Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.08.494 2019;26(10):2386-90

Original Article

The value of blood parameters as a diagnostic inflammatory biomarker for inverted papilloma

Mustafa Celik

Harran University Faculty of Medicine, Department of Otorhinolaryngology, Sanliurfa, Turkey

Abstract

Aim: We aimed to determine the diagnostic value of blood parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) values for sinonasal inverted papilloma (IP) and to investigate its relationship with severity of the disease.

Material and Methods: In this retrospective study, 33 patients (22 males, 11 females; mean age 52.60±8.99 years) diagnosed with IP and 44 healthy individuals (25 males, 19 females; mean age 50.97±9.28 years) were included. NLR, PLR and MPV values of IP and control groups were calculated and compared statistically. In IP group, NLR values and stages of the disease in accordance with the Krouse Staging system were evaluated statistically.

Results: NLR levels were significantly higher in the IP group than the control group. (Mean NLR: IP group= 2,484±1.132; Control group= 1.971±0.884; p=0.029). Lymphocyte, PLR and MPV values were not statistically significant between the two groups. A strong correlation was found between the NLR value and IP stages.

Conclusion: In cases with inverted papilloma, the NLR value obtained by easy-to-perform and low-cost tests, can be used as a new inflammatory biomarker and to predict the severity of the disease. In order to confirm these findings, further studies with larger patient series are needed.

Keywords: Inverted papilloma, inflammation, neutrophil, platelet, lymphocyte, ratio.

INTRODUCTION

Sinonasal inverted papilloma (IP) is a benign sinonasal tumor of ectodermal origin, usually originating from the lateral nasal wall, middle concha and middle meatus, and rarely from the paranasal sinuses (1-3). IP is a rare tumor that accounts for approximately 0.5 % to 7 % of all nasal tumor cases; approximately 4 % of all nasal polyps and approximately 70 % of all cases of sinonasal papilloma (1). Although, chronic inflammation, allergens, cigarettes, bacterial and viral agents and environmental factors have been implicated in its etiology, it could not be fully elucidated (1). Despite being a benign tumor histologically, it may cause bone erosion due to its local aggressive properties (1-3). The recurrence rate in IPs is reported to be between 10 % and 25.3 % (1-3). IP can show a high degree of dysplastic characteristics and can develop into an invasive squamous cell carcinoma at a rate of 2-27 % (1-3).

IP is a chronic, inflammatory, T-cell mediated disease (4, 5). It has been shown that in addition to inflammatory cells, many different cytokines play roles in the physiopathogenesis of IP (4,5). There are evidences that inflammation plays a critical role in the development and progression of many diseases (6). Neutrophils and lymphocytes play important roles in inflammatory and immunological processes (4-10). Mean platelet volume (MPV) can also be used as an indicator of inflammation (11,12). In the light of this information, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) can be used as systemic inflammatory markers (6-10). These parameters have been suggested to reflect inflammatory response and disease activity in many inflammatory and autoimmune diseases such as chronic otitis media with effusion, Familial mediterranean Mediterranean fever, Bell palsy, idiopathic sudden sensorineural hearing loss, SLE, cardiovascular diseases such as coronary artery diseases

Received: 25.08.2019 **Accepted:** 07.10.2019 **Available online:** 22.10.2019
Corresponding Author: Mustafa Celik, Harran University Faculty of Medicine, Department of Otorhinolaryngology, Sanliurfa, Turkey
E-mail: mustafareyhan@yahoo.com

(13-19). Furthermore, it has also been suggested that these parameters are high in some malignancies and are associated with poor prognosis (20-23). Chronic inflammation may be a common factor underlying IP etiopathogenesis, as in many nasal pathologies. We hypothesize that blood parameters such as NLR, PLR, MPV can be used as systemic inflammation and infection indicators in cases with IP.

In this study, we evaluated the systemic inflammation parameters such as NLR, PLR and MPV levels in the patients assuming that there is an underlying inflammation in the process of IP formation. In addition, we aimed to investigate whether levels of these parameters are associated with the severity of disease or not.

MATERIAL and METHODS

In this retrospective case-control study, 33 patients, who were diagnosed with nasal-paranasal masses and underwent endoscopic sinus surgery and had inverted papilloma confirmed by pathological examination at Harran University Medical School, Department of Otorhinolaryngology, between August 2005 and February 2019, were included in the study. The control group consisted of 44 healthy individuals with matching age and sex with that of patient group. The files of the cases included in the study were analyzed retrospectively through a systematic database search. The study protocol was approved by the Ethics Committee of Harran University School of Medicine (07.01.2019/01-06) and was conducted in accordance with the ethical principles described by the Helsinki Declaration.

Paranasal computed tomography, routine complete blood count results, routine biochemical results, pathology report results and demographic data of all patients were obtained from the database records of hospital computer. Blood samples were taken from healthy volunteers for the control group for routine complete blood count and routine biochemical examination. The patients were staged according to the IP Krouse staging system (24). This staging was performed according to the findings of preoperative endoscopic examination recorded in the patient files and preoperative paranasal sinus computed tomography images. The mean postoperative follow-up period was detected to be 17.24(14-120) months.

Krouse Staging System in Inverted papilloma; T1: The tumor is completely localized in the nasal cavity. It has not extended into the sinuses or extranasal structures. T2: The tumor is confined to the medial wall of the ostiomeatal complex, ethmoid sinus and maxillary sinus. It may be associated with nasal cavity involvement or isolated. T3: Tumor involvement is present in lateral, inferior, superior, anterior and posterior wall of the maxillary sinus and in sphenoid sinus or frontal sinus. T4: The tumor extends beyond the nasal cavity or sinus boundaries. Invasion of the orbita, intracranial region or pterygo maxillary region may be observed.

The criteria for exclusion include one or more of the following: Patients with allergic rhinitis, infectious rhinosinusitis, history of nasal and paranasal sinus surgery, history of chronic drug use, systemic or local steroid, antihistaminic or anti-inflammatory drug use for the treatment of nasal polyposis in the last three months, obstructive sleep apnea, inflammatory or infectious diseases, or autoimmune diseases, diabetes mellitus, systemic hypertension, hyperlipidemia, acute or chronic kidney failure, chronic liver disease, chronic obstructive pulmonary disease, coronary artery disease, connective tissue disease, hematological, metabolical, neurological, psychiatric and malignant diseases and a white cell count $<4x10^3$ and $>11x10^3$, were excluded from the study.

Laboratory methods

Blood samples of all participants taken from the peripheral vein were studied using the Cell-Dyne Ruby fully automated hemogram device using the optical laser scatter method (Abbott Cell-DyneRuby; IL 60064, Chicago, USA). CBC parameters, white blood cell (WBC: leukocytes), hemoglobin, erythrocytes, neutrophils, lymphocytes, platelet counts and MPV of all the participants were analyzed with an automated hematology analyzer. The NLR value was calculated by dividing neutrophil count by the lymphocyte count and PLR value was calculated by dividing platelet count by lymphocyte count.

Leukocyte, neutrophil, lymphocyte, platelet, NLR, PLR and MPV values of both groups were statistically compared separately. The difference between IP density and NLR values of the IP group was statistically evaluated according to the Krouse staging system. Statistically significant differences found between NLR, PLR and MPV values of two groups were compared with Krouse staging system.

Statistical Analysis

Statistical analyzes were performed using SPSS 25.0 (IBM Corporation, Armonk, NY, USA). Parametric tests were used for normally distributed data and non-parametric tests were used for non-normally distributed data in the comparison of blood parameters of the patient group and control group. $p<0.05$ was considered significant.

RESULTS

The demographic and laboratory characteristics of the groups are shown in table 1.

According to the Krouse staging system, 16(48.48%) of the cases were recorded as stage 3;9(27.27%) were recorded as stage 2;5(15.15%) were recorded as stage 1and 3(9.09%) of the cases were recorded as stage 4. As shown in Table 2, as the stage progressed, the NLR values were observed to be significantly increased. According to Kruskal-Wallis H Test results, there are significant difference between groups $X2$ $(df=3,n=33)=24.556$, $p<0.01$. Afterwards, we conducted Mann Whitney U test between all groups and we determined that there are significant differences between all groups.

Table 1. The demographic characteristics and laboratory values of the patients and control groups

	Patients group (n=33)	Control group (n=44)	P value
Age (years)	52.60 ± 8.99	50.97 ± 9.28	0.443
Gender (male/female)	22/11	25/19	
Hb. mg/dL	14.24 ± 0.355	15.27 ± 0.243	0.623
WBC	8.115 ± 1.251	7.453 ± 1.289	0.027
Neutrophil, ×103/L s,	5.855 ± 1.470	5.138 ± 0.878	0.009
Lymphocytes, ×103/L	2.62 ± 0.820	2.56 ± 0.852	0.731
PLT, ×103/L	311.85757±77.89005	276,31136±74,09106	0.045
MPV, fL	9.834±4.48	9.628±4.57	0.844
NLR	2.484±1.132	1.971±0.884	0.029
PLR	128.145±47.259	121.362±56.020	0.576

Data are presented as means ± standard deviation. Hb: hemoglobin. WBC: white blood cell. NLR: neutrophil to lymphocyte ratio. PLR: platelet to lymphocyte ratio. MPV: mean platelet volume. PLT: platelet.

Table 2. Descriptive statistics about krouse paranasal computed tomography scores and neutrophil/lymphocyte ratio of inverted papilloma group

Stages	Patients (n)	NLR (Mean±SD)*	Mean Rank	Chi-Square	p
1	5	1.398±0.262	4.5	24.556	0.000
2	9	1,744±0.312	9.94		
3	16	2.773±0.740	22.13		
4	3	4.972±0.707	31.67		
Total	33	2.484±1.132			

*Data are presented as means ± standard deviation). NLR: neutrophil / lymphocyte ratio.
According to Kruskal-Wallis H Test results, there are significant difference between groups X2 (df=3, n=33) = 24.556, p<0.01.

DISCUSSION

In our study, we found that NLR, leukocyte, neutrophil and platelet levels were significantly higher in IP group compared to healthy control group. Lymphocyte, PLR and MPV levels were higher in the IP group than in the control group, but they were not statistically significant. A strong correlation was found between NLR values and Krouse staging values. To the best of our knowledge, this is the first study to investigate NLR, PLR and MPV levels as inflammatory biomarkers in patients with IP. In addition, it is the first study to evaluate the relationship between the NLR levels and the Krouse staging system, which differ significantly in two groups. We did not find a similar study, when we searched the literature.

IP physiology could not be fully understood. It was suggested that many factors such as inflammation, genetic factors, environmental factors, bacterial, and viral infections play a role in IP etiopathogenesis (4). In IP physiology, chronic inflammation, which causes stromal edema, plays an important role. Histopathologically, papilloma tissue contains high levels of neutrophil, macrophage, eosinophil, CD8 + T cells and B cells. In addition, several different cytokines, such as TGF-β and IL-10, which are secreted from inflammatory cells, play an important role in the physio pathogenesis of IP (4,5).

The tendency to use NLR, PLR and MPV values as systemic inflammation and infection indicators is increasing all over the world. NLR, PLR and MPV values are cheap and easy to calculate parameters.

In a study conducted on patients with Nasal Polyposis (NP), it was shown that leukocyte and platelet levels were significantly higher in the polyps group compared to the control group (7). The mean NLR value was shown to be statistically significantly higher in the NP group than in the control group.

Yenigün et al. (8) in a study conducted on 158 patients with chronic rhinosinusitis with nasal polyps (CRSwNP), reported that preoperative NLR values were significantly higher in patients with recurrent CRSwNP than those without recurrence.

In another study, it was suggested that the high number of neutrophils in CRSwNP patients meant more serious chronic inflammation (9). In this study, it was shown

that NLR values were significantly higher in patients with recurrence than in patients without recurrence (9).

In a study of 240 CRSwNP case series, recurrence rates were significantly higher in patients with high mean NRL, ELR and BLR values after endoscopic sinus surgery (10). It was stated that all three ratios can be considered as markers of inflammation. In addition, higher rates of these markers were suggested to increase the risk of recurrence of CRSwNP disease.

In addition, Eryılmaz et al. (12) examined MPV, NLR, PLR and erythrocyte distribution width values in pediatric patients with cholesteatomatous or noncholesteatomatous pediatric chloric chronic otitis media. In this study, there was no statistically significant difference in parameters other than MPV in both groups. However, MPV values were shown to be significantly lower in patients with cholesteatoma compared to control group (12). In order to determine cholesteatoma in com patients, it was suggested that MPV level could be used as independent predictor with high sensitivity and specificity.

In a study examining the relationship between cronic chronic otitis media with effusion (COME) and NRL and PLR values, it was found that the NLR value was significantly higher in the patient group compared to the control group (13). It was claimed that NLR could be used as a diagnostic parameter in patients with COME (13). In another study, NLR values of Familial Mediterranean fever (FMF) patients with frequent exacerbations were shown to be higher than in non-exacerbated FMF patients and healthy control group (14).

In a study by Bucak et al. (15), neutrophil and NLR values were found to be significantly higher in patients with Bells palsy Bell palsy compared to control group. In a study, NLR and MPV values were found to be significantly higher in patient group with unrecovered sudden hearing loss (16). It was suggested that NLR and MPV could be used to predict prognosis for patients with sudden hearing loss (16). In another study, a decrease in response to treatment was observed in patients with sudden hearing loss and high NL values, and this condition was described as a poor prognostic factor (25).

In a study conducted on patients with Systemic Lupus Erythematosus (SLE), NLR, PLR and MPV levels were found to be higher (17). It was suggested that high NLR and PLR levels showed positive correlation with inflammatory markers and disease activity.

It was suggested that the NLR value as inflammatory marker might help the risk classification and prognosis prediction of acute coronary syndrome cases. In a study, the mortality rate of patients with a higher NLR value, was increased (18). In another study, it was reported that NLR could be used as a prognostic marker for the evaluation of coronary artery bypass graft results (19).

In addition, it has been suggested that parameters such as NLR and PLR are found to be high in various malignancies and these high parameters are associated with poor prognosis (6,20-23).

The findings of this study are generally consistent with the literature. Another important finding of this study is the relationship between the disease stages and the NLR values. As the disease progressed from Stage 1 to stage 4, we found a significant increase in NLR values. This relationship has to be confirmed with studies to be conducted when the number of cases increases in our center or with multi-center studies where the number of cases is very high. If this relationship can be demonstrated in large series studies with recurrence and/or focus of carcinoma, it may provide valuable information for prognosis determination and prediction of malignancy. In this way, valuable predictive findings can be obtained by looking at the NLR values that are very easy to obtain at the beginning of the disease, before the surgery is applied. There are some limitations of this presented study. First; the number of cases is less. Second; long-term follow-up results, which include recurrent cases or malignancies, are absent. Third; a retrospective case study may not be accurate because of the possibility that the characteristics of the patient may not be fully recorded. Fourth; infection conditions such as acute/chronic sinusitis cannot be treated adequately in the preoperative period, and this may affect the laboratory values.

CONCLUSION

As a result, NLR values were significantly higher in cases with inverted papillomas compared to control group. To the best of our knowledge, the relationship between IP and NLR has been shown for the first time. Based on these data, it can be said that NLR values, which can be easily calculated at low cost, can be used as an appropriate auxiliary parameter in the demonstration and staging of inflammation in IP patients. Further studies are needed to determine the possible relationship between the IP staging system and NLR, PLR and MPV.

Competing interests: The authors have no financial conflicts of interest.
Financial Disclosure: The authors declared that this study has received no financial support
Ethical approval: The study was approved by the local ethics committee of the Harran University Faculty of Medicine (07.01.2019 / 01-06).

Mustafa Celik ORCID: 0000-0002-6237-2518

REFERENCES

1. Sauter A, Matharu R, Hormann K, et al . Current advances in the basic research and clinical management of sinonasal inverted papilloma (review). Oncol Rep 2007;17:495-04.
2. Mirza S, Bradley PJ, Acharya A, et al. Sinonasal inverted papillomas: recurrence, and synchronous and metachronous malignancy. J Laryngol Otol 2007;121:857-64.
3. Lawson W, Kaufman MR, Biller HF. Treatment outcomes in the management of inverted papilloma: an analysis of 160 cases. Laryngoscope 2003;113:1548-56.
4. Wang MJ, Noel JE. Etiology of sinonasal inverted papilloma: A narrative review. World J Otorhinolaryngol Head Neck Surg 2016;3:54–8.
5. Yang YH, Lin C. Impact of virus infection and related

immunity factorson nasal inverted papilloma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2016;30:1029-33.
6. Kemal O, Kemal Y, Atmaca S, et al. The value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in salivary gland tumors. B-ENT 2019;15:33-7.
7. Atan D, Özcan KM, Köseoğlu S, et al. New predictive parameters of nasal polyposis: neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. Kulak Burun Bogaz Ihtis Derg 2015;25:97-01.
8. Yenigün A. Assessment of patients with nasal polyposis by the neutrophil-to-lymphocyte ratio and eosinophil-to-lymphocyte ratio. Kulak Burun Bogaz Ihtis Derg 2015;25:193-9.
9. Boztepe OF, Gün T, Demir M, et al. A novel predictive marker for the recurrence of nasal polyposis following endoscopic sinus surgery. Eur Arch Otorhinolaryngol 2016;273:1439-44.
10. Brescia G, Pedruzzi B, Barion U, et al. Are neutrophil-, eosinophil-, and basophil-to-lymphocyte ratios useful markers for pinpointing patients at higher risk of recurrent sinonasal polyps? Am J Otolaryngol 2016;37:339-45.
11. Aktas G, Sit M, Tekce H, et al. Mean platelet volume in nasal polyps. West Indian Med J 2013;62:515-8.
12. Eryilmaz MA, Derin S. Mean Platelet Volume as a Potential Predictor of Cholesteatoma in Children. J Craniofac Surg 2016;27:575-8.
13. Atan D, Apaydin E, Ozcan KM, et al. New diagnostic indicators in chronic otitis media with effusion: neutrophil to lymphocyte ratio and thrombocyte lymphocyte ratio. ENT Updates 2016;6:12-5.
14. Uluca Ü, Ece A, Şen V, et al. Usefulness of mean platelet volume and neutrophil-to-lymphocyte ratio for evaluation of children with Familial Mediterranean fever. Med Sci Monit 2014;20:1578–82.
15. Bucak A, Ulu S, Oruc S, et al. Neutrophil-to-lymphocyte ratio as a novel potential marker for predicting prognosis of Bell palsy. Laryngoscope 2014;124:1678-81.
16. Ulusoy B, Bozdemir K, Akyol M, et al. The effectiveness of neutrophil-to-lymphocyte ratio for predicting prognosis of idiopathic sudden hearing loss. B-ENT 2018;13:71-6.
17. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016;26:372-6.
18. Tamhane UU, Aneja S, Montgomery D, et al . Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653–7.
19. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013;11:55-9.
20. Wang D, Yang JX, Cao DY, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. Onco Targets Ther 2013;6:211-6.
21. Peng W, Li C, Wen TF, et al. Neutrophil to lymphocyte ratio changes predict small hepatocellular carcinoma survival. J Surg Res 2014;192:402–8.
22. Templeton AJ, Knox JJ, Lin X, et al. Change in neutrophil-to-lymphocyte ratio in response to targeted therapy for metastatic renal cell carcinoma as a prognosticator and biomarker of efficacy. Eur Urol 2016;70:358–64.
23. Cedrés S, Torrejon D, Martínez A, et al. Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol 2012;14:864-9.
24. Krouse JH. Development of a staging system for inverted papilloma. Laryngoscope 2000;110:965-8.
25. Ulu S, Ulu MS, Bucak A, et al. Neutrophil-to-lymphocyte ratio as a new, quick, and reliable indicator for predicting diagnosis and prognosis of idiopathic sudden sensorineural hearing loss. Otol Neurotol 2013;34:1400-4.