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Original Article

The uses of platelet indices, NLR (Neutrophil to Lymphocyte Ratio) and PLR (Platelet to Lymphocyte Ratio) in the predictive value diagnosis of benign and malignant masses of the parotid gland

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Abstract

Aim: Parotid gland tumors are uncommon in the head and neck surgery practice and difficult to surgically treat. Planning is very important, especially while planning parotid gland surgery, considering the difficulty of revision surgery. In this context, fine-needle aspiration cytology and radiological imaging stand out. However, preoperative diagnosis is sometimes difficult due to the nature of the salivary gland. At this point, additional methods in preoperative diagnosis are questioned. In our study, it was aimed to determine the surgical modality based on the predictive value in parotid benign and malignant masses with inexpensive, fast and easily obtainable platelet indices, NLR (Neutrophil to Lymphocyte Ratio) and PLR (Platelet to Lymphocyte Ratio).

Materials and Methods: The data of 236 patients who were operated on with parotid masses between 2010 and 2020 in our clinic were retrospectively analyzed. The data of the patients and the control group were evaluated statistically.

Results: A total of 356 participants were included in the study, including 236 patients who had undergone parotid gland surgery and a control group of 120 healthy individuals. When the data of the participants were reviewed, there was no significant difference between the groups in terms of age. In terms of sex, the number of the male patients was significantly higher than the female participants in the group with only parotid benign neoplasia. Based on the collected data, the mean MPV (Mean Platelet Volume) values were mean 9.1548 ± 1.55152 in the parotid cancer patient group (n1), 9.3810 ± 1.57825 in the inpatient group with parotid benign mass (n2) and 10.49250± 1.05314 in the control group (n3). The mean NLR values were found as 3.6395 ± 3.36035 in the parotid cancer patients (n1), 2.0145 ± 1.04293 in the parotid benign masses (n2) and 1.9689 ± 1.54979 in the control group (n3). The mean PDW (Platelet Distribution Width) values were found as 14.1258 ± 2.82536 in the parotid cancer patient group (n1), 14.5220 ± 2.69823 in the parotid benign mass group (n2), and 12.5150 ± 2.49953 in the control group (n3).

Conclusion: In our study, we observed that the MPV, PDW and NLR values were significantly changed in the parotid gland tumors. We concluded that NLR values may be used effectively, especially in the predictive diagnosis of malignant masses and in planning surgery.

Keywords: Neutrophil to lymphocyte ratio; platelet index; parotid gland surgery; parotid gland tumors; platelet to lymphocyte ratio

INTRODUCTION

Salivary gland tumors have a rate of 3-6% among all head and neck neoplasms (1,2), and this rate was expressed as 3-10% in some regional studies (3,4). Approximately 80% of these tumors are seen in the parotid gland (1-5), approximately 10-17% of these tumors are malignant (1,2,6). In general, they constitute 3-5% of head and neck cancers (4). Tumors are seen especially in the 5th and 6th decades of life, and the rate of male patients is higher (2). Although simple surgical enucleating used to be performed before 1940s (7), superficial parotidectomy and total parotidectomy are standard treatment protocols used for parotid tumors with a clear understanding of the parotid gland and facial nerve anatomy (7-9). In recent years, with the increase in endoscopic approaches, extra-capsular dissection has become popular due to complications such as facial paralysis, Frey's syndrome and cosmetic deformities (7). Therefore, the preoperative diagnosis has become important in determining the surgical modality. For the preoperative diagnosis, clinical evaluation, fine-needle cytology and radiological imaging come to the fore. However, sometimes, a preoperative

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diagnosis cannot be made due to the diversity of salivary gland tumors, intratumoral heterogeneity and the need for a good cytopathologist.

Especially recently, many studies have been focusing on the relationship between the tumor and the systemic immune response. Here, the main hypothesis is based on obtaining information about predictive factors and/or surveying the relationship between inflammation and tumors. In this context, research has been focused especially on platelet indices, neutrophil and lymphocyte values. Many publications have shown that measuring the systemic immune response in head and neck tumors and cancer physiopathology is beneficial in terms of diagnosis and prognosis (2-4,10,11). The clinical use of platelet indices, NLR (Neutrophil/lymphocyte) and PLR (Platelet / Lymphocyte) values are highly questioned due to their easy, inexpensive and fast availability. In our study, we investigated the role of preoperative thrombocyte indices and NLR (Neutrophil / Lymphocyte ratio) and PLR (Platelet / Lymphocyte ratio) values in predicting the type of neoplasm in patients who underwent parotid surgery due to parotid neoplasms in our clinic, as well as the ability to determine the type of surgical procedure based on this role.

MATERIALS and METHODS

Design of the Study

This study was retrospectively planned to be conducted at a tertiary university hospital. The data of patients who had received parotid surgery due to their parotid tumors between 2015 and 2020 in our clinic were retrospectively collected. The data were grouped as benign and malignant parotid masses. Additionally, a control group was formed out of healthy individuals. The data were organized based on the inclusion and exclusion criteria and statistically analyzed.

Sample Selection

The patient group included patients who had received surgeries due to their parotid masses in the period of 2015-2020 in our clinic who were divided into two groups as the benign and malignant mass groups. All patients that were treated in our clinic in the specified 5-year period and met the inclusion criteria were included in the patient group. While forming the control group, attention was paid to ensure a statistically similar distribution to the patient group in terms of age and sex.

Inclusion Criteria

Patients who received surgical treatment in our clinic in the period of 2015-2020 due to parotid tumors whose assessments including all examinations at the stages of diagnosis and treatments, laboratory tests and pathological examinations had been performed in our clinic and who had complete data available were included.

Exclusion Criteria

Patients with incomplete data, patients with hematological disorders, cardiac disorders, autoimmune diseases, inflammatory or infective diseases, endocrinological diseases, malignancy, liver and kidney diseases, and patients taking drugs that would affect coagulation cascades were excluded.

Standardization

It was ensured that the examined data of all patient and control groups that were included in the study were data that belonged to our hospital records. While forming the control group, it was paid attention to form it statistically similarly to the other groups in terms of age and sex. At our hospital, for hemogram data, three ml of blood is collected in EDTA vacuum tubes (lavender cap), and the samples are tested within 30 minutes by using a Sysmex XN-1000 automated hematology analyzer (Sysmex, Kobe, Japan).

Statistical Analysis

The data collected in the study were analyzed using the SPSS "Statistical Package for Social Sciences (SPSS17.0, version 17.0)" program. Percentages, mean, median, standard deviation, minimum and maximum values were calculated. Since the variables were not normally distributed according to the results of the Kolmogorov-Smirnov test ($p < 0.05$), non-parametric test statistics were used. Kruskal Wallis Test was used to compare more than two groups, and Mann Whitney U test was used to compare two groups. Chi-Squared Test was used for the comparisons of the qualitative variables. In the statistical analyses, an alpha error level of $p<0.05$ was considered statistically significant.

Ethical Approval

Approval for the study was obtained from Scientific Research and Publication Ethics Committee of Inonu University (Decision No: 2020/649).

RESULTS

A total of 356 participants were included in the study, and the participants were divided into three groups. The first group was the group of parotid cancer patients (n1 = 31) who underwent total parotidectomy, the second group was the patient group with parotid benign mass (n2 = 205) who underwent partial parotidectomy, and the third group was the control group consisting healthy individuals (n3 = 120). There was no significant difference in terms of age between the groups. However, in the patient group with benign parotid mass, the male / female ratio was significantly higher ($p < 0.05$). The demographic data of the study are presented in Table 1.

The histological types of the patients with parotid cancers and parotid benign masses who were included in the study are shown in Table 2.

When the platelet indices of the participants were examined in our study, there were statistically significant differences in the MPV, PDW and NLR values among the parotid cancer, parotid benign mass and control groups. There was no statistically significant difference in other parameters (PLR, PLT / MPV) among the groups (Table3).

In this study, the mean MPV (Mean Platelet Volume) values were determined as 9.1548 ± 1.55152 in the parotid

cancer patient group (n1), 9.3810 ± 1.57825 in the parotid benign mass group (n2) and 10.49250 ± 1.05314 in the control group. Based on the intergroup comparison of these data, there was a statistically significant difference (p = 0.0001 **) between the patients with parotid cancer / benign mass (n1 ± n2) and the control group (n3). When the patient groups were compared to each other, there was no statistically significant difference between the parotid cancer patient group (n1) and the patient group with parotid benign masses (n2) (p = 0.061). Accordingly, the MPV values were found to be significantly different between the parotid cancer patients (n1) and the control group (n3) (p = 0.0001 **) and between the parotid benign mass group (n2) and the control group (n3) (p = 0.001 **) (Table 4).

Table 1. Demographic data of the study

	Gender			Age	
	Male n (%)	Female n(%)	p	Mean±S.Deviation	p
Parotid Cancer Groups (n1)	18	13		54.38710 ± 21.37861	
	%58.1	%41.9			
Parotid Bening Mass Groups (n2)	129	76	0.017**	50.66830 ±15.97723	0.630
	%62.9	%37.1			
Control Groups (n3)	56	64		51.44170 ± 20.49792	
	%46.7	%53.3			

p<0.05** was considered statistically significant

Table 2. Distribution of histologic types of benign and malignant parotid gland tumors

Benign	Patient(n)	Malign ant	Patient(n)
Pleomorphic adenoma	96	Mucoepidermoid carcinoma	10
Wharthin tm	69	Acinic cell carcinoma	4
Basal cell adenoma	1	Adenocystic carcinoma	3
Hemangioma	3	Adenocarcinoma	1
Lymphangioma	1	Undifferentiated carcinoma	1
Lipoma	6	Squamous cell carcinoma	3
Oncocytoma	4	Carcinoma ex pleomorphic adenoma	1
Myoepithelioma	4	Myoepithelial carcinoma	2
Neurofibroma	1	Lymphoma	2
Chronic sialadenitis	20	Malignant Melanoma	1
		Liposarcoma	1
		Papillary Cystadenocarcinoma	1
		Plasma cell tumor	1
Total	**205**		**31**

Table 3. Hematological parameters and platelet indexes

Hematologic parameters and platelet index	Parotid Cancer Group n1=31 Mean±S.Deviation	Bening parotid Mass Group n3=205 Mean±S.Deviation	Control Groups (n3) Mean±S.Deviation	P	Test value
MPV (Mean Platelet Volume)	9.1548 ± 1.55152	9.3810 ±1.57825	10.4925 ± 1.05314	0.0001**	43.275
PDW (Platelet Distribution Width)	14.1258 ± 2.82536	14.5220 ± 2.69823	12.5150 ± 2.49953	0.0001**	43.010
PLT/MPV	28.3769 ± 9.61633	28.1738 ±10.48799	26.3566998 ± 6.84991681	0.574	1.112
NLR (Neutrophil-Lymphocyte Ratio)	3.6395 ± 3.36035	2.0145 ±1.04293	1.9689052 ±1.54978835	0.0001**	14.400
PLR (Platelet-Lymphocyte Ratio)	133.1727 ± 87.63275	109.3872 ± 37.40104	119.7489607 ± 45.15337342	0.127	4.123

p<0.05** was considered statistically significant

In our study, the mean NLR (Neutrophil to Lymphocyte Rate) values were found as 3.6395 ± 3.36035 in the parotid cancer patients (n1), 2.0145 ± 1.04293 in the parotid benign mass group (n2) and 1.9689 ± 1.54979 in the control group. In the intergroup comparison of these data, there was a statistically significant difference (p = 0.001 **) between the patients with parotid cancer / benign mass (n1 ± n2) and the control group (n3). When two groups were compared to each other, these significant differences were between the parotid cancer patient group (n1) and the parotid benign mass (n2) (p = 0.002 **) and between the parotid cancer patient group (n1) and the control group (n3) (p = 0.0001**). However, there was no statistically significant difference in the NLR values between the parotid benign mass group (n2) and the control group (n3) (p = 0.094) (Table 4).

In this study, the mean PDW (Platelet Distribution Width) values were found as 14.1258 ± 2.82536 in the parotid cancer patient group (n1), 14.5220 ± 2.69823 in the parotid benign mass group (n2) and 12.5150 ± 2.49953 in the control group (n3). According to the intergroup comparison of these data, there was a statistically significant difference (p = 0.0001 **) between the patients with parotid cancer / benign mass (n1 ± n2) and the control group (n3). When two groups were compared among these three, there was no statistically significant difference between the parotid cancer patient group (n1) and the patient group with parotid benign mass (n2) in terms of their PDW values (0.623). However, the PDW values were found to be significantly different between the parotid cancer patient group (n1) and the control group (n3) (p = 0.004 **) and between the patient group with parotid benign masses (n2) and the control group (n3) (p = 0.0001 **) (Table 4).

Table 4. Comparative results of MPV, PDW, and NLR ratios among the groups

	Groups	n	Mean	Median	p	z value
MPV	Parotid Cancer Groups (n1)	31	9.1548	9.10000	0.061	-1.550
(Mean Platelet Volume)	Bening Parotid Mass Groups (n2)	205	9.3810	9.5000		
	Parotid Cancer Groups (n1)	31	9.1548	9.10000	0.0001**	-3.720
	Control groups(n3)	120	10.4925	10.3000		
	Bening Parotid Mass Groups (n2)	205	9.3810	9.5000	0.001**	-3.090
	Control groups (n3)	120	10.4925	10.3000		
PDW	Parotid Cancer Groups (n1)	31	14.1258	14.9000	0.623	-0.491
(Platelet Distribution Width)	Bening Parotid Mass Groups (n2)	205	14.5220	15.8000		
	Parotid Cancer Groups (n1)	31	14.1258	14.9000	0.004**	-2.885
	Control groups(n3)	120	12.5150	11.7000		
	Bening Parotid Mass Groups (n2)	205	14.5220	15.8000	0.0001**	-6.571
	Control groups (n3)	120	12.5150	11.7000		
NLR	Parotid Cancer Groups (n1)	31	3.6395	2.1679	0.002**	-3.030
(Neutrophil-Lymphocyte Ratio)	Bening Parotid Mass Groups (n2)	205	2.0145	1.7826		
	Parotid Cancer Groups (n1)	31	3.6395	2.1679	0.0001**	-3.676
	Control groups (n3)	120	1.9689	1.6215		
	Bening Parotid Mass Groups (n2)	205	2.0145	1.7826	0.094	-1.673
	Control groups (n3)	120	1.9689	1.7826		

p<0.05 was considered statistically significant**

DISCUSSION

The parotid glands are the largest salivary glands in humans and are frequently involved in disease processes. Salivary gland tumors are uncommon tumors among all head and neck tumors and are most common in the parotid gland. Recently, different centers have reported an increase in the prevalence of parotid gland tumors (2,11,12). In the classification made by the World Health Organization in 2017, parotid gland tumors were revised, and there are controversial subclassifications in this classification (13). Due to the problems arising from the nature of the salivary glands, the diagnosis sometimes becomes problematic, and preoperative evaluation of the mass becomes important. In our study, we examined platelet indices, NLR and PLR values, and determination of the diagnosis and treatment modality in parotid gland lesions.

After the relationship between inflammation and cancer was expressed by Rudolf Virchow, studies on this topic have intensified. The relationship between tumor cells and stroma provides information about the initiation, progression and even prognosis of the disease (14). Tumors attract inflammatory cells first into the microenvironment during the initial and developmental

stages. They control the activities of other cells for tumor growth through these cells. They perform this control process through various mediators secreted from cell groups such as lymphocytes, neutrophils, monocytes and macrophages. Interleukin 6 (IL-6) and the Tumor Necrosis Factor α (TNF-α) are thought to induce neutrophilia by promoting paraneoplastic production of myeloid growth factors by cancer cells (3,15-17).

It has been stated that the role of neutrophils in the pathophysiology of tumors and cancers is realized through neutrophil extracellular trapping (NET) (4,18,19). Neutrophil extracellular traps are extracellular DNA clusters associated with cytotoxic enzymes produced by neutrophils to capture and destroy microorganisms (19). It was stated in the literature that cancer cells activate leukocytes through NETs (18). On the one hand, the precise role of neutrophils in tumor microenvironments is still controversial, whereas Tumor-Associated Neutrophils (TAN) appear to contribute to tumor progression, angiogenesis and immune tolerance. TAN is also stimulated to release proteases in tumor microenvironments that facilitate invasion and nodal metastasis (20,21). All these changes in the immune response cause an increase in the number of neutrophils and therefore in NLR. The increasing NLR reported in various malignancies in the medical literature supports the aforementioned pathophysiological mechanisms (10).

Lymphocytes are an important component of the immune system and play a major role in cancer pathophysiology with their antitumor properties. Lymphocyte dominance gives us information that the prognosis will be better (22). On the contrary, lymphopenia is associated with a poor prognosis in tumor pathophysiology (23). Wee et al. reported that lymphopenia was strongly associated with increased serum IL-6 levels and the TNF-α receptor, reflecting cancer-induced immunosuppression (24). Haghshenas et al. stated that helper and cytotoxic T lymphocytes in the subgroups of lymphocytes decreased in both benign and malignant salivary gland tumors, but this decrease was significantly higher in malignant salivary gland tumors (25). In vitro studies have shown that the cytolytic activities of lymphocytes and natural killer cells can be suppressed by neutrophils, and the degree of suppression is closely related to the neutrophil count (26). In our study, the NLR value was found to be significantly higher in the parotid cancer patient group. The parotid cancer patient group with a high mean NLR value was easily separated from the patient group with parotid benign masses, and NLR was observed as a convenient marker in planning surgical modality. Moreover, the mean NLR value was found to be higher in the patient group with parotid benign mass in comparison to the control group, but this difference was not statistically significant. Kuzucu et al. emphasized that NLR values were higher in malignant and benign parotid tumors in comparison to the control group, but they were especially significantly higher in malignant parotid tumors (4). Damar et al. found that NLR values were higher in malignant and benign parotid tumors in comparison to the control group, but they were especially significantly higher in malignant parotid tumors (3). Seng et al. determined that the pre-treatment NLR rate was significantly associated with prognosis in the pediatric patient group with parotid cancer (27). Gao et al. observed that the rate of NLR in the pediatric group with pediatric mucoepidermoid cancer was significantly associated with prognosis (28).

Proinflammatory factors, chemokines, growth factors and platelets have an important role in causing cancer to develop based on inflammation (29,30). The platelet (PLT) count, platelet distribution width (PDW) and mean platelet volume (MPV) are known as platelet indices. In recent years, it has been recommended to use these indices in cardiovascular, cerebrovascular, thromboembolic and inflammatory diseases, as well as using PLT and platelet indices in cancer patients as an inflammatory marker. Low cost and high reproducibility rates increase the availability of PLT and platelet indices (30,31). Increased proinflammatory cytokines trigger proliferation, and megakaryocytes are converted into platelets (32). Platelets provide the production and release of the vascular endothelial growth factor (VEGF), which plays a role in tumor angiogenesis and inflammation (33). Larger platelets are more active than smaller ones, and MPV shows platelet function. When the MPV values were examined in our study, the MPV values in the parotid malignant/benign lesions were observed to be significantly lower than those in the control group. Mean Platelet Volume values can be used in lesions that cause inflammation in the parotid gland, but they cannot distinguish benign and malignant lesions in the parotid gland. Kuzucu et al. emphasized that MPV values were higher in malignant and benign parotid tumors in comparison to the control group, but they were especially significantly higher in malignant parotid tumors (4). The platelet distribution width is the standard deviation of the log transforms data of platelets, and higher levels indicate that abnormally small and large platelets are in circulation. Compared to MPV, PDW is a more reliable marker for predicting whether thrombocytopenia has a hypo-productive or hyper-destructive etiology (34). When the PDW (Platelet Distribution Width) values were examined in our study, the PDW rates in the parotid malignant/benign lesions were observed to be significantly higher than those in the control group. PDW values can be used in lesions that cause inflammation in the parotid gland, but they cannot distinguish benign and malignant lesions in the parotid gland. In our study, we found that PDW was correlated with MPV in defining lesions. The data provided by different authors in cancer studies on PDW are contradictory (30). Kuzucu et al. found no significant difference in MPV values in terms of PDW in malignant and benign parotid tumors (4).

Based on lymphocytes, platelets and PLR (Platelet to Lymphocyte Ratio) have been investigated for use as inflammatory markers (4,35). In our study, there was no statistically significant difference between the groups in terms of their PLR values. Kuzucu et al. emphasized that

PLR values were higher in malignant and benign parotid tumors in comparison to the control group, but they were especially significantly higher in malignant parotid tumors (4). Our study may be criticized for its retrospective design. Since the incidence of parotid malignant neoplasms is low, the number of patients in the total parotidectomy group was limited. However, the other groups had a large number of participants and reflected our 10 years of experience.

CONCLUSION

In our study, we observed that the MPV, PDW and NLR values were significantly different in the parotid gland tumor cases. We found that MPV and PDW decreased and increased, respectively, in the benign and malignant masses that caused inflammation in the parotid gland. However, we found that there was no useful marker in distinguishing benign and malignant mass. Nevertheless, the NLR ratio increased in parotid masses and clearly distinguished malignant masses from benign masses. We concluded that NLR values can be used effectively, especially in the predictive diagnosis of malignant masses and in planning surgery.

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