RESEARCH ARTICLE

WILEY

The role of neutrophil-lymphocyte ratio, and mean platelet volume in detecting patients with acute venous thromboembolism

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Abstract

Background: Acute venous thromboembolism (VTE) refers to deep venous thrombosis (DVT) of the extremities or pulmonary embolism (PE), or to both. Reliable imaging is not always available making a serologic diagnosis, or biomarker, highly desirable.

Objective: This study aimed to examine the role of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) in detection patients with acute VTE.

Methods: A total of 327 patients with initial diagnosis of acute VTE who were admitted to Ziv hospital were evaluated. Of them, 272 patients with definitive diagnosis of VTE, and 55 patients without VTE were used as control group. Complete blood count (CBC), measurements of NLR, MPV, and PLR were determined at admission.

Results: Patients with VTE were older than controls (62 ± 18.9 vs 55.4 ± 15.1 years, respectively, $P = .03$). Female gender was predominant in the two groups. In the study group, 178/272 (66%) had DVT, 84/272 (31%) had pulmonary embolism (PE), and the rest had DVT and PE. NLR, MPV, and PLR were found to be significantly elevated in acute VTE compared to control ($P < .001$, $P = .008$, $P = .014$, respectively). A ROC curve analysis of NLR and MPV for predicting acute VTE was performed which found a cut-off value of 5.3 for NLR, an area under curve of (0.67 (0.60-0.75), $P < .001$, with a sensitivity of 69% and specificity of 57%. and a cut-off value of 8.6 for MPV, an area under curve of (0.61 [0.53-0.68], $P = .014$, with a sensitivity of 52% and specificity of 67%. Multivariate logistic regression model found that NLR (OR 1.2, 95% CI [1.01-1.4], $P = .041$) and MPV (OR 1.5, 95%CI [1.07-2.12], $P = .5$) were associated with acute VTE.

Conclusions: Neutrophil-lymphocyte ratio and MPV could be beneficial predictors for the early detection of potential acute VTE.

KEYWORDS

mean platelet volume, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio (PLR), venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE causes cardiovascular death and disability.[1] The risk of PE-associated mortality and morbidity extends far beyond the acute phase of the disease. In earlier follow-up studies, as many as 30% of the patients died during a follow-up period of up to 3 years, and up to 50% of patients continued to complain of dyspnea and/or poor physical performance 6 months to 3 years after the index event.[2] It is declared that PE is the most preventable cause of death among hospitalized patients. The pathophysiology of DVT and PE is inflammation and platelet activity. Virchow's triad of inflammation, hypercoagulability, and endothelial injury leads to recruitment of activated platelets that contain pro-inflammatory mediators.[1]

Diagnosis of VTE is often difficult, and point score criteria help to estimate the clinical likelihood of DVT and PE. Patients with a low-to-moderate likelihood of DVT or PE should undergo initial diagnostic evaluation with D-dimer testing alone without obligatory imaging tests.[1,3] However, patients with a high clinical likelihood of VTE should skip D-dimer testing and undergo imaging as the next step in the diagnostic algorithm. Score system for low clinical likelihood of DVT is zero points; moderate likelihood is score 1 to 2; high likelihood if score is 3 or greater. However, the D-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, D-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.[1,3] Adding markers is highly desirable. In recent years, more and more attention is given to the role of inflammatory markers in different diagnosis.[4-6] Few studies have been done about inflammatory factors in correlation to DVT and PE. These studies show clear correlation between some inflammatory factors as red blood cell distribution width (RDW), mean platelet volume (MPV), P-selectin, E–selectin, and DVT.[7-10]

While the traditional diagnosis of VTE relies on primarily imaging studies, a multimodality approach including serologic testing continues to evolve. Ongoing data support the use of molecular markers (biomarkers) that may not only aid in the diagnosis of VTE, but also predict recurrence risk and guide length and modality of treatment.[11]

These biomarkers hold promise to both explain the pathogenesis of thrombosis and serve as useful markers for diagnostic purposes. In this work, we will examine the correlation between DVT and selected inflammatory markers such as MPV, RDW, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR).

2 | MATERIAL AND METHODS

A retrospective cohort study which aimed to examine the association and correlation between VTE and various new inflammatory markers as RDW, MPV,PLR and NLR taking from medical records of patients admitted with venus thromboembolism. The study was conducted between the years 2010 and 2016 in the departments of internal medicine in Ziv medical center, Safed, affiliated to Azrieli Faculty of Medicine Bar Ilan University, Galilee, Safed, Israel. The study was approved by local Helsinki committee.

A total of 327 patients with initial diagnosis of acute VTE who met the inclusion and exclusion criteria were enrolled. Of them, 272 patients with definitive diagnosis of VTE, and 55 subjects, who were suspected to have VTE and admitted in the same period without evidence of VTE, served as a control group. We excluded patients with acute renal failure, patients treated with hemodialysis, with bone fractures, hepatic failure, and/or manifest active heart disease, such as cardiac failure, acute coronary syndrome, arrhythmia, and cardiac valve disease. Similarly, patients with infection, sepsis, chronic systemic inflammatory disease, and those who had been receiving medications affecting the number of leukocytes were excluded.

We compared between the two groups those with VTE and the controls in term of age, gender, RDW, MPV, PLR, and NLR.

Red blood cell distribution width, MPV, NLR, and PLR were obtained and calculated from the complete blood count which executed in our hematology unit with Beckman-Coulter Gen-S system device (Beckman-Coulter Inc). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. RDW and MPV were obtained from the results of CBC.

Deep venous thrombosis was diagnosed by ultrasound performed by senior and expert radiologists. PE was diagnosed by lung computed angiography which was interpretation by expert radiologists.

TABLE 1 Demographic and laboratory data of all study groups

Variable	Patients with VTE N = 272	Controls N = 55	P value
Age (y)	62.7 ± 18.9	55.4 ± 15.1	.003
Gender, female (%)	142 (52.4)	31 (57.4)	.501
WBC	9.5 ± 4.3	7.5 ± 2.4	<.001
HB	12.8 ± 2.2	12.9 ± 1.6	.665
MPV	8.6 ± 1.1	8.3 ± 0.8	.008
RDW	14.9 ± 1.9	14.6 ± 1.5	.262
NLR	5.3 ± 5.3	3.1 ± 1.9	<.001
PLR	180.2 ± 127.8	149.4 ± 70.5	.014
Platelet	248.3 ± 93.6	240.3 ± 58.8	.421
Neutrophils	7.3 ± 6.6	4.9 ± 2.1	.01
Lymphocytes	1.9 ± 2.3	1.8 ± 0.8	.847
Deep venous thrombosis	178 (66)		
Pulmonary embolism	84 (31)		
PE with DVT	8 (3)		

Abbreviations: DVT, deep venous thrombosis; MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio; PE, pulmonary embolism; PLR, platelet-lymphocyte ratio; RDW, red blood cell distribution width; VTE, venous thromboembolism.

2.1 | Statistical analysis

Data were analyzed using SPSS version 19 (IBM SPSS). Continuous variables are expressed as the mean standard deviation. The chi-square test was used to test differences in categorical variables between the cases and controls, and analysis of variance (ANOVA) or Student's t test was used for comparisons of continuous variables. Univariate analysis (Pearson correlation) was used in order to assess potential variables with significant correlation with VTE. The independent association of the inflammatory markers with VTE was investigated by multivariable logistic regression analysis. The odd ratio (OR) and 95% confidence interval (CI) were calculated for every associated variables. Receiver-operating characteristic (ROC) curve analysis was performed to identify the sensitivity and specificity of the inflammatory markers for the prediction of VTE $P < .05$ was considered significant in all statistical analysis.

3 | RESULTS

A total of 327 patients were enrolled in this retrospective study. Table 1 shows the demographic and laboratory data of all participants. A total of 272 patients (83%) patients were classified as belonging to acute VTE group, while 55 patients belonged to the control group. Among patients within the VTE group, 66% of them were diagnosed with DVT, 31% with PE, and 3% with PE and DVT. There was a no significant difference in gender between the two groups. There was a significant difference in baseline characteristics between the study group and controls regarding the age, and patients with VTE were older than the controls (62 ± 18.9 years vs 55.4 ± 15.1 years, $P = .003$, respectively). In the acute VTE group, the median value of WBC, PLR NLR, and MPV was statistically significant and higher than the control group.

A ROC curve analysis of NLR and MPV for predicting acute VTE was performed which indicated a cut-off value of 5.3 for NLR, an area under curve of (0.67 [0.60-0.75], $P < .001$, with a sensitivity of 69% and specificity of 57%, and a cut-off value of 8.6 for MPV, an area under curve of (0.61 [0.53-0.68], $P = .014$, with a sensitivity of 52% and specificity of 67% (Figure 1).

Univariate analysis showed significant associations between WBC, NLR, and MPV and VTE. Table 2 summarizes the multivariate logistic regression analysis which showed that age ≥ 62 year (OR 1.02, 95% CI [1.00-1.04], $P = .033$), WBC ≥ 9.5 (OR 1.15, 95% CI [1.02-1.3], $P = 0.026$), NLR ≥ 5.3 (OR 1.2, 95% CI [1.01-1.4], $P = .041$), and MPV ≥ 8.6 (OR 1.5, 95% CI [1.07-2.12], $P = .020$) were associated with acute VTE.

4 | DISCUSSION

This retrospective, observational, cohort study showed that NLR and MPV could be beneficial predictors for the early detection of potential acute VTE.
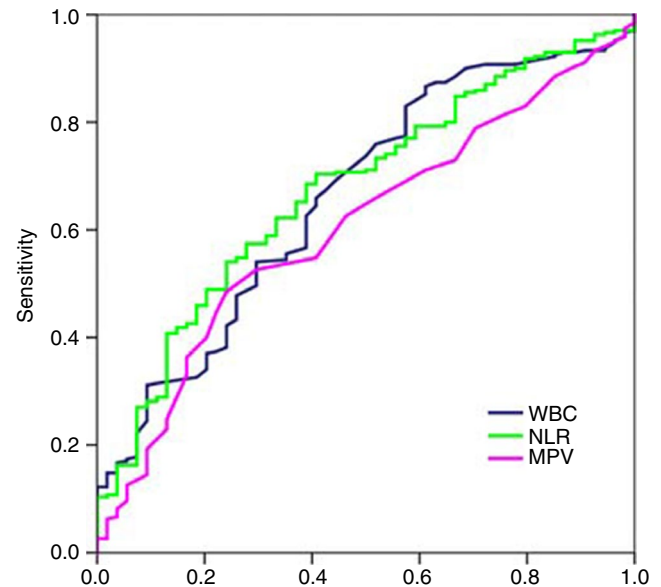

FIGURE 1 Receiver-operating characteristic (ROC) curve of WBC, NLR, and MPV to predict VTE. NLR is presented by green line with an AUC of 67% with a sensitivity of 69% and specificity of 57%. MPV is presented in pink line with an AUC of 61% with a sensitivity of 52% and specificity of 67%. MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio

TABLE 2 Multivariate logistic regression model for the association between venous thromboembolism and inflammatory markers

Variable	OR (95% CI)	P value
Age (y)	1.02 (1.00-1.04)	.033
WBC	1.15 (1.02-1.30)	.026
NLR	1.20 (1.01-1.40)	.041
MPV	1.50 (1.07-2.12)	.020

Abbreviations: MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio.

The present study investigated the role of potential and simple inflammatory markers in detecting patients with acute VTE. We included hematological inflammatory markers such as MPV, PLR, RDW, and NLR. We showed a significance utility of NLR and MPV in predicting acute VTE.

The diagnosis of VTE is often difficult, and the D-dimer is useful only for excluding acute venous thromboembolism; it lacks the specificity necessary for diagnosis confirmation. Therefore, the search for additional diagnostic measures is essential. Recently, inflammatory markers such as MPV, PLR, RDW, and NLR were used as predictors for diverse diseases.[12,13]

Neutrophil-lymphocyte ratio is accessible, cheap, and easy calculated. The importance of this inflammatory marker is related to the pathophysiological mechanism of inflammation and prothrombotic factors, which is characterized by an increased number of circulating leukocytes and cytokines.[14] On the other hand, lymphocytopenia appears as a consequence of lymphocyte margination and

redistribution in the lymphatic system, with accelerated apoptosis.[15] The predictive role of NLR has been evaluated in patients with infections, cancers, cardiovascular diseases, or intestinal inflammatory diseases. We consider that NLR will be a useful prognostic marker in patients with VTE.

Mean platelet volume is another inflammatory marker, which has gained importance in patients with lung, pancreatic cancer.[16,17] One of the key factors for VTE development is the platelet's contribution to the clot formation.[18] The MPV, among other markers related to platelet functions and platelet number, is one of the most commonly available hematological parameters. There is evidence that MPV is a surrogate of platelet turnover, because larger platelets are younger and more reactive compared to their counterparts and the association between increased MPV with VTE and cardiovascular risks has been well established.[19,20] In our study, we found that MPV might help in predicting the acute VTE event.

The potential limitations in this study include its retrospective nature, performance in a single center, and many exclusion criteria.

5 | CONCLUSIONS

Our study showed that NLR and MPV are significant predictors of acute VTE. Larger, prospective studies are needed in order to confirm these results.

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