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RESEARCH ARTICLE

IS CRP - ALBUMIN RATIO A BETTER DIAGNOSTIC BIOMARKER THAN NEUTROPHIL - LYMPHOCYTE RATIO IN RECURRENT APHTHOUS STOMATITIS? - A CROSS-SECTIONAL STUDY

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Abstract

Background: Painful, recurrent, round or ovoid ulcers on the oral mucosa are a defining feature of recurrent aphthous stomatitis (RAS). C-reactive protein to albumin ratio (CAR) is a developing measure for predicting inflammation that captures the intensity of inflammatory reactions. On the other hand, neutrophil-to-lymphocyte ratio (NLR), which combines the functions of innate and adaptive immunity has been proven as a biomarker that is elevated in RAS cases.

Aim: To analyze the diagnostic role of CAR and NLR ratio as biomarkers in patients with aphthous ulceration by comparing with healthy controls.

Materials and Methods: This cross-sectional study was conducted on 50 patients clinically diagnosed with recurrent aphthous stomatitis and 50 patients without the oral ulceration. Blood samples were obtained from all participants to study the levels of inflammatory markers. Complete blood count was obtained to evaluate neutrophils, lymphocyte, C-reactive protein (CRP) and albumin levels. CAR and NLR values were calculated and compared between cases and control to elicit possible association with RAS.

Results: The neutrophil-lymphocyte ratio in cases was approximately 1.24 times higher than in controls. CRP-albumin ratio is about 6.75 times higher in cases than in controls. These differences were found to be highly significant statistically. The Receiver operating characteristic (ROC) curve analysis suggests that CRP-Albumin ratio is a more effective diagnostic marker for identifying RAS as indicated by the better sensitivity (88.0) and specificity (84.0) compared to that of NLR (sensitivity = 66.0, specificity = 64.0).

Conclusion: This study claims to be among the first to compare the diagnostic accuracy of CAR to that of NLR in RAS, in the Indian population. Given its strong diagnostic performance, CAR could be prioritized as a primary marker in the clinical assessment of recurrent aphthous stomatitis. Although the neutrophil-to-lymphocyte ratio (NLR) also shows statistical significance and reasonable discriminatory power, it may be more suitable as a complementary marker alongside CAR in evaluating RAS.

Keywords: *Inflammation, Biomarker, Predictor, Canker sore, Stomatitis.*

INTRODUCTION

Recurrent aphthous stomatitis (RAS), also known as canker sores, is a common disorder of the oral mucosa, featuring painful, recurrent ulcerative lesions that typically occur on non-keratinized areas, including the buccal mucosa, lips, tongue, and mouth floor. RAS is divided into three types: minor, major, and herpetiform.[1,2] Although it significantly affects patients' quality of life, its exact cause remains unclear. Both systemic and local factors such as genetic predisposition, immune dysregulation, and environmental triggers like trauma, infections, and certain food allergies are thought to play roles in its development.[3,4] Histopathological analyses reveal that RAS ulcers involve a cell-mediated immune response, with prominent infiltration of neutrophils, monocytes, and T-cells, indicating that immune system dysregulation is a key factor in this condition The neutrophil-to-lymphocyte ratio (NLR), which is measured in peripheral blood, also functions as a biomarker by combining the functions of adaptive and innate immunity.[5]

In recent years, research has increasingly turned to inflammatory biomarkers to deepen understanding of RAS's underlying mechanisms and to develop potential diagnostic and prognostic indicators.[6] A key indicator of systemic inflammation, the neutrophil-to-lymphocyte ratio (NLR) shows the equilibrium between immune-modulating lymphocytes and pro-inflammatory neutrophils.[7] The severity and prognosis of certain chronic inflammatory disorders as well as several types of cancer have been linked to higher NLR levels.[8,9] Similarly, the C-reactive protein (CRP)-to-albumin ratio (CAR), an indicator of inflammation that combines the positive acute-phase reactant CRP with the negative acute-phase reactant albumin, has shown promise in forecasting outcomes for a variety of conditions, including rheumatoid arthritis, heart disease, and certain types of cancer. Standard blood tests provide easy access to both NLR and CAR, providing an economical method of assessing systemic inflammation.[10]

Given the existing evidence of NLR as biomarker for diagnosis of RAS and considering the emerging relevance of CAR as a potential inflammatory marker, this study aims to compare the diagnostic accuracy of NLR with that of CAR in aphthous stomatitis.

MATERIALS & METHODS

Study design

This was a cross-sectional study conducted in Saveetha Dental College and Hospitals, Chennai. Patients were divided into 2 groups:

Group I (cases) included 50 patients clinically diagnosed with RAS during the given time frame.

Group II (controls) included 50 healthy were recruited for this study.

Prior to sample collection, informed consent was sought from each participant and ethical approval was received from the Saveetha University (India) institutional review board.

Inclusion criteria

Individuals aged between 18 and 60 years with a diagnosis of RAS established based on patient history and clinical examination were included in the case group.

The control group consisted of healthy individuals matched for age and sex, who exhibited no history of oral lesions.

Exclusion criteria

Participants with history of autoimmune conditions, recent infections, Behçet's disease, pregnancy, acute trauma, malignancies, recent use of corticosteroids or immunosuppressive medications were excluded from the study.

Principle of the assay

To evaluate inflammatory indicators, blood samples were taken from each participant. Using the enzyme-linked immunosorbent assay (ELISA) method, the levels of C-reactive protein (CRP) were measured. Albumin levels were measured through standard biochemical methods. For each participant, the CRP-to-albumin ratio was calculated. Complete blood counts were also conducted to determine neutrophil and lymphocyte levels, and the neutrophil-to-lymphocyte ratio (NLR) was computed by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical analysis

Excel 2016 was used to enter the data, and IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY: IBM Corp.), was used for analysis. Whereas means and standard deviations were employed for continuous variables, descriptive statistics such as frequency and percentage analysis were applied for categorical variables. To find significant differences between independent groups, the independent sample t-test was employed. Relationships between variables were evaluated using Pearson's correlation coefficient. PANC 3's predictive effectiveness in determining the severity of pancreatitis was assessed using the Receiver Operating Characteristics (ROC) curve, which included cut-off values, sensitivity, and specificity. The chi-square test was utilized to determine the relevance of categorical data. All tests were deemed statistically significant at a p-value of 0.05.

RESULTS

The study included a total of 100 participants, consisting of 50 Group I (cases) individuals diagnosed with recurrent aphthous stomatitis (RAS) and 50 Group II healthy controls.

A p-value of 0.829 and 0.876 in Pearson Chi-Square test comparing gender and age, respectively, between cases and controls indicates that there was no statistically significant association. In other words, the distribution of gender and age was similar between the two groups (Table 1, 2).

Table 1. *Association of gender between cases and controls*

		Groups		Total	P value
		Cases (I)	Controls (II)		
Gender	Females n (%)	35 (70)	34 (68)	69 (69)	0.829
	Males n (%)	15 (30	16 (32)	31 (31)	
Total	Total	50 (100)	50 (100)	100 (100)	

Pearson Chi-Square test

Table 2. *Association of age between cases and controls*

		Groups		Total	P value
		Cases (I)	Controls (II)		
Age groups	18-20 years	9 (18)	7 (14)	16 (16)	0.876
	21-30 years	30 (60)	31 (62)	61 (61)	
	31-40 years	8 (16)	10 (20)	18 (18)	
	41-50 years	3 (6)	2 (4)	5 (5)	
Total	Total	50 (100)	50 (100)	100 (100)	

Pearson Chi-Square test

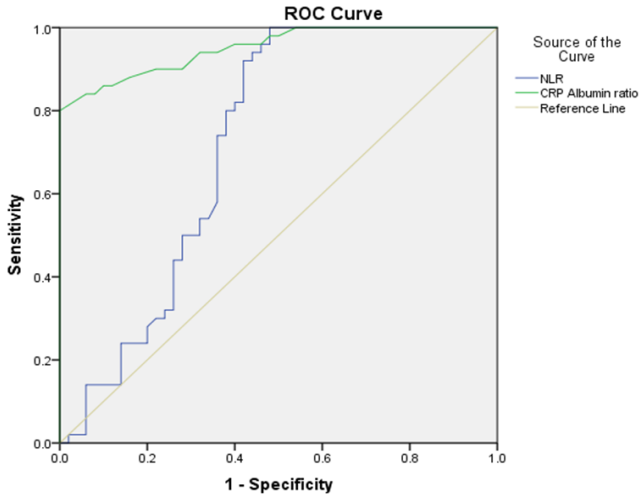
The neutrophil-lymphocyte ratio in cases was approximately 1.24 times higher than in controls. CRP-albumin ratio is about 6.75 times higher in cases than in controls. Despite both values being close to zero, this substantial difference suggests that cases tend to have a relatively higher CRP-albumin ratio than controls. Both these differences were found to be statistically highly significant (p value = 0.0005) (Table 3).

Table 3. *Association of NLR and CAR with cases and controls*

Groups		Count (n)	Mean	SD	P value
NLR	Cases	50	2.408	0.419	0.0005
	Controls	50	1.940	0.810	
CAR	Cases	50	0.000358102629183557	0.000229023805379329	0.0005
	Controls	50	0.000053144924077127	0.0000383392017726237	

Independent Samples T-Test

The ROC curve suggests that the CRP-Albumin ratio is a more effective diagnostic marker than the Neutrophil-Lymphocyte Ratio for identifying cases versus controls in your study. This is indicated by the CRP-Albumin ratio curve lying closer to the top-left corner, which reflects better sensitivity (88.0) and specificity (84.0) at various thresholds compared to that of NLR (sensitivity = 66.0, specificity=64.0) (Figure 1).



CRP-Albumin Ratio (CAR), with an AUC of 0.951, is a highly effective biomarker for distinguishing cases from controls in this study. Neutrophil-Lymphocyte Ratio (NLR), with an AUC of 0.79, is a good but less effective biomarker compared to CAR. Both markers are statistically significant (p = 0.0005), but CAR stands out for its high accuracy and potential clinical utility as a primary diagnostic tool in this context (Table 4).

Table 4. *Area Under the Curve*

	AUC	Std. Error	p-value	95% CI	
				LB	UB
NLR	.719	.054	.0005	.613	.825
CAR	.951	.020	.0005	.912	.990

DISCUSSION

A systematic review and meta-analysis conducted by Rahimi et al. (2024) provides key evidence on the role of NLR in RAS. The analysis included 1,239 RAS patients and 1,167 healthy controls across 13 studies. Results showed that, with a standardized mean difference (SMD) of 0.50, NLR levels were considerably greater in people with RAS than in people without. This SMD of 0.50 represents a moderate effect size for the mean difference in NLR between RAS cases and controls. Additionally, Rahimi et al. classified the included studies as either retrospective or prospective, concluding that elevated NLR levels were evident in retrospective studies but not in prospective ones.[11] Contrarily, our study employed a cross-sectional design, providing data in a snapshot view during a particular point of time.

Suat Terzi and associates assessed the mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) in patients with RAS.The mean NLR reported was 3.37±1.74 in cases and 1.95 ± 1.21 in controls (<0.05). The association of PLR was not statistically significant with RAS and they did not consider the CAR value. Also, the mean NLR for RAS patients in our study (2.408 ± 0.419) was lower compared to the mean NLR reported for RAS patients in their study.[12]

Sinan Uluyol and Saffet Kilicaslan found that patients with active RAS had considerably higher NLR values than those with inactive RAS in different prospective research (3.74 ± 1.9 vs. 2.1 ± 1.43). Also, NLR values in inactive RAS patients did not show a significant difference from those in the control group (2.1 ± 1.43 vs. 2.07 ± 0.96).[13] However, in our study we did not classify the lesions into active and inactive which hindered further analysis. A study done by Tanacan E et al showed that NLR had a positive significant correlation with RAS (r= 0.74, p<0001). Instead of CRP-albumin ratio they assessed the correlation of CRP individually, which was found to have a moderate correlation with RAS (r= 0.36, p<0.001).[14] This study is not comparable to the current study as the former has reported the correlation coefficient and the latter has plotted the ROC curve. Nevertheless, both the studies indicate a significant favourable relationship between NLR and CRP with RAS.

Although, a number of researchers have evaluated the importance of neutrophil lymphocyte ratio being a predictive biomarker in aphthous stomatitis, the role of CAR in the same context has not been exploited thoroughly yet. CAR has been reported to have good diagnostic ability for other immune mediated ulcerative disorders of oral cavity such as Behçet's disease and pemphigus.[15,16] However, studies on RAS were found to be scarce in literature. One another study similar to the current study was conducted by Kayabasi et al which studied the relationship between NLR along with CAR in RAS. They reported that both the parameters were higher in the cases compared to controls. Their ROC analysis revealed an AUC of 0.836 for CAR compared 0.719 found in our study. The AUC for NLR reported by them was (0.807) greater than that seen in our study (0.719). Since CAR's sensitivity and specificity were lower than those found in our study—74% and 72%, respectively it was determined that it was a stronger predictor of RAS than NLR.[17]

Overall, this study boasts of being one of first studies done in Indian population which assessed the diagnostic accuracy of CAR in RAS and has compared it to NLR. NLR has been proved to be raised in RAS in quite many studies, but the studies are mostly from Middle East.[11-14,17] Additionally, baseline NLR values seem to differ based on geographic region and ethnicity,[18-20] which could help account for the discrepancies observed between previous studies and the current study.

This study demonstrates that the neutrophil-to-lymphocyte ratio (NLR) and the C-reactive protein-to-albumin ratio (CAR) differ considerably between people with recurrent aphthous stomatitis (RAS) and healthy controls, highlighting their potential as predictive biomarkers for RAS. The increased NLR and CAR observed in the RAS group suggests a heightened neutrophilic response, possibly due to an overwhelming inflammatory process and immune imbalance. This shift in immune homeostasis could predispose individuals to recurrent ulceration.

Nevertheless, this study had few limitations. Given the case-control design, this study offers only a single-point snapshot of inflammatory markers. Various factors, including stress, smoking, and other underlying health conditions, may influence these markers and potentially confound their association with RAS. Controlling for these factors can be challenging in case-control studies. Furthermore, correlation of the inflammatory markers was not

assessed with relation to severity of RAS. Future research, particularly longitudinal studies, could further clarify how changes in CAR and NLR correlate with disease activity and patient-reported outcomes. This approach could ultimately lead to more personalized and effective strategies for managing RAS, with a focus on targeting underlying inflammatory pathways.

CONCLUSION

The CRP-albumin ratio (CAR), with an AUC of 0.951, demonstrates excellent diagnostic accuracy and could be considered a highly reliable tool for identifying RAS cases. Given its strong performance, CAR might be prioritized as a primary marker in the clinical evaluation of this condition. While the neutrophil-to-lymphocyte ratio (NLR) also shows statistical significance and reasonable discriminatory ability, it may serve better as a supportive or secondary marker in conjunction with CAR.

The elevated CAR and NLR suggest that individuals with RAS may experience a heightened inflammatory response, potentially contributing to the recurrence and severity of ulcerations. By integrating these inflammatory markers into clinical practice, healthcare providers may gain valuable insights for managing RAS more effectively. This study, therefore, adds to the growing evidence on the link between systemic inflammation and RAS, advocating for a more holistic approach to patient care, which could ultimately improve outcomes.

DECLARATIONS

Conflicts of interest and financial disclosures

The author declares that he has no conflict percent and there was no external source of funding for the research in question.

Ethical approval

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of the World Medical Association.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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