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Is the neutrophil-to-lymphocyte ratio a marker for differentiating between benign and malignant submandibular gland masses?

Adem Bora[1*]

SUMMARY

OBJECTIVE: This study aimed to evaluate the effect of the neutrophil-to-lymphocyte ratio on the differentiation of benign and malignant masses in the submandibular triangle.

METHODS: We retrospectively evaluated 48 patients who underwent surgery for submandibular gland masses between January 2013 and February 2023. The patient's age, gender, preoperative complete blood count and imaging findings, postoperative histopathological diagnosis, and hemogram data were analysed. Patients were evaluated according to their postoperative histopathological diagnoses and categorised into four main groups: sialolithiasis, sialadenitis, benign tumours, and malignant tumours. Benign submandibular gland disease formations were evaluated under group B and malignant tumour formations under group M.

RESULTS: A preoperative fine needle aspiration biopsy was performed on 19 patients due to sialadenitis, pleomorphic adenoma, and malignant diseases other than sialolithiasis. One patient died among the patients with malignant disease and the remaining 7 patients were compared with the benign group of 40 patients regarding preoperative and postoperative neutrophil-to-lymphocyte ratio. In the benign group, the neutrophil-to-lymphocyte ratio was 2.64 preoperatively and decreased to 2.34 in the first postoperative year. The preoperative neutrophil-to-lymphocyte ratio decreased from 4.79 to 1.77 postoperatively in the malignant group. A statistically significant difference was observed ($p<0.05$).

CONCLUSION: This is the first study to demonstrate that the neutrophil-to-lymphocyte ratio can be used as a biomarker in submandibular gland masses and has prognostic significance in malignant masses. In addition to fine needle aspiration biopsy results, neutrophil-to-lymphocyte ratio can be used as a biomarker.

KEYWORDS: Submandibular gland neoplasm. Fine needle biopsy. Blood cell count. Malignancy. Inflammation.

INTRODUCTION

The submandibular triangle is a clinically significant area in head and neck surgery practice, and patients may present with an isolated submandibular mass. The differential diagnosis of submandibular masses includes salivary gland, lymph node, soft tissue, vascular, and neural pathologies. The most common submandibular gland pathologies are sialadenitis, sialolithiasis, benign tumours, and carcinomas. Inflammatory diseases of the salivary glands and sialolithiasis are more commonly observed in the submandibular gland[1]. Salivary gland tumours are rare, and it has been reported that only 10–15% of them are seen in the submandibular gland[2]. The primary approach for submandibular gland tumours is surgery, and the indication for surgery varies based on the tumour's histopathology and local spread. Therefore, differentiating between benign and malignant lesions and distinguishing low-grade from high-grade malignancies during the preoperative period is vital. Fine needle aspiration biopsy (FNAB) is widely performed and is the preferred intervention in the differential diagnosis of salivary gland pathologies[3]. However, considering the wide variety of tumours in the salivary glands, there are many diagnostic challenges in salivary gland cytopathology, including the need for a uniform reporting system. For this purpose, the "Milan Classification System for Reporting Salivary Gland Cytopathology" has been established under the leadership of the American Society of Cytopathology and the International Academy of Cytology. According to the Milan System, cytopathological diagnoses are classified into six main categories: (1) non-diagnostic (insufficient, ordinary salivary gland); (2) non-neoplastic; (3) atypia of undetermined significance; (4) neoplastic group: (a) benign neoplasia and (b) salivary gland neoplasm of uncertain malignant potential; (5) suspicion of malignancy; and (6) malignant cytology[4]. According to the Milan System, 25% of cytopathological diagnoses fall into the first three categories, and a malignancy risk ranging from 10 to 25% has been estimated for these categories[5]. This rate is significant and cannot be ignored.

[1]Cumhuriyet University, Faculty of Medicine, Department of Otorhinolaryngology – Sivas, Turkey.
*Corresponding author: adembora@yahoo.com

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Numerous studies have shown that inflammation plays a significant role in cancer prognosis in recent years. Previous studies have shown that high levels of inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index are associated with poor prognosis in many types of cancer. Many disorders have inflammation as a key factor in their development. For example, rheumatoid arthritis produces more inflammation, while others produce only less. NLR is an inflammatory marker, and its diagnostic and prognostic role has been shown in irritable bowel disease, COVID-19 infection, diabetes mellitus, gastrointestinal conditions, cardiac conditions, and thyroiditis[6-11]. Moreover, there is a clear link between inflammation and cancer[12]. Thus, it is rational to study NLR in the differentiation of benign and malignant conditions. In recent years, considerable evidence has shown that inflammation plays a significant role in cancer prognosis[13].

In their study in 2016, Damar et al. included major and minor salivary glands and reported that a high NLR and low lymphocyte count could differentiate malignant tumours from benign tumours. They also reported that these parameters significantly predicted low-grade and high-grade malignancies[14]. However, our literature search did not find a specific study that used NLR values as a marker for malignant tumours in cases where submandibular gland excision was performed.

Therefore, this study aimed to evaluate the importance of demographic data, preoperative FNAB results, and NLR values in comparison with postoperative histopathological results in differentiating between benign and malignant submandibular gland masses in cases where submandibular gland excision was performed in a third-level healthcare institution over 10 years.

METHODS

In this study, patients who underwent surgical intervention for submandibular gland mass in the Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Sivas Cumhuriyet University, between the years 2013 and 2023 were retrospective. Inclusion criteria were as follows: having a previous diagnosis of submandibular gland mass, a history of surgical intervention for this diagnosis, and sufficient pre- and postoperative information. Exclusion criteria included cases that underwent submandibular surgery for a different diagnosis or as part of a more extensive resection and had insufficient follow-up data. Additionally, patients with inflammatory, autoimmune, acute or chronic infectious diseases, haematological disorders, diabetes, obese patients (body mass index >30), hypertension, obstructive sleep apnea, a history of corticosteroid treatment, or chronic kidney failure that could affect inflammatory parameters were excluded, except for five patients. Neutrophil and lymphocyte counts were recorded from complete blood count samples obtained approximately 1 week before surgery (venous blood samples taken at 10:00–11:00 in the morning). The NLR was calculated from these values. All sample analyses were performed on automated haematology analysers purchased from Sysmex XN-9100TM (Kobe, Japan).

After obtaining verbal and written consent from all cases accepting to participate in the study according to the Declaration of Helsinki principles, medical history, age, gender, FNAB results, histopathological diagnosis, and hemogram data were retrospectively reviewed. According to the postoperative histopathological diagnoses, patients were evaluated under four main categories: sialolithiasis, sialoadenitis, benign tumours, and malignant tumours. Sialolithiasis, sialoadenitis, and benign tumours were considered benign disease categories (group B), while malignant tumours were evaluated as malignant (group M). Ethical approval for this study was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (Date: 22.02.2023; Decision number: 2023-02/04).

Statistical methods

The SPSS (SPSS Inc., Chicago, IL) 23.0 software was used for data evaluation in the study. After necessary corrections, descriptive statistics and frequency tables were used to describe the population's demographic characteristics. The normality of the data was analysed using the Kolmogorov-Smirnov test, and since the normality criterion was not provided, non-parametric tests were performed. Due to the non-normal distribution of scale means, Mann-Whitney U and Wilcoxon rank tests were used to calculate the difference between two categorical variables. Differences between categorical variables were investigated using Chi-square analysis. All analysis results were interpreted at a 95% confidence level.

RESULTS

A total of 48 patients were included in the study, with 35.40% (n=17) females and 66.6% (n=32) males. The mean age of the patients was 50.08±20.46 years (13–94 years). The mean age of female patients was 55.24±20.54 years (13–94 years), and male patients was 47.26±20.18 years (14–89 years), with no significant difference in age between males and females. The mean age of the benign disease group, which consisted of sialolithiasis, sialadenitis, and benign tumours, was 47.88±20.13 years (ranging from 13 to 94 years), while the mean age of the malignant

disease group was 61.12±19.62 years (ranging from 25 to 89 years) (Figure 1A). The youngest patient in the benign disease group underwent surgery at 13 years, who was in the malignant disease group and was operated on for adenocystic carcinoma at 25 years. There was no statistically significant difference in age between benign and malignant diseases.

In group B, 9 (18.80%) patients underwent surgery due to sialolithiasis, 23 (47.90%) patients due to sialadenitis, and 8 (16.70%) patients due to pleomorphic adenoma. On the contrary, 8 (16.70%) patients underwent surgery due to group M (Figure 1B).

The patients who underwent surgery due to malignant diseases were reported as three cases of adenocystic carcinoma, two cases of mucoepidermoid carcinoma, adenocarcinoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma, respectively.

In all, 19 patients underwent FNAB preoperatively due to sialoadenitis, pleomorphic adenoma, and malignant diseases, excluding the sialolithiasis group. Among the 13 patients whose preoperative FNAB results were reported as benign cytology, 9 were confirmed as benign and 4 as malignant, according to postoperative histopathology. All three cases with FNAB results reported as insufficient cytology had benign postoperative histopathology. Among the three cases with suspicious malignant cytology in preoperative FNAB, one was reported as benign and two as malignant in postoperative histopathology (Figure 2A).

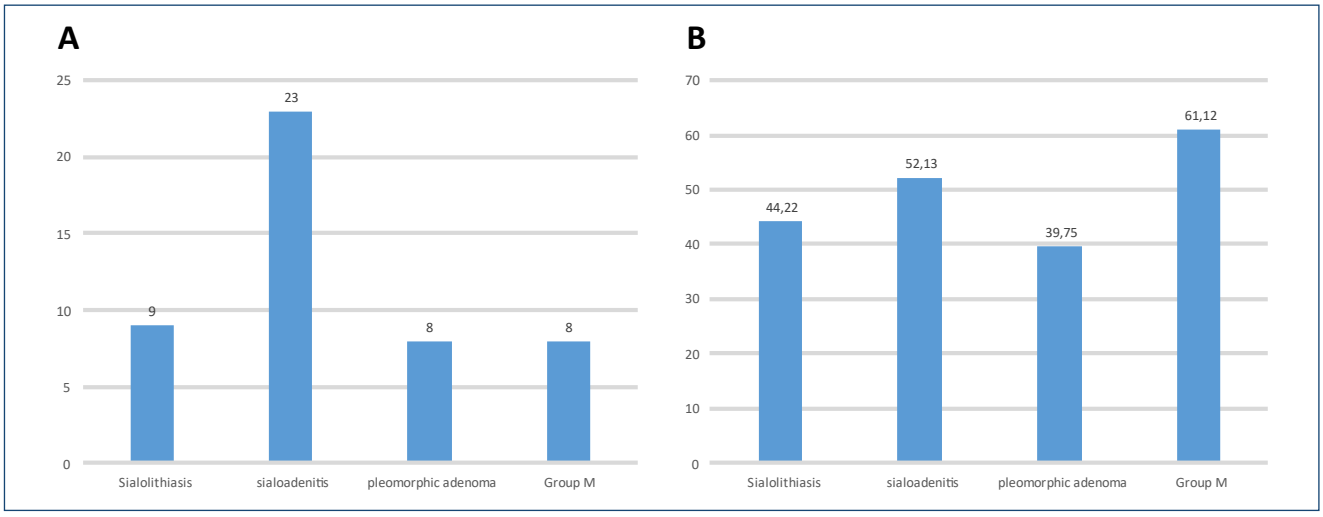

Figure 1. (A) Average age in benign and malignant diseases. (B) Distribution of patients who underwent submandibular gland excision according to the histopathological results.

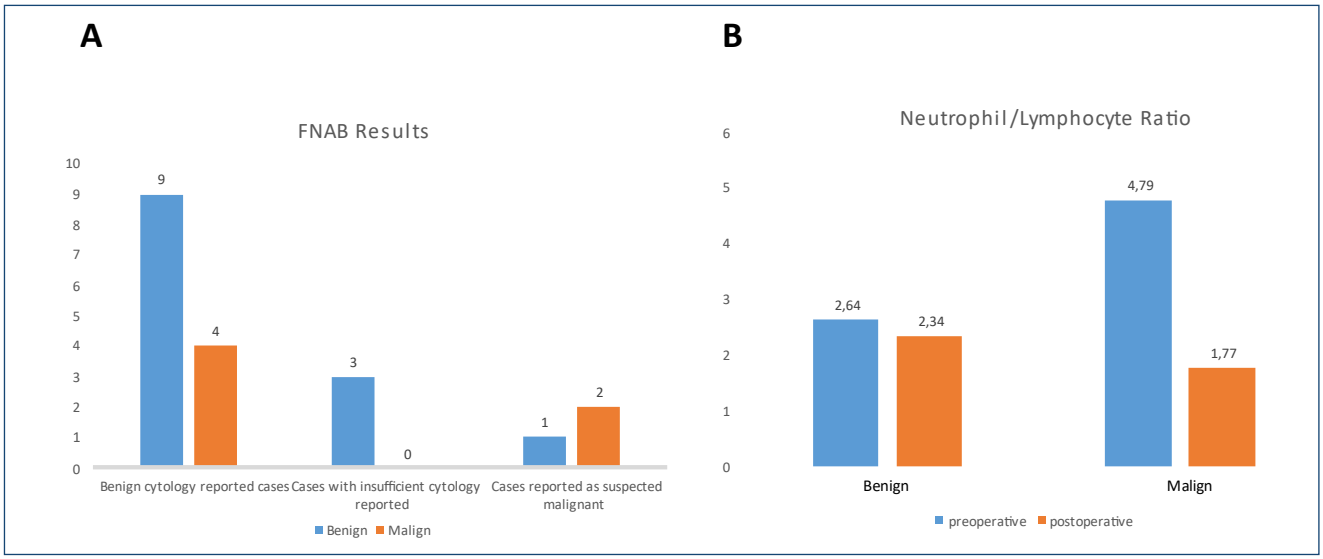

Figure 2. (A) Comparison of preoperative fine needle aspiration biopsy results with postoperative histopathological results. (B) Comparison of the neutrophil-to-lymphocyte ratio of benign and malignant diseases before and after surgery.

One patient has died due to a malignant disease. When the preoperative and postoperative hemogram values of 7 other patients and 40 patients in group B were compared, the preoperative value in group B was 2.64, while it was 2.34 in the first year after surgery. In malignant cases, the preoperative value decreased from 4.79 to 1.77 postoperatively. A statistically significant difference was observed ($p<0.05$) (Figure 2B). The demographic data of the patients along with NLR and histopathological results are summarized in Table 1.

DISCUSSION

Non-neoplastic lesions may resemble neoplastic lesions clinically and pathologically, and their differentiation is significant. The definitive diagnosis is a histopathological evaluation of the surgical material[15]. FNAB is important in the preoperative diagnosis and treatment of patients with submandibular masses[16]. However, due to the high rates of false positives and false negatives in salivary gland pathologies, the predictive value of FNAB is low[17]. In our study, among 13 cases with benign cytology, 4 were reported as malignant and 2 of the cases with suspicious malignant cytology resulted in malignancy. Therefore, due to its misleading outcomes, surgical and medical treatments should not be determined solely based on the FNAB results. The most significant result of our study is that, upon comparing the preoperative and postoperative hemogram values of 7 patients with malignant disease and 40 patients in group B, we observed a decrease in the preoperative value of group B from 2.64 to 2.34 in the first year after surgery. In cases diagnosed with malignancy, the preoperative value decreased significantly from 4.79 to 1.77 after surgery ($p<0.05$). Numerous studies have described the association between malignancy and inflammation[18]. Therefore, we aimed to utilise inflammatory criteria in the differentiation of malignant lesions. NLR values can serve as a dependable indicator of inflammation. Additionally, NLR proves to be valuable in distinguishing between benign and malignant nodules in patients with thyroid nodules. Sit et al. found that the mean NLR of the malignant nodule group (2.1±0.9) was higher compared to both the benign nodule group (1.7±0.9) and the control group (1.7±0.6). The observed difference between the groups was statistically significant ($p=0.002$)[19]. In our study, similar results were obtained, with the additional finding of higher values in malignant patients. This state may be attributed to the assessment based on preoperative values, which differs from the approach taken in the study conducted by Sit et al.[19].

Recently, high preoperative NLR and PLR values have been reported to be associated with increased recurrence risk, tumour aggressiveness, and poor prognosis in various

Table 1. Demographic data, and biochemical and histopathological results of patients with submandibular gland masses.

Age Mean±SD (min–max)		**50.1±20.5 (13–94)**				
Male (n=31)		47.26±20.18 (14–89)				p=0.215
Female (n=17)		55.24±20.54 (13–94)				
Mean age of patients with submandibular gland masses [Mean±SD (min–max)]	Benign diseases	47.88±20.13 (13–94)				p=0.105
	Malignant diseases	61.12±19.62 (25–89)				
Submandibular diagnoses, n (%)	Sialolithiasis	9 (18.8)				
	Sialadenitis	23 (47.9)				
	Pleomorphic adenoma	8 (16.7)				
	Malignant diseases	8 (16.7)				
Fine needle aspiration biopsy results, n (%)		None	Insufficient cytology	Benign	Suspicious malignant	p-value
Sialolithiasis		9 (31)	0 (0)	0 (0)	0 (0)	**0.001**
Sialoadenitis		17 (58.6)	2 (66.7)	3 (23.1)	1 (33.3)	
Pleomorphic adenoma		1 (3.4)	1 (33.3)	6 (46.2)	0 (0)	
Malignant diseases		2 (6.9)	0 (0)	4 (30.8)	2 (66.7)	
Neutrophil-to-lymphocyte ratio	Benign diseases	2.64–2.34 (preoperative–postoperative)				0.387
	Malignant diseases	4.79–1.77 (preoperative–postoperative)				**0.043**

Bold values indicate statistical significance at the $p<0.05$ level.

head and neck malignancies[20]. Kuzucu et al. found a significant difference in the NLR between benign and malignant tumours on parotid gland malignant tumours[21]. The preoperative NLR was significantly different in this study, with an average value of 2.64 in benign tumours and 4.79 in malignant tumours. Similar results were also obtained in our study. Our data showed a very close correlation. We concluded that NLR can be utilised in the discrimination between benign and malignant lesions of submandibular gland tumours. The prevalence of malignancy in submandibular gland tumours varies in the literature. In some series, the prevalence of malignant tumours ranges from 40 to 60%, and this rate is lower in Western populations[22]. In the recent studies, it has been reported that the prevalence of submandibular gland malignancies is approximately 20%[23]. This prevalence rate is also observed in our clinic.

Another important finding of our study is that there was no age-related difference between benign and malignant pathologies. Although the mean age of malignant cases may be slightly higher, the youngest patient with adenocystic carcinoma was 25 years. Therefore, it is necessary to approach every patient presenting with a mass complaint in the submandibular area as a potential malignancy until proven otherwise.

The most common reason for submandibular gland excision in the past was sialolithiasis, but in our study, the most common etiological cause was sialoadenitis[24]. This change is due to the development of new methods, which now allows for the preservation of the gland through endoscopic stone removal and extracorporeal shock wave lithotripsy.

Pleomorphic adenomas are the most common benign submandibular gland tumours, and our study is consistent with the literature[22]. In addition, incomplete resection of pleomorphic adenoma has been reported to result in a high tumour recurrence rate. Therefore, meticulous preservation of the tumour capsule and complete removal of the entire gland are necessary[25]. In our study, we did not have any cases of recurrence due to pleomorphic adenoma.

The limitations of this study include the retrospective study design, single-centre experience, and small sample size (n=48), particularly in histological subtypes and treatment. Survival data should be tested and confirmed in a prospectively designed study.

If there is a mass in the submandibular triangle, careful history-taking, physical examination, and endoscopic examination should be performed first. Ultrasonography is preferred for the initial radiological evaluation. If there is a high suspicion of infection, antibiotic therapy and anti-inflammatory treatment should be initiated while eliminating the submandibular mass. If there is no clinical and radiological improvement with medical treatment, a histopathological examination should be performed to evaluate the risk of malignancy. FNAB is the initial step in histopathological evaluation for submandibular masses. If repeated FNABs are unsuccessful, an excisional biopsy should be performed.

CONCLUSION

This study discussed the demographic data and histopathological evaluation of patients with submandibular masses. Sialadenitis was the most common condition, and benign and malignant tumours were encountered similarly. Although the average age of malignant diseases was slightly higher, no significant difference was observed between benign and malignant tumours based on age. FNAB results for submandibular gland masses can be misleading. Therefore, it is necessary to keep malignancies in mind until proven otherwise in patients presenting with submandibular mass complaints. The NLR and FNAB results may indicate malignant tumours in submandibular gland masses.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The protocol of the study was approved by the Institutional Review and Animal Ethics Use Committee of Sivas Cumhuriyet University School of Medicine, and the study was carried out based on the accepted guidelines on the care and use of laboratory animals (Date: 22.02.2023; Decision number: 2023-02/04).

DATA ACCESSIBILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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