

Research Article

Relevance of Inflammatory Biomarkers in Salivary Gland Cancers Management

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Abstract

Objectives: Preoperative diagnostic investigation of salivary neoplasms leaves a fair share of doubtful cases that complicate the therapeutic choices. The aim of our study was to look for new means to support the decision-making process for their management. Inflammatory biomarkers could play an important role in this process.

Methods: A retrospective chart review of salivary glands tumors was performed between January 2016 and September 2020 in our Department. The samples were divided in 2 groups basing on the histological result after surgery: 191 patients with benign salivary glands tumors (SGbt), and 47 with salivary glands cancer (SGc). 90 patients were randomly selected to form the control group (C group).

Results: Statistically significant increase of platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) was reported in SGc group compared to SGbt group and control group ($p < 0.001$). Statistical evaluation established optimal threshold for PLR (164,2), NLR (3,11) and SII (517.5) that can discriminate the doubtful cases with specificity of 85-86% and 62% respectively, and sensitivity of 40-45% and 64% respectively.

Conclusion: Inflammatory biomarkers can have a relevant role as diagnostic tools in doubtful cases. They could be performed in the clinical setting for guiding the treatment of these neoplasms.

Keywords: Blood inflammatory biomarkers, NLR, PLR, Salivary glands tumors, SII

Cite This Article: Abbate V, Orabona GDA, Barone S, Troise S, Bonavolontà P, Pacella D, et al. Relevance of Inflammatory Biomarkers in Salivary Gland Cancers Management. *EJMO* 2021;5(4):311–317.

Salivary gland tumors (SGTs) are an heterogeneous group of tumors that, according with the current 4th World Health Organization (WHO) classification of 2017, include: benign tumours that are the most frequent types, corresponding to 54-79% of the total salivary gland tumours while malignant tumors account for 21-46% of total.^[1]

Among the benign tumours, Pleomorphic adenoma is

the most common and accounts for nearly 50% of all neoplasms of this anatomical site. The second most frequent is Warthin's tumour, also called papillary lymphomatous cystadenoma, corresponding to 4-14% of all tumours.^[2-4]

Salivary gland cancers (SGc) are more than 20 distinct histopathologic entities. Mucoepidermoid carcinoma is the most frequent primary salivary malignancy, followed by adenoid cystic and acinic cell carcinoma.^[5-6]

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Submitted Date: September 14, 2021 **Accepted Date:** November 18, 2021 **Available Online Date:** December 01, 2021

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Diagnostic imaging but above all the Fine needle aspiration cytology (FNAC) is widely used as a first-line investigative technique distinguishing between benign and malignant salivary gland pathologies.^[7-9] 25% of cytological diagnoses fall into the first three categories of the Milan system. A risk of malignancy ranging from 10 to 25% has been estimated for these categories. This percentage is not negligible.^[10,11]

This diagnostic complexity can leave a fair share of inconclusive or doubtful diagnoses that complicate therapeutic choices. Therefore the goal of our study was to look for new elements that could support the therapeutic choice in doubtful cases.

In recent years, several evidences proved that inflammation plays a key role in the prognosis of cancers. Previous studies have shown that high level of inflammatory biomarkers, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and Systemic Immune Inflammation Index (SII) were associated with poor prognosis in several types of cancer.^[12-17] Thus we conducted a retrospective study with the aim of evaluating the role of inflammatory markers as a useful diagnostic tools in cases with a dubious cyto-radiological diagnosis.

Methods

A retrospective chart review of all patients affected by benign and malign salivary glands tumours was performed between January 2016 and September 2020 in the Department of Maxillofacial Surgery of the University of Naples "Federico II". On a total of 678 examined reports, 238 patients were eligible for this study, satisfying the following inclusion criteria: histological confirmation of benign or malign salivary glands tumours; complete medical records available; preoperative blood counts routine laboratory data.

Patients were not included in the study if they had any inflammatory, autoimmune, acute or chronic disease; history of others cancers; previously treatment with non-steroid anti-inflammatory drugs and immunotherapy; fever or systemic infections; acute myocardial infarction or coronary revascularization within 6 month before surgery; incomplete clinical data.

The samples was divided in 2 groups basing on the histological result: 191 patients with benign salivary gland tumours (SGbt group), and 47 with salivary gland cancers (SGc group).

90 patients were randomly selected from our database and were included in the control group (C group).

Relevant clinical-pathological data such as sex, age, tumor

entity, location and routine laboratory data performed before surgery, were collected from the medical records. These data include white blood cell (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute eosinophils count (AEC), absolute basophils count (ABC), platelets, albumin, alpha 1 and 2 proteins, beta 1 and 2 proteins, red blood cells, hematocrit, hemoglobin, glycemia, sideremia, lactate dehydrogenase (LDH), Glutamic Oxaloacetic Transaminase (GOT) and Glutamic Pyruvic Transaminase (GPT). The pre-treatment baseline NLR, PLR, SII were calculated using the following formulae:

$SII = \text{platelet counts} \times \text{neutrophil counts} / \text{lymphocyte counts}$,

$NLR = \text{neutrophil counts} / \text{lymphocyte counts}$,

$PLR = \text{platelet counts} / \text{lymphocyte counts}$,

Statistical Analysis

Quantitative variables are expressed as mean and standard deviation. Comparisons between two groups are performed using Student's t test or with Mann-Whitney U test, as appropriate. Comparisons among more than two groups are performed with ANOVA or Kruskal-Wallis test as appropriate. Categorical variables are expressed as absolute frequencies and percentages. Comparisons between groups for categorical variables are performed with the chi-square test. Receiver operating curves (ROCs) are constructed and the corresponding areas under the curves (AUCs) are computed to evaluate the diagnostics and predictive performances of SII, PLR and NLR. Optimal cut-offs are determined maximizing the Youden index and corresponding accuracy, sensitivity and specificity are provided. For all analyses, a p-value < 0.05 was considered statistically significant. Analyses are performed using the statistical software R, version 4.0.3.

Results

Baseline Features of Patients

SGbt group included 191 patients with benign salivary glands tumours, 99 male and 92 females, the mean age was 55. In control group, 90 patients were included respectively 65 male and 25 female, mean age was 38. SGc group included 47 patients with malign salivary gland tumours 24 male and 23 female, mean age was 65. The site of the neoplasia was more frequently the parotid gland for both benign and malignant tumors. Main features of the three groups are shown in table 1.

In the benign group 94 (49%) Warthin's Tumor and 97 (51%) Pleomorphic Adenoma were found. In the malign-

Table 1. Main features of the three groups

	Control Group	SBGT Group	SGc Group
Sex	F 25 (28%) M 65 (72%)	F 92 (48%) M 99 (52%)	F 23 (49%) M 24 (51%)
Mean Age	38	55 (range 18-84)	65 (range 35-85)
Site		Parotid 187 (98%)	Parotid 39 (8,3%)
		Submandibular 3 (1,5%)	Submandibular 4 (8,5%)
		Minor Salivary Glands 1 (0,5%)	Minor Salivary Glands 4 (8,5%)
Histology		Warthin's Tumor 97 (51%)	Adenoid cystic carcinoma 9 (19%)
		Pleomorphic Adenoma 94 (49%)	Squamous cell carcinoma 13 (28%)
			Adenocarcinoma 3 (6%)
			Carcinoma ex pleomorphic adenoma 4 (9%)
			Mucoepidermoid carcinoma 15 (32%)
			Others 3 (6%)

SBGT: salivary gland benign tumors; SGc: salivary gland cancers.

nant group the histological variants were more: there were 12 patients with squamous cell carcinoma (11 parotid gland and 1 submandibular gland) 7 of them were metastasis of cutaneous carcinoma; 9 patients with adenoid cystic carcinoma (6 parotid gland, 2 submandibular gland and 1 minor salivary glands); 15 patients with mucoepidermoid carcinoma (12 parotid gland, 1 submandibular gland and 2 minor salivary glands); 4 patients with carcinoma ex pleomorphic adenoma; 4 patients with adeno-

carcinoma (3 parotid gland and 1 minor salivary glands) and 3 patients with other malignant tumors (1 lymphoepithelial carcinoma; 1 sarcoma ex pleomorphic adenoma and 1 B-cell lymphoma). The distribution of malignant histological types is shown in Table 2.

The statistical analysis of all the considered variables in the three groups is shown in table 3. In the last column of the table the statistical significance is shown: the difference between the three groups results statistically significant ($p < 0.001$) for SII, NLR, PLR, white blood cell (WBC) absolute neutrophil count (ANC), red blood cells hematocrit, hemoglobin, albumin, alpha 1 and 2 proteins, beta 1 and 2 proteins, glycemia sideremia ($p = 0.012$), lactate dehydrogenase (LDH) ($p = 0.003$), Glutamic Oxaloacetic Transaminase (GOT) and Glutamic Pyruvic Transaminase (GPT) ($p < 0.001$). Furthermore, Figure 1 showed a statistically significant correlation for SII, NLR ($p < 0.05$), and PLR ($p < 0.01$) between malignant group and controls group (Fig. 1).

ROC Analysis

ROC analysis was performed to identify the optimal cut-off point with the highest sensitivity and specificity, which was 3.11 for NLR, 164.2 for PLR, and 517.5 for SII (sensitivity and specificity: 0.45 and 0.85 for NLR, 0.40 and 0.86 for PLR, and 0.64 and 0.62 for SII, respectively). The complete Roc analysis with the AUC and the accuracy of each test is shown in Figure 2.

Discussion

The management of salivary glands neoplasia is still a controversial topic due to the diagnostic difficulties that have sometimes been encountered.

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) represents a standardized, evidence-based reporting system for salivary gland fine-needle aspiration cytology (FNAC).^[18]

Jaslyn Jie Lin Lee et al showed that about 25% of cytological diagnoses fall into the first three categories of Milan

Table 2. Distribution of histological types of Malignant Salivary Gland Tumors in the minor and Major glands

Malign salivary glands	Parotid, n (%)	Submandibular, n (%)	Minor salivary glands, n (%)
Squamous cell carcinoma	11 (23.5)	1 (2.1)	
Adenoid cystic carcinoma	6 (12.7)	2 (4.3)	1 (2.1)
Mucoepidermoid carcinoma	12 (25.6)	1 (2.1)	2 (4.3)
Carcinoma ex pleomorphic adenoma	4 (8.6)		
adenocarcinoma	3 (6.3)		1 (2.1)
Others	3 (6.3)		
Total	39 (83)	4 (8.5)	4 (8.5)

Table 3. Statistical analyses of the considered variables in the three groups

Variable	n	Benign, n=191	Controls, n=90	Malignant, n=47	p
Age	325	55 (15)	38 (16)	65 (14)	<0.001
Sex	328				0.004
f	92 (48%)	25 (28%)	23 (49%)		
m	99 (52%)	65 (72%)	24 (51%)		
White blood cell	328	7.54 (2.08)	6.55 (1.76)	7.83 (2.80)	<0.001
neutrophils	328	4.76 (1.76)	3.77 (1.38)	5.46 (2.70)	<0.001
lymphocytes	328	2.05 (0.65)	2.09 (0.54)	1.83 (0.73)	0.057
monocytes	328	0.46 (0.16)	0.44 (0.17)	0.48 (0.20)	0.338
eosinophils	328	0.17 (0.12)	0.19 (0.22)	0.14 (0.12)	0.108
basophils	328	0.039 (0.022)	0.085 (0.436)	0.033 (0.025)	0.251
platelets	328	235 (61)	230 (43)	239 (62)	0.660
alfa1	323	4.07 (0.62)	3.70 (0.44)	4.50 (0.89)	<0.001
alfa2	323	10.25 (1.77)	9.01 (1.26)	11.15 (1.87)	<0.001
beta1	323	6.20 (0.75)	5.81 (0.58)	6.23 (0.61)	<0.001
beta2	323	5.16 (0.96)	4.65 (0.82)	5.45 (1.39)	<0.001
hematocrit	328	44.2 (5.0)	44.4 (3.9)	41.4 (4.8)	<0.001
hemoglobin	328	14.48 (1.56)	14.71 (1.38)	13.48 (1.72)	<0.001
Red blood cell	328	5.01 (0.52)	5.04 (0.43)	4.63 (0.52)	<0.001
ck	322	109 (72)	137 (111)	150 (241)	0.053
ldh	328	218 (75)	189 (40)	211 (50)	0.003
iron	325	84 (37)	96 (33)	81 (28)	0.012
glycemia	326	92 (23)	82 (13)	99 (28)	<0.001
AST	326	22 (13)	22 (7)	24 (14)	0.378
ALT	325	22 (19)	23 (13)	25 (20)	0.581
creatinine	326	0.84 (0.19)	0.88 (0.14)	0.88 (0.26)	0.224
albumin	326	4.43 (0.33)	4.89 (1.96)	4.24 (0.41)	<0.001
SII	328	601 (433)	433 (183)	851 (722)	<0.001
PLR	328	125 (54)	116 (28)	152 (66)	<0.001
NLR	328	2.55 (1.74)	1.88 (0.73)	3.55 (2.82)	<0.001

Data are presented as Mean (SD) for continuous variables and as Frequency (%) for categorical variables. P-values are computed with one-way ANOVA or chi square test. Significant values are highlighted in bold.

System. They reported a percentage ranging from 10 to 25% of estimated risk of malignancy for these categories.^[19]

Howard H Wu et al collected a total of 1,560 fine-needle aspirations of the salivary glands from two institutions for a 12-year period measuring the Real world risk of malignancy based on 694 histologic follow-up cases. The real world risk of malignancy, defined as objective, unbiased risk, result of an actuarial-probabilistic assessment.^[20] For each category was: 18.3% for non diagnostic (Category I), 8.9% for non neoplastic (Category II), 37.5% for atypia of undetermined significance (AUS – Category III).^[21]

This high rate risk for malignancy translates into a concrete possibility of inadequate management for the clinician. Thus, the inflammatory background in these patients may support the decision-making process.

As remarked by several studies, inflammation has been

recognized as a promoter of cancer development and progression.^[22-24]

Immune and inflammatory cells such as neutrophils, platelets and lymphocytes contribute to the invasion of cancer cells into the peripheral blood.^[25,26]

The increase in pretreatment inflammatory biomarker values was positively correlated with a worse prognosis in many major salivary gland tumors and in a large number of epithelial and mesenchymal neoplasms.^[12-15,27]

Guangyan Cheng et al noted that different increasing values of NLR were related to the different stages of malignancy in primary parotid cancer patients.^[28]

Kawakita et al described an NLR cut-off > 2.5 in patients with salivary duct carcinoma, indicating that there was an almost 2-fold greater risk of death than baseline levels.^[29]

To our knowledge the first Authors whose analyze the values

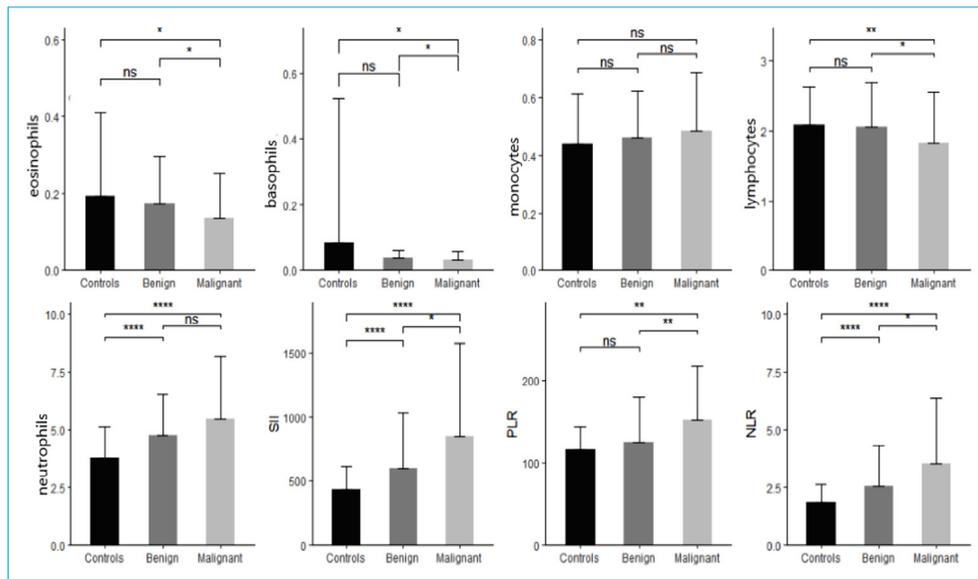


Figure 1. Comparison graphs of blood inflammatory indices in the three Groups.
Significance level: ns = not significant, * = $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$.

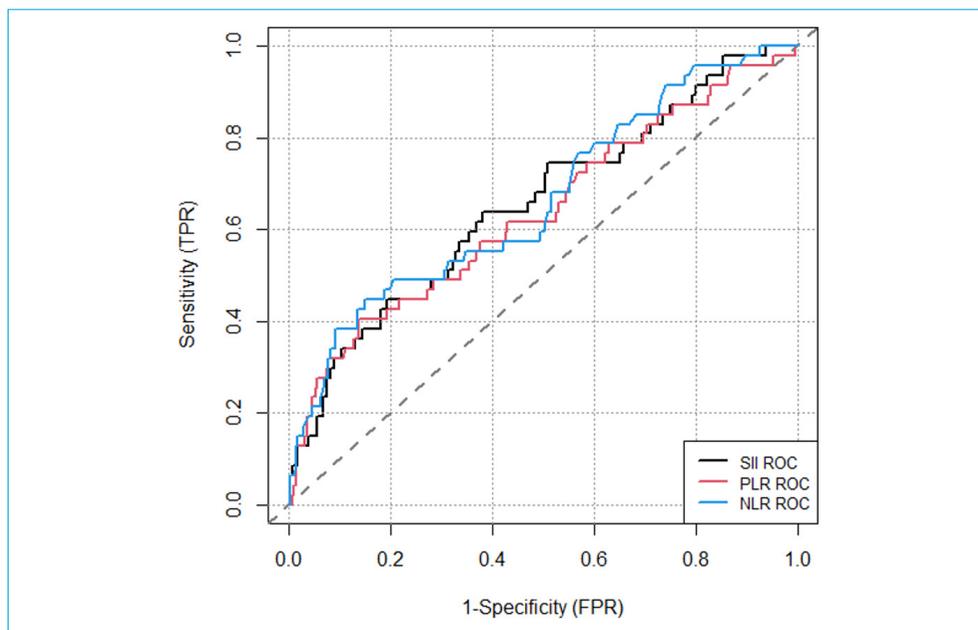


Figure 2. Receiver operating curves (ROCs) and obtained optimal cut offs for the three variables SII, NLR and PLR.

SII AUC = 0.6532, PLR AUC = 0.6366, NLR AUC = 0.6618.

Variable	Optimal Threshold	Accuracy	TN	TP	FN	FP	Specificity	Sensitivity
SII	517.5	0.622	174	30	17	107	0.62	0.64
PLR	164.2	0.796	242	19	28	39	0.86	0.40
NLR	3.11	0.793	239	21	26	42	0.85	0.45

of these biomarkers in benign and malignant salivary gland tumors were Murat Damar et al in 2016.^[30] In their study the Authors analyzed preoperative NLR values in patients with malignant and benign salivary gland tumors. They reported

an increase of NLR value in malignant tumors compared to benign. On the other hand mean lymphocyte count and rate were lower in patients with malignant salivary gland tumors than in patients with benign salivary gland tumours. These

results suggested that the combination of NLR and lymphocyte percentage may be used as a potential inflammatory marker in patients to differentiate low- from high- grade malignant parotid gland tumors.

These preliminary studies have remarked the role of the inflammatory state in benign and malignant salivary pathology. The analysis of the results coming out from our study showed that there is a statistically significant increase of NLR, PLR and SII indices in salivary glands cancers compared to benign salivary gland tumours and control group. It's important to underline the role that the optimal threshold defined for NLR (3,11), PLR (164,2) and SII (517.5) could have in doubtful cases .

In particular, the optimal threshold values of NLR and PLR seem to be particularly useful in discriminating true negatives with a sensitivity of 85%. Conversely, the SII threshold values would seem to be more effective in discriminating true positives with a sensitivity of 64%. Thus, the cut-off value, as defined in our study, assume an important role in the decision-making process for the management of salivary tumors. They provide the clinician useful information to guide the therapeutic choices aimed at repeating the FNAC or moving towards an enucleoresection surgery vs parotidectomy.

The study has some limitations: this is a retrospective study based on a single center data set; the predictive value of these markers has not yet been tested on a prospective population. Therefore, our future goal will be to conduce a prospective study to evaluate these cut-offs both as a diagnostic tools in dubious diagnoses at FNAC and as predictive prognostic values.

Conclusion

In conclusion, the encouraging results of our study show that inflammatory markers values increase in Salivary glands cancer. They could be a standard laboratory measurements which may be routinely performed in the clinical setting guiding the surgical treatment of these neoplasms. A prospective trial with a larger number of patients is mandatory to confirm our preliminary results.

Disclosures

Ethics Committee Approval: Signed patients consents were obtained for all the participants in the study in accordance with declaration of Helsinki. No ethical approval was required by our local IRB as a retrospective study based on collecting data.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – V.A.; Design – V.A.; Supervision – G.I.; Materials – P.B.; Data collection &/or processing – S.B.;

Analysis and/or interpretation – D.P.; Literature search – S.T.; Writing – S.B., S.T.; Critical review – L.C.

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