Original Article

Neutrophil to Lymphocyte Ratio as a Marker in Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy in HRH Princess Maha Chakri Sirindhorn Medical Center

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Background: Non anterior ischemic optic neuropathy (NAION) is the most common form of ischemic optic neuropathy. usually associated with systemic vasculopathy disease and has variable visual outcomes. The mechanism of NAION is not fully understood and there is no treatment have been proven to be standard treatment.

Objective: To evaluate Neutrophil to Lymphocyte Ratio in Non-arteritic Anterior Ischemic Optic Neuropathy patients in HRH Princess Maha Chakri Sirindhorn Medical Center.

Design: Retrospective crossectional study.

Materials and Methods: 90 patients in the present study were categorized equally into three groups. Group one was those who were diagnosed with NAION. Group two and three as control groups were those who were diagnosed with cataract with and without systemic diseases respectively. The complete blood count was examined at the first visit of NAION or at the pre-operative day. NLR in each group was calculated and compared.

Results: The average of NLR in the group one was 2.25, in the group two and group three were 1.69 and 1.74 respectively. The comparison of mean continuous variable between 3 groups using Oneway ANOVA was analysed. NLR in group one was higher with statistical significance ($p<0.05$) when compared with group two but there was no statistical significance between group one and group three or group two and group three. The level of NLR has the negative correlation with the improvement of BCVA at 3 months.

Conclusion: NLR ratio is one of the marker that can be found elevated when there is an inflammatory reaction, in the present study there is a significant higher of NLR ratio in NAION group and has negative correlation with vision at three months, NLR could be used as a prognostic indicator for the prediction of Visual outcome.

Keywords: Non arteritic anterior ischemic optic neuropathy; Neutrophil lymphocyte ratio (NLR); Prognostic indicator; Prediction; Visual outcome

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Anterior ischemic optic neuropathy (AION) is one of common ophthalmic diseases. Patients present with acute painless visual loss. There are two types of AION differentiated by pathophysiology: Arteritic anterior ischemic optic neuropathy (AAION), which is the result of an arterial inflammation and Non-arteritic anterior ischemic optic neuropathy (NAION)[8], which is due to non-inflammatory arterial disease. NAION also accounts for 90% of AION[3].

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NAION is commonly found in patients older than 50 year. Clinical presentations include visual loss in hours to days, visual field defect, presence of relative afferent pupillary defect in unilateral case and optic disc swelling which may precede declination of visual acuity. Optic disc swelling can be found in diffuse or segmental form and accompany with disc hyperemia. In contralateral asymptomatic eye mostly find crowded disc appearance[3]. NAION can be either stable or progressive on its clinical course.

Pathophysiology of NAION results from insufficiency of blood circulation around optic disc. There are many etiologies which can cause an insufficiency e.g. ischemia or stenosis of optic disc vessels, venous drainage obstruction, nocturnal hypotension[2,9,10]. Patients who have crowded disc and underlying diseases of Diabetes mellitus, Hypertension, Hyperlipidemia, Obstructive sleep apnea are at risk developing NAION[1,4,5].

Laboratory investigations that help differentiation AAION from NAION are ESR (erythrocyte sedimation rate), CRP (C reactive protein) and CBC (complete blood count). The level of ESR, CRP and platelet in AAION is usually

higher than NAION [6,7]. Other blood parameters in complete blood count e.g. neutrophil lymphocyte ratio is found to be high in Diabetes mellitus and Hypertension patients. Systemic inflammatory reaction from DM and hypertension causes neutrophilia and lymphopenia leading to higher NLR. As in pathophysiology of NAION which produce some degree of inflammation in early course of disease. We believe that NLR level may rise and help diagnosing NAION.

Objective

The present study is evaluate Neutrophil to Lymphocyte Ratio in Patients with Non-arteritic Anterior Ischemic Optic Neuropathy in HRH Princess Maha Chakri Sirindhorn Medical Center Thailand.

Materials and Methods

The present study is retrospective study comparing blood parameters in patients with NAION, patients who were diagnosed with cataract and had underlying diseases and those with cataract without any underlying diseases in HRH Princess Maha Chakri Sirindhorn Medical Center between January 2005 and June 2020.

This research was approved by from the ethics committee of Srinakharinwirot University Thailand (SWUEC-064/2563E).

90 patients were participated in the present study. There were three groups in this study. Each group had 30 patients. Group one was those who were diagnosed with NAION which was our study group.

Inclusion criteria: 1) Acute painless visual loss, 2) Presence of relative afferent pupillary defect, 3) Arcuate or altitudinal Visual field defect which is compatible with optic disc edema, 4) Segmental or diffuse Optic disc edema with peripapillary flame-shaped hemorrhages, 5) Spontaneous resolution of optic disc edema was observed, 6) No other abnormal ophthalmic findings that can mimic other ophthalmic disease or other neurological diseases, 7) Laboratory in first time examination (CBC, ESR, CRP, VDRL, Anti HIV) and MRI result was normal.

Exclusion criteria: 1) Subjects with underlying disease effected a blood test result e.g. inflammatory diseases, leukemia, thrombocytosis, and Multiple myeloma, 2) History of smoking and alcohol drinking, 3) Retinal diseases e.g. diabetic retinopathy, retinal vein occlusion and hypertensive retinopathy, 4) Glaucoma diseases, 5) Other Neuro-ophthalmic diseases, 6) The patient who received any kind of treatment for NAION.

Group two were those who were diagnosed with senile nuclear cataract and had either diabetes, hypertension or dyslipidemia as theirs underlying diseases. And group three were those were diagnosed with senile nuclear cataract and did not have any underlying disease. Our study was retrospective study. we included the patients with senile cataract for reason that laboratory testing is performed routinely for pre operation. We defined group two and three as control group. All of patients were undergone complete ocular and fundoscopic examination. Best corrected visual acuity (BCVA) evaluated by snellen chart at the initial and 3 months follow-up examination was recorded. Color vision test was also recorded in every subject. Visual field testing was performed by Humphrey field analyzer with strategy of 30-2.

The complete blood count from every participant was examined at the visit the diagnosis of NAION was made and at the pre-operative day for cataract surgery. Other blood tests that we collected from patients with NAION were ESR, CRP, VDRL, Anti HIV, Bun/Cr.

The authors used comparing two independent means to calculate sample size in the present study. Values of $Z_{\alpha/2}$ and Z_{β} were set as 1.96 and 0.84 respectively for significance level of 0.05 and statistical power of 80%. Standard deviation and mean difference values were both set as 1. After calculation, the smallest sample size per group is 16.

PASW Statistic (SPSS) 18.0 (SPSS, Inc., Chicago, IL, USA) program was used for statistical analysis. Descriptive statistics, including frequency and percentage, were used for categorical variables. Continuous variables were reported as mean, standard deviation for normally distributed variables and median (Percentile 25 and Percentile 75) for non-normally distributed variables. The comparison of mean continuous variables between three groups was used the Oneway ANOVA and compare between two groups was used Student t-test. The comparison of categorical variables were performed using Chi-square test or Fisher's exact test. Pearson correlation or Spearman rank correlation was used to relate the NLR with ESR, Platelet, MPV and BCVA. The receiver operating characteristic curve (ROC) analysis was performed to determine the cutoff values of NLR for predicting NAION. For all tests performed, a two-tailed p-value <0.05 was considered to be statistically significant.

Results

There was no difference in sex between three groups. But there was statistically significant difference in the age, Control without underlying disease group and control with underlying disease the mean age was higher than NAION group. Female subjects account for 55.6% (n=50). Conversely, number of male subjects is 40 (44.4%). In NAION group, there were patient with underlying disease for 80% (n=24) and up to 33% (n=10) had diabetes mellitus, hypertension and hyperlipidemia as their underlying disease. Demographic data are shown in Table 1.

The Comparison of blood parameters are summarized in Table 2. Level of white blood cell and platelet were higher in NAION group than the other groups. The average of NLR in the group diagnosed with NAION was 2.25. While the average NLR in the group of patients with cataract who had one of the underlying diseases and without underlying disease were 1.69 and 1.74 respectively. The comparison of mean continuous variable between 3 groups using Oneway ANOVA was analyses. It found that NLR in group one was higher with statistical significance ($p<0.05$)

Table 1. Demographic characteristics and systemic disorders of all participants

	Total (n=90)	NAION (n=30)	Control no U/D (n=30)	Control with U/D (n=30)	p-value	p-value of multiple comparison
Age (years), mean±SD	64.13±12.45	59.20±11.32	63.10±13.72	70.10±9.79	0.002	0.002[b]
Sex (female), n (%)	50 (55.6)	13 (43.3)	16 (53.3)	21 (70.0)	0.110	
Sex (male), n (%)	40 (44.4)	17 (56.7)	14 (46.7)	9 (30.0)		
Underlying disease, n (%)	54 (60.0)	24 (80.0)	0 (0.0)	30 (100)	<0.001	<0.001[a], 0.024[b], <0.001[c]
HT, n (%)	47 (52.2)	18 (60.0)	0 (0.0)	29 (96.7)	<0.001	<0.001[a], <0.001[b], <0.001[c]
DM, n (%)	32 (35.6)	16 (53.3)	0 (0.0)	16 (53.3)	<0.001	<0.001[a], <0.001[c]
DLP, n (%)	40 (44.4)	13 (43.3)	0 (0.0)	27 (90.0)	<0.001	<0.001[a], <0.001[b], <0.001[c]
DM and DLP, n (%)	2 (2.2)	1 (3.3)	0 (0.0)	1 (3.3)	1.000	
HT and DM, n (%)	3 (3.3)	2 (6.7)	0 (0.0)	1 (3.3)	0.770	
HT and DLP, n (%)	14 (15.6)	2 (6.7)	0 (0.0)	12 (40.0)	<0.001	0.002[b], <0.001[c]
HT and DM and DLP, n (%)	24 (26.7)	10 (33.3)	0 (0.00	14 (46.7)	<0.001	0.001[a], <0.001[c]

HT = Hypertension; DM = Diabetes mellitus; DLP = Dyslipidemia
Compare mean between 3 groups by Oneway ANOVA and Multiple comparison ([a] NAION vs. control no U/D, [b] NAION vs. control with U/D, [c] Control no U/D vs. control with U/D).

when compared with group two but there was no statistical significance when comparing NLR in both group one with group three and group two with group three. Mean platelet volume and Hemoglobin values did not show any significant difference between groups. ROC curve analysis showed that the optimal NLR cut-off point for NAION was 1.89 with a sensitivity of 66.7% and specificity of 65% (Figure 1).

Relationship between NLR and best corrected visual acuity (log mar unit) was shown on table 3. The correlation coefficient was positive between NLR and BCVA at 3 months follow-up which can interpret that the higher NLR was, the more BCVA (log mar unit) at 3 month escalated (Figure 2). There was a negative correlation between NLR and change of VA (initial to 3-month). As the NLR increased, the difference of VA became lower (Figure 3).

Discussion

Many types of white blood cell could be one of inflammatory markers in body. NLR was one of makers that usually rise in inflammatory reaction[2]. The upsurge of NLR resulted from ischemia of cellular tissues. NLR was associated with cardiovascular disease[11,12], hyperlipidemia[11,13,14] and diabetes mellitus[11,15,16]. Optic neuritis[17,18], Thyroid eye disease[19], Keratoconus[20,21], Primary open angle glaucoma[22] and AION[8-10] were also related to an uprise of NLR. NLR can be easily calculated and taken from a complete blood count result.

The present study was the first study that evaluated neutrophil to lymphocyte Ratio in patients with NAION Thailand. Polat et al showed that NLR was significantly higher in patients with NAION compare to normal populations[9]. We found that NLR in NAION group was higher with statistical significance ($p<0.05$) when compared with control with underlying disease group but there was no statistical significance when comparing NLR in NAION group with control without underlying disease group. Even though there was up to 80% of patients with NAION who had underlying disease, NLR was still higher than control with underlying disease group. It meant that NAION caused an immoderate inflammatory reaction. However, patients with underlying disease who was undergone a preoperative evaluation would make a good control of their blood pressure or fasting blood sugar. Inflammatory reaction would decline and NLR would also deescalate. In the group of control without underlying disease because of our limitation from retrospective study we used taking past history from patients and preoperative laboratory to get their underlying disease. We did not use any other investigations so that we might still miss some others underlying disease which could have effect with NLR. Platelet values might associate with inflammatory processes. Polat et al stated that platelet value was

Table 2. Comparison of blood parameters of all participants

	Total (n=90)	NAION (n=30)	Control no U/D (n=30)	Control with U/D (n=30)	p-value	p-value of multiple comparison
WBC count (/mm^3)	7,608.21±2,376.13	9,025.67±2,936.02	6,613.63±1,373.05	7,185.33±1,880.20	0.001	0.001[a], 0.015[b]
Neutrophil (/mm^3)	4,487.41±1,938.96	5,609.84±2,532.56	3,815.13±1,255.29	4,037.24±1,252.12	<0.001	0.001[a], 0.003[b]
Lymphocyte (/mm^3)	2,386.96±728.30	2,593.35±816.24	2,093.66±611.53	2,473.88±668.41	0.019	0.022[a]
NLR	1.97±0.84	2.25±0.95	1.96±0.90	1.69±0.51	0.030	0.505[a], 0.024[b]
Platelet (/mm^3)	278,455.76±65,526.01	316,133.33±75,927.25	254,100.00±50,241.04	265,133.93±51,207.22	0.002	0.001[a], 0.010[b]
Mean platelet volume (fL)	9.89±0.74	9.67±0.77	9.99±0.66	10.04±0.77	0.124	
Hb (g/dL)	13.01±1.58	13.01±2.08	13.13±1.17	12.89±1.39	0.848	
ESR (mm/hr)	30.5 (15.0 to 57.0)	32.0 (15.0 to 57.0)	-	26.0 (26.0 to 26.0)	NA	

Mean±SD and median (percentile 25 to Percentile 75). Not Available (NA).
Compare mean between 3 groups by Oneway ANOVA and Multiple comparison ([a] NAION vs. control no U/D, [b] NAION vs. control with U/D

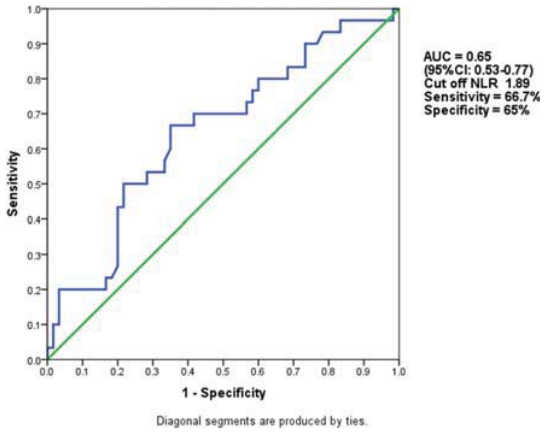

Figure 1. ROC curve of NLR and NAION.

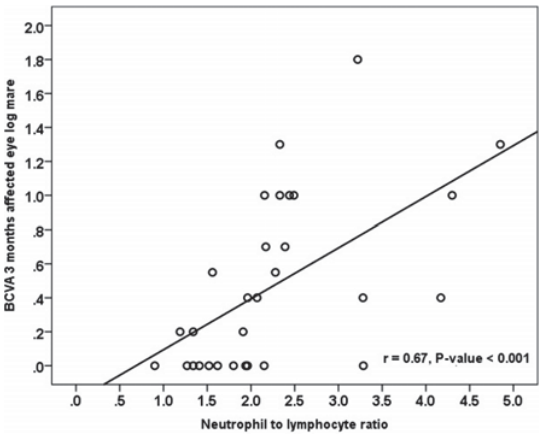

Figure 2. Correlation of NLR and Best Corrected Visual Acuity 3 months affected eye (log mar unit) within NAION.

Table 3. Correlation of Best Corrected Visual Acuity (BCVA) affected eye log mar unit and NLR within NAION

BCVA	n	r	p-value
Initial	30	0.24	0.205
3 month	30	0.67	<0.001
Difference of Initial and 3 month	30	-0.49	0.006

Correlation of BCVA affected eye log mar and NLR within NAION was used Spearman rank correlation

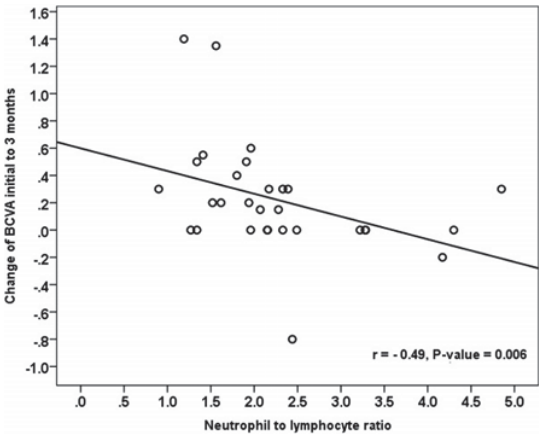

Figure 3. Correlation of NLR and Change Best Corrected Visual Acuity initial and 3 months affected eye (log mar unit) within NAION.

significantly higher in NAION group[9]. In the present study we also found that platelet level was significantly higher in NAION group compared to other groups.

In our study we choose the patients with senile cataract for control group with reason that laboratory testing was performed routinely for pre operation because the present study was retrospective study so there was some limitation about laboratory testing in control group, our idea was senile nuclear cataracts is aged related diseases which has not been reported to be related to NLR.

The present study found a NLR cut off value of 1.89 to differentiate patient with NAION. The sensitivity was 66.7% and the specificity of 65% were too low to use it as a diagnostic tool. History taking and complete ocular examination together with NLR would help in the diagnosis. Gunes et al reported that high NLR value is associated with worse visual results[10]. As in our study, NLR could be a predictive factor for the visual acuity of the patients. According to correlation between NLR and difference of Visual acuity from initial to 3 months with no treatment in all patients, the more NLR increased, the lower change of visual acuity occurred. Comparison of ESR between groups could not be established due to the absence of ESR values in control group. Gunes et al found that Mean platelet volume (MPV) did not differ between NAION and control group[10]. The present study also found that there was no difference in MPV between groups.

The authors compared the present study with other literatures. The present results seemed to correlate with a study conducted by Polat et al[9] and Gunes et al[10] in the way that NLR ration were signification higher in NAION patients and could be used as prognostic factor for visual outcome, both of researches were carried out in Turkey, our study was the first one that study in Thai population.

For the further study, we suggested that the sample

size should be higher in order to make the difference statistically significant and to make the result more valid, until now NAION still has no proven effective treatment, In one a large, noncontrolled, retrospective study Hayreh et al found that oral corticosteroid has positive potential effect on visual outcome[23] but there is still many controversies and was suggested only to use in progressive type NAION (progressive declination of visual acuity over 2 to 3 weeks and persistent optic disc edema) because steroid could make worsening of the underlying disease of NAION's patients then if NLR could predict the prognosis or severity this might help in decision making of treatment with steroid. And in the future with more sample size and with prospective design, it would be advanced if the alteration of NLR, the change of visual acuity and visual field was followed periodically and find the correlation in further study. Hence, NLR might be utilized as a predictive value for NAION.

Conclusion

The neutrophil lymphocyte ratio could be one of the marker that increase in NAION patients. The advantages of the neutrophil lymphocyte ratio were the low cost and the high availability of the resource. Moreover it could be used as the predictive factor for the visual outcomes of the NAION patients.

What is already known on this topic?

The neutrophil to lymphocyte ratio (NLR) is an indicator of systemic inflammation, an elevated NLR has proven its prognostic value in cardiovascular diseases, infections, inflammatory diseases and in several types of cancers.

What this study adds?

There is a significant higher of N/L ratio in patients with NAION and has negative correlation with vision at three months, the level of NLR could be used as a prognostic factors for the predication of Visual outcome.

Potential conflicts of interest

The authors declare no conflict of interest.

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