Correlation between Neutrophil to Lymphocyte Ratio (NLR) and Degree of Myopia in Medical Students from University of Sumatera Utara

Annisa Putri Siregar[1], Masitha Dewi Sari[2], Aryani Atiyatul Amra[2]
[1]Ophthalmology Resident, University of Sumatera Utara, Indonesia
[2]Ophthalmologist, University of Sumatera Utara, Indonesia

Abstract. *Introduction.* Visual impairment caused by myopia has been a major global health issue. The incidence of myopia has increased rapidly in the past two decades. Inflammatory factors are one of the factors causing myopia. Previous study shows there is a correlation between NLR and degree of myopia.

Purpose. This study aims to determine the correlation between NLR and degree of myopia in medical students from Faculty of Medicine, University of Sumatera Utara.

Material and Methods. This study was a cross sectional design with an observational analytical study. The measurements were refraction examination and NLR values. Statistical analysis used was Kruskal Wallis and Anova correlation with 5% significance.

Results. This study consisted of 42 myopic subjects detailed as 20 male subjects (47.6%) and 22 female subjects (52.4%) with mean age 25.64±2.99 years old. Distribution of mild, moderate and high myopia was 38.1%, 42.9% and 8% respectively with mean spherical equivalent -3.57±2.11 D. Mean NLR values were 2.07±0.88. NLR values were not statistically significant with degree of myopia (p=0.082)

Conclusions. There was no statistically significant correlation between NLR and degree of myopia in medical students from Faculty of Medicine, University of Sumatera Utara.

Keyword: refractive error, myopia, neutrophil-to-lymphocyte ratio, inflammation

Introduction

Refractive errors are the most common eye disorders that can occur at all ages and are a public health challenge. The World Health Organizations (WHO) report that refractive errors are the first cause of visual impairment and the second cause of vision loss worldwide. The prevalence of refractive errors worldwide is astigmatism (40.4%), hypermetropia (30.9%) and myopia (26.5%) (Hashemi et al., 2017; Holden et al., 2016).

The incidence of myopia has increased rapidly in the past two decades. The prevalence of myopia and high myopia in Indonesia is estimated at 26.1% and 0.8% (Icel et al., 2019). Most cases of myopia can be corrected but uncorrected refractive errors still account for nearly 33% of visual impairment (Lin et al., 2016; Flitcroft et al., 2019).

The main causes of myopia are still not entirely known. Genetic, environment and lifestyle factors have been identified to be associated with the development of myopia. Many studies have reported that the prevalence of myopia increases with age, lack of outdoor activities, and near work activities (American Academy of Ophthalmology, 2020; Walline et al., 2020).

Nugroho et al.'s study found that the development of myopia in medical schools was higher compared to nursing and nutrition schools, but was similar between boys and girls (Nugroho et al., 2020). The development of myopia in children and adolescents occurs gradually. In addition, early-onset myopia is associated with high myopia (Zhao et al., 2019). The Rotterdam Eye Study demonstrated of bilateral visual impairment in high myopia with 39% of patients developing myopic maculopathy, 17% with open-angle glaucoma and 5% with cataracts (Vagge et al., 2018).

Research on the pathophysiology of myopia has progressed very rapidly, both in the field of genetics and cellular. Myopia is associated with inflammation, oxidative stress, genetics and

environment (Coviltir et al., 2019). Several studies have suggested that various inflammatory mediators have been correlated to the development of myopia. In myopia, expression of Transforming Growth Factor-β (TGF-β) and Matrix Metalloproteinase (MMP) are increased, while expression of Collagen-1 (COL-1) is downregulated. TGF-β regulates cell growth, inflammation, wound healing and differentiation. MMPs play role in reconstruction and vascularization of tissue during the inflammatory and breakdown extracellular matrix (Wojciechowski et al., 2013). MMPs's dysregulation has also been considered as pathogenetic mechanism in myopia. TGF-β regulates MMP2 levels through activation of nuclear factor (NF)-κB is a transcription factor that modulates various inflammatory cytokines's expression in fibroblasts (Yang et al., 2010).

The neutrophil to lymphocyte ratio (NLR) is calculated as the absolute number of neutrophils divided by the absolute number of lymphocytes. NLR is an index to differential diagnosis, prognostic prediction of disease and marker to patient's inflammatory activity. Potential inflammatory marker in eye diseases such as dry eye, keratoconus, and retinal vein occlusion also has been described by NLR (Icel et al., 2019).

Based on previous studies, this study are aimed to understand more about the relationship between NLR with myopia in medical students from Medical Faculty, University of North Sumatra, Medan, Indonesia.

Material and Methods

This study was cross sectional design at Department of Ophthalmology, Faculty of Medicine, University of Sumatera Utara, University of Sumatera Utara Hospital, Medan, Indonesia and was approved by the Health Research Ethical Clearance Committee of the Medical Faculty of University of Sumatera Utara, Medan, Indonesia.

Inclusion criteria of the study were subject aged between 21 and 33 years old with refractive error valued at -0.50 D that divided into mild myopia, moderate myopia and high myopia. Exclusion criteria were systemic inflammatory diseases affecting blood NLR, such as anemia, malignancy, diabetes mellitus, hypertension, coronary artery disease, infection, liver diseases, kidney failure, thyroid pathologies, smoking, and any ocular problems beside than ocular problems.

All subjects filled informed consent and demographic form. Ocular examinations including anterior segment, posterior segment and intraocular pressure was evaluated to rule out another eye disease. And then venous blood samples were collected. Complete Blood Count were performed with hematology analyzer (Sysmex xn 1000) by taking 3 ml venous blood. NLR values were obtained by dividing the neutrophil count by the lymphocyte count. NLR values were then presented to statistical analysis.

Data was then analyzed and presented in the data tabulation, by displaying frequency values and percentages for categorical data. Numerical data was presented by displaying mean, median, standard deviation, minimum and maximum values. Normality of the data was determined with Shapiro Wilk test. Bivariate analysis was used to determine the relationship between the independent and dependent variables using Kruskal Wallis test and Anova test with a significance level of p-value <0,05.

Results

In the demographic data of this study, the number of samples that fulfilled the criteria in this study were 42 subjects. The data in this study are primary data in form of demographic data (gender and age) obtained through interviews; data on refraction status obtained through refractive examination, as well as data on NLR levels obtained through complete blood count at the University of Sumatera Utara Hospital.

Table 1. Demographic characteristics of research subjects

Demographic Characteristics	n (%)
Sex	
Male	20 (47,6)
Female	22 (52,4)
Age	
Mean (SD)	25,64 (2,99)
Median (Min – Max)	26 (21 – 33)
21 – 25 years	18 (42,9)
26 – 30 years	20 (47,6)
31 – 35 years	4 (9,5)
Degree of myopia	
Mild	16 (38,1)
Moderate	18 (42,9)
High	8 (19)
Spherical Equivalent	
Mean (SD)	3,57 (2,11)
Median (Min – Max)	3,5 (0,75 – 9)
NLR	
Mean (SD)	2,07 (0,88)
Median (Min – Max)	1,93 (0,92 – 4,61)

Based on Table 1, it could be concluded that in this study, there were more female myopia students of Medical Faculty, University of Sumatera Utara, which were 22 subjects (52.4%) more than men, that were 20 people (47.6%). In addition, the median and mean age of myopia students from Medical Faculty, University of Sumatera Utara were 26 years old and 25.64±2.99 years old, with the youngest being 21 years old and the oldest being 33 years old. Characteristics of the subjects based on the degree of myopia. The most category consisted of 18 subjects (42.9%) who had moderate degree myopia, followed by 16 subjects (38.1%) with mild degree myopia and 8 subjects (19%) with high degree myopia. Characteristics of the subject based on the spherical equivalent value. The mean value of the spherical equivalent was 3.57 ± 2.11 D, with the lowest value of 0.75 D and the highest value of 9.00 D. The average NLR value was 2.07, with the lowest value was 0.92 and the highest was 4.61.

Table 2. Correlation between NLR and degree of myopia

Myopia	NLR		p
	Mean (SD)	Median (Min – Max)	
Mild	1.78 (0.55)	1.76 (0.93 – 2.56)	0.082*
Moderate	2.02 (0.9)	1.8 (0.92 – 4.05)	
High	2.77 (1.07)	2.37 (1.68 – 4.61)	

Table 2 showed the relationship between the NLR and the degree of myopia. In subjects with mild myopia, the mean value was 1.78±0.55. Subjects with moderate myopia showed a slightly higher mean value compared to subjects with mild myopia with a mean value of 2.02±0.9. The highest mean NLR value was seen in subjects with severe myopia with a mean value of 2.77±1.07. Using the Kruskal Wallis test, there was no significant relationship between the NLR value and the degree of myopia (p = 0.082).

Discussion

In this study, more than half of the subjects was female. This study was in line with research conducted by Gao et al. (2014) on the Handan tribe in China, that the majority of myopia patients were female. This was not only influenced by environment factors, but also influenced by a family history with refractive errors (Gao et al., 2014).

The mean age in this study was 25 years old, similar with a study conducted by Jones and Luensmann (2012) in East Asia, where the prevalence of myopia patients were 73% of 15-25 years old subjects. In Indonesia, the prevalence of myopia patients aged 15-25 years old was 62% - 66% (Hyman et al., 2015).

In this study, the majority of the samples had moderate myopia, which was 42.9%. This study was in line with the study by Reddy et al. (2020) that found subjects with moderate degree of myopia of 56.54% (Reddy et al., 2020). This study was different with the study conducted by Jones and Luensmann (2012) in East Asia, with the highest prevalence was severe myopia at 38.4% (Jones & Luensmann, 2012). The study was also different from Arsa's study in 2019 with the prevalence of mild, moderate and high myopia being 64.3%, 20.2% and 15.5% respectively (Arsa et al., 2019).

This study found that the mean spherical equivalent of myopia students from Medical Faculty, University of Sumatera Utara was 3.57±2.11 D. This is in line with research by Hu et al. (2019) in Melbourne that the mean spherical equivalent was -3.00±0.50 D and Tanjung et al.'s (2021) study that mean spherical equivalent was -2.94±2.08 D. However, the spherical equivalent value in this study was lower compared to the study by Reddy et al. (2020) in Malaysia that the spherical equivalent was -4.25 D (Hu et al., 2019; Reddy et al., 2020; Tanjung et al., 2021).

In this study, the mean predictive value of NLR was 2.07±0.88. This result was comparable with the results from Icel et al. (2018), that had average predictive value of NLR in the severe myopia group that was 2.23± 0.78. Meanwhile, research conducted on patients with ocular hypertension revealed an average NLR value of 2.12±0.78. In patients with acute primary open-angle glaucoma, the mean NLR was 2.33± 0.90. However, no recent study had showed the cutoff value of NLR in myopia patients. Based on the result of previous studies, it could be concluded that the average value of the NLR tended to show a slightly higher result (Icel et al, 2019).

In this study, the mean value of NLR was differentiated based on the degree of myopia, detailed as mild, moderate, and severe myopia, with higher mean value depending on myopia severity. However, this study showed that there was no significant relationship between the NLR value and the degree of myopia ($p>0.05$). This results was different from Icel et al. (2019) that found a significant relationship between NLR values and the incidence of myopia by comparing them in a healthy control group. This difference could occur due to limited number of samples in this study, which was 42 subjects, compared to Icel E. et al.'s study with 79 subjects. Undetected comorbid systemic disease in this study subjects could also affected the result of the study (Icel et al., 2019).

This study had several limitations such as this study did not include control group and number of subjects in this study were relative small, therefore further research was required in addition to more variables and larger sample size. Furthermore, additional laboratory testing of systemic disease should be added to reduce bias.

Conclusions

This study found differences in NLR values based on the degree of myopia that severity of myopia was correlated with higher the NLR value, but no statistically significant correlation was found between NLR and the degree of myopia in medical students from Faculty of Medicine, University of Sumatera Utara ($p = 0.082$).

Conflict of Interest

The authors declare that there is no conflict of interest.

References

American Academy of Ophthalmology. (2019). *Clinical Optics*. San Francisco: American Academy of Ophthalmology.

Arsa, D.M. (2019). *Hubungan Panjang Aksial, Ketebalan Kornea Sentral dan Kedalaman Bilik Mata Depan dengan Kejadian Miopia pada Etnis Melayu, India, dan Cina Mahasiswa Fakultas Kedokteran Universitas Sumatera Utara*. Medan: USU Press.

Coviltir, V., Burcel, M., & Cherecheanum, A.P. (2019). Update on Myopia Risk Factors and Microenvironmental Changes. *J Ophthalmol*. doi:10.1155/2019/4960852

Flitcroft, D.I., He, M., Jonas, J.B., Jong, M., Naidoo, K., Matsui, K.O., et al. (2019). Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *IOVS J., 60,* M20-M30.

Gao, T.Y., Zhang, P., Li, L., Lin, Z., Jhanji, V., Peng, Y., et al. (2014). Rationale, design, and demographic characteristics of the handan offspring myopia study. *Oph Epidemiologi J, 21*(2), 124-132. doi: 10.3109/09286586.2014.887734

Hashemi, H., Fotouhi, A., Yekta, A., Pakzad, R., Ostadimoghaddam, H., & Khabazkhoob, M. (2017). Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol, 30*(1), 3-22. doi:10.1016/j.joco.2017.08.009

Holden, B.A., Fricke, T.R., Wilson, D.A., et al. (2016). Global Prevalence of Myopia and High Myopia and Tempora; Trends from 2000 through 2050. *Ophthalmology, 123*(5), 1036-1042. doi:10.1016/j.ophtha.2016.01.006

Hu, Y., Ding, X., Long, W., et al. (2019). Longitudinal Changes in Spherical Equivalent Refractive Error Among Children With Preschool Myopia. *Investigate Ophthalmology & Visual Science*. 10.1167/iovs.18-24862.

Hyman, L., Gwiazda, J., Hussein, M., Norton, T.T., Wang, Y., Tootle, W.M., et al. (2015). Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *ArchOph, 123*, 977-985.

Icel, E., Ucak, T., Karakurt, Y., Yilmaz, H., Tasli, N.G., & Turk, A. (2019). The relation of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with high axial myopia. *Ocular Immunology and Inflammation, 28*(3), 396-401.

Jones, D., & Luensmann, D. (2012). The prevalence and impact of high myopia. *Contact Lens Research, 38*(3), 188-196.

Lin, H.J., Wei, C.C., Chang, C.Y., Chen, T.H., Hsu, Y.A., Hsieh, Y.C., et al. (2016). Role of chronic Inflammation in myopia progression: clinical evidence and experimental validation. *EBioMedicine, 10*, 269-281.

Nugroho, A., Prayogo, M.E., Widyandana, E., Indrawati, S.G., & Suhardjo. (2020). Progression of Myopia Among Medical Students: A one-year cohort study. *Journal of Community Empowerment for Health, 3*(1), 28-33. doi: 10.22146/jcoemph.42887

Reddy, S.C., Shariff, M.M., & Dasrilsyah, A.M. (2020). Correlation between Central Corneal Thickness and Degree of Myopia among Malaysian Patients Undergoing Laser Keratorefractive Surgery. *Journal of Advances in Medicine and Medical Research*. doi:10.9734/jammr/2020/v32i2230705

Tanjung, F.N., Amra, A.A., & Sari, M.D. (2021). Association between Vitamin D and Ocular Lens Thickness in Myopic Eyes. *International Journal of All Research Education and Scientific Methods*, 2455-6211.

Vagge, A., Ferro, D.L., Nucci, P., Serafino, M., Giannaccare, G., & Traverso, C.E. (2018).

Prevention of Progression in Myopia: A Systematic Review. *Diseases, 6*(4), 92. doi:10.3390/diseases6040092

Walline, J.J., Lindsley, K.B., Vedula, S.S., et al. (2020). Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev, 1*(1), CD004916. doi:10.1002/14651858.CD004916

Wojciechowski, R., Yee, S.S., Simpson, C.L., Bailey-Wilson, J.E., & Stambolian, D. (2013). Matrix metalloproteinases and educational attainment in refractive error: evidence of geneenvironment interactions in the age-related eye disease study. *Ophthalmology, 120*, 298–305.

Yang, S.R., Ye, J.J., & Long, Q. (2010). Expressions of collagen, matrix metalloproteases-2, and tissue inhibitor of matrix metalloproteinase-2 in the posterior sclera of newborn guinea pigs with negative lens-defocused myopia. *Acta Academiae Medicinae Sinicae, 32*, 55–59.

Zhao, Y., Feng, K., Liu, R.B., et al. (2019). Atropine 0.01% eye drops slow myopia progression: a systematic review and Meta-analysis. *Int J Ophthalmol, 12*(8), 1337-1343. doi:10.18240/ijo.2019.08.16