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Diagnostic performance of inflammatory biomarkers and cytological analysis in salivary gland tumors

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Abstract

Background: This study aimed to evaluate the diagnostic performance of serum inflammatory biomarkers in salivary gland tumors with dubious results following cytological analysis.

Methods: A retrospective analysis of 239 cases following surgery between January 2011 and June 2022 was performed. Receiver Operating Characteristic curves were drawn and areas under the curves were computed to evaluate the diagnostic performance of the inflammatory biomarkers (SII, SIRI, PLR, and NLR). Optimal cut-offs for each marker were determined by maximizing the Youden index.

Results: Analysis showed that among the major biomarkers examined, SIRI performed an AUC of 0.77. The best SIRI cut-off was 0.94 with an accuracy of 79.9%. The accuracy, sensitivity, and specificity of cytological analysis were 77.8%, 59.6%, and 90.7% respectively. By combining SIRI with cytological analysis we demonstrated an increase in sensitivity to 82.8%.

Conclusions: Inflammatory biomarkers could be evaluated to support the diagnosis and treatment of salivary gland tumors in difficult cases.

KEYWORDS

fine needle aspiration cytology, NLR, salivary gland tumors, SII, SIRI

1 | INTRODUCTION

Accurate diagnosis of preoperative salivary gland tumors (SGTs) is necessary to guide the proper treatment of these lesions. Fine needle aspiration cytology (FNAC) is considered today as the gold standard test for presurgical diagnosis.[1–3] The accuracy of the procedure is often debated in the literature, as it depends on the experience

of the operator and cytopathologist.[4–6] Sensitivity and specificity of FNAC for parotid gland lesions were reported to be 78% and 98%, respectively.[7,8]

The Milan system for reporting salivary gland cytopathology (MSRSGC) was conceived during the 39th European Cytology Congress held in Milan in 2015. It provides a guide for diagnosis and management according to the risk of malignancy (ROM) as divided into six categories. These are (1) nondiagnostic, (2) non-neoplastic, (3) atypia of undetermined significance, (4) neoplasm (further subdivided into benign neoplasms and salivary gland neoplasms of uncertain malignant potential), (5) suspicious for malignancy, and (6) malignant. The ROM of each category are 25%, 10%, 20%, 5%, 35%, 60%, and 90% respectively.[9]

Thus, while the introduction of this system has made the stratification of lesions based on cellularity easier from a cytopathological point of view, it has not resolved diagnostic problems in a clinical setting. Use of this system still leaves a considerable margin of diagnostic uncertainty making therapeutic and management decisions potentially controversial. Diagnostic imaging investigations provide helpful support for selection of therapy, however, they are not enough to guide the decision-making process alone.[10]

In such cases, a significant role could be played by inflammatory biomarkers. Several authors have discussed the role of inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and more recently systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) in patients with malignant salivary gland tumors and other cancers.[11–15] The efficacy of these biomarkers as a prognostic factor in salivary gland tumors has already been widely demonstrated, but no evidence investigates a potential role for them as a preoperative diagnostic tool in SGT.[16]

Based on this evidence, a retrospective study was conducted to evaluate the diagnostic performance of the main inflammatory biomarkers, compared to FNAC alone, for salivary gland tumors.

2 | MATERIALS AND METHODS

2.1 | Study design

From January 2011 to June 2022 data were collected from all patients surgically treated for salivary gland tumors admitted to the Department of Maxillofacial Surgery of the University of Naples "Federico II" and a retrospective study was performed.

Ethical review and approval were waived for this study due to its observational and retrospective nature. Informed consent was obtained from all subjects involved in the study in accordance with the Helsinki declaration. A total of 905 salivary gland tumors surgically treated in our department were collected from our clinic's digital records. Among these, 239 were eligible for this study, satisfying the following inclusion criteria.

- The presence of salivary gland tumor(s) was confirmed histologically;
- Complete medical records were available;
- A routine preoperative blood count was conducted;
- Patient age > 18;
- Preoperative ultrasound-guided FNAC examination was conducted.

The exclusion criteria were:

- Patients with inflammatory diseases with potential to alter NLR, PLR, SII, and SIRI values were excluded (such as chronic or acute inflammatory disease; autoimmune hematological disorders, and anti-inflammatory/steroidal treatments).
- Presence of previous cancers at any other sites;
- Radiotherapy or chemotherapy was included in the clinical history;
- Incomplete clinical data.

Two hundred sixty-six patients were excluded due to incomplete clinical data; 270 for chronic or acute inflammatory disease, autoimmune hematological disorders, and/or anti-inflammatory/steroid treatments; 64 were less than 18 years old; 66 had tumors at any other site, and/or had received radiation or chemotherapy.

2.2 | Data collection

The diagnostic workup for all the patients involved a complete physical examination, routine blood count, fine needle aspiration cytology of the tumor, neck ultrasound, head and neck CT scan, and/or MRI with contrast.

Relevant clinical and pathological data such as demographic information (age, sex), FNAC report, histological diagnosis, tumor site, and routine laboratory data performed before surgery, were collected from the medical records.

From 2018 to 2022, the results of the FNAC were categorized according to the Milan System. Therefore, to standardize the sample, we considered categories III, IVa, and IVb benign (ROM: 20%, <5%, and 35%) and categories V and VI malignant (ROM: 60% and 90%).

Surgical management of benign salivary gland tumors was performed according to the European Salivary Gland Society guidelines.[17]

Superficial parotidectomy was performed for T1 or T2 low-grade superficial tumors and a total parotidectomy was performed for high-grade or T3–T4 tumors.[10]

Submandibular sialoadenectomy was performed for any tumor located in the submandibular gland. Excision including a margin of 1 cm of healthy tissue was performed for any tumor located in the minor salivary glands. Neck Dissection was performed in selected cases, based on the clinical, radiological, and cytological analysis according to current guidelines for the treatment of malignant tumors of the salivary glands.[18,19]

Pretreatment baseline NLR, PLR, SII, and SIRI were calculated using the following formulae:

$$\text{NLR} = \text{Neutrophil counts}/\text{Lymphocyte counts},$$

$$\text{PLR} = \text{Platelet counts}/\text{Lymphocyte counts},$$

$$\text{SII} = \text{Platelet counts} \times \text{Neutrophil counts}/\text{Lymphocyte counts},$$

$$\text{SIRI} = \text{Neutrophil count} \times \text{Monocyte count}/\text{Lymphocyte count}.$$

2.3 | Statistical analysis

Quantitative variables are expressed as mean and standard deviation while categorical variables are expressed as frequency and percentage. The diagnostic performance of the cytological examination was summarized using raw accuracy, sensitivity, and specificity. To evaluate the diagnostic performance of the inflammatory biomarkers (SII, SIRI, PLR, and NLR), receiver operating characteristic curves (ROCs) were constructed and the corresponding areas under the curves (AUCs) were calculated. Optimal cut-offs for each marker were determined maximizing the Youden index. Additionally, the diagnostic performance of the cytological examination combined with the best-performing inflammatory marker was evaluated. The combination of the inflammatory marker at the specified threshold with the FNAC was considered dichotomous and in particular was defined as having a value of 1 if at least FNAC or the marker was positive and as 0 if neither was positive. Differences in the diagnostic performances achieved were computed with the Mc Nemar's test. Simple and multinomial logistic regression was used to investigate predictors of discordance between the FNAC and histology. For all analyses, a p-value <0.05 was considered statistically significant. Analyses were performed using the statistical software R, version 4.0.3.

TABLE 1 Sample characteristics.

Variables	Total cases 239
Age (years)	
≤60	145 (61%) 87 Benign 58 Malignant
>60	94 (39%) 53 Benign 41 Malignant
Gender	
Female	111 (46.5%) 63 Benign 48 Malignant
Male	128 (53.5%) 78 Benign 50 Malignant
Smoking	
Yes	55 (23%) 28 Benign 27 Malignant
No	184 (77%) 112 Benign 72 Malignant
Alcohol	
Yes	27 (11%) 17 Benign 10 Malignant
No	212 (89%) 123 Benign 89 Malignant
Tumor types	
Benign tumors	140 (58.5%)
Malignant tumors	99 (41.5%)
Tumor location	
Major salivary glands	221 (92%)
Minor salivary glands	18 (8%)
Tumor size (cm)	
≤4	167 (70%) 83 Benign 84 Malignant
>4	72 (30%) 57 Benign 15 Malignant

3 | RESULTS

The study sample included 239 patients with salivary gland tumors (128 males and 111 females; mean age 55 ± 16 years; age range 18–87 years).

The preoperative FNAC results were available for all 239 patients of whom 167 (70%) and 72 (30%) were

TABLE 2 Histopathological types of tumor and their location.

Tumor location	Number of cases	Histopathological types
Parotid gland	208	• Pleomorphic adenoma: 68 (33%) • Warthin tumor: 63 (30%) • Mucoepidermoid cancer: 11 (5.25%) • Adenocarcinoma: 11 (5.25%) • Squamous cell carcinoma: 8 (4%) • Myoepithelial carcinoma: 8 (4%) • Oncocytoma: 7 (3%) • Carcinoma ex pleomorphic adenoma: 7 (3%) • Adenoid cystic carcinoma: 5 (2.5%) • Secretory carcinoma: 4 (2%) • Lymphoepithelial carcinoma: 4 (2%) • Acinic cell carcinoma: 3 (1.5%) • Basal cell adenoma: 2 (1%) • Undifferentiated carcinoma: 2 (1%) • Carcinosarcoma: 2 (1%) • Intraductal carcinoma: 1 (0.5%) • Salivary duct carcinoma: 1 (0.5%) • Oncocytic carcinoma: 1 (0.5%)
Submandibular gland	13	• Adenoid cystic carcinoma: 4 (31%) • Squamous cell carcinoma: 3 (23%) • Carcinosarcoma: 2 (15%) • Carcinoma ex pleomorphic adenoma: 2 (15%) • Adenocarcinoma: 1 (8%) • Myoepithelial Carcinoma: 1 (8%)
Minor salivary glands	18	• Mucoepidermoid Cancer: 5 (27.5%) • Adenocarcinoma: 4 (22.5%) • Adenoid cystic carcinoma: 4 (22.5%) • Myoepithelial carcinoma: 2 (11%) • Carcinoma ex pleomorphic adenoma: 1 (5.5) • Acinic cell carcinoma: 1 (5.5) • Clear cell carcinoma: 1 (5.5)
TOTAL	239	• Pleomorphic adenoma: 68 (28.5%) • Warthin tumor: 63 (26.5%) • Adenocarcinoma: 16 (7%) • Mucoepidermoid cancer: 16 (7%) • Adenoid cystic carcinoma: 13 (5%) • Myoepithelial carcinoma: 11 (4.5%) • Squamous cell carcinoma: 11 (4.5%) • Carcinoma ex pleomorphic adenoma: 10 (4.5%) • Oncocytoma: 7 (3%) • Secretory carcinoma: 4 (1.5%) • Acinic cell carcinoma: 4 (1.5%) • Lymphoepithelial carcinoma: 4 (1.5%) • Carcinosarcoma: 4 (1.5%) • Basal cell adenoma: 2 (0.75%) • Undifferentiated carcinoma: 2 (0.75%) • Intraductal carcinoma: 1 (0.5%) • Salivary duct carcinoma: 1 (0.5%) • Clear-cell carcinoma: 1 (0.5%) • Oncocytic carcinoma: 1 (0.5%)

suggestive of benign and malignant salivary gland tumors, respectively.

The histological examination revealed 140 (58.5%) benign lesions and 99 (41.5%) malignant tumors. In 167 (70%) patients, the tumor size was ≤4 (84 malignant and 83 benign) while in 72 (30%), the tumor size was >4 cm (15 malignant and 57 benign). The main demographic, clinical, and pathological findings are shown in

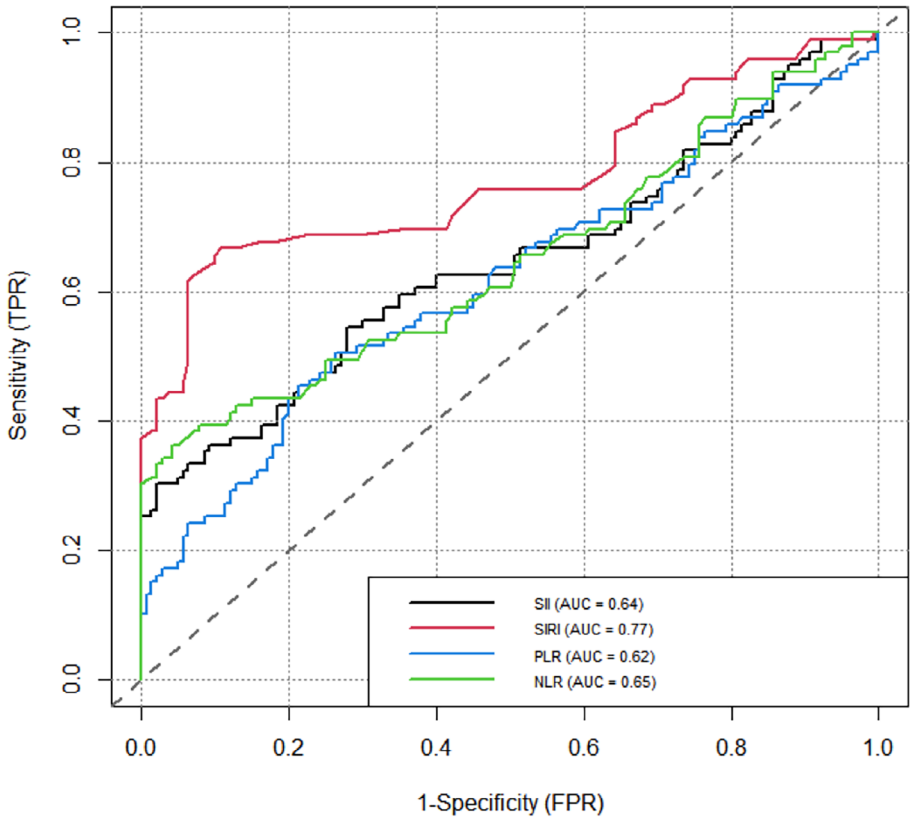

FIGURE 1 Receiver operating characteristic curves of the main inflammatory biomarkers. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. All 140 benign tumors were located in the parotid gland, of the 99 malignant tumors, 68 (68.5%) were located in the parotid glands, 13 (13%) in the submandibular gland, and 18 (18.5%) in the minor salivary glands. Pleomorphic adenoma was the most common in the benign tumor group (48.5%), while mucoepidermoid carcinoma and adenocarcinoma (32.3%) were most common in the malignant tumor group. The final histological diagnoses of the included tumors are summarized in Table 2.

3.1 | Diagnostic performance of fine needle aspiration cytology and inflammatory biomarkers

Cytological diagnosis did not match with the definitive histological diagnosis in 53 cases (22%). Among these, a mismatch between cytological diagnosis of benignity and histopathological diagnosis of malignancy was reported in 40 cases (75%). Furthermore, through the Youden index method, the optimal cut-offs of each individual biomarker were calculated to discriminate the tumor from benign to malignant (SII:788, SIRI:0.94, PLR: 129, and NLR:3.09). With the Youden index method, the accuracy, sensitivity, and specificity of cytological analysis were 77.8%, 59.6%, and 90.7% respectively.

Among the major biomarkers examined (SII, PLR, and NLR) SIRI performed an AUC of 0.77 (Figure 1). The best SIRI cut-off was 0.94 with an accuracy of 79.9% and a sensitivity of 66.7% (Table 3).

Logistic regression analysis of the main clinical outcome for cytological–histological discordance was statistically significant for tumor size (<0.001; Table 4).

3.2 | Diagnostic performance combining SIRI and FNAC

Since among the biomarkers SIRI showed better accuracy than the others, we decided to combine the positivity to the SIRI+ FNAC (i.e., considering a subject positive if at least one of the two indices is positive) to evaluate the diagnostic performance.

The ROC curve constructed using the combination of SIRI + FNAC had an AUC of 0.81 (Figure 1).

Combining the positivity to the best SIRI cut-off (0.94) and FNAC (suspicion for malignancy) the accuracy, sensitivity, and specificity were 81.2%, 82.8%, and 80.0%, respectively.

In particular, this SIRI + FNAC combination shows an increase in sensitivity to 82.8% compared to 59.6% at FNAC ($p < 0.001$) and 66.7% at SIRI ($p < 0.001$) taken individually (Figure 2).

TABLE 3 Diagnostic performance of cytological analysis and inflammatory biomarkers.

Measure	TP	FP	TN	FN	Raw accuracy	Sensitivity	Specificity
Cytologic examination	59	13	127	40	77.8%	59.6%	90.7%
Inflammatory markers							
SII (cut-off Youden index = 788)	30	3	137	69	69.9%	30.3%	97.9%
SIRI (cut-off Youden index = 0.94)	66	15	125	33	79.9%	66.7%	89.3%
PLR (cut-off Youden index = 129)	50	37	103	49	64.0%	50.5%	73.6%
NLR (cut-off Youden index = 3.09)	36	6	134	63	71.1%	36.4%	95.7%

TABLE 4 Simple logistic regression outcome for cytological–histological discordance.

Outcome discordant yes/no	*N*	OR	95% CI	*p*-value
Gender	239			
Female		—	—	
Male		1.02	0.55, 1.88	0.958
Age	239	0.98	0.96, 1.00	0.066
Tumor_location	239			
Major		—	—	
Minor		1.00	0.27, 2.94	0.996
Tumor_size	239			
≤4		—	—	
>4		0.19	0.06, 0.45	**<0.001**
Lymph_node_metastasis	239			
N−		—	—	
N+		0.70	0.23, 1.81	0.497
Adjuvant_radiotherapy	239	1.83	0.85, 3.81	0.110
Smoking	239	1.63	0.81, 3.20	0.162
Alcohol	239	1.80	0.73, 4.16	0.181
NLR (continuous)	239	0.92	0.73, 1.10	0.438
PLR (continuous)	239	0.99	0.99, 1.00	0.112
SII (continuous)	239	1.00	1.00, 1.00	0.321
SIRI (continuous)	239	0.95	0.65, 1.18	0.707
NLR > 3.09 (Youden cutoff)	239	0.66	0.25, 1.50	0.346
PLR > 129 (Youden cutoff)	239	0.56	0.27, 1.07	0.089
SII > 788 (Youden cutoff)	239	0.44	0.13, 1.19	0.143
SIRI > 0.94 (Youden cutoff)	239	1.69	0.90, 3.16	0.099

4 | DISCUSSION

The preoperative diagnosis of SGTs is still a widely debated topic in the literature.[20,21] Current evidence advises against a surgical open biopsy for SGTs; this makes preoperative diagnosis of these lesions difficult. Liu et al have shown that open surgery for histological sampling may result in spillage or seeding, scarring, nerve damage, and salivary fistulas.[7] Core needle biopsy (CNB) is another method of obtaining tissue for histological sampling in salivary gland neoplasms. This technique involves the collection of salivary tissue through a cutting needle with gauges ranging from 12G to 19G.

Although it is generally considered a safe technique, needle thickness may increase the risk of complications. Witt et al. highlighted that CNB is a more invasive technique that requires local anesthesia and may lead to tumor spread along the needle tract, hematoma (1.6%), and temporary facial nerve weakness (0.2%).[22,23]

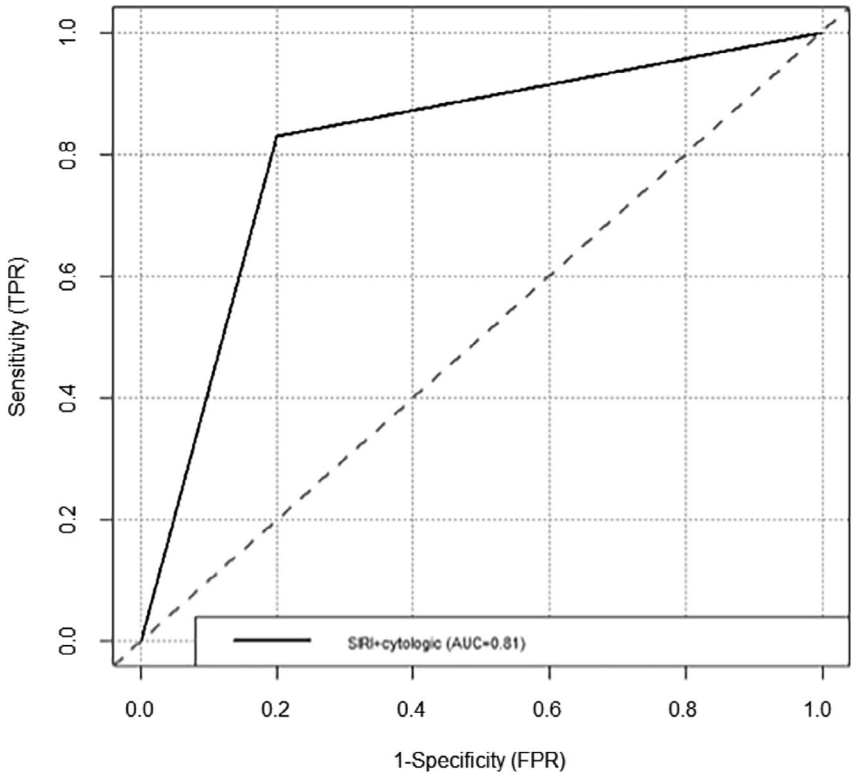

FIGURE 2 Diagnostic performance of SIRI and cytological analysis.

Measure	TP	FP	TN	FN	Raw accuracy	Sensitivity	Specificity
SIRI (cut-off Youden index) + cytology = 1	82	28	112	17	81.2%	82.8%	80.0%

In this scenario, FNAC of salivary gland tumors is considered a safer and simpler method to achieve preoperative diagnosis.[24]

This technique allows preservation of the integrity of surrounding tissues and parenchyma maintaining a low complication rate.

In 2018, the Milan System was introduced to classify the cytology of the salivary glands; this classification includes six categories: I, nondiagnostic; II, non-neoplastic; III, atypia of indeterminate significance (AUS); IV, neoplastic, which is further subdivided into IVa benign – IVb salivary gland neoplasm of uncertain malignant potential (SUMP); V, suspicious for malignancy; and VI, malignant.[9]

The Milan system has helped facilitate pathological analysis by offering a standardized criterion for classifying salivary neoplasms based on cytological characteristics.

However, as shown by Rossi et al., this system comports a certain degree of uncertainty that is expressed using the Risk of Malignancy (ROM)score ranging from <5% to >90%.[9] Several authors have recently highlighted the inaccuracy of cytological sampling with FNAC.

Singh et al. observed four cases of discordance between diagnoses based on cytology versus those based on histopathology in 56 examined cases. One case of carcinoma ex pleomorphic adenoma was diagnosed as pleomorphic adenoma on cytology; one case of pleomorphic adenoma was diagnosed as mucoepidermoid carcinoma on cytology; one case of adenoid cystic carcinoma was diagnosed as pleomorphic adenoma; and one case of metastatic malignant melanoma was diagnosed as chronic sialoadenitis on cytology.[25]

Iftikhar et al. reported discordance between FNAC and histopathology in patients with mucoepidermoid carcinoma of the parotid gland. Specifically, eight cytology specimens proved falsely negative upon analysis as mucoepidermoid carcinoma could not be detected with FNAC. Three cases were reported as high-grade mucoepidermoid carcinoma on histopathology and were underdiagnosed as pleomorphic adenoma on cytology.[26] In view of the above, the mucoepidermoid carcinoma (MEC) may be underdiagnosed by FNAC and, depending on the portion aspirated, may be mistaken for pleomorphic adenoma or abscess.[27,28]

Moreover, some cells of the adenoid cystic carcinoma often resemble normal acinar cells in FNAC, therefore the tumor may evade diagnosis.[29]

Cong-Gai Huang et al. reported four misdiagnosed cases of ACC of the salivary gland. When analyzing their causes: 4 cases (12.5%) were misdiagnosed by cell morphology as benign tumors (Iva); 2 cases were misdiagnosed as pleomorphic adenomas (PA); 2 other cases were misdiagnosed as basal cell adenomas (BCA).[30,31]

Thus, diagnostic uncertainty complicates the clinical decision-making process. Hence, the need to identify new tools capable of supporting the surgeon when choosing the best treatment.

Several authors have highlighted how the values of inflammatory biomarkers vary according to tumor histotype. In our previous study, we underlined the role of the inflammatory status in benign and malignant salivary pathology, demonstrating a statistically significant increase in NLR, PLR, and SII indices in malignant salivary gland tumors compared to benign tumors.[32,33]

Based on this evidence, we conducted a retrospective study to evaluate the diagnostic performance of inflammatory biomarkers in preoperative SGTs diagnosis.

In our samples, the accuracy, sensitivity, and specificity of FNAC were 77.8%, 59.6%, and 90.7%, respectively.

SIRI has proven to be the biomarker with the highest diagnostic performance. It was accurate in 79.9% of cases, with a sensitivity and specificity of 66.7% and 83.3%, respectively. Furthermore, when the performance of SIRI is combined with cytological analysis sensitivity increases to a statistically significant value of 82.8%.

This indicates that a lesion that appears clinically benign with either a suspicious cytology or a suprathreshold SIRI carries an 82.8% risk that the lesion will be revealed as malignant upon histological examination.

Moreover, it is noteworthy that regression analysis demonstrates that tumor size has a large impact on the extent of discordance between the results of cytological and histopathological analyses.

Furthermore, we found discordance between the preoperative FNAC results and final histopathological diagnoses to be higher in patients with tumor sizes of >4 cm.

According to Yildiz et al., the reason might be that tumors with a larger volume carry a higher risk that nondiagnostic tissue will be included in the cytological aspirate.[2]

Our study has some limitations. This is a retrospective single-center study of 239 patients with SGTs, the cytological examination was performed by different operators with 11 years of experience; unknown inflammatory diseases that remained unreported when taking each patient's history could influence the results of inflammatory biomarkers. Moreover, the small size of the sample did not allow the differential analysis of the cutoffs values based on the tumor localization. The result turned out statistically not significant in the sample examined and therefore was not reported. Further studies with larger patient cohorts are mandatory for the validation of our results.

In conclusion, the encouraging results of our study show that the SIRI score can be routinely collected in SGTs patients as a supplement to FNAC to achieve preoperative diagnosis, especially in dubious cases. When combining SIRI with cytological analysis, sensitivity significantly increases to 82.8%.

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CONFLICT OF INTEREST STATEMENT

Vincenzo Abbate, Simona Barone, Gerardo Borriello, Stefania Troise, Paola Bonavolontà, Daniela Pacella, Luigi Angelo Vaira, Mario Turri-Zanoni, Carlos Navarro Cuéllar, Luigi Califano, Giovanni Dell'Aversana Orabona declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

Ethical review and approval were waived for this study due to its observational and retrospective nature. Informed consent was obtained from all subjects involved in the study in accordance with the Helsinki Declaration.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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