Brief Report

Novel Inflammatory Markers Associated With Cutaneous Leukocytoclastic Vasculitis Etiology

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Abstract

Objectives: We aimed to compare inflammatory markers and determine their potential role in distinguishing secondary leukocytoclastic vasculitis (SLV) from idiopathic leukocytoclastic vasculitis (ILV). **Materials and Methods:** We included in this cross-sectional study patients with cutaneous leukocytoclastic vasculitis (CLV) diagnosed on cutaneous biopsy. We assessed clinical and laboratory data and then calculated platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP)-to-albumin ratio (CAR), and fibrinogen-to-albumin ratio (FAR). We have also defined the number of positive etiological examination (NPE) as the sum in a unique patient of the positive paraclinical examinations involved in the etiological assessment of CLV. **Results:** In total 77 patients were included, with 52 SLV group patients and 25 in the ILV group, mean age was 44+/-18 vs 49+/-21, and gender ratio was 29/23 vs 11/14. Comparison of PLR, NLR, CAR, and FAR showed significant differences in mean values between SLV and ILV groups with 199.1 (117.3-309.8) vs 126.8 (79-193) (P = 0.01) for PLR, 3.6 (1.9-5.1) vs 2.3 (1.7-3.4) (P = 0.048) for NLR, 1.9 mg.g-1 (0.4-3.6) vs 0.6 mg g-1 (0.2-1.9) (P = 0.043) for CAR, and 155.8 mg.g-1 (90.7-192.3) vs 108.7 mg.g-1 (82.2-148.1) (P = 0.034) for FAR. PLR, CAR, and FAR were positively correlated to NPE (r = 0.463, P < 0.001; r = 0.434, P < 0.001; and r = 0.411, P < 0.001, respectively), and there was no significant correlation between NLR and NPE (r = 0.165, P = 0.151). **Conclusion:** This is the first study to investigate PLR, NLR, CAR, and FAR in CLV, and it demonstrates that elevation of these ratios is associated with SLV, which leads us to suggest to exhaustively explore patients with elevated ratios.

Keywords: *Inflammation, Laboratory diagnosis, Skin, Sjogren's syndrome, vasculitis*

Introduction

Cutaneous leukocytoclastic vasculitis (CLV) typically presents as infiltrated non-blanching erythematous cutaneous lesions, sometimes necrotic and usually involving the lower limbs. Such features suggest wall damage to small vessels of the skin. Although skin biopsy confirms the diagnosis of CLV, rarely does it provide findings toward its cause. Establishing the etiology of CLV can be challenging given the variety of diseases that could be responsible for this condition. This leads to a costly investigation process, which in turn results in a concerning high rate of idiopathic leukocytoclastic vasculitis (ILV).[1]

Many of the diseases responsible for CLV are associated with an increase in inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein (CRP). These laboratory findings often have poor contribution to the investigation process. Novel inflammatory markers have recently been described in various inflammatory diseases: ratios such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), CRP-to-albumin ratio (CAR), and fibrinogen-to-albumin ratio (FAR).[2,3]

Although increase in inflammation markers is common in such clinical condition, the role of laboratory inflammation markers as well as the status held by previously cited novel inflammatory markers in the investigation process of CLV has yet to be determined.

We conducted a study aiming to compare inflammatory markers in ILV as opposed to secondary leukocytoclastic vasculitis (SLV). We also evaluated new inflammatory markers for their potential to distinguish between both groups.

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Methods

Subjects

Patients with CLV hospitalized in our internal medicine department in Tunis, from January 2001 to November 2022, were included in this cross-sectional study, data were collected from January 2023 to March 2023. The diagnosis of CLV was established based on skin biopsy findings in patients with normal platelet count and normal hemostasis assessment.

Patients presenting a concurrent condition that could also explain the elevated inflammatory markers, such as infections, active cancer, active inflammatory diseases, or thromboembolic diseases, were excluded from the study when the latter was not considered as a CLV etiology.

Assessment of CLV etiology

All patients were hospitalized and have undergone etiological assessment for CLV. They were then divided into two different groups:

Patients who responded to one of the following classification criteria were classified in the SLV groups:

Systemic lupus erythematosus (SLE): 2019 EULAR/ACR Classification criteria.[4]

Sjögren's syndrome (SS): criteria of the American-European Consensus Group (AECG 2002).[5]

Rheumatoid arthritis (RA): criteria of the EULAR 2010.[6]

Anti-phospholipid syndrome (APS): classification criteria of Sapporo/Sydney 2006.[7]

Systemic vasculitis: classification criteria from the 2012 Chapel Hill consensus conference.[8]

Infectious endocarditis (IE): modified Duke criteria (2000).[9]

Other infections were considered after positivity of specific serology and PCR when needed, cancers were diagnosed according to histopathologic examination, and diagnosis of drug-induced vasculitis was established after eliminating other causes with concordant history of drug intake and favorable outcome after drug withdrawal.

ILV patients were classified when aetiological investigation remained unfruitful.

We also defined the number of positive etiological examination (NPE) as the sum in a unique patient of:

- Ophthalmologic examination finding keratoconjunctivitis sicca, keratitis, scleritis, episcleritis, uveitis, or retinal vasculitis.
- Proteinuria >0.5 g/24 or glomerular haematuria.
- Electromyogram (EMG) showing peripheral nerve involvement related to the underlying etiology.
- Pulmonary function test showing restrictive or obstructive lung disease because of the underlying etiology of CLV.
- Elevation of liver enzymes when related to the underlying etiology.
- Positive blood culture.
- A positive infectious serology from the following screening: hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus B19 (PB19), anti-Strepto-Lysine O (ASLO), and chlamydia.
- Histopathologic findings specific to cancers, lymphoproliferative diseases, inflammatory diseases, or tuberculosis.
- A positive immunological screening including antinuclear antibodies (ANA), anticitrullinated protein antibodies (ACPA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), antiphospholipid (APL) antibodies, complement proteins measurement abnormalities, and cryoglobulinemia.
- Imaging findings related to the underlying etiology of CLV.
- Endoscopic findings showing ulcers, intestinal bleeding, or mucosal inflammation because of the underlying etiology of CLV.
- Positive direct immunofluorescence (DIF) contributing to the diagnosis of SLV, such as IGA deposits in IGA vasculitis.

Clinical assessment and laboratory data

Clinical and laboratory data were collected during the initial presentation of active CLV and included age, gender, clinical presentation and extension of the CLV lesions, leukocyte count (WBC), neutrophil (NEU) count, lymphocyte (LYM) count, platelet (PLT) count, CRP, albumin (ALB), gamma globulin (GG), ferritin (FER), and fibrinogen (FG). Laboratory evidence of inflammation (LEI) was defined as the increase of at least two classic inflammatory markers. All blood samples were collected from peripheral veins, after a minimum of 8 hours of fasting, in the morning according to the requirements of each measure. Laboratory testing was performed within 2 hours of blood sampling for complete blood count parameters (Celltac Es MEK-7300K) and biochemical tests (COBAS INTEGRA 400 plus).

PLR, NLR, CAR, and FAR were calculated according to the results of individual items following the formulas:

$$PLR = \frac{PLT}{LYM}; \quad NLR = \frac{NEU}{LYM}; \quad CAR = \frac{CRP}{LYM}; \quad FAR = \frac{FG}{LYM}$$

Statistical analysis

The data analysis was performed by SPSS statistical software (SPSS for Windows, version 22.0) and RStudio for Windows. The normality of data distribution was checked by the Kolmogorov-Smirnov test. Quantitative variables were presented as mean ± standard

deviation (SD) or median (interquartile range), as appropriate. The categorical variables were expressed as percentages. Categorical variables were compared with the $\chi 2$ test. Comparison of the differences of continuous variables was performed by the Mann-Whitney *U* test or Student's *t*-test. Pearson correlation ratio was used for linear correlation analysis. Binary logistic regression analysis was used to assess association of PLR, NLR, CAR, and FAR with SLV. *P* values < 0.05 were considered statistically significant.

Results

Demographic and clinical data in our study groups

A total of 77 patients were included in this study with 52 patients in the SLV group and 25 patients in the ILV group. Sixty-five (84%) patients exhibited systemic involvement associated with CLV. Sex ratios (female/male) in ILV and SLV groups were, respectively, 0.78 and 1.26, but this difference was not statistically significant ($P = 0.333$). The rest of demographic and clinical variables evaluated in our study showed no significant statistical difference between both groups as portrayed in Table 1. The etiologies observed in the SLV group are reported in Figure 1.

Laboratory results

Laboratory findings for ILV and SLV are represented in Table 2. SLV group had significantly higher levels of ESR ($P = 0.013$), GG ($P = 0.038$), PLR ($P = 0.010$), NLR ($P = 0.048$), CAR ($P = 0.043$), and FAR ($P = 0.034$), whereas LYM count was significantly lower ($P = 0.012$). SLV group also presented higher levels of PLT, CRP, FG, and FER. However, these differences were not statistically significant. Differences in WBC and NEU between the two groups were not statistically significant. Comparison between ILV and SLV concerning PLR, NLR, CAR, and FAR is illustrated in Figure 2. LEI was significantly more frequent in the group of SLV ($P = 0.027$).

Correlation between PLR, NLR, CAR, FAR, and classic inflammatory markers in CLV

Linear correlation analysis of NLR, PLR, CAR, FAR, and other classic inflammatory markers was performed using a bivariate Pearson correlation analysis. Results are shown in Table 3. PLR was also positively correlated to NLR (r = 0.494, $P < 0.001$) and CAR (r = 0.237, $P = 0.038$), whereas NLR was positively correlated to CAR (r = 0.226, $P = 0.048$). CAR and FAR were positively correlated (r = 0.714, $P < 0.001$).

Correlation of PLR, NLR, CAR, FAR, and other inflammatory markers to the NPE

Correlation of PLR, NLR, CAR, and FAR with NPE is represented in Figure 3, PLR, CAR, and FAR were positively correlated to NPE (r = 0.463, $P < 0.001$; r = 0.434, $P < 0.001$ and r = 0.411, $P < 0.001$, respectively), and there was no significant correlation between NLR and NPE (r = 0.165, $P = 0.151$). NPE was positively correlated to ESR (r = 0.631, $P < 0.001$), CRP (r = 0.390, $P < 0.001$), gamma globulin (r = 0.472, $P < 0.001$), and PLT (r = 0.302, $P = 0.008$). NPE was negatively correlated to ALB (r = -0.568, $P < 0.001$) and LYM (r = -0.280, $P = 0.014$).

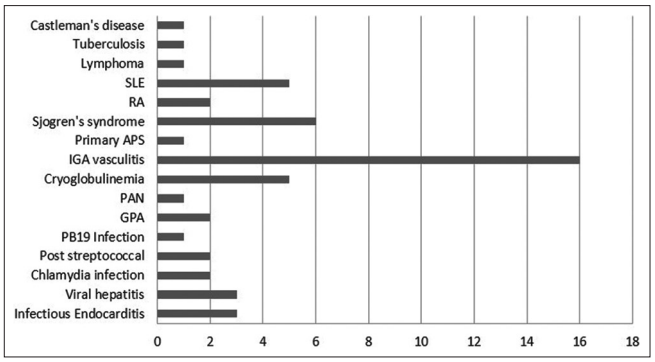

Figure 1: Etiologies of secondary leukocytoclastic vasculitis. SLE: systemic lupus erythematosus, RA: rheumatoid arthritis, APS: antiphospholipid syndrome, PAN: periarteritis nodosa, GPA: granulomatosis with polyangiitis, PB19: parvovirus B19

Table 1: Demographic and clinical presentation of both cutaneous leukocytoclastic vasculitis groups

	ILV	SLV	*P* value of the t/χ^2 Test
Age +/- SD	49.12 +/- 21.29	44.31 +/-17.94	0.303
Gender (F/M)	11/14	29/23	0.333
Petechial purpura	23 (92%)	46 (89%)	0.634
Ecchymotic purpura	13 (52%)	33 (64%)	0.337
Necrotic purpura	7 (28%)	24 (46%)	0.128
Bullous lesions	3 (12%)	7 (14%)	0.858
Pustular lesions	0 (0%)	2 (4%)	0.320
Trunk involvement	10 (46%)	12 (31%)	0.282
Upper-limb involvement	12 (55%)	19 (50%)	0.734
Face involvement	1 (5%)	2 (5%)	0.902

ILV=idiopathic leukocytoclastic vasculitis, SLV=secondary leukocytoclastic vasculitis, F/M=female/male, SD=standard deviation

Multivariate logistic regression analysis of novel inflammatory markers independently associated with SLV

We have also performed multivariate logistic regression analysis to estimate the association of PLR, NLR, CAR, and FAR with SLV as illustrated in Table 4. Only PLR was found to be an independent predictor for SLV (OR = 1.006, 95% CI (1.001–1.009), $P = 0.037$).

Discussion

CLV is often associated with a strenuous investigation process to determine its cause as treatment depends

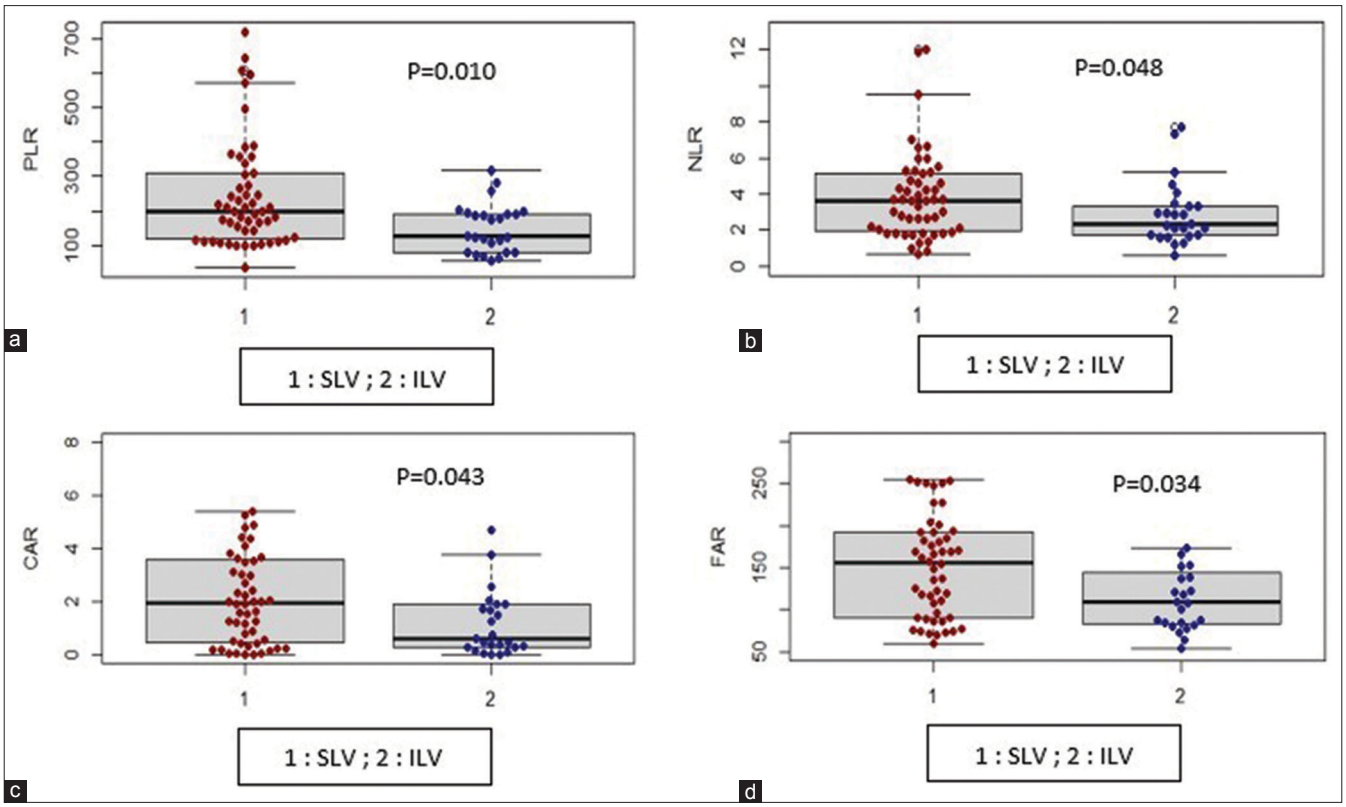

Figure 2: Comparison of PLR (a), NLR (b), CAR (c) and FAR (d) between ILV and SLV groups. ILV: idiopathic leukocytoclastic vasculitis, SLV: secondary leukocytoclastic vasculitis, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, CAR: C-reactive protein-to-albumin ratio, FAR: fibrinogen-to-albumin ratio

Table 2: Comparison of laboratory features between ILV and SLV groups

	ILV	SLV	*P*
WBC (109 L−1)	8560 (6450-9925)	7830 (6462-10950)	0.617
Neutrophils (109 L−1)	5520 (4040-7095)	5310 (3838-8475)	0.970
Lymphocytes (109 L−1)	2374 +/- 947	1801 +/- 892	0.012
Platelets (109 L−1)	317720 +/- 129904	348961 +/- 120758	0.303
CRP (mg L−1)	19.0 (9.6-72.5)	54.5 (18.2-84.8)	0.148
ESR (mm H−1)	57 +/- 38	81 +/- 39	0.013
Albumin (g L−1)	36.8 +/- 6.4	31.4 +/- 8.5	0.006
Gamma globulin (mg L−1)	11.3 (8.8-16)	13.9 (9.7-20.8)	0.038
Fibrinogen (mg.L-1)	3955 (3400-4775)	4570 (3500-5050)	0.275
Ferritin (ug.L-1)	56 (44-385)	79 (40-298)	0.823
LEI (%)	13 (52%)	40 (76%)	0.027
PLR	126.8 (79.1-193.0)	199.1 (117.3-309.8)	0.010
NLR	2.3 (1.7-3.4)	3.6 (1.9-5.1)	0.048
CAR (mg g−1)	0.6 (0.2-1.9)	1.9 (0.4-3.6)	0.043
FAR (mg g−1)	108.7 (82.2-148.1)	155.8 (90.7-192.3)	0.034

ILV=idiopathic leukocytoclastic vasculitis, SLV=secondary leukocytoclastic vasculitis, WBC=white blood cells, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, LEI=laboratory evidence of inflammation, PLR=platelet-to-lymphocyte ratio, NLR=neutrophil-to-lymphocyte ratio, CAR=C-reactive protein-to-albumin ratio, FAR=fibrinogen-to-albumin ratio

essentially on the etiology. Such investigation is required to be cost-effective, given the variety of possible causes. As such, identifying patients in whom investigations must be thorough as an underlying disease is highly suspected, whereas using accessible laboratory analysis could be beneficial.

Our study mainly showed that in patients with no significant differences in age, gender, clinical presentation, and extension of CLV lesions, the plasma levels of the following inflammatory markers: ESR, GG, PLR, NLR, CAR, and FAR were significantly higher in patients with SLV compared with ILV patients, whereas ALB and LYM counts

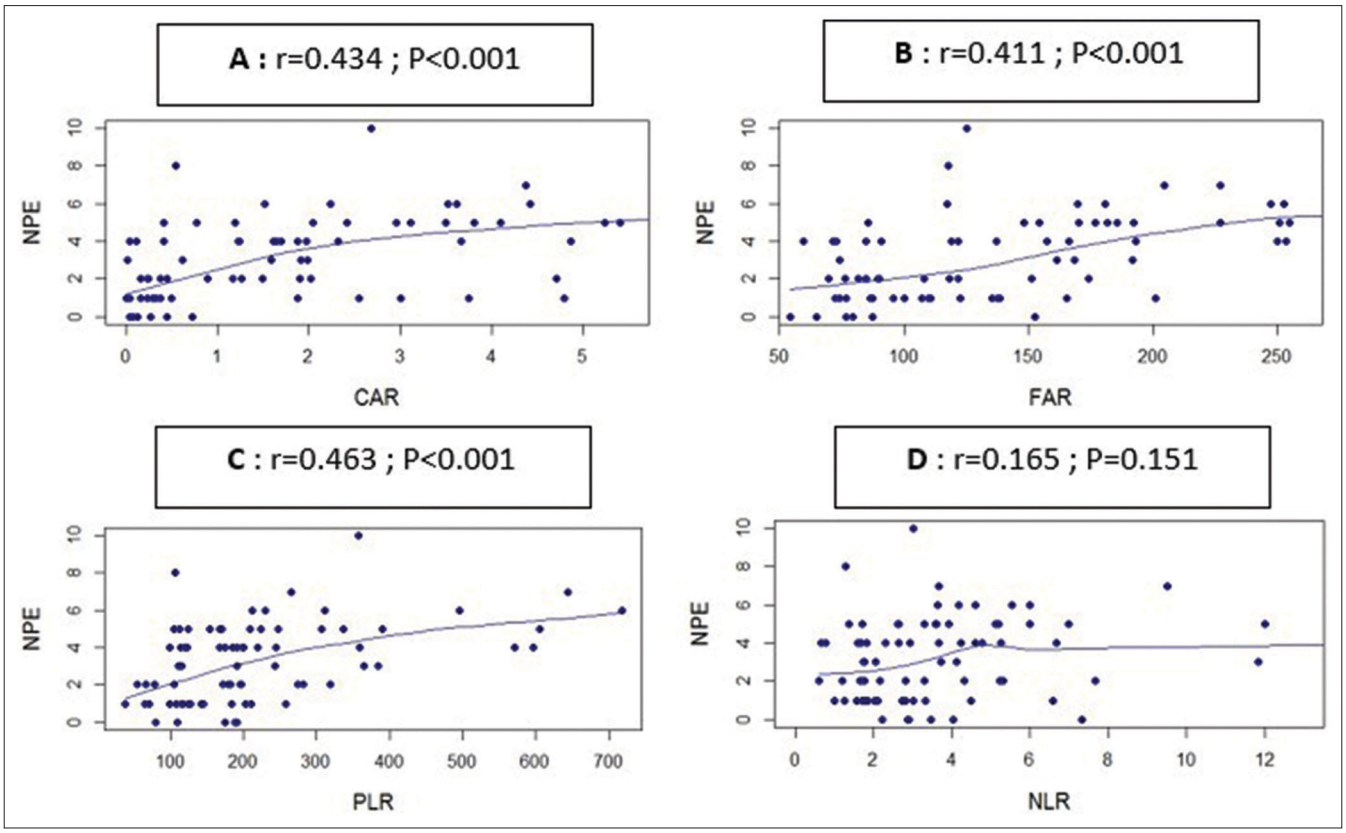

Figure 3: Correlation of CAR (A), FAR (B), PLR (C) and NLR (D) to NPE in leukocytoclastic vasculitis patients. NPE: Number of positive etiologic examinations, CAR: C - reactive protein-to-albumin ratio, FAR: fibrinogen-to-albumin ratio, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio

Table 3: Correlation of PLR, NLR, CAR, and FAR to classic inflammatory markers in cutaneous leukocytoclastic vasculitis patients

Classic inflammatory markers	PLR		NLR		CAR		FAR	
	r	*P*	*r*	*P*	*r*	*P*	*R*	*P*
WBC	-0.096	0.407	0.549	<0.001	0.419	<0.001	0.311	0.007
NEU	0.067	0.565	0.703	<0.001	0.424	<0.001	0.304	0.009
LYM	-0.653	<0.001	-0.413	<0.001	-0.016	0.893	0.106	0.369
PLT	0.470	<0.001	0.137	0.235	0.355	0.002	0.380	0.001
Ferritin	-0.171	0.268	-0.068	0.659	0.469	0.001	0.306	0.046
ALB	-0.391	<0.001	-0.189	0.099	-0.616	<0.001	-0.775	<0.001
GG	0.185	0.108	-0.015	0.896	0.348	0.002	0.323	0.005
CRP	0.213	0.063	0.223	0.042	0.976	<0.001	0.633	<0.001
ESR	0.207	0.070	-0.059	0.611	0.531	<0.001	0.540	<0.001
FG	0.004	0.971	0.015	0.900	0.556	<0.001	0.855	<0.001

WBC=white blood cells, NEU=neutrophils, LYM=lymphocytes, PLT=platelets, ALB=albumin, GG=gamma globulin, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, FG=fibrinogen, PLR=platelet-to-lymphocyte ratio, NLR=neutrophil-to-lymphocyte ratio, CAR=C-reactive protein-to-albumin ratio, FAR=fibrinogen-to-albumin ratio

were significantly lower when comparing the same groups. LEI rate was significantly higher in the SLV group compared with the ILV group. Also, PLR was negatively correlated to ALB, whereas NLR was positively correlated to WBC and CRP. CAR and FAR both showed positive correlation to WBC, NEU, PLT, Ferritin, CRP, GG, ESR, and FG in CLV patients. Adding to that CAR, FAR, and PLR were positively correlated to NPE. Regression analysis showed PLR was an independent predictor of SLV in our study.

CLV can be the main clinical feature for a wide spectrum of underlying diseases.[10] For the majority of these conditions, association with increased serum levels of inflammatory markers has often been reported.[11-13] Inflammatory markers have not been, to the best of our knowledge, previously described specifically in ILV. Our data show a significant difference in inflammatory markers and LEI between ILV and SLV. These results can be due to the fact that ILV is generally limited to inflammation

Table 4: Multivariate logistic regression analysis of novel inflammatory markers in cutaneous leukocytoclastic vasculitis patients

Risk value	Odds ratio (95% CI)	*P*
PLR	1.006 (1.001-1.009)	0.037
NLR	1.199 (1.046-1.352)	0.148
CAR	1.175 (1.029-1.321)	0.188
FAR	1.006 (1.001-1.011)	0.202

PLR=platelet-to-lymphocyte ratio, NLR=neutrophil-to-lymphocyte ratio, CAR=C-reactive protein-to-albumin ratio, FAR=fibrinogen-to-albumin ratio

and wall damage in small cutaneous vessels,[14] whereas SLV implies systemic vasculitis with a more generalized inflammatory process.

Few data exist on PLR, NLR, CAR, and FAR in systemic vasculitis that suggest that these novel inflammatory markers are associated with inflammation, activity, and poor prognosis.[15-18] However, none exists as to their utility in CLV investigation process. Our study showed that PLR, CAR, and FAR were correlated with classic inflammatory markers in CLV, and their serum levels were significantly higher in SLV compared with ILV. This should encourage taking into consideration such easily measurable inflammatory markers when assessing the presence of an underlying disease in patients presenting with CLV.

NPE was established in this study as a mean of compiling the investigations with significant contributions to identifying the underlying etiology in patients with CLV. This allowed the assessment of its correlation with novel inflammatory markers. Our findings showing that PLR, CAR, and FAR were correlated to NPE strengthen furthermore their association with SLV. Such results would equally suggest that clinicians should consider a more throughout investigation if the serum level of these ratios is increased. Screening using previously discussed ratios as inflammatory markers may lead to a less costly and more efficient investigation. To the best of our knowledge, these results have not been published anteriorly.

The use of these ratios in inflammatory diseases was first described in RA where values of PLR and NLR were elevated in RA patients when compared with healthy controls. These ratios also correlated with multiple inflammatory markers and disease activity scores thereby offering an additional evaluative tool alongside conventional markers for assessing systemic inflammation and activity in RA.[19] A recent meta-analysis evaluated PLR in IGA vasculitis, which was the most frequently observed etiology in our study. The authors stated a significant increase in PLR in comparison with healthy controls as well as its role in predicting gastrointestinal complications in this disease.[20] In our study, PLR was the only independent marker of SLV after logistic regression. This highlights the importance of this marker in evaluating patients with CLV, while being, as all other ratios studied, derived from quick and routinely performed blood analysis.

Some limitations are to be stated about this study. It is a cross-sectional study so by definition subject to confounding bias; nevertheless, our groups were matched with no significant difference in age, gender, extension, and clinical presentation of CLV lesions. We have also performed logistic regression to reduce the effect of such bias. Another limitation of this study is the retrospective and monocentric model and the lack of a healthy control group. Correlating inflammatory markers to NPE was an indirect method of linking them to the presence an underlying cause of CLV. Such a method was chosen as the diversity of CLV aetiologies contrasted with choosing one specific quantitative measurement that could precisely express SLV.

Conclusion

This is the first study to explore the role of PLR, NLR, CAR, and FAR in CLV. PLR, CAR, and FAR were correlated with NPE in CLV, which suggests considering these inexpensive and very accessible markers in CLV patients. Patients with a higher risk of SLV would then be proposed for thorough investigations to avoid missing underlying causes while effectively management investigations cost.

This approach would allow to stratify the diagnostic approach of CLV patients with more exhaustive initial workup for patients presenting with elevated inflammatory ratios.

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Conflicts of interest

There are no conflicts of interest.

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