Original Article
Hematology & Cardiology
DOI: 10.56016/dahudermj.1249255

DAHUDER Medical Journal
e-ISSN: 2791-9250

The atherogenic index of plasma complicates the thrombotic tendency of chronic myeloproliferative disorders: A retrospective cohort study

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ABSTRACT

Objectives: Chronic myeloproliferative diseases (CMPD) are neoplastic disorders leading to hypercoagulability and thrombosis. The critical hemostatic abnormalities include alterations in the blood viscosity and a history of recent thrombus. The aim of this study is to assess the interrelationships among the atherogenic index of plasma (AIP) and thromboembolism of CMPD with JAK2 V617F mutation.

Methods: Ninety-two patients diagnosed as CMPD with JAK2 V617F mutation and 73 controls were included into the study. The patients were evaluated for the presence of any venous or arterial thromboembolic events. AIP was calculated by using the formula log (Tg/HDL) from serum triglyceride and high-density lipoprotein values.

Results: The study group consisted of 30 patients (33%) with myelofibrosis (MF), 42 patients (46%) with polycythemia vera (PV) and 20 patients (21%) with essential thrombocythemia (ET). Two study groups were similar in terms of sex, age and other comorbidities ($p > 0.05$). CMPD group had higher levels of right blood cell count (RBC), red blood cell distribution width (RDW), platelets (PLT), hemotocrit (Hct) and AIP. Univariate and multivariate logistic regression analysis revealed that platelet count, RBC and AIP were independent predictors for thrombosis in both groups. The comparison of ROC curve analysis disclosed that AIP was superior to platelet count and RBC in predicting thrombosis.

Conclusion: AIP can be used to determinate higher risk of thromboembolism in patients with CMPD. As a reliable and 'easy-to-assess' diagnostic tool, AIP could be useful for the determination of thrombotic events in CMPD clinicobiological disease course.

Keywords: Atherogenic index, myeloproliferative, Janus kinase, thromboembolism,

BCR-ABL negative chronic myeloproliferative diseases (CMPD) namely; essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) are driven by functional pathogenic mutation. [1, 2] The Janus kinase 2 (JAK 2) V617F mutation is the most common genetic mutation. It is detected in almost all of the patients with PV and about half of PMF and ET patient population. [3, 4] Numerous symptoms including fatigue, weight loss, loss of appetite, abdominal swelling, early satiety, rapid bleeding/bruising, painful joint swellings, tinnitus and pain radiating from the left upper quadrant to

Received: *.February 8, 2023;* ***Accepted:*** *April 26, 2023;* ***Published Online:*** *April 29, 2023*

How to cite this article: *Karadeniz M, Ozcan Abacioglu O, Malkan UY, Haznedaroğlu IC. The atherogenic index of plasma complicates the thrombotic tendency of chronic myeloproliferative disorders: A retrospective cohort study. DAHUDER MJ 2023;3(2):54-61. DOI: 10.56016/dahudermj.1249255*

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the left shoulder could be observed during the clinical course of CMPD, especially in MF. [5] Thrombotic and hemorrhagic anomalies are among the leading causes of the morbidity and mortality in all subgroups of CMPD. [6] Arterial and venous thromboses are associated with adverse outcome in PV. The symptoms of PV primarily occur due to elevated red blood cell count (RBC) which results in the increased blood viscosity and beyond this high platelet counts contribute to the occlusion of vessels. Thrombosis is responsible for 45% of the deaths in those patients with CMPD. [7-9] Thrombosis of the greater arteries is an important cause of mortality due to ET or can trigger severe neurological, cardiac or peripheral arterial events. [10, 11] Anemia is detected in most of the cases at the time of diagnosis in PMF. Besides leukocytosis, leukopenia, thrombocytosis and thrombocytopenia could also be seen. Thrombotic or bleeding complications are common particularly in the presence of thrombocytosis. While focusing on the question of whether there is another condition that predisposing to the generation of thrombosis in CMPD; atherogenic index of plasma (AIP), which is a parameter that causes an increase in the incidence of clot formation in the normal population, shall be one of the first to be considered from the clinical point of view. [12] In those patients with CMPD, there is no extensive data regarding whether the atherogenic index of plasma causes an extra risk for the genesis of thrombus in addition to the RBC and platelet elevation and/or dysfunction. The aim of this study is to assess the atherogenic index of plasma in the patients with CMPD and reveal its relationship between thrombosis, due to the disease course.

METHODS

Study population

Ninety-two patients followed in our clinic with the diagnosis of CMPD and positive for JAK2 V617F gene mutation with real time polymerase chain reaction test and 73 controls randomly selected from patients who applied to the outpatient clinic and had no mutation for CMPD and no CMPD diagnosis pathologically were included in this retrospective cohort study. The sample width was determined by power analysis. The diagnosis of CMPD was made according to the 2016 revision to the World Health Organization classification. 42 of the patients in study group were diagnosed as PV, 30 of them as PMF and the remaining 20 patients as ET. Laboratory data, demographic properties and comorbidities of all participants were retrospectively scanned and noted. Sub-diagnostic groups (ET, PV and PMF) of the patients in the CMPD group and laboratory results used in the diagnosis were recorded. The history of arterial / venous thrombosis was investigated in detail for both groups. Acute myocardial infarction, thromboembolic stroke, deep vein thrombosis, pulmonary embolism, splenic or portal vein thrombosis, acute arterial occlusion defined by imaging methods such as doppler ultrasonography, coronary arteriography or magnetic resonance imaging was defined as the presence of thromboembolic event. The treatments for the primary disease of the patients in the study group were obtained from the from hospital information recorded at patients' regular check-ups. Hypertension (HT) was defined as a systolic blood pressure of 140 mmHg, a diastolic blood pressure of 90 mmHg or more, or a person using antihypertensive medication as mentioned in American Heart Association guidelines. Diabetes mellitus (DM) was defined by according to the American Diabetes Association's 2022 revision criteria as fasting blood glucose is 126 mg/dl and above in at least two tests performed on different days, or if > 200 mg/dL is detected in at least two random blood glucose measurements or if HbA1c values are 6.5% or higher. Smoking habit, a major trigger of thrombosis in CMPD could not be accessible for the patients and control group because of the retrospective design of the study.

Laboratory parameters and calculation of atherogenic index of plasma

Blood samples were collected, and the laboratory measurements of serum values of hematocrit (Hct), hemoglobin (Hb), mean platelet volume (MPV), platelets, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell distribution width (RDW), lipid parameters, kidney function tests were performed and analysed with appropriate kits and atherogenic index of plasma was calculated by using the formula log (Tg/HDL) from serum triglyceride and HDL values. [13] Lipid values were directly measured.

Ethical approval

The study was approved by the local Clinical Research Ethics Committee of our hospital (2022/05-42, 16969557/543). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's hu-

man research committee.

Statistical analyses

All analyses were performed on SPSS 17.0 (SPSS for Windows 20.0, Chicago, IL, USA) and MedCalc for Windows. Data were expressed as mean ± SD for continuous variables and as number and percentage for categorical variables. Normality of the distribution of continuous variables was assessed using Kolmogorov-Smirnov test. The comparisons of the continuous variables between groups were performed using the independent samples t-test and categorical variables with Chi-square test. Univariate and multivariate logistic regression analysis were used to determine the relation between thrombosis and other variables and variables with a p value < 0.25 in univariate analysis were analyzed in multivariate regression. Receiver operating characteristics (ROC) curve analysis was performed to demonstrate the cut-off values and sensitivity and specificity of atherogenic index of plasma for predicting the thrombosis in CMPD. *p* value < 0.05 for all comparisons was considered as significant.

RESULTS

The study group consisted of 30 MF, 42 PV and 20 ET patients. It was estimated that the study would end

Table 1. Baseline demographic properties and laboratory results of the groups

	CMPD group (n = 92)	Control group (n = 73)	*P*
Age, years	63.3 ± 15.2	60.8 ± 13.3	0.281
Sex, male, n (%)	41	25	0.179
HT, n (%)	27	13	0.086
DM, n (%)	9	9	0.772
HF, n (%)	7	3	0.271
COPD, n (%)	2	1	0.637
CKD, n (%)	9	5	0.384
Malignancy, n (%)	8	3	0.278
Hb (g/dL)	12.6 ± 2.5	12.0 ± 2.3	0.147
HTC (%)	39.0 ± 7.8	35.9 ± 6.7	0.008
WBC (10^3/ µL)	8.8 ± 4.3	7.6 ± 5.3	0.125
RBC (10^6/ µL)	4.6 ± 1.1	4.1 ± 0.8	0.002*
MCH (pg)	28.4 ± 4.9	29.3 ± 3.7	0.207
MCV (fL)	87.6 ± 13.0	88.0 ± 9.4	0.831
RDW (%)	19.4 ± 6.1	15.0 ± 2.7	< 0.001*
MPV (fL)	8.7 ± 0.9	8.7 ± 1.2	0.845
PLT (10^3/ µL)	337.5 ± 213.8	247.8 ± 132.4	0.002*
Glucose (mg/dL)	80.2 ± 15.7	72.2 ± 18.2	0.194
Creatinine (mg/dL)	1.0 ± 0.7	0.8 ± 0.3	0.075
Albumin (g/dL)	4.1 ± 0.5	4.2 ± 0.4	0.437
Total protein (g/dL)	7.1 ± 0.6	7.2 ± 0.6	0.808
Total cholesterol (mg/dL)	160.6 ± 50.7	165.4 ± 35.8	0.505
Triglyceride(mg/dL)	134.2 ± 61.6	153.4 ± 65.9	0.060
HDL (mg/dL)	42.0 ± 15.9	49.4 ± 12.6	0.002*
LDL (mg/dL)	102.2 ± 36.4	109.4 ± 31.2	0.186
Tg/glucose index	3.8 ± 2.8	3.3 ± 2.9	0.250
AIP	0.14 ± 0.26	0.01 ± 0.26	0.003*

Abbreviations: CMPD: chronic myeloproliferative diseases, HT: hypertension, DM: diabetes mellitus, HF: heart failure, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell count, RBC: red blood cell count, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, RDW: red blood cell distribution width, MPV: mean platelet volume PLT: platelet count, HDL: high density lipoprotein, LDL: low density lipoprotein, Tg: trigliseride, AIP: atherogenic index of plasma.

Table 2. Univariate and multivariate logistic regression analysis of the studied parameters

	Univariate analysis			Multivariate analysis		
	OR	CI 95%	P	OR	CI 95%	*P*
Age	1.004	0.971-1.037	0.818	-		
Sex	1.450	0.598-3.514	0.411	-		
RBC	1.384	0.912-2.100	0.127	1.152	0.739-1.795	0.043*
WBC	1.060	0.981-1.145	0.340	-		
Hb	1.044	0.869-1.254	0.648	-		
HTC	1.023	0.963-1.087	0.462	-		
MCV	0.992	0.955-1.031	0.697	-		
MCH	0.957	0.866-1.058	0.392	-		
RDW	1.015	0.940-1.097	0.699	-		
MPV	1.244	0.825-1.876	0.298	-		
PLT	1.004	1.002-1.006	0.001	1.003	1.001-1.006	0.003*
Glucose	0.999	0.987-1.011	0.858	-		
Total protein	0.776	0.398-1.515	0.458	-		
Albumin	0.680	0.277-1.667	0.399	-		
Total cholesterol	0.998	0.989-1.008	0.765	-		
Triglyceride	1.004	0.998-1.011	0.267	-		
HDL	0.976	0.946-1.008	0.338	-		
LDL	0.994	0.981-1.007	0.384	-		
AIP	16.291	1.632-16.260	< 0.001	12.580	11.609-13.630	< 0.001*
Tg/HDL	1.104	0.974-1.251	0.121	1.066	0.936-1.213	0.338

Abbreviations: Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell count, RBC: red blood cell count, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, RDW: red blood cell distribution width, MPV: mean platelet volume PLT: platelet count, HDL: high density lipoprotein, LDL: low density lipoprotein, AIP: atherogenic index of plasma, Tg: trigliseride.

with 95% reliability and 80% power, with a minimum of 63 patients for each group. The mean age of the patients in this group was 63.3 ± 15.2 and 60.8 ± 13.3 in the controls ($p = 0.281$). The groups were not different in terms of sex, HT, DM, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), heart failure (HF) and malignancy ($p > 0.005$, for all) but the patients with CMPD had a higher percentage of arterial or venous thrombosis (20% vs 6%) than the controls ($p = 0.019$). Nineteen patients (4 MF, 2 ET and 12 PV) in the CMPD group and 5 patients in the control group had a history of arterial or venous thrombosis. 4 patients in PV and 1 patient in ET had arterial thrombosis (mesentery infarct in two patients, acute ischemic stroke in two patients and myocardial infarction in one patient) and the remaining had venous thrombosis (portal or splenic infarct except one, who had deep vein thrombosis). Four of the patients in the controls had arterial thrombosis (2 myocardial infarction, 2 acute ischemic stroke) and one had deep vein thrombosis in their history. When the groups were compared in terms of laboratory results; we found out that the patients in CMPD group had lower levels of high-density lipoprotein cholesterol (HDL). Although triglyceride to HDL (Tg/HDL) ratio was similar between groups, atherogenic index of plasma was higher in CMPD group and the difference was statistically significant ($p = 0.250$, $p = 0.003$; respectively). Baseline demographic properties and laboratory results of the groups are depicted in Table 1.

Univariate and multivariate logistic regression analysis revealed that platelet count, RBC and AIP were independent predictors for thrombosis in both groups (Table 2). A moderate correlation was found between RBC, AIP, platelet count and thrombosis in correlation analysis ($r = 0.290$, $p < 0.001$; $r = 0.387$, $p < 0.001$ and $r = 0.282$, $p < 0.001$, respectively) and the correlation coefficient of AIP in CMPD group was higher than in the total patients ($r = 0.478$, $p < 0.001$). In ROC curve analysis the platelet count >

Table 3. The comparison of ROC curve analysis of AIP, RBC and platelet count for predicting the risk of thrombosis

	Difference between AUC	SE	CI 95%	Z statistic	P
RBC-PLT	0.0530	0.0948	-0.133-0.239	0.559	0.5759
AIP-RBC	0.2550	0.0921	0.0749-0.436	2.773	0.0056
AIP-PLT	0.2020	0.0750	0.0555-0.349	2.700	0.0069

Abbreviations: SE: standard error, CI: confidence interval, AIP: atherogenic index of plasma, RBC: red blood cell count, PLT: platelet count

270 x 10^3/ µL (sensitivity 78.3%, specificity 45.1%, AUC:0.577), AIP > 0.2 (sensitivity 100%, specificity 43.2%, AUC:0.779) and RBC > 3.34 x 10^6/ µL (sensitivity 39.1%, specificity 77.5%, AUC:0.519) predicted arterial or venous thrombosis risk in study population. Furthermore, the specificity of AIP to predict the risk of thrombosis was better in CMPD group (AUC:0.779, sensitivity 72.2%, specificity 70 %). Comparison of ROC curve analysis showed that AIP was superior to platelet count and RBC in predicting the risk of thrombosis (Table 3, Fig. 1).

DISCUSSION

Vascular complications, especially thrombotic events have commonly seen (nearly one third) in the patients with CMPD who had the JAK2 V617F mutation. [14, 15] Patients with JAK2 V617F mutation had enhanced procoagulation activity and the mutation also itself promotes megakaryocytopoiesis. [7, 16] Two-thirds of thrombosis are arterial in origin. [17] In a previous study by the Italian Polycythemia Working Group 40% of PV patients had arterial or venous thrombosis. Thrombosis has been detected in 12 (28%) of 42 patients with PV in our study, thus the thrombotic rate was lower when compared to the Italian study. In our cohort, microvascular thrombosis is more common and the incidence of transient ischemic attack and unusually located venous thrombosis have increased in the patients with ET. We were able to detect clinical thrombosis within 10% of the patients with diagnosed as ET.

JAK2 V617F positivity is observed in 6,7% patients with Budd-Chiari syndrome and 41% of these patients had the diagnosis of CMPD at the time of thrombosis occurrence or in a year. [18] Trembley and co-workers disclosed that unusual site thrombosis especially in the portal and hepatic veins occurred concurrently (26%) or just after (44%) the diagnosis of

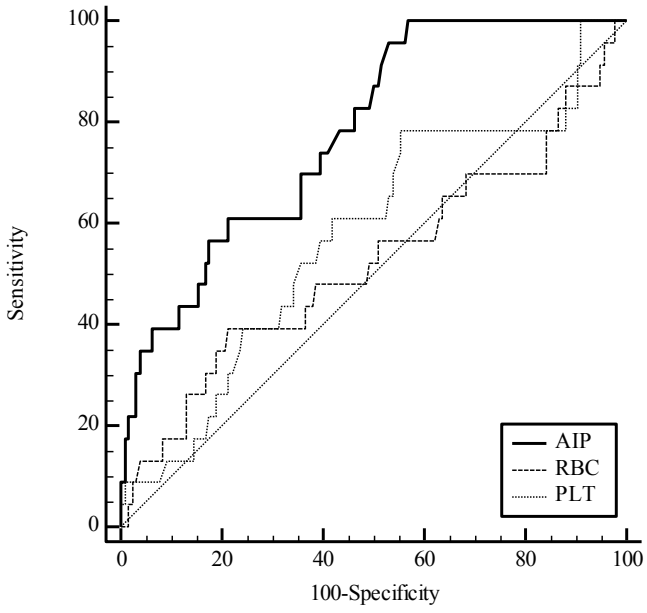

Fig. 1. The comparison of ROC curve analysis
Abbreviations: AIP: atherogenic index of plasma, RBC: red blood cell count, PLT: platelet count

CMPD. [19] Splanchnic vein thromboses were detected 8.1% of the CMPD patients. [20]

Among numerous causes of CMPD thrombosis, the most important factors are the alterations of the elevated number and destructed structure of erythrocytes and platelets. JAK2 V617F mutation carrying newly formed hyperactive thrombocytes can cause platelet aggregation due to the increased turnover. [21] Moreover, over 60 years of age, smoking, the presence of JAK2 V617F mutation especially for ET and any history of thrombosis are considered the most important clinical risk factors for thromboembolic events in various publication and prognostic thrombosis risk scoring models such as International Prognostic Score for Thrombosis in ET (IPSET) and revised IPSET. [22-31] Additional risk factors for thrombosis include cardiovascular risk factors like hypertension, diabetes mellitus and male sex. [32, 33] The results of our study are comparable with those classical concepts of CMPD. Beyond those classical risk factors, there is no study on the existence of different factors that may play a role in clot formation. Kubong *et al*. found that high AIP levels were associated with an increase in oxidative stress in patients with sickle cell anemia, which is also a hematological disease and has a genetic background. [34] Sherief and colleagues determined higher AIP levels in children with beta-thalassemia major and claimed that premature atherosclerosis is related with AIP in those children. [35] There is no other detailed study on this critical biomarker in the hematological diseases. AIP allows us to have information about the viscosity of the blood and is calculated using lipid parameters. AIP has a significant value in terms of both the risk of coronary artery disease and the prognosis of the disease. Likewise, high AIP values were predictive of adverse outcomes in acute ischemic stroke. [36]

There are some limitations of this present study; it is a single centre study with relatively small number of patients and retrospectively designed. Patient dependent factors like smoking or physical activity could not be recorded due to the retrospective nature of the study. This study is including only CMPD patients with JAK2 V617F mutation and the results and the relationship between AIP and thrombosis cannot be generalized for other hematological malignancies and also for other mutations as calreticulin or MPL which are also seen in CMPD. We cannot access the JAK2 V617F allelic burden information of the patients and in this respect, we cannot make comparisons between the groups.

CONCLUSION

In this study, AIP is found to be related with thromboembolism in CMPD patients. Therefore, not only complete blood counts but also other biochemical laboratory values should be closely followed in the CMPD patients. Thrombogenicity biomarkers such as AIP should be taken into account in terms of complications and lipid values follow up should be optimized for the overall management plan of CMPD. Our study with these results contributes to the literature as it provides a little important information on the AIP and CMPD. This small population, single-center study highlights the need for prospective multicenter studies involving other mutations and allelic burden in a large patient population to identify patients with high thrombotic risk.

Authors' Contribution

Study Conception: MK, ÖÖA, ÜYM, İH; Study Design: MK, ÖÖA, ÜYM, İH; Supervision: MK, ÖÖA, İH; Materials: MK, ÖÖA, ÜYM; Data Collection and/or Processing: MK, ÖÖA; Statistical Analysis and/or Data Interpretation: MK, ÖÖA, İH,; Literature Review: MK, ÖÖA; Manuscript Preparation: MK, ÖÖA, ÜYM, İH and Critical Review: MK, ÖÖA, ÜYM, İH.

Conflict of interest

In this article, all authors have stated that there is no conflict of interest between them.

Acknowledgements

None to declare

Financing

There is no financial or non-financial support for the article.

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