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Eosinophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio in Allergic Rhinitis: A Systematic Review with Meta-analysis

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ABSTRACT

A growing number of literatures explores the diagnostic role of serum eosinophil-to-lymphocyte ratio (ELR) and platelet-to-lymphocyte ratio (PLR) in patients with allergic rhinitis (AR), yielding variable findings and lacking control of potential confounding variables and standardized cut-offs for clinical application. We aim to clarify their role through a systematic review and meta-analysis.

Web of Science, PubMed, Embase, Scopus, Cochrane Central Register of Control Trials, Google Scholar, and Medline were systematically searched up to October, 2025. The search strategy was described by a combination of relevant medical subheadings (MeSH) and keywords. Eligible English language studies were reviewed, and their quality was appraised. This review adhered to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

A total of 12 studies, including 3 449 individuals, met the inclusion criteria. AR group had

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significantly higher ELR (SMD: 0.64) and insignificantly lower PLR (SMD−0.02) than control. Patients with persistent AR had, numerically but not significantly, higher ELR (SMD: 1.19) and PLR (SMD: 0.58) compared to intermittent AR. ELR value of greater than 0.085 had a pooled AUC of 67% in discrimination of patients with AR from control. This AUC rate was statistically significant.

This review investigated that no clear correlation was found between mean PLR and AR. However, mean ELR was found to be significantly increased in patients with a diagnosis of AR, and a numerical trend toward higher ELR with greater disease severity was observed. Though further research is necessary to determine its clinical utility.

Keywords: Allergic rhinitis; Diagnosis; Eosinophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Severity

INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated type 1 hypersensitivity reaction characterized by the presence of ≥ 1 of the following symptoms: nasal congestion, rhinorrhea, sneezing, and nasal pruritis.[1] Though largely clinical, a formal diagnosis of AR can be made with allergen-specific serum IgE, and skin prick testing.[2] However, diagnosis can be complicated by the vague nature of the presenting symptoms, the expense of serum IgE testing, and a lack of standardized skin prick testing between centers.[3] These challenges, as well as the fact that AR affects 15% to 25% of the world's population, highlight the necessity to develop accessible, affordable, and non-invasive laboratory markers for diagnosis of AR.[4]

Inflammation in AR is not limited to the nasal mucosa; there is systemic inflammation as well. A vital role within this inflammatory orchestra is played by overproduction and activation of mast cells, eosinophils, basophils, platelets, lymphocytes, and neutrophils.[5] Platelet-to-lymphocyte ratio (PLR) and Eosinophil-to-lymphocyte ratio (ELR) are two markers of systemic inflammation that have been shown to have diagnostic value in inflammatory and infectious disease processes.[6-9] Thus, they may be potential markers for the diagnosis of AR.[10] While other studies have investigated the diagnostic value of serum ELR and PLR in AR,[4,11-13] they lack control of potential confounding variables and standardized cut-offs for clinical application. This systematic review and meta-analysis aims to: (1) compare ELR and PLR between patients with AR and healthy controls; (2) investigate the diagnostic utility of ELR and PLR in AR; (3) investigate the association between mean ELR and PLR and AR severity.

MATERIALS AND METHODS

Study Design

This systematic review with meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[14] and aimed to evaluate the diagnostic role of serum ELR and PLR in patients with AR. The research question was defined using the following Population or Participants, Intervention, Comparison, Outcome (PICO) statement: Population/Participants: Patients with definite diagnosis of AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.[15] Intervention: Blood sampling for measuring the serum levels of eosinophils, platelets, and lymphocytes. Comparison: Mean serum ELR and PLR between: (1) AR vs control; (2) mild AR vs moderate to severe AR (as defined by ARIA guidelines);[15] (3) persistent vs intermittent AR (as defined by ARIA guidelines);[15] (4) patients with positive vs negative skin prick test. Outcome: Mean ELR and PLR.

Search Strategy

A literature search using English keywords was performed across Medline, Web of Science, PubMed, Google Scholar, Embase, Cochrane Central Register of Control Trials, and Scopus through October, 2025. The systematic search was carried out by a combination of medical subheadings (MeSH) and keywords including: ["Allergic rhinitis" OR "Seasonal rhinitis"] AND ["Eosinophil-to-Lymphocyte Ratio" OR "Eosinophil/Lymphocyte Ratio" OR "Eosinophil Lymphocyte Ratio" OR "ELR" OR "Eosinophil" OR "Lymphocyte"] AND/OR ["Platelet-to-Lymphocyte Ratio" OR "Platelet/Lymphocyte Ratio" OR "Platelet Lymphocyte Ratio" OR "PLR" OR "Platelet" OR

"Lymphocyte"]. The generated list of articles was reviewed for potentially relevant studies that met the inclusion criteria. Also, gray literature and unpublished studies were searched to minimize publication bias.

Eligibility Criteria

There was no limitation on geographical location, race, age bracket, or publication date. When multiple studies enrolled the same population, the most comprehensive one was included, prioritizing those with larger sample sizes and data collected over a longer period. We included English papers comparing the levels of ELR and PLR between: (1) AR vs control, (2) mild AR vs moderate to severe AR, (3) persistent vs intermittent AR, (4) patients with positive vs negative skin prick test. If a study reported only one of the indices (ELR or PLR), we manually calculated the other, if possible.

The following were excluded: conference abstracts; case reports; reviews; case series with <5 patients; studies that did not report neither of ELR nor PLR; and non-English studies. Also excluded were studies of patients who had a diagnosis of lower airway pathology including, asthma, chronic obstructive respiratory diseases, or anatomical abnormality; patients with concomitant systemic disease including cancer, cardiovascular, renal or hepatic disease, diabetes mellitus, haemato-oncologic disorders; patients with nasal polyposis; patients on medications that may affect CBC parameters including Nebivolol; patients receiving systemic corticosteroids within the last month.

Selection Process

Two authors independently screened papers according to the predefined criteria. In case of any disagreement, a third reviewer was consulted to reach an agreement. Reference checking of reviews and the review of full-texts of articles that met the inclusion criteria were done by the same two authors. Only variables assessed in at least 2 papers were included in this review, those assessed in only 1 study were excluded.

Data Extraction

Relevant data including country, date of publication, first author, sample size, study design, age range, and severity of AR were manually extracted from each study that met inclusion criteria. Subsequently, two researchers extracted serum ELR and PLR data. The extracted data was checked by a third author for errors.

Quality Appraisal

All studies included were case-control. Two independent researchers examined the quality of each study using the Newcastle - Ottawa Scale (NOS) for quality assessment of non-randomized studies. This scale contains eight questions to evaluate studies on three key domains: Exposure, Comparability, and Selection.[16] Each domain is scored via specified criteria and a total score of > 6 (out of a possible 9) is considered high quality. All studies included in the meta-analysis were high quality (score > 6).

Statistical Analysis

MedCalc software version 23.0.8 (MedCalc Software Ltd., Ostend, Belgium) listed the results of each study. The pooled standardized mean difference (SMD) ELR and PLR with 95% confidence interval (CI) were given for both fixed-effects model and the random-effects model. Hedges' g metric was used to estimate SMD. Given the disproportionate contribution of the sample sizes between studies, we employed a random-effects model, which accounts for both between-study and within-study variability. This method mitigated the impact of the larger studies on the overall effect size. I^2 statistics and Cochran's Q were used to check the homogeneity. Egger's and Begg's tests were used to assess the publication bias. Forest plot was used to show the parameters, and Funnel plot was used to check the errors. High heterogeneity was defined as a significance level of $p<0.05$ and $I^2 \geq 75\%$. Based on the heterogeneity level, fixed-effects (inverse variance) or random-effects (DerSimonian–Laird) models were applied to obtain pooled estimates. For analyses performed on small number of included studies, publication bias assessment was not reliable.

RESULTS

Study Selection and Baseline Features

Initially, 709 studies were identified across all platforms using the search parameters outlined above. 429 duplicates were removed leaving 280 records for abstract screening. Of these, 231 failed to meet the inclusion criteria leaving 49 studies for full-text screening. Ultimately, 12 studies[4,11-13,17-24] met the inclusion criteria providing 3 449 individuals for data analysis (Figure 1).

The characteristics of the included studies are demonstrated in Table 1; all were case-control, with

sample sizes ranging from 43 to 695 patients. Eight studies compared mean ELR between AR and control.[11-13,20-24] Nine studies compared mean PLR between AR and control.[4,11-13,18-21,24] Six studies compared mean ELR and PLR as a function of AR severity.[4,12,17-20] The mean ELR and PLR of different groups across the studies are summarized in supplementary information 1.

Meta-analyses on Comparisons of ELR and PLR between AR and Control

Eight studies, including 1 793 patients (n=1 054 AR and n=739 control), compared ELR between AR and control.[11-13,20-24] (Table 2). Data analysis demonstrated a higher mean ELR in patients with AR as compared to healthy controls (SMD: 0.64; CI: 0.35 to 0.92; p=0.001). The number of studies on children was not enough to perform a specific meta-analysis on this age group. However, analysis of only adult patients revealed a higher mean ELR in adults with AR as compared to healthy controls (SMD: 0.498; CI: 0.25 to 0.82, p=0.001) (see supplementary information 2).

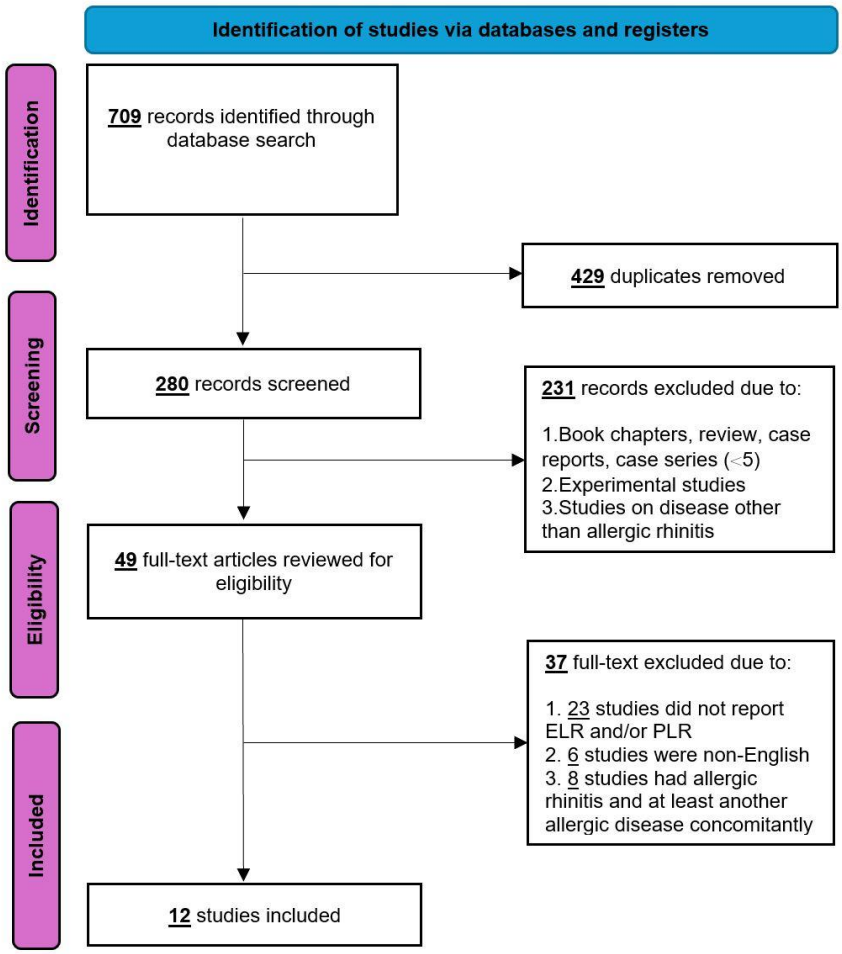

Figure 1. Flow diagram of the studies selection process.

Nine studies, including 2 131 patients (n=1 231 AR and n=900 control), compared PLR between AR and control.[4,11-13,18-21,24] (Table 2). Analysis of these studies showed that patients with AR had lower mean PLR than their healthy controls (SMD: −0.02; CI: −0.72 to 0.67). However, this difference was not statistically significant (p=0.94). Again, the number of studies on children was not enough to perform a specific meta-analysis on this age group. However, analysis of only adult patients revealed a lower mean PLR in adults with AR as compared to healthy controls (SMD: −0.03; CI: −0.91 to 0.69) (see supplementary information 2). This difference was not statistically significant (p=0.79).

Table 1. Baseline characteristics of included studies.

Study (Year)	Country	Age group	Total subjects	Comparisons (ELR)	Comparisons (PLR)	NOS score
Kant et al. (2021)[12]	Turkey	Adults	254	AR vs control/ Between various severity of AR	AR vs control/ Between various severity of AR	8
Altas et al. (2023)[17]	Turkey	Children	230	Between various severity of AR	Between various severity of AR	7
Yalim et al. (2024)[11]	Turkey	Adults	439	AR vs control	AR vs control	7
Gurlek et al. (2017)[13]	Turkey	Adults	271	AR vs control	AR vs control	8
Rohila et al. (2023)[18]	India	Adults	140	NR	AR vs control/ Between various severity of AR	8
Goker et al. (2019)[19]	Turkey	Adults	452	NR	AR vs control/ Between various severity of AR	8
Cansever et al. (2022)[4]	Turkey	Children	360	Between various severity of AR	AR vs control/ Between various severity of AR	8
Yazici et al. (2019)[20]	Turkey	Adults	92	AR vs control/ Between various severity of AR	AR vs control	8
Selcuk et al. (2023)[21]	Turkey	Adults	338	AR vs control	AR vs control	8
Akgedik et al. (2017)[22]	Turkey	Adults	135	AR vs control	NR	7
Yenigun et al. (2016)[23]	Turkey	Children	695	AR vs control	NR	8
Cinar et al. (2021)[24]	Turkey	Adults	43	AR vs control	AR vs control	8

AR: allergic rhinitis; ELR: eosinophil-to-lymphocyte ratio; NOS: Newcastle-Ottawa Scale; NR: not reported; PLR: platelet-to-lymphocyte ratio.

Meta-analyses on Comparisons of ELR and PLR between: Mild vs Moderate to Severe AR; AR with Positive vs Negative Skin Prick Test; Persistent vs Intermittent AR

Three studies, including 509 patients (n=235 mild and n=274 moderate to severe), compared mean PLR between patient with varying severity of AR.[17-19] (Table 3). Analysis of these studies demonstrated that patients with mild AR had lower mean PLR than those with moderate to severe AR (SMD: −0.51; CI: −1.01 to 0.07). However, this difference was not statistically significant (p=0.09).

Two studies, including 276 patients (n=181 positive and n=95 negative), compared ELR between AR with positive skin prick testing and AR with negative skin prick testing.[17,20] (Table 3). Analysis of these studies revealed that patient with AR in the setting of positive skin prick testing had significantly higher mean ELR than their counterparts with negative skin prick testing (SMD: 0.54; CI: 0.29 to 0.79; p=0.001).

Two studies, including 405 patients (n=247 persistent and n=158 intermittent), compared ELR between persistent AR and intermittent AR.[4,12] (Table 3). Analysis of these studies showed that patients with persistent AR had higher mean ELR than those with intermittent AR (SMD: 1.19; CI: −0.34 to 2.72). However, this difference was not statistically significant (p=0.13).

The same two studies, including 405 patients (n=247 persistent and n=158 intermittent), also compared PLR between persistent AR and intermittent AR.[4,12] (Table 3). Analysis of these studies demonstrated that persistent AR had higher mean PLR than those with intermittent AR (SMD: 0.58; CI: −1.00 to 2.15). Again, this difference was not statistically significant (p=0.47).

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Accuracy of ELR in Differentiating AR From Control

Three studies, including 617 patients, investigated potential ELR threshold values for the diagnosis of AR.[12,13,20] (Table 4). An ELR cut-off value greater than 0.085 demonstrated a statistically significant pooled AUC of 0.67 (95% CI: 0.61–0.74, $p<0.001$) for discriminating AR patients from controls.

Table 2. Comparing ELR and PLR between AR and control.

Study	Subjects (AR)	Subjects (Control)	SMD	SE	95% CI	t-value	*p*	Weight (%)
ELR								
Kant	205	49	0.65	0.16	[0.33; 0.96]			12.73
Yalim	179	103	1.28	0.13	[1.02; 1.54]			13.36
Gurlek	182	89	0.35	0.13	[0.1; 0.61]			13.47
Yazici	46	46	0.73	0.21	[0.31; 1.16]			11.37
Selcuk	121	116	0.24	0.13	[−0.01; 0.49]			13.46
Akgedik	60	75	0.66	0.17	[0.31; 1.01]			12.33
Yenigun	242	237	0.97	0.09	[0.78; 1.16]			14.15
Cinar	19	24	0.00	0.3	[−0.6; 0.6]			9.14
Overall	1054	739	0.64	0.14	[0.35; 0.92]	4.399	0.001	100
PLR								
Kant	205	49	−0.26	0.15	[−0.57; 0.05]			11.16
Yalim	179	103	−3.00	0.17	[−3.34; −2.65]			11.10
Gurlek	182	89	0.21	0.12	[−0.03; 0.47]			11.25
Rohila	70	70	1.04	0.17	[0.69; 1.39]			11.09
Goker	209	243	0.59	0.09	[0.4; 0.78]			11.32
Cansever	200	160	0.94	0.11	[0.72; 1.16]			11.29
Yazici	46	46	0.02	0.2	[−0.38; 0.43]			10.99
Selcuk	121	116	−0.10	0.13	[−0.35; 0.15]			11.25
Cinar	19	24	0.29	0.3	[−0.32; 0.9]			10.54
Overall	1231	900	−0.02	0.35	[−0.72; 0.67]	−0.072	0.94	100

For ELR: Heterogeneity= Q: 51.58 ($p<0.001$), I^2: 86.43%; Publication Bias= Egger's test: −3.26 ($p=0.36$), Begg's test: 0.00 ($p=1.0$). For PLR: Heterogeneity= Q: 426.79 ($p<0.001$), I^2: 98.13%; Publication Bias= Egger's test: −8.52 ($p=0.33$), Begg's test: −0.22 ($p=0.4$). AR: allergic rhinitis; CI: confidence interval; ELR: eosinophil-to-lymphocyte ratio; NR: not reported; PLR: platelet-to-lymphocyte ratio; SE: standard error; SMD: standardized mean difference.

Table 3. Comparing ELR and PLR between: mild vs moderate to severe; positive vs negative skin test; persistent vs intermittent.

Study	Subjects (Group 1)	Subjects (Group 2)	SMD	SE	95% CI	t-value	*p*	Weight (%)
PLR between mild vs moderate to severe AR								
Altas	124	106	−0.03	0.13	[−0.29; 0.23]			35.22
Rohila	35	35	−0.66	0.24	[−1.15; −0.18]			30.25
Goker	76	133	−0.87	0.15	[−1.17; −0.58]			34.54
Overall	235	274	−0.51	0.3	[−1.01; 0.07]	−1.71	0.09	100
ELR between positive vs negative skin prick test								
Altas	154	76	0.62	0.14	[0.34; 0.9]			81.05
Yazici	27	19	0.2	0.29	[−0.39; 0.79]			18.95
Overall	181	95	0.54	0.13	[0.29; 0.79]	4.22	0.001	100
ELR between persistent vs intermittent AR								
Kant	160	45	0.41	0.17	[0.08; 0.75]			50.02
Cansever	87	113	1.97	0.17	[1.63; 2.31]			49.98
Overall	247	158	1.19	0.78	[−0.34; 2.72]	1.53	0.13	100
PLR between persistent vs intermittent AR								
Kant	160	45	−0.23	0.17	[−0.56; 0.1]			49.93
Cansever	87	113	1.39	0.16	[1.07; 1.69]			50.07
Overall	247	158	0.58	0.8	[−1.00; 2.15]	0.72	0.47	100

[a]or PLR (mild vs moderate to severe): Heterogeneity= Q: 19.06 (p=0.001), I^2: 89.5%. For ELR (positive vs negative): Heterogeneity= Q: 1.63 (p=0.2), I^2: 38.65%. For ELR (persistent vs intermittent): Heterogeneity= Q: 41.25 (p<0.001), I^2: 97.58%. For PLR (persistent vs intermittent): Heterogeneity= Q: 48.32 (p<0.001), I^2: 97.93%.

AR: allergic rhinitis; CI: confidence interval; ELR: eosinophil-to-lymphocyte ratio; NR: not reported; PLR: platelet-to-lymphocyte ratio; SE: standard error; SMD: standardized mean difference.

Table 4. Accuracy analysis based on AUCs and suggested cut-offs of ELR for distinguishing AR from control.

Study	Subjects	Suggested cut-off	AUC	SE	95% CI	z-value	*p*	Weight (%)
Prediction of AR using ELR								
Kant	254	0.067	0.74	0.03	[0.67; 0.8]			31.55
Gurlek	271	0.088	0.6	0.02	[0.54; 0.65]			34.22
Yazici	92	0.105	0.7	0.02	[0.64; 0.75]			34.22
Overall	617	0.085	0.67	0.03	[0.61; 0.74]	19.98	<0.001	100

Heterogeneity= Q: 13.63 (p=0.001), I^2: 85.33%; Publication Bias= Egger's test: 18.0 (p=0.52), Begg's test: 0.81 (p=0.2). AR: allergic rhinitis; AUC: area under curve; CI: confidence interval; ELR: eosinophil-to-lymphocyte ratio; NR: not reported; SE: standard error.

DISCUSSION

In summary this meta-analysis demonstrated several important findings: (1) patients with AR had a significantly higher mean ELR than their healthy controls, and there was a numerical trend between mean ELR and AR severity. (2) patients with AR and positive skin prick testing had significantly higher mean ELR than those with AR and negative skin prick testing. (3) patients with AR had lower mean PLR than control group; this difference was not statistically significant. (4) patients with mild AR had lower mean PLR than patients with moderate to severe AR; this difference was not statistically significant. (5) patients with persistent AR had higher mean ELR and PLR than those with intermittent AR; these differences were not statistically

significant. (6) ELR value of greater than 0.085 had a pooled AUC of 67% in discrimination of patients with AR from control.

The pathophysiology of AR supports the utility of ELR as a diagnostic marker. AR is an IgE-mediated type 1 hypersensitivity reaction that results in systemic inflammation in addition to local inflammation of the nasal mucosa.[25] Mast cells, dendritic cells, basophils, eosinophils, neutrophils, and T helper (T_H) lymphocytes all play a key role in this inflammatory cascade a downstream effect of which is increased serum eosinophils and lymphocytes.[26,27] In our meta-analysis, mean ELR was significantly higher in patients with AR as compared to healthy controls (SMD: 0.64; p=0.001). This was still true after excluding pediatric patients from the data analysis; mean ELR in adults with AR was significantly higher than in healthy controls (SMD: 0.498; p=0.001). There were not enough studies on children for specific subgroup analysis on this population. Future research is needed to determine if this relationship holds true in the pediatric population. To examine the clinical utility of this statistically significant difference we also aimed to assess the accuracy of ELR in differentiating patients with AR from healthy subjects. Our meta-analysis, conducted on AUCs for ELR, showed that ELR > 0.085 had a pooled AUC of 67% in discrimination of patients with AR from healthy control. Taken together ELR shows potential as a biomarker for AR diagnosis.

Unlike ELR, the difference in PLR between patients with AR and healthy controls was not significantly different. This may be due to several confounding variables. Most notably, platelet count can be affected by multiple demographic variables including age, gender, race as well as variations in genetic and climate.[28,29]

The other statistically significant difference found in this meta-analysis was that in the mean ELR between patients with AR and positive versus negative skin prick testing. The nasal mucosa is exposed to environmental allergens which enter the body via the respiratory tract. These aeroallergens are primarily responsible for the hypersensitivity reaction of allergic diseases including AR.[30] This reaction may be against one allergen or multiple allergens. Skin prick testing can be used to formally diagnose AR based on reactions to injected allergens.[31] Our review found that AR patient with positive skin prick testing had significantly higher mean ELR than AR patients with negative skin prick testing (SMD: 0.54; p=0.001). This provides further support for the diagnostic role of ELR in AR.

Since both eosinophils and lymphocytes play a major role in pathophysiology of AR, prior studies have investigated the correlation between ELR and AR severity. Our meta-analysis did not find a statistically significant difference in mean ELR between intermittent versus persistent AR. However, only two studies were available for pooled analysis of this potential correlation.

Current guidelines rely heavily on clinical history in the diagnosis of AR and in the determination of its severity. Though objective testing in the form of skin prick testing is available diagnosis, it has its disadvantages. Clinically, the diagnosis of AR can be difficult as: (1) assessment of symptoms in the pediatric population can be challenging since these patients may not be reliable historians; (2) the existing objective tests are operator dependent, poorly standardized between centers and require a baseline level of patient cooperation and tolerance. ELR, along with other inflammatory biomarkers and clinical history, may be a useful biomarker in the diagnosis of AR and affords the following advantages: 1. ELR can be calculated from a CBC, which can be easily obtained at a routine outpatient laboratory. 2. ELR requires less time and patient cooperation than skin prick testing; it is easier to interpret and subject to less variability than skin prick testing. 3. ELR is less expensive than serum IgE testing. 4. ELR is numerically, but not significantly, correlated with severity of AR.

This review had some limitations: First, there were potential confounding variables between the included studies, including demographic variables, genetic variations, different CBC analyzers, different exclusion criteria, and geographic distribution. Second, some of analyses had a high level of heterogeneity, owing to the disproportion samples sizes of the included studies, inclusion of both adult and pediatric population, and most studies were on Turkish populations. For this reason, the random effect model, which accounts for both within-study and between-study variability, was used to mitigate the influence of this heterogeneity. Third, most of the included studies were carried out in Turkey potentially limiting the generalizability of the results. Fourth, the duration of AR was different across the studies, which may affect ELR and PLR values. Fifth, this project was not registered in PROSPERO. These limitations emphasize the need for more

comprehensive and standardized research with larger samples size. Future research should focus on current gaps in the knowledge by including among a more diverse population, specifically with respect to geographic distribution and age as the results included in this review came primarily from Turkish studies and did not include sufficient number of children to do a subgroup analysis on the pediatric population. This future research would also benefit from the evaluation of ELR, PLR, and NLR within the same study, as these biomarkers are all associated with both AR severity and sensitization to different allergens. Still, to our knowledge, this review provides the best overall evidence to date on ELR and PLR in AR.

This systematic review and meta-analysis investigated the diagnostic role of ELR and PLR in patients with AR. No clear correlation was found between mean PLR and AR. However, mean ELR was found to be significantly increased in patients with a diagnosis of AR, and a numerical trend toward higher ELR with greater disease severity was observed. ELR, along with other inflammatory biomarkers and clinical history, may be a useful biomarker in the diagnosis of AR. However, further research is necessary to determine its clinical utility, this data provides evidence to support mean ELR as a potential biomarker in the diagnosis of AR.

STATEMENT OF ETHICS

For this type of study formal consent is not required.

FUNDING

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Not applicable.

DATA AVAILABILITY

Upon reasonable request from the corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

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