

Mean Platelet Volume as A Marker of Thrombosis in Antiphospholipid Syndrome Patients

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ABSTRACT

Antiphospholipid Antibody Syndrome (APS) is a systemic autoimmune disease associated with venous and/or arterial thrombosis with the presence and persistence of antiphospholipid antibodies (aPL). One of the currently discussed markers related to a high risk of thromboembolism is increased Mean Platelet Volume (MPV). This study aimed to determine the association between MPV and thrombosis events in APS patients. Systematically searched and reviewed studies from MEDLINE, Science Direct and the Cochrane Controlled Trials registry (CENTRAL) were performed from October until November 2018. Appraisal instruments from the Critical Appraisal Skills Programme (CASP-UK) for cohort studies were used. Two relevant studies were included in our review. In total, 389 patients consisting of 92 APS patients, 297 APS-negative patients, and healthy controls were involved. In two studies, the mean of MPV in APS group with thrombosis ranged from 7.85 to 9.22 fl. MPV in the APS group with thrombosis was higher than in the APS group without thrombosis and in healthy controls. The platelet size, measured as MPV, reflects platelet reactivity, including aggregation, glycoprotein IIb-IIIa expression, and production of more thrombogenic factors. In summary, there was a positive correlation between MPV and thrombosis in APS patients. Mean platelet volume might also be a potential clinical predictor for recurrence of thrombosis in APS patients. Future prospective studies with larger sample size were needed to validate this potential marker.

Keywords: Mean platelet volume, thrombosis, antiphospholipid syndrome

INTRODUCTION

Antiphospholipid Antibody Syndrome (APS) is a systemic autoimmune disease associated with venous or arterial thromboembolism and/or recurrent miscarriage with the presence and persistence of antiphospholipid antibodies (aPL).¹ The updated (Sydney) classification criteria for definite APS require the presence of a lupus anticoagulant (LA) and/or IgG or IgM anticardiolipin antibodies (aCL) present in medium or high titer, and/or anti-b2 glycoprotein-1 (aβ2GPI) (IgG and/or IgM) in serum or plasma (in titer >99th percentile). These aPL should be persistent, with a presence on two or more consecutive occasions at least 12 weeks apart.² The prevalence of aPL in asymptomatic subjects is approximately 1 to 5.6%.³ APS can occur primarily or secondarily (mostly caused by Systemic Lupus Erythematosus/SLE).^{4,5} About 30% of SLE patients developed APS, while only 20% of those were considered clinically significant.^{3,6}

The true prevalence of antiphospholipid-antibody positivity in the general population is not known due

to a lack of population-based study. Transient aPL can occur due to infections, supported by a study which found 10% aCL-positive and 1% LA-positive healthy blood donors but then decreased to less than 1% for both after 12 weeks.

The pathogenesis of thrombosis mediated by antiphospholipid antibody is multifactorial and involves numerous mechanisms, including activation of endothelial cells, platelets, and monocytes which triggers procoagulant and proinflammatory signal; inhibition of natural anticoagulant pathways such as tissue factor inhibitor, protein C, and annexin A5; activation of the complement system; and impairment of the fibrinolytic system.⁷

Platelets play a crucial role in hemostasis, inflammation, and thrombosis. Platelet activation, a central factor in many disorders, may be triggered by the presence of aPL. Upon activation, platelets release vasoactive and thrombogenic agents, which are considered as a mechanism of thrombosis in APS. Several investigators have used a series of platelet indices measured by hematologic analyzers, considering that platelet activation causes changes in

the morphology of platelets identified by Mean Platelet Volume (MPV).⁸ Furthermore, APS-related thrombosis due to platelet activation occurs through at least two mechanisms: facilitating β 2-glycoprotein I dimerization and enhancing surfaces that promote coagulative reaction.⁹

Several meta-analysis and prospective studies have reported the correlation between increased MPV with the risk of thromboembolism.^{10,11} Therefore, authors would like to determine the correlation between MPV and thrombosis in APS patients. To the best of our knowledge, there is limited knowledge about the value of MPV and its prognostic significance for thrombosis occurrence in patients with confirmed APS. It was hypothesized that MPV correlates with thrombosis in APS patients and MPV was expected to be a useful marker to manage a better prophylaxis strategy for thromboembolism in APS patients.

This study was performed and reported following the guideline from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and involved all studies to determine the correlation between MPV and thrombosis events in APS patients, irrespective of the publication status and language.¹² The participants were patients with antiphospholipid syndrome and healthy controls with the age of more than 18 years old. All studies on animals, which predominantly comprised neonates, post or perioperative patients and cancer patients were excluded.

Systematically searched MEDLINE, Science Direct and the Cochrane Controlled Trials registry (CENTRAL) was performed from October until November 2018, using the following key words: ("Antiphospholipid syndrome" or "Anti-phospholipid" or APS or Antiphospholipid) and ("Mean Platelet Volume" or MPV or Platelet) and (Platelet or RDW or "Red Cell Distribution Width" or PLR) and (Thrombosis or Thromboembolism or Thrombotic). To ensure a comprehensive literature search, reference lists from retrieved articles and reference literature (guidelines and systematic reviews) were investigated. Abstracts and other grey literature were also included through hand searching. Eligible studies were studies which assessed the level and correlation of MPV in APS patient with thrombosis. Review articles, animal studies, and studies in cancer or post-surgery patients were excluded. The authors of ongoing or unpublished trials were contacted to obtain additional details and information on these studies.

Two reviewers (MD and JHH) independently screened and decided on the inclusion of available studies. The studies were filtered a priori based on the title and the abstracts. Duplicated references were removed. The full texts of the included studies were assessed for eligibility. Any disagreement regarding the extracted data was resolved through discussion. The process of selecting the studies was plotted in the PRISMA flow diagram.

The methodological quality of included studies was assessed independently by two observers (MD and JHH) using the instrument from the Critical Appraisal Skills Programme (CASP-UK) for cohort studies or Oxford's Center of Evidence-Based Medicine (CEBM) for RCTs.^{13,14}

DISCUSSION

Twenty-six references from MEDLINE, 2 references from the Cochrane Central Register of Controlled Trials (CENTRAL), and 857 references from Science Direct were identified. Eleven references were retrieved by manually searching the references of identified papers. Thirty-five duplicate studies were removed, abstracts were filtered, and 878 studies which met the exclusion criteria were excluded. Eleven studies with full-text were assessed for eligibility, while nine studies were excluded because they did not use MPV as a laboratory indicator and the subjects involved were not diagnosed with APS.

Two relevant studies were found and included in our review.^{15,16} Three hundred and eighty nine patients consisting of 92 APS patients and 297 APS-negative patients and healthy controls were included.

A study by Korkmaz *et al.* found that MPV values in the APS group with thrombosis were higher (9.22 ± 1.00) than the same population at three months after the thrombosis event (8.20 ± 1.10), ($p = 0.0001$).¹⁵ Mean platelet volume in the APS group with thrombosis was also higher (9.22 ± 1.00) than the healthy controls (8.18 ± 0.97 respectively) ($p < 0.05$). In the study by Rupa-Matysek *et al.*, the MPV was significantly higher in APS with thrombosis group (mean 7.85, range 4.73 – 12.2 fl) compared to control group (6.85, range 5.01–7.93 fl, $p = 0.004$).¹⁶

In a study by Rupa-Matysek *et al.*, recurrent thrombosis was observed in 83 patients of the cohort study ($n = 247$). Among the APS group, recurrent thrombosis was documented in 66.3% of patients. The Receiver Operating Characteristic (ROC) analysis indicated a cut-off value of 7.4 fl for MPV with 86%

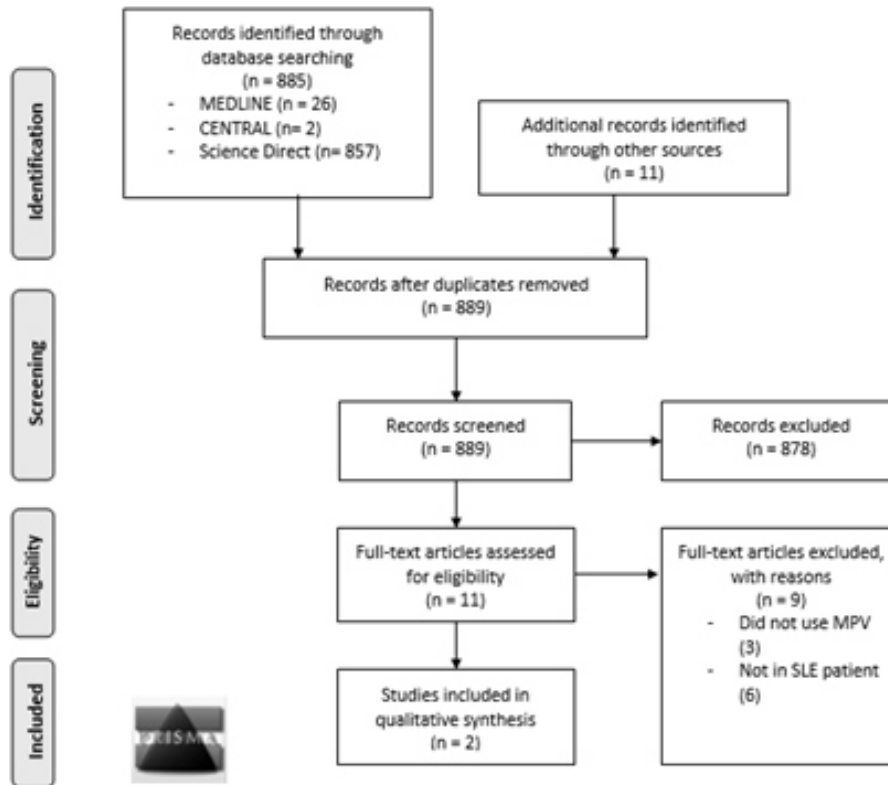


Figure 1. PRISMA flowchart of this review¹²

Table 1. Critical appraisal of included studies using appraisal instruments from CASP-UK¹³

Checklist	Korkmaz <i>et al.</i> (2014)	Rupa-Matysek <i>et al.</i> (2014)
Did the study address a clearly focused issue?	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes
Was the exposure accurately measured to minimize bias?	Can't tell	Yes
Was the outcome accurately measured to minimize bias?	Yes	Yes
Have the authors identified all the important confounding factors?	Yes	No
Was the follow up of subjects complete and enough?	Yes	Can't tell
Do you believe the results?	Yes	Yes
Can the results be applied to the local population?	Can't tell	Can't tell
Do the results of this study fit with other available evidence?	Yes	Yes

sensitivity and 82% specificity for prediction of thrombosis recurrence. The Area Under Curve (AUC) was 0.86 (p=0.0001). Based on the result of univariate analysis, MPV ≥ 7.4 fl, the history of pulmonary embolism, and hereditary thrombophilia were the only factors which were significantly correlated with thrombosis recurrence. Upon multivariate analysis, only MPV >7.4fl3.65, p=0.009) significantly associated with the risk of thrombosis recurrence in APS patients.¹⁶

Thrombosis has resulted from a hyper coagulable

state caused by direct activation of platelets, endothelial cells, and monocytes.¹⁷ Platelet activation, a major contributing feature of thrombosis, might be involved in APS-related thrombosis in at least two mechanisms. First, due to the presence of multiple receptors which interact with antibodies, platelets can facilitate the dimerization of β2-glycoprotein I enhancing the coagulation. Second, platelets provide a surface for the coagulation process.¹⁸ The platelet size, measured as MPV, reflects the activity of platelets,

Table 2. Summary table of included studies

Author/ Year	Level of Evidence/ Study Design / Participant / Inclusion Criteria	Intervention and Control Groups	Outcome Measures	Results
Korkmaz <i>et al.</i> / 2014 ^[15]	Level III Retrospective cohort N: 22 APS patients (both primary and secondary APS) & 22 healthy controls Inclusion criteria: All patients diagnosed with APS based on updated Sapporo classification criteria (2006)	Group 1: All patients on the first day of the thrombotic event Group 2: all the same patients at three months after the thrombotic events Control group: Healthy controls	Primary: MPV levels. Secondary: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, platelet count	There was a higher significance of MPV, ESR, and CRP in group 1 compared to group 2 and healthy controls
Rupa- Matysek, <i>et al.</i> / 2014 ^[16]	Level III Prospective Cohort N: 247 patients & 98 healthy controls Inclusion criteria: All patients with a history of thrombotic episodes and/or pregnancy loss were analyzed between 2009 and 2012. All patients were white Caucasians with a median age of 38 (range 18–66) years.	APS group: 70 APS-positive patients based on APS & thrombophilia tests APS-negative group: 177 APS-negative patients based on APS & thrombophilia tests Control group: 98 healthy controls	Primary: MPV Secondary: LA, aCL, a β 2GPI, ROC curve	There was a higher significance of MPV, in the APS group compared to controls. There was a positive correlation between LA and $a\beta$ 2GPI for the value of MPV in the APS group. The cut-off value of 7.4 fl for MPV showed 86% sensitivity & 82% specificity for prediction of thrombosis recurrence.

APS: antiphospholipid syndrome; MPV: Mean Platelet Volume; LA: Lupus Anticoagulant; ROC: Receiver Operating Characteristic

including glycoprotein IIb-IIIa expression, aggregation, and production of more thrombogenic factors (β -thromboglobulin, thromboxane A₂, platelet-derived growth factor, and P-selectin). The mechanism of the platelet size variation is multifactorial.¹⁹

In this review, it was found that MPV were significantly higher in patients with confirmed APS, especially if a thrombotic event was also observed, in comparison to healthy controls. Mean platelet volume was also higher in the APS group compared

to the APS-negative group. A significantly positive correlation between Lupus Anticoagulant (LA) and $a\beta$ 2GPI for MPV values was observed in the APS group; however, the mechanism remained unclear.

Both in the univariate and multivariate analysis by Rupa-Matysek *et al.*, MPV was significantly correlated with thrombosis recurrence in APS patients. Mean platelet volume values >7.4 fl was identified as a prognostic marker of thrombosis recurrence in APS patients with high sensitivity, sensitivity, and AUC. This finding was similar to other

studies which yielded a promising result of MPV as a marker for other thrombosis-related diseases. Evidence derived from several retrospective and prospective studies suggests that large platelets and high MPV values are associated with thrombotic events in several arterial disorders, such as coronary artery disease, restenosis following coronary angioplasty and ischemic stroke.^{11,19-21} Also, it has been demonstrated that higher MPV values were reported in venous thromboembolism such as deep vein thrombosis, and pulmonary thromboembolism.^{10,22-23} A Study by Tromsø, one of the largest population-based study on MPV, revealed a strong independent association of high MPV (> 9.5 fl) with VTE without other underlying conditions such as surgery, trauma, immobilization, or cancer.¹⁰

By far, only a small number of studies investigating the role of MPV in thrombotic events in APS and its related disorders; however, the evidence was rather contradictory. In one study comparing two different hematological analyzers, a lower level of MPV was reported in some 14.3% and 65.7% of cases with rheumatoid disease, not specifically in APS. Unfortunately, the relation of MPV with the thrombotic risk was not studied.²⁴ However, a more recent study reported that approximately 55% of patients with the antiphospholipid syndrome had increased MPV.²⁴ According to theory by Gasparyan *et al*, high MPV in APS and some rheumatoid diseases at remission are associated with a presence of large-sized platelets in thrombi. Whereas, low MPV in some high-grade inflammatory condition such as in rheumatoid arthritis and active SLE is possibly due to increased consumption of platelets at the sites of active inflammation.²⁵

Our findings of the association between an elevated MPV and thrombosis event in patients with APS is probably best explained by previous theory and hypothesis suggesting that an increased MPV is an indicator of larger-sized platelet in thrombi, which are enzymatically and metabolically more active than smaller platelets. These platelets also have greater prothrombotic potential due to higher levels of intracellular TXA2 and an increased procoagulant surface, although this hypothesis needs confirmation.^{9,27} Elevated MPV is also associated with other markers of platelet activity, such as increased platelet aggregation and increased expression of adhesion molecules.^{27,28}

In clinical practice, the measurement of MPV as a marker of thrombosis still has some limitations. Discordance of results between different cell

counters may be one of the issues.²⁴ In appropriate blood sampling and storage also may cause inaccurate estimation of platelet indices. It has been showed that platelet indices are sensitive to differences in blood sample anticoagulation, delay in processing, and in appropriate storage temperature. For instance, samples anticoagulated with ethylenediaminetetraacetic acid (EDTA) can result in an increase of the MPV due to platelet swelling in test tube.²⁹ It was found that within one hour of sampling, MPV value of blood samples anticoagulated in EDTA is 9% was higher than those anticoagulated with citrates. It can be minimized by rapid processing of samples (within less than one hour) using tubes with sodium citrate.³⁰

To the best of our knowledge, this is the first systematic review which determined the utility of MPV as a marker of thrombosis in antiphospholipid syndrome patients. Although MPV seemed promising, our systematic review also had several limitations. First, both of our included studies were cohort studies with a limited number of participants. Second, only one study performed a sufficient follow up to analyze the potential of MPV for thrombosis recurrence in APS patient. Thus, future prospective studies were needed to validate this finding.

CONCLUSION

In conclusion, there was a significant correlation between MPV and thrombotic events in antiphospholipid syndrome patients. The MPV may also be a potential predictor of thrombosis recurrence in APS patients; however, the evidence is still lacking. Future prospective studies with larger sample size and sufficient follow-up were needed to validate this potential marker.

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