001**
Median (Range)	20 (10 – 35)	13 (8 – 30)	5.35	**(S)**
Serum Albumin (g/L)			t	**<0.0001**
Mean± SD	34.56 ± 6.53	41.73 ± 4.98	5.67	**(S)**
Creatinine (µmol/L)			t	0.799
Mean± SD	93.65 ± 26.75	92.28 ± 26.39	-0.26	(NS)
HbA1c (%)			t	0.255
Mean± SD	8.92 ± 1.48	8.52 ± 2.05	-1.15	(NS)
MPV (fL)			t	**0.0001**
Mean± SD	10.77 ± 1.79	9.51 ± 1.52	-3.95	**(S)**
hsCRP			**MW**	**<0.0001**
Median (Range)	22 (5 – 55)	4.5 (1 – 19)	7.93	**(S)**

Note: t = Independent sample (t) test, MW = Mann Whitney U test, χ^2 Chi-squared test, DM = Diabetes mellitus, HbA1c= hemoglobin A1c, MPV= mean platelet volume, hsCRP= high-sensitivity C-reactive protein

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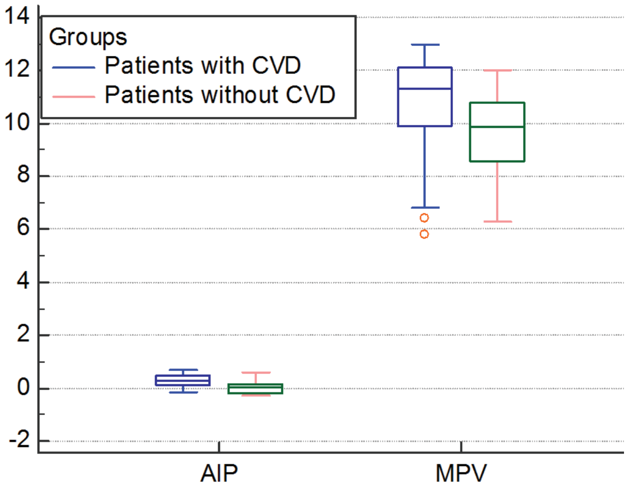

Figure 1: A box-plot showing the differences between patients with diabetes with or without CVD considering AIP and MPV.

Regarding MPV, it was found to be higher in group I (M=10.77, SD=1.79) compared to group II (M=9.51, SD=1.52); t(106)= -3.59, p=0.0001 (Figure 1).

AIP levels were found to be higher in group I (M=0.29, SD=0.21) compared to group II (M=0.03, SD=0.21); t(106)= -6.32, p<0.0001 (Figure 1).

In this study, after breaking the total population per tertile according to the level of AIP, we have found that 43 (39.8%) patients had a low risk (group A) (AIP<0.11); 18 (16.7%) patients had intermediate-risk (group B) (AIP=0.11-0.21) and 47 patients (43.5%) patients had a high risk (group C) (AIP> 0.21). Group I with proven ACVD had 11 (20.4%) patients in the low-risk group, 6 (11.1%) patients in the intermediate-risk group, and 37 (68.5%) patients in the high-risk group. Group II with no proven ACVD had 32 (59.3%) patients in the low-risk group, 12 (22.2%) patients in the intermediate-risk group, and 10 (18.5%) patients in the high-risk group. Other lipid parameters are summarized in Table 2.

Based on the AIP risk profile, MPV was higher in patients with high AIP (group C) compared to the other two groups by one-way ANOVA (F(2,105) =8.96, p<0.001). LSD post-hoc test revealed that MPV is significantly different in group C (10.87 ± 1.78) compared to group A (9.40 ± 1.52, p=0.001), while there was no statistically significant difference between group B and the other two groups.

The FRS in diabetic patients without ACVD (group II) varied between 5.39% and 63.5%, with a mean of 23.38 ± 13.73%. Ten participants (18.5%) had a low risk of ACVD (FRS<10 %), 17 participants (31.5%) had a moderate risk (FRS=10–20%), and 27 participants (50%) had a high risk of ACVD (FRS>20%).

Based on FRS, there was a statistically significant difference in diabetic patients without ACVD regarding MPV between the three groups as determined by one-way ANOVA (F(2,51) =9.55, p<0.001). LSD post-hoc test revealed that MPV is significantly different between high FRS (10.29 ± 1.37) compared to moderate

Table 2: Different lipid parameters, including AIP, between the study groups (n=108).

	Group I (Patients with diabetes and CVD) (n=54)	Group II (Patients with diabetes without CVD) (n=54)	Test	P-value
Total Cholesterol (mmol/L) Mean± SD	5.33 ± 1.30	5.52 ± 0.94	t 0.90	0.370 (NS)
TG (mmol/L) Median (Range)	1.67 (0.71 – 3.67)	1.47 (0.71 – 3.32)	**MW** 1.84	0.066 (NS)
LDL-c (mmol/L) Mean± SD	3.61 ± 1.25	3.35 ± 0.97	t -1.25	0.215 (NS)
HDL-c (mmol/L) Mean± SD	0.89 ± 0.23	1.45 ± 0.35	t 9.62	**<0.0001 (S)**
Non HDL-c (mmol/L) Mean± SD	4.43 ± 1.28	4.08 ± 1.06	t -1.57	0.12 (NS)
AIP Mean± SD	0.29 ± 0.21	0.03 ± 0.21	t -6.32	**<0.0001 (S)**

Note: t = Independent sample (t) test, MW = Mann Whitney U test, TG= triglycerides, LDL-C= low density lipoprotein cholesterol, HDL-C= high density lipoprotein cholesterol, AIP= atherogenic index of plasma.

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FRS (8.68 ± 1.14, p<0.0001) and low FRS (8.79 ± 1.46, p=0.003). Also, AIP by one-way ANOVA was (F(2,51) =9.67, p<0.001). LSD post-hoc test revealed that AIP is significantly higher in patients with high FRS (0.14 ± 0.20) compared to patients with moderate (-0.04 ± 0.17, p= 0.004) and low FRS (-0.12 ± 0.14, p= 0.001).

Concerning the other parameters, a Kruskal-Wallis H test showed that there was a statistically significant difference between the three groups regarding the systolic blood pressure X2 (2) = 21.57, p= 0.00002, with a mean rank systolic blood pressure of 11.85 for low FRS, 22.12 for moderate FRS and 36.69 for high FRS. Also, regarding DM duration, there was a statistically significant difference, determined by one-way ANOVA (F(2,51) =5.27, p=0.008). LSD post-hoc test revealed that DM duration is significantly different between high FRS (16.04 ± 4.90) compared to low FRS (10.5 ± 2.17, p= 0.002).

The correlation between AIP, MPV, and other study parameters was tested using appropriate correlation analysis. Positive correlation between AIP or MPV and FRS in patients with diabetes and without proven ACVD (n= 54, r = 0.595, P < 0.0001 and r = 0.473, P=0.0003) were determined. Another correlation analysis between AIP and other study parameters is summarized in Tables 3 and 4.

Table 3: Correlation between AIP and study parameters in patients with diabetes with and without CVD (n=108).

	Whole Population with diabetes (n=108)		Group I (Patients with diabetes and CVD) (n=54)		Group II (Patients with diabetes without CVD) (n=54)	
	r	p	r	p	r	p
Age	0.069*	0.478	0.074*	0.594	-0.094*	0.497
HbA1c	0.170*	0.081	0.096*	0.499	0.068**	0.626
FPG	0.272**	0.065	0.371**	0.158	-0.01**	0.958
SBP	0.396**	<0.0001	0.117**	0.399	0.609**	<0.0001
Albumin	-0.434*	0.0001	-0.295*	0.068	-0.097*	0.529
MPV	0.456*	<0.0001	0.427*	0.001	0.236*	0.086
hsCRP	0.711**	<0.0001	0.252**	0.084	0.670**	0.0001
FRS CVD risk	-	-	-	-	0.595*	<0.0001

Note: r= correlation analysis, HbA1c= hemoglobin A1c, AIP= atherogenic index of plasma, FBP= fasting plasma glucose, SBP= systolic blood pressure, FRS= Framingham risk score, MPV= mean platelet volume, hsCRP= high-sensitivity C-reactive protein, CVD= cardiovascular disease
* Pearson correlation coefficient, ** Spearman's coefficient of rank correlation

Table 4: Correlation between MPV and study parameters in patients with diabetes with and without CVD (n=108).

	Whole Population with diabetes (n=108)		Group I (Patients with diabetes and CVD) (n=54)		Group II (Patients with diabetes without CVD) (n=54)	
	r	p	r	p	r	p
Age	0.114**	0.24	-0.003**	0.98	0.163*	0.239
HbA1c	0.047**	0.630	-0.134**	0.345	0.097**	0.487
FPG	0.542**	0.0001	0.348**	0.187	0.391**	0.03
SBP	0.297**	0.002	0.267**	0.051	0.335**	0.013
Albumin	-0.203**	0.065	-0.051**	0.759	0.286*	0.036
TC	0.027**	0.779	0.046**	0.741	0.114**	0.41
TG	0.328**	0.0005	0.358**	0.008	0.219**	0.111
LDL-c	0.124**	0.2	0.042**	0.763	0.157*	0.256
HDL-c	-0.506**	0.0001	-0.350**	0.009	-0.188*	0.173
Non-HDL-c	0.175**	0.069	0.098**	0.482	0.192**	0.165
hsCRP	0.465**	<0.0001	0.099**	0.501	0.211**	0.1261
FRS CVD risk	-	-	-	-	0.473*	0.0003

Note: r= correlation analysis, HbA1c= hemoglobin A1c, TG= triglycerides, LDL= low density lipoprotein cholesterol, HDL-c= high density lipoprotein cholesterol, MPV= mean platelet volume, FBP= fasting plasma glucose, SBP= systolic blood pressure, FRS= Framingham risk score, hsCRP= high-sensitivity C-reactive protein, CVD= cardiovascular disease
* Pearson correlation coefficient, ** Spearman's coefficient of rank correlation

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Significant relationship between FRS (as the dependent variable) and AIP (β = 37.63, 95% CI: 22.82 – 52.44; p = <0.0001; R2 = 0.33) and MPV (β = 3.69, 95% CI: 1.62 – 5.76; p=0.0008; R2 = 0.197) by using univariate linear regression analysis. In multivariate regression model that include MPV and AIP with adjustment for DM duration, SBP and hsCRP. AIP and MPV still could have the ability to affect the ACVD risk. In this adjusted model, the adjusted β coefficients for AIP and MPV were 17.21, p=0.049 and 1.79, p=0.047, respectively.

For the prediction of ACVD in patients with diabetes, at the best cut-off value of AIP (> 0.199), the sensitivity and specificity was 68.52% and 81.48% respectively, and AUC was 0.80, and at the best cut-off value of MPV (>11.2 fL), the sensitivity and specificity were 53.7% and 92.6% respectively, and AUC was 0.74 (Figure 2).

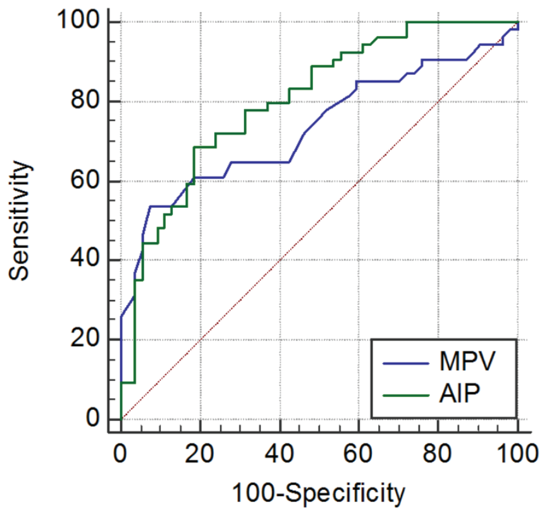

Figure 2. ROC curve analysis to determine the best cut-off value of MPV and AIP used to predict CVD in patients with diabetes.

Discussion

Despite the multifactorial and heterogeneous pathogenesis of ACVD in diabetes, it was found that dyslipidemia is a powerful predictor and a substantial risk factor to be considered in such population and the state of chronic low-grade inflammation that predispose to many complications related to atherothrombosis. We have examined standard lipid profile parameters together with the calculation of AIP. We have also measured MPV, which reflects platelet function and activation that is increased in many inflammatory states [10].

MPV is one of the most commonly used surrogate platelet activation markers in which greater platelet volume means being enzymatically and metabolically more active than smaller platelets [11]. MPV is higher in hypertensive and diabetic patients with disease progression and the presence of target organ damage [12, 13]. In this study, we have found that MPV is significantly higher in diabetic patients with ACVD. In diabetic patients without ACVD with high FRS, MPV was higher than those with low FRS. The findings of Marković et al. were consistent with our results; they found a higher MPV in patients with high FRS; however, this difference was not statistically significant [14]. We found a positive statistically significant correlation between MPV and some CV risk factors, including systolic blood pressure (SBP) and FPG; again, this was not the case in the study of Marković et al. [14].

In our study, we found that there was a statistically significant correlation between MPV and FRS in diabetic patients without ACVD. Also, Maluf et al. have found a significant correlation between MPV and FRS; this relation persisted after the adjustment of confounders, and it was concluded that MPV was independently correlated with higher CVD risk based on FRS [15]. Also, in a study by Kim et al., the mean CVD 10-year risk (FRS) increased significantly by increasing levels of MPV in patients with hyperglycemia compared to those with normal glucose tolerance [16].

In our study, there was no significant correlation between MPV and HbA1c in diabetic patients. In the study by Ulutas et al. conducted on individuals with DM, the values of MPV were higher for those with HbA1c >7% (8.30 ± 1.3 fL) compared to those with HbA1c <7% (7.50 ± 1.1 fL; p = 0.039). MPV presented a positive correlation with HbA1c (r=0.39, p<0.001) and plasma glucose (r=0.41, p<0.001), as well as with diabetes duration (r=0.22; p=0.02) [17]. We found a significant positive correlation between fasting plasma glucose and MPV in diabetic patients without ACVD. Contrary to us, Hekimsoy et al. did not find any correlation between MPV and FPG in patients with type 2 diabetes mellitus [18]. Consistent with our findings, Shimodaira et al., and Ulutas et al. also confirm a relationship between MPV and FPG in prediabetic subjects [17, 19].

Abnormal platelet-endothelial interactions have been identified as an essential pathogenic mechanism in atherosclerosis development [20]. In the case of diabetic subjects, MPV was found to be greater in those with microangiopathy (i.e., retinopathy, microalbuminuria), inflammation, diabetic nephropathy, atherothrombotic vascular disease and heart failure [21].

In our study, AIP was higher in diabetic patients with ACVD compared to those without ACVD; also, AIP showed a statistically significant increment in diabetic patients with high FRS, denoting the predictable capacity of AIP to determine the high-risk of diabetic individuals. AIP calculation involves the ratio of TG and HDL-C; a core lipoprotein abnormality in diabetes consists of elevated serum concentrations of TG-rich lipoproteins, high prevalence of LDL-C and low cholesterol-rich lipoprotein (HDL-c) concentrations [22]. While LDL-C is a powerful contributor to ACVD, such as coronary artery disease, significant hypercholesterolemia is less frequent in diabetic patients [23]. This was shown in our study, where the total cholesterol and LDL-c were not different between diabetic patients with or without ACVD.

In our study, there was a statistically significant correlation between AIP in diabetic patients without ACVD and each of the following parameters: systolic blood pressure, MPV and FRS. Niroumand et al. found that AIP was significantly correlated with risk factors for CVD and could be used in everyday practice as a regular CVD monitoring index, especially in people with other cardiovascular risk factors [24].

To date, more than a dozen large-scale studies have shown that hsCRP levels are a solid, independent predictor of future vascular events and that hsCRP adds prognostic risk information at all levels of LDL-C, Framingham Risk Score, and metabolic syndrome [25]. The addition of hsCRP to the definition of metabolic syndrome has been shown to improve the prediction of CVD [26].

In our study, there was a statistically significant positive correlation between AIP, MPV, and hsCRP in diabetic patients; a study conducted by Parrinello et al. showed that significant or persistent elevation of hsCRP over a 6-year duration was correlated with subsequent elevated diabetes risk. Also, people with a sustained increase in hsCRP were at the highest risk of CVD and death; similar findings were reported by Chuengsamarn et al. [27, 28].

The results of this study showed that AIP, MPV and the risk of future ACVD in diabetic patients (assessed by the FRS) were significantly correlated. Furthermore, after adjusting for confounders (DM duration, SBP, and hsCRP), AIP and MPV still could have the ability to affect the ACVD risk. Contrary to our findings, Nansseu et al. found that after adjustment for confounders (BMI, FPG, uric acid, DBP, and LDL-C), AIP did not appear to be an independent factor affecting the onset of ACVD ($p = 0.487$) [29].

Conclusions

The present study showed that high MPV and AIP were associated with an increased risk of future CV disease based on FRS. From a practical point of view, clinicians should be aware that patients with high MPV and AIP are at increased risk of developing ACVD, and they could be used in combination and with other conventional cardiovascular risk factors as inexpensive, non-invasive, easily measured markers for potential cardiovascular events.

Conflict of Interest

The authors declare that there is no conflict of interest.

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