ORIGINAL RESEARCH

Complete Blood Count-Derived Inflammation Indices and Retinal Vein Occlusion: A Case–Control Study

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ABSTRACT

Introduction: This study evaluated complete blood count-derived inflammation indices in patients with retinal vein occlusion (RVO).

Methods: Participants in this case–control study were 54 patients with RVO and 54 age- and sex-matched control subjects. All participants underwent a thorough ophthalmic examination, as well as blood sample testing for complete blood count. Comparison of all parameters derived from complete blood count as well as calculation of specific indices was performed between patients with RVO and controls.

Results: Patients with RVO presented significantly higher white blood cell count ($p = 0.033$), neutrophil count ($p = 0.003$), neutrophil-to-lymphocyte ratio (NLR, $p = 0.002$), red cell distribution width (RDW, $p = 0.009$), mean platelet volume (MPV, $p = 0.023$), and systemic immune-inflammatory index (SII, $p = 0.007$) compared to controls. Receiver operator characteristic curve (ROC) analysis showed that NLR was superior to other inflammatory indices, having the greatest area under the curve. The optimal cutoff value for NLR to predict RVO was 2.29 with 46.2% sensitivity and 77.8% specificity.

Conclusion: Patients with RVO presented increased NLR, RDW, MPV, and SII, providing evidence that inflammation plays an important role in the pathogenesis of RVO. Complete blood cell count-derived indices can be easily calculated and may serve as an easy, simple, and cost-effective tool to evaluate the degree of systemic inflammation in patients with RVO, so as to potentially guide treatment.

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Key Summary Points

Patients with retinal vein occlusion (RVO) presented high inflammatory indices (i.e., neutrophil-to-lymphocyte ratio and systemic immune-inflammatory index) compared to controls.

Inflammation plays a significant role in RVO pathogenesis.

Complete blood cell count-derived indices may serve as a simple and cost-effective tool to evaluate the degree of systemic inflammation in patients with RVO.

INTRODUCTION

Retinal vein occlusion (RVO), either central (CRVO) or branch (BRVO), is the second most common retinal vascular disease after diabetic retinopathy with a global prevalence in people aged 30–89 years of 0.77% in 2019 [1]. Today it is estimated that about 16 million people worldwide suffer from RVO [2, 3], which is considered as a significant cause of visual loss if left untreated, especially due to macular edema and retinal ischemia [4].

The exact pathogenesis of RVO is multifactorial, but it is thought to follow the principles of Virchow's triad; compression of the vein by the adjacent artery at the lamina cribrosa or at sites of arteriovenous crossing, degenerative changes of the vessel wall, and abnormal hematological factors lead to stasis, thrombosis, and consequent occlusion [5]. Several risk factors have been associated with RVO development, with the most common being hypertension, atherosclerosis, dyslipidemia, smoking, diabetes mellitus, and hypercoagulability [5, 6]. Since platelets play an essential role in hemostasis, alterations in platelet activation or function may predispose to thrombosis and RVO, while a recent meta-analysis has demonstrated that mean platelet volume (MPV) and platelet distribution width (PDW) are

significantly elevated in patients with RVO compared to controls [7].

Furthermore, inflammation has been implicated in the pathogenesis of RVO [6, 8–10]. Increased concentrations of inflammatory mediators, such as interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein 1 (MCP-1), intracellular adhesion molecule 1 (ICAM-1), placental growth factor (PlGF), platelet-derived growth factor (PDGF), and erythropoietin, have been found in patients with RVO and have shown correlation to the severity of the disease, with the most prominent being vascular endothelial growth factor (VEGF) [10].

Recently, cell counts in the peripheral blood sample and their combinations, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been identified as indicators of systemic vascular and inflammatory conditions [11–13]. Their predictive value has been also discussed regarding ocular vascular and inflammatory diseases, such as diabetic retinopathy, age-related macular degeneration, glaucoma, uveitis, and dry eye disease [14–19]. In addition, systemic immune-inflammation index (SII), a combination of three peripheral inflammatory cells, is a novel inflammatory biomarker, which has been proposed as a prognostic indicator in several clinical entities, including coronary artery disease, cancer, and autoimmune disorders [20, 21]. Interestingly, SII has been found to be elevated in primary open-angle glaucoma and dry eye disease [22, 23], while the clinical relevance of SII in patients with RVO has not been described to date.

In light of the aforementioned, the purpose of this study was to investigate the potential association between complete blood count-derived inflammation indices and RVO.

METHODS

Participants in this prospective study were 54 patients, diagnosed with acute RVO (35 with CRVO and 19 with BRVO) at the 2nd Department of Ophthalmology, University of Athens, Athens, Greece, between September 2019 and December 2020. Diagnosis of RVO was made

clinically on the basis of the presence of retinal hemorrhages, retinal vein dilatation, tortuosity, flame-shaped and dot-blot hemorrhages, while confirmed by retinal imaging, including fundus fluorescein angiography (FFA) and spectral domain-optical coherence tomography (SD-OCT). Moreover, 54 age- and gender-matched subjects without RVO, who were examined at this clinic during the same period, served as controls. Patients with other retinal diseases than RVO, corneal disease, uveitis, glaucoma, dry eye disease, trauma, and any previous intraocular surgery during the last 6 months, as well as patients with infectious pathologies and malignancies, were excluded from the study. In addition, subjects using anti-inflammatory medications, steroids, or any medication affecting platelet function were excluded from the study. The study was approved by the Institutional Review Board of Attikon University Hospital (Reference number 699/2019). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent to participate in the study and to publish their data was obtained from all participants in the study.

Demographic characteristics and medical history of the participants were recorded. All participants underwent a thorough ophthalmic examination, including best-corrected visual acuity (BCVA) measurement by means of Snellen charts, intraocular pressure measurement, slit-lamp examination, dilated fundoscopy, SD-OCT and FFA using Heidelberg Spectralis (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) to confirm the diagnosis of RVO.

At the same day of ocular examination and following an 8-h overnight fast, all participants underwent an antecubital venous puncture for peripheral blood extraction. Complete blood count samples were drawn into vacutainer tubes containing 0.04 ml of 7.5% K3 salt of ethylenediaminetetraacetic acid and analyzed within an hour after sampling using a Sysmex XE-2100 analyzer (Sysmex Corp. Kobe, Japan). All complete blood count parameters and specific inflammation indices (NLR, PLR, and SII) were recorded. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, PLR by dividing the platelet count by the lymphocyte count, while SII was calculated as platelet count × neutrophil count/lymphocyte count.

Statistical Analysis

The normality of distribution of the continuous variables was determined using the Kolmogorov–Smirnov test. Student's t test and Mann–Whitney–Wilcoxon test were appropriately used for the comparison of continuous variables. Receiver operator characteristic curve (ROC) analyses were performed to identify the optimal cutoff points at which sensitivity and specificity would be maximal for the prediction of RVO for indices proven significant in univariate analysis. Areas under the curve (AUCs) were also calculated as measures of the accuracy of the tests. Statistical analysis was done by the SPSS statistical software package (IBM SPSS version 25.0, Chicago, IL, USA). Statistical significance was defined at $p < 0.05$.

RESULTS

Table 1 shows the demographic characteristics and the results of complete blood count parameters, as well as specific inflammation indices in patients with RVO and in control subjects. The mean age of patients with RVO and controls was 68.6 ± 9.9 years and 67.8 ± 9 years, respectively. The male-to-female ratio was 30:24 in the RVO group and 29:25 in the control group. There were no statistically significant differences between the two groups in terms of age ($p = 0.649$) and gender ($p = 0.848$). Regarding comorbidities, 39 out of 54 patients with RVO had hypertension (72.2%), 16 (29.6%) had diabetes mellitus, and 22 (40.7%) had dyslipidemia. In addition, 14 out of 54 patients (25.9%) presented the ischemic type of RVO. Patients with RVO had significantly higher levels of white blood cells (WBC, $p = 0.033$), neutrophil count ($p = 0.003$), MPV ($p = 0.023$), red cell distribution width (RDW, $p = 0.009$), NLR ($p = 0.002$), and SII ($p = 0.007$). Other complete blood count indices

Table 1 Demographic characteristics and results of the complete blood count testing between patients with retinal vein occlusion and control subjects

	Retinal vein occlusion ($n = 54$)	Controls ($n = 54$)	p
Age (mean ± SD, years)	68.6 ± 9.9	67.8 ± 9	0.649
Gender (M/F)	30:24	29:25	0.848
Red blood cells (mean ± SD, $10^6/\mu l$)	4.80 ± 0.50	4.67 ± 0.47	0.181
White blood cells (mean ± SD, $10^3/\mu l$)	7.84 ± 1.91	7.08 ± 1.75	0.033
Neutrophils (mean ± SD, $10^3/\mu l$)	4.90 ± 1.51	4.07 ± 1.32	0.003
Lymphocytes (mean ± SD, $10^3/\mu l$)	2.14 ± 0.68	2.23 ± 0.69	0.506
Monocytes (mean ± SD, $10^3/\mu l$)	0.55 ± 0.14	0.56 ± 0.16	0.845
Platelets (mean ± SD, $10^3/\mu l$)	251.15 ± 64.81	245.95 ± 55.01	0.654
Plateletcrit (mean ± SD, %)	0.26 ± 0.07	0.25 ± 0.07	0.897
Platelet distribution width (mean ± SD, fl)	12.76 ± 1.81	12.77 ± 2.65	0.976
Mean platelet volume (mean ± SD, fl)	10.37 ± 1.40	9.65 ± 1.82	0.023
Mean corpuscular volume (mean ± SD, fl)	88.02 ± 5.11	89.41 ± 7.02	0.240
Mean corpuscular hemoglobin (mean ± SD, pg)	29.70 ± 2.31	30.17 ± 2.97	0.363
Red cell distribution width (mean ± SD, fl)	13.70 ± 1.61	12.92 ± 1.39	0.009
Hb (mean ± SD, g/dl)	14.02 ± 1.29	13.86 ± 1.27	0.526
Hematocrit (mean ± SD, %)	42.07 ± 3.47	41.73 ± 3.80	0.628
Neutrophil-to-lymphocyte ratio	2.47 ± 1.00	1.94 ± 0.72	0.002
Platelet-to-lymphocyte ratio	125.42 ± 42.24	119.29 ± 42.16	0.452
Systemic immune-inflammatory index	622.73 ± 332.95	477.17 ± 205.34	0.007

Table 2 Results of the receiver operator characteristic curve analysis

Index	AUC	95% CI	p value	Cutoff	Sensitivity	Specificity
NLR	0.648	0.544–0.752	0.009	2.29	46.2%	77.8%
RDW	0.645	0.539–0.750	0.010	13.25	61.5%	59.3%
MPV	0.618	0.509–0.727	0.037	10.0	67.3%	57.4%
SII	0.640	0.535–0.745	0.013	525.5	55.8%	68.5%

AUC area under the curve, *MPV* mean platelet volume, *NLR* neutrophil-to-lymphocyte ratio, *RDW* red cell distribution width, *SII* systemic immune-inflammatory index

did not differ significantly between the two groups.

Table 2 shows the results of the ROC analysis regarding the factors that were significant in the univariate analysis. Since WBC and neutrophils are parameters affecting NLR, RDW, MPV, and SII, we examined only the latter indices. The predictive value of NLR, RDW, MPV, and SII was evaluated by comparing the AUC values. The AUC of NLR, RDW, MPV, and SII was 0.648,

0.645, 0.618, and 0.640, respectively, indicating that NLR is superior to other inflammation indices. The optimal cutoff value of NLR to predict RVO was 2.29 with 46.2% sensitivity and 77.8% specificity. As far as the other indices are concerned, the optimal cutoff value of RDW was 13.25 with 61.5% sensitivity and 59.3% specificity; for MPV the optimal cutoff value was 10.0 with 67.3% sensitivity and 57.4% specificity, while for SII the optimal cutoff value was 525.5 with a sensitivity of 55.8% and a specificity of 68.5%. The ROC curve analyses are depicted in Fig. 1.

DISCUSSION

In the present study, we investigated several indices derived from complete blood count examination, as potential biomarkers of inflammation in patients with RVO. Compared to healthy control subjects, patients with RVO were found to have higher WBC, neutrophils count, MPV, RDW, NLR, and SII; the last of these was examined in patients with RVO for first time. Furthermore, on the basis of ROC analysis, we found that NLR was superior to other indices in predicting the inflammatory status of the disease.
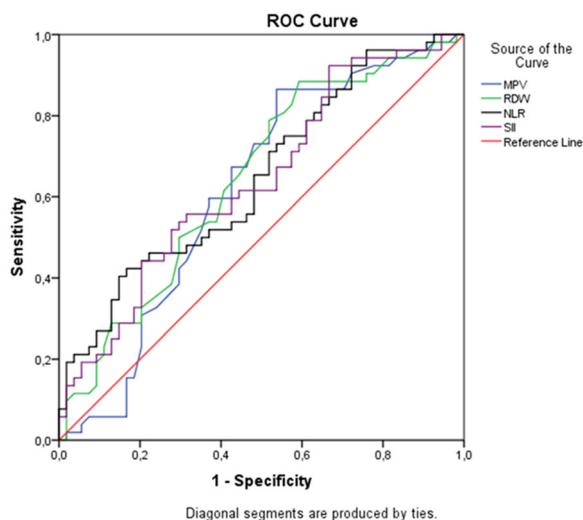

Fig. 1 Receiver operator characteristic curve for the complete blood count-derived inflammation indices

Both systemic and local inflammation are thought to play an important role in the etiology or RVO. Under systemic inflammation status, levels of inflammatory cytokines are elevated, activating coagulation, as well as pathways that inhibit fibrinolysis [24]. Among the immune system elements, WBC have a crucial role in the control of inflammation, since their activation leads to the synthesis of inflammatory cytokines. [24]; thus, they can serve as biomarkers of inflammation. Of note, neutrophil is an indicator of inflammation, while lymphocyte is an indicator of physiologic stress [24]. Neutrophil-to-lymphocyte ratio combines the predictive value of two parameters and is considered more powerful to predict inflammation than subtypes of WBC alone [25]. Few studies exist in the literature examining the association between NLR and RVO, showing conflicting results. Some authors have reported a significant association between higher NLR and RVO, suggesting that it could be used as a predictor marker for identifying the risk of RVO [26–28], while higher RDW has been also associated with RVO [29]. However, other studies found no association between NLR, as well as RDW, and RVO [30, 31]. In our study, NLR was found to be superior in RVO detection compared to other complete blood count-derived indices, although its sensitivity was low (46.2%).

Besides WBC, platelets are a source of inflammatory mediators and directly modulate the activation of vascular endothelium [7]. Platelets have been previously demonstrated to be involved in the pathogenesis of RVO [5]. In the current literature, some reports mentioned an association between altered hemorheological variables and RVO development, while other studies did not confirm these findings [7]. Mean platelet volume, a marker of platelet activation, has been investigated in patients with RVO, with a recent meta-analysis reporting that MPV is significantly elevated in patients with RVO compared to controls [7]. This is in line with the majority of studies [31–37], while Ornek et al. observed lower MPV values in patients with RVO [38] and Turkseven Kumral et al. observed unaffected indices [30].

The association between MPV and RVO can reflect the role of platelets in thrombosis. In particular, MPV measures platelet size and mechanistically larger platelets possess denser granules and have been linked to increased rate and extent of platelet aggregation, synthesis of thromboxane A2 and serotonin, release of beta-thromboglobulin, procoagulant function, and expression of adhesion molecules [39]. Functionally, raised MPV has been related to both venous and arterial thrombotic vascular disorders [39, 40]. However, it is worth noting that the main pathogenetic mechanism in RVO is based on the anatomic relationship between retinal artery and vein. Therefore, the primary factor in the development of RVO seems to be the change in the adjacent arteries and not systemic hematologic abnormalities, differentiating RVO from other systemic venous occlusive disorders [38]. This is the reason why treatment with anticoagulants seems not to be beneficial in patients with RVO [41]. Of note, Hayreh et al. reported that antiplatelet therapy was associated with worse visual acuity outcomes and no apparent benefit in patients with RVO [42].

Another interesting finding of this study is that SII was reported to be significantly higher in patients with RVO compared to controls for the first time, enhancing the theory about the involvement of inflammation in RVO pathogenesis. This specific index is the combination of the three main factors of inflammatory response measured in complete blood count, i.e., platelets, neutrophils, and lymphocytes, and has been found to be elevated in other inflammatory disorders, such as coronary artery disease and autoimmune diseases [20, 21], as well as in patients with dry eye disease [23].

One limitation of the study is the fact that it was single-centered, while inflammatory cytokines were not measured to examine their association with RVO and with the herein-examined indices. However, it is a case–control study with a relatively large study sample, and it has to be mentioned that this is the first time that SII is examined in patients with RVO.

CONCLUSIONS

This study showed that patients with RVO presented increased NLR, RDW, MPV, and SII, providing evidence that inflammation plays an important role in the pathogenesis of RVO. Of note, NLR was found to be superior compared to other indices. Complete blood cell count-derived inflammation indices can be easily calculated and are an easy, simple, and cost-effective tool to evaluate the degree of systemic inflammation in patients with RVO. Our findings may probably suggest these indices as predictors of the possibility of impending RVO, while their role in prognosis of RVO could be also considered. In addition, inflammation indices may define in which cases of RVO an inflammatory component is high, potentially guiding treatment decision with intravitreal steroids as first-line or adjunct treatment. Further multicenter studies are needed to obtain stronger evidence and justify our results.

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Compliance with Ethics Guidelines. The study was approved by the Institutional Review Board of Attikon University Hospital (Reference number 699/2019). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent to participate in the study and to publish their data was obtained from all participants in the study.

Data Availability Statement. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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