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Diagnostic significance of neutrophil-to-lymphocyte ratio in non-arteritic anterior ischemic optic neuropathy: a meta-analysis

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Abstract

Background We aimed to determine the association of neutrophil-to-lymphocyte ratio (NLR) with non-arteritic anterior ischemic optic neuropathy (NAION).

Methods We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Scopus and Web of Science were searched from the establishment of the database to May 5, 2022 to find the relevant studies. The quality of the included literature was evaluated with the Newcastle–Ottawa scale (NOS). The results are reflected in the form of standard mean difference (SMD) and 95% confidence interval (CI).

Results Finally, six articles were included in our study. Compared with healthy controls, patients' NLR levels were significantly higher (SMD = 0.47; CI 95% = 0.30–0.65, p<0.001). The included studies were not statistically heterogeneous (I^2 = 0.0%, p = 0.60); thus, the analysis used the fixed-effect model. The pooled sensitivity of NLR was 0.69 (95% CI 0.60–0.67), and the pooled specificity was 0.59 (95% CI 0.50–0.67). The pooled positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio (DOR) of NLR were 1.71(95%CI 1.48–1.98), 0.50 (95%CI 0.41–0.62), and 3.38 (95%CI 2.57–4.44), respectively.

Conclusions Our findings suggest NLR to be a potential marker of NAION, while also implicating a role for inflammation in underlying pathophysiology.

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Background

Non-arteritic anterior ischemic optic neuropathy (NAION) is one of the most common and prevalent diseases leading to vision loss in middle-aged patients and elderly [1]. It is the most common subtype of ischemic optic neuropathy characterized by sudden onset vision loss, optic edema upon presentation, and cup-to-disc ratio of 0.2 or less ("disc at risk") in the same eye [1, 2]. Exact pathophysiology remains unknown; however, it is generally thought to be preceded by relative hypoperfusion to optic nerve head leading to progressive edema and infarction of the optic nerve fibers [2]. Patients with history of hypertension, hypercholesterolemia, diabetes mellitus, cardio- and cerebrovascular disease, and obstructive sleep apnea are at higher risk of developing NAION [2]. A majority of these predisposing conditions are regulated by inflammatory mechanisms [3–6]. Furthermore, there is evidence that cellular inflammation plays a major role after the initial infarct to clear debris and stimulate tissue remodeling [7]. Together, these suggest that inflammatory markers may be useful in diagnosing and assessing clinical progression of NAION, especially given the absence of objective and quantitative measures for diagnosis.

Peripheral blood neutrophil-to-lymphocyte ratio (NLR) is an emerging prognostic biomarker of inflammation and immune function in cardiovascular disease, respiratory disease, kidney disease, lung disease, infection, and cancer [8]. Independent of disease, NLR is also associated with overall mortality [8]. NLR reflects a balance between inflammatory activity and immune response, offering insights into the extent and phase of these processes [9]. Effective regulation of NLR is essential for both disease progression and recovery. Since inflammation may play a role in the development of NAION, recent studies have examined the potential link between NAION and peripheral blood NLR, suggesting an association between higher NLR levels and NAION. Although prior systematic reviews [10–14] have covered NAION risk factors and treatment options, none have explored the NLR–NAION relationshiExisting studies on this topic are all original research [15–20]. This systematic review and meta-analysis aim to compile data from these studies to evaluate the potential of NLR as a biomarker for NAION in the appropriate clinical context. To the best of our knowledge, this is the first manuscript on this context.

Methods

Search strategy

We used the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) standards to perform a systematic review and meta-analysis to collect all published materials, such as grey literature and preprints [21] **(**Fig. 1**).** Three main data bases (Scopus, PubMed, and Web of Science) were systematically searched using these key words: "Neutrophil to lymphocyte ratio", NLR, and "Nonarteritic Anterior Ischemic Optic Neuropathy". Table 1 illustrates the precise search methodology. The latest update to the search occurred on May 5, 2022. Our search approach was not limited by language or publishing year.

Inclusion and exclusion criteria

The PICOS concept is used to determine whether investigations are eligible. The following were the inclusion criteria:

a) Population: patients with NAION
b) Intervention: NLR
c) Control: healthy controls
d) Outcomes: the prognostic performance of NLR in NAION
e) Case–control, nested case–control, and cross-sectional studies

Duplicate studies, experimental or animal investigations, editorials, letters, articles with insufficient data, case reports, case series, and studies with overlapping data were excluded.

Data extraction and quality assessment

EndNote software was used for study screening [22]. Duplicate studies were first eliminated. Following that, two writers independently reviewed the titles and abstracts of articles found during the first database search, concentrating on those that were closely related. The same writers received and evaluated the full texts of the studies listed. The meta-analysis eventually contained studies that satisfied the criteria. In addition, we looked through the references of relevant original publications and review papers to see if we could find any more relevant research. A third person was brought in to mediate disagreements among the two writers doing the screening. The following information was separately collected from the included articles by two reviewers: study design and location, first author's name, publication year, number of controls and cases, mean age, gender, best-corrected visual acuity (BCVA), NAION phase (acute or chronic), mean± standard deviation (SD) of NLR level in cases and controls, or sufficient data for estimating the mean± SD such as median and interquartile range (IQR) or/and range. Two writers independently assessed the quality of the included studies using the Newcastle–Ottawa Scale (NOS) [23].

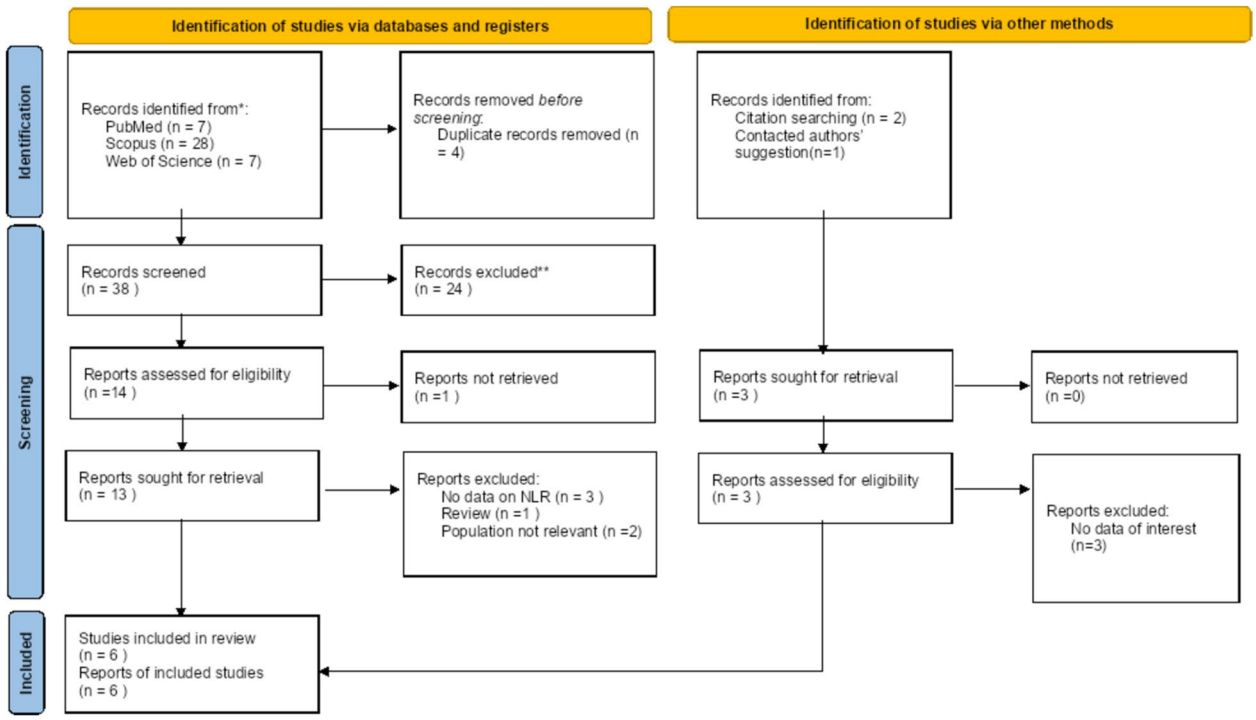

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which includes searches of databases, registers and other sources

Table 1. Exact search strategy of databases

Database	Search strategy	Limitation	Date of search	Number of studies
PubMed	("Neutrophil to lymphocyte ratio"[All Fields] OR "NLR"[All Fields]) AND ("Nonarteritic Anterior Ischemic Optic Neuropathy"[All Fields] OR "Non-arteritic Anterior Ischemic Optic Neuropathy"[All Fields])	None	May 5, 2022	7
Scopus	[ALL ("Neutrophil to lymphocyte ratio" OR NLR) AND ALL ("Nonarteritic Anterior Ischemic Optic Neuropathy" OR "Non-arteritic Anterior Ischemic Optic Neuropathy")]	None	May 5, 2022	28
Web of Science	"Neutrophil to lymphocyte ratio" OR NLR (All Fields) and "Nonarteritic Anterior Ischemic Optic Neuropathy" OR "Non-arteritic Anterior Ischemic Optic Neuropathy" (All Fields)	None	May 5, 2022	7

Statistical analysis

The Standardized Mean Difference (SMD) was provided along with a 95% confidence interval (CI) to indicate the NLR level. Due to variations in laboratory standards for NLR across countries and the impact of factors like ethnicity and geographic location, we opted to use the standardized mean difference (SMD) rather than the mean difference (MD) in our study. SMD enables comparisons across studies with different measurement scales or units, as it standardizes effect size, allowing for a more consistent and widely applicable metric when pooling results. While MD might offer greater statistical power, it is constrained to studies with comparable outcomes and units, which could limit broader relevance. We evaluated the heterogeneity among the outcomes of the studies using both the chi-squared ($\chi 2$) test and the I^2 statistic. Results with an I^2 value exceeding 75% and a P value less than 0.05 for the $\chi 2$ test were regarded as indicative of significant result heterogeneity. In such instances, we employed a random effect model for the meta-analysis of the heterogeneous results. Alternatively, if the conditions mentioned earlier were not met, we applied the fixed-effect model. We evaluated the diagnostic efficacy of NLR for NAION through the utilization of a summary receiver operating characteristic (SROC) curve.

To detect potential publication bias, we employed Egger's linear-regression test along with the funnel plot. For conducting statistical analyses, we employed STATA 12.0

software provided by Stata Corporation in College Station, TX, USA. We considered a *P* value equal to or less than 0.05 as indicative of statistical significance.

Results

Search and selection of literature

A total of 45 records were retrieved in the database search and manual search of citation list of articles. After the exclusion of duplicates and not relevant records, six studies were included in the systematic review and meta-analysis [15–20], for a total of 251 patients with NAION and 252 healthy controls. The process of inclusion and exclusion is detailed in the PRISMA flow diagram, provided in Fig. 1. The PRISMA checklist for this investigation is included in Supplementary File 1.

Characteristics of the included studies

This meta-analysis included six studies, of whom four were conducted in Turkey, one in Italy and one in Thailand. In terms of document language, all of the documents were written in English language. All of them were retrospective studies. Table 2 shows the overall characteristics of the studies and their quality scores. In total, six research examined NLR levels in patients with NAION and healthy controls[15–20], and five studies reported diagnostic value of NLR for differentiating between patients with NAION and healthy controls, based on ROC curve analysis[15, 17–20]. NOS score of included studies ranged between 6 and 7. In all studies, subjects without any systemic disease were considered as healthy controls. With regards to risk factors affecting the immune system and eyes, all of included studies excluded people with such risk factors including other ocular pathologies, medications that may affect blood parameters, chronic inflammatory disease or autoimmune disease, and any systemic diseases such as renal or liver failure.

Difference in NLR level between patients with NAION and healthy controls

Compared with healthy controls, patients' NLR levels were significantly higher (SMD = 0.47; CI 95% = 0.30–0.65, $p < 0.001$). The included studies were not statistically heterogeneous ($I^2 = 0.0\%$, $p = 0.60$); thus, the analysis used the fixed-effect model Fig. 2.

Diagnostic value of NLR for differentiating between patients with NAION and healthy controls

The pooled sensitivity of five studies was 0.69 (95% CI 0.60–0.67), and the pooled specificity was 0.59 (95% CI 0.50–0.67). The pooled positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio (DOR) of NLR were 1.71(95%CI 1.48–1.98),0.50 (95%CI 0.41–0.62), and 3.38 (95%CI 2.57–4.44), respectively Fig. 3.

Publication bias

As shown in Fig. 4, there was no publication bias among included studies (Egger's test $p = 0.34$).

Discussion

Our study found that NLR was higher in patients with NAION than in healthy controls in six retrospective studies. No significant publication bias was measured. SROC analysis of the pooled data demonstrates a relationship between NLR and NAION. This could be used to help identify mechanisms of pathology and treatment, both of which remain elusive.

NAION is the most common ischemic optic neuropathy in general and most common optic nerve disorder for patients over 50 years of age [24]. It is distinguished clinically from arteritic anterior ischemic optic neuropathy (AAION), which is from giant cell arteritis. NAION is characterized by acute and painless loss of vision [25]. A swollen, pallid optic disk (the optic nerve head [ONH]), with a small or absent cup is a pathognomonic finding that results from obstructions in the posterior ciliary artery and associated vasculature. The exact mechanism is unknown and likely multifactorial. Loss of vision generally stabilizes following the initial incident, and occurrence in one eye does not guarantee the same contralateraly [26]. Associations between smoking, hypertension, and diabetes and NAION have been consistently reported [2, 27], along with obstructive sleep apnea, renal failure, and other inflammatory processes [28, 29].

There are several possibilities for the inadequate perfusion and subsequent optic disk injury seen in NAION: Thrombotic and hypoperfusion ischemia have both been reported [7, 30]. Arnold et al. found delayed filling of the prelaminar nerve head vasculature to precede disk edema, axonal atrophy and swelling [31]. They also described axoplasmic stasis as contributing to laminar crowding and a compartment syndrome mechanism [31]. Co-occurring inflammatory conditions, like those commonly found in NAION patients, exacerbate preexisting variations in microvascular and orbital anatomy and influence the nerve sheath's propensity for injury [30]. Cell and molecular pathology that follows injury is difficult to study, however, because NAION is not lethal and so histology is rare. Since the optic nerve is a CNS structure, it is reasonable to believe NAION pathology could mirror that of other, better-understood CNS ischemic conditions [32]. Post-injury CNS tissue, for example, shows neutrophils peaking within the first week, coinciding with disruption of the blood–brain barrier and thrombus forming NETs [33]. Resident microglia and

Table 2. General characteristics of included studies

First author	Years	Country	Design	Mean age	Gender (male percentage)	NLR cutoff value	Sensitivity	Specificity	BCVA	NAION group		Healthy controls		Healthy control definition	Exclusion criteria	NAION phase	NOS score
										N	NLR	N	NLR				
Polat [19]	2015	Turkey	R	60.1	51.11%	1.94	60	63	3.13	45	2.44 ± 1.00	50	1.85 ± 0.50	Subjects without any systemic disease	Other ocular pathologies, using antiplatelet or anticoagulant agents, malignancy, coronary artery disease, chronic liver or heart disease	Acute	7
Gunes [15]	2017	Turkey	R	54.7	42.9%	1.64	85	41	1.08	56	3.62 ± 4.37	56	2.09 ± 0.96	Subjects without any systemic disease	Other ocular pathologies, neurological disease, chronic autoimmune disease or inflammatory disease, active infection,	Acute	6

Table 2. (continued)

First author	Years	Country	Design	Mean age	Gender (male percentage)	NLR cutoff value	Sensitivity	Specificity	BCVA	NAION group		Healthy controls		Healthy control definition	Exclusion criteria	NAION phase	NOS score
										N	NLR	N	NLR				
Inanc [16]	2018	Turkey	R	66.66	41.66%	2.25	66	73	–	33	2.04 ± 0.42	35	1.97 ± 0.31	Healthy people from outpatient clinic of ophthalmology with simple refractive errors	Other ocular pathologies, alcohol abuse, chronic smoking, inflammatory diseases, atrial fibrillation, any systemic disease, hepatic or renal failure	Acute	6
Kocak [17]	2020	Turkey	R	64.7	42.85%	1.79	71	59	–	50	2.57 ± 1.49	44	1.98 ± 1.05	Healthy people from outpatient clinic of ophthalmology	Other ocular pathologies, using medications that may affect blood parameters, chronic inflammatory disease or autoimmune disease, any systemic diseases	Acute	7
Pinna [18]	2021	Italy	R	–	–	_	_	_	–	37	2.44 ± 0.99	37	1.95 ± 0.81	Subjects without NAION	Not declared	Acute	7

Table 2. (continued)

First author	Years	Country	Design	Mean age	Gender (male percentage)	NLR cutoff value	Sensitivity	Specificity	BCVA	NAION group		Healthy controls		Healthy control definition	Exclusion criteria	NAION phase	NOS score
										N	NLR	N	NLR				
Sinsawad [20]	2021	Thailand	R	59.20	56.7%	1.89	66.7	65	–	30	2.25 ± 0.95	30	1.96 ± 0.90	patients with cataract without any systemic disease	Using any kind of treatment for NAION, other neuro-ophthalmic diseases, glaucoma diseases, retinal diseases, alcohol drinking and smoking, underlying disease that can affect the blood test results	Acute	7

N: Number; NLR: Neutrophil-to-lymphocyte ratio; R: Retrospective; BCVA: best-corrected visual acuity; NOS: the Newcastle–Ottawa scale

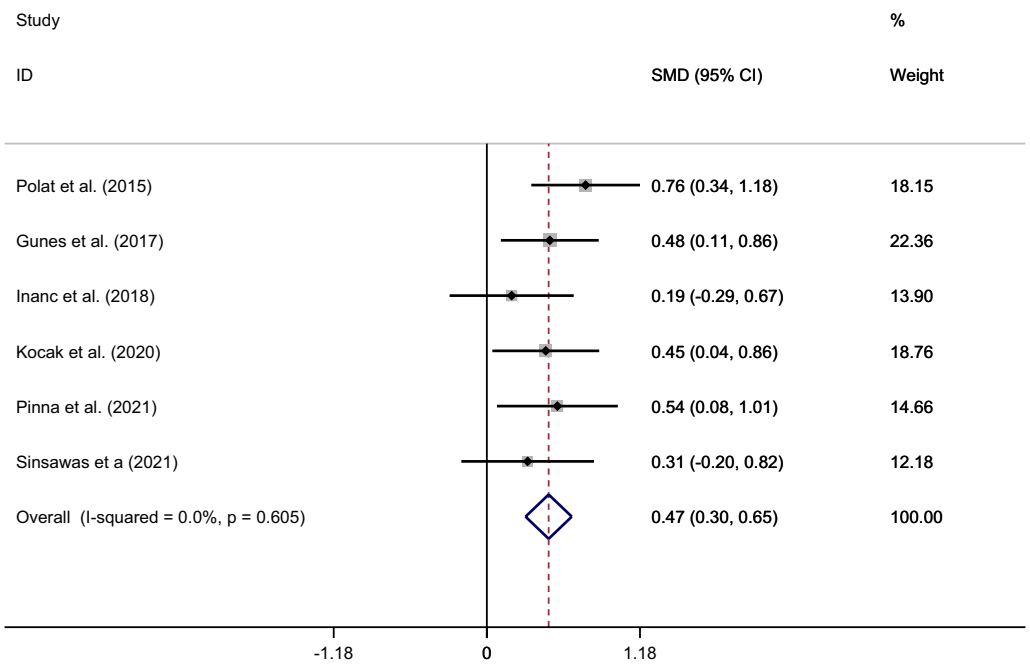

Figure 2. Meta-analysis of differences in NLR level between patients with NAION and healthy controls

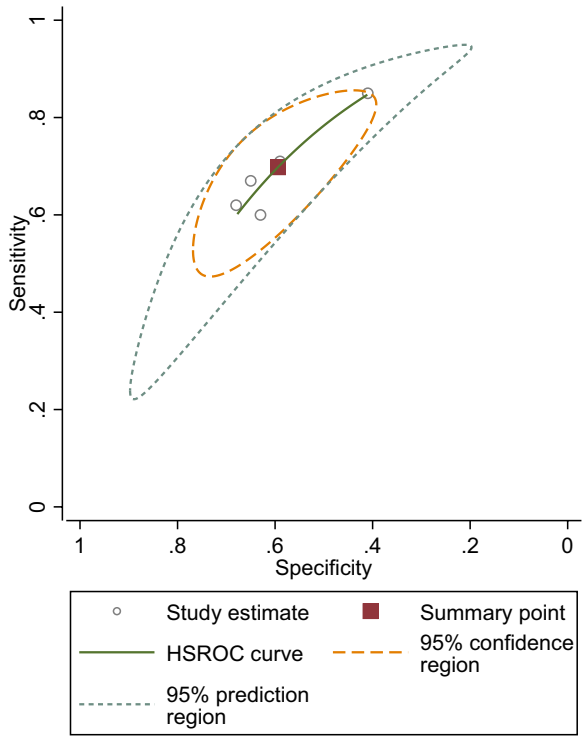

Figure 3. SROC curve of included studies assessing diagnostic value of NLR for NAION

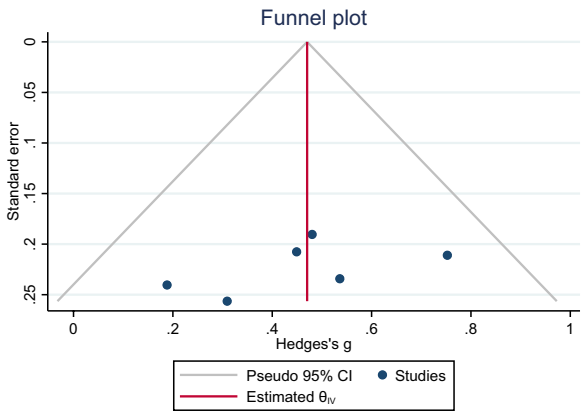

Figure 4. Funnel plot assessing publication bias

peripheral macrophage levels remain elevated over a longer period (on the order of a month), with myeloid subtypes remaining active for different lengths of time [34]. The composition of leukocytes in the injured tissue, moreover, predicts hemorrhagic complications and outcomes more broadly, even when considered independently of infection [35].

Histology of animal and human NAION lesions are consistent with the inflammatory cellular progression of CNS ischemia overall [7]. Tissue edema in a non-human primate model (pNAION) increases in the first week and reperfusion can be seen between 3 and 7 days [36].

Neutrophils respond to the site of injury and peak before microglia and peripheral macrophages take hold, with the monocytes peaking around 21–35 days. Early breakdown of the blood–retinal barrier (BRB) in pNAION resolves by day 14 [32]. Rodent (rAION) models, as well, have shown acute inflammation of the optic nerve axon 24 h post-infarct, with peripheral macrophages appearing between days 3 and 14 [37]. Evidence, thus, suggests the optic nerve is exposed to complex immunological interplay in a manner consistent with more common systemic diseases [37].

The NLR is an easy value to calculate that shows a relationship to disease progression and activity in a number of conditions [8, 38–41]. The ratio is more stable than the absolute counts of either cell type, making it a better indicator of overall immune activity than each value on its own. Neutrophils respond to sterile injury—such as hypoxic, inadequately perfused optic nerve tissue—in essentially the same pro-inflammatory manner as used to clear infection [42].

The elevated NLR value in our investigation might be explained by two different mechanisms. First, it has been discovered that the early stage of NAION is characterized by neutrophil-mediated cellular inflammation [7, 37]. Elevated neutrophil count has been linked to ischemic injury, according to several publications [43–45]. An indication of neutrophil-mediated microvascular plugging may be the relationship between impaired microvascular perfusion and neutrophilia. The relationship between low-grade inflammation and atherosclerosis is the second potential mechanism. Immune cells and different inflammatory factors have a significant contribution to the development and progression of atherosclerotic lesions [46, 47]. Given that atherosclerosis is a risk factor for NAION, increased NLR levels may suggest low-grade chronic inflammation.

In addition to NLR, other complete blood count (CBC)-based biomarkers have been shown to play a significant role in the diagnosis and prediction of NAION. For instance, Pinna et al. in 2019 revealed that median values of mean platelet volume (MPV; $p = 0.01$), dNLR [dNLR = neutrophils/(white blood cells−neutrophils)] ($p = 0.01$), and red cell distribution width (RDW; $p = 0.015$) were all significantly higher in NAION patients. In the mentioned study, there were no significant differences between two groups in terms of neutrophils, lymphocytes, white blood cells, and PLR [18]. In Kocak et al.'s study monocyte, platelet, and neutrophil counts were greater in the NAION group compared to control group, but the difference was statistically insignificant ($p > 0.05$). The SII in the NAION group were greater than in the control group ($p = 0.011$). SII had an area under the curve of 0.66, and SII of > 417 indicated NAION with a specificity of 49% and sensitivity of 71%. Monocyte-to-lymphocyte ratio (MLR) and PLR did not significantly vary between the groups ($p = 0.347$ and $p = 0.105$, respectively) [17]. Inanc et al. in 2018 demonstrated that mean platelet volume (MPV), Plateletcrit, and platelet distribution width (PDW) is higher among NAION and patients with arteritic anterior ischemic neuropathy (AAION) groups compared with healthy controls. Just in the AAION group compared to the control and NAION groups, the mean NLR was significantly higher, indicating that platelet function plays a critical role in AIONs and that NLR may be utilized to distinguish AAION from NAION [16]. Recently, other inflammatory biomarkers have been researched in addition to the biomarkers that are based on CBC. Micieli et al. in 2017 illustrated that in Aqueous Humor, the mean level of IL-2 (5.56 ± 1.27 pg/mL) was significantly lower in the NAION group when compared to the cataract control group (16.6 ± 14.0 pg/mL; P = .002) and the mean level of vascular endothelial growth factor (VEGF) (94.1 ± 40.4 pg/mL) was significantly higher in the NAION group than in the cataract control group (52.2 ± 20.8 pg/mL; P = .010). However, there was not a significant difference in term of IL-1β, TNF-α, IL-6, and IL-8 [48]. According to Mesentier-Louro et al.'s research in 2021, the best biomarker candidates for acute NAION were MCP-2, Eotaxin-3, TRAIL, and TPO. CXCL10 and IL-1α were shown to be the most effective treatment targets in chronic NAION [49]. In this research, comprehensive plasma profiling showed considerable differences in cytokine profiles between mouse model and human with NAION compared with controls, which validates increased inflammation. In human NAION, 21 cytokines elevated more than 1.5 times over control levels, whereas none dropped more than 0.5 times. Four cytokines rose > 1.5x in mouse NAION, whereas two dropped to 0.5x. Monocyte–chemoattractant protein MCP3 and C–C motif chemokine CCL11 (the protein which is associated with human aging) were the most increased cytokine in both mouse models and human with NAION. IL1a, CXCL5, and CXCL13 were the cytokines that increased the highest in human chronic NAION, along with CCL11. Bilateral NAION exhibited the most dramatic elevations in these cytokines. Plasma from three human NAION patients increased angiogenesis and disrupted the endothelial barrier in cultured human retinal endothelial cells [50].

Our analysis is limited by the retrospective design of the included studies, their relatively small sample sizes,

and the lack of blood samples drawn at multiple points over the course of a clinically relevant period.

Conclusion

Our study showed that NLR could predict NAION with high sensitivity and specificity. NLR level is elevated in patients with NAION than healthy controls. However, prospective studies, preferably randomized and multicenter, are needed to establish whether NLR has predictive value for visual acuity and prognosis in NAION. Furthermore, future studies could address whether use of other biomarkers, such as ESR, systemic immune inflammation index (SII), platelet-to-lymphocyte ratio (PLR), or platelet distribution width, which have also been found to correspond to NAION, help refine NLR's diagnostic value.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Abbreviations

NLR	Neutrophil-to-lymphocyte ratio
NAION	Non-arteritic anterior ischemic optic neuropathy
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
NOS	Newcastle–Ottawa scale
SMD	Standard mean difference
CI	Confidence interval
IQR	Interquartile range
SROC	Summary receiver operating characteristic
AAION	Arteritic anterior ischemic optic neuropathy
BRB	Blood–retinal barrier
rAION	Rodent
CBC	Complete blood count
RDW	Red cell distribution width
MLR	Monocyte-to-lymphocyte ratio
MPV	Mean platelet volume
PDW	Platelet distribution width
VEGF	Vascular endothelial growth factor
SII	Systemic immune inflammation index
PLR	Platelet-to-lymphocyte ratio
BCVA	Best-corrected visual acuity

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Author contributions

E.K: study design, draft the initial manuscript, revision of the manuscript, data collection; Sh.N: supervision of data collection, drawing the tables, searching the databases; J.V: data collection, statistical analysis; I.S: supervision of data collection, initial analysis; H.B: statistical analysis, data collection; A.Gh: design and conceptualization of the study, writing the initial draft; B.L-W, A.M.E.M: revision of the manuscript, data collection; Sh.Kh: statistical analysis, study design, revision of the manuscript. All authors read and approved the final manuscript and are responsible for data review.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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