REVIEW

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Diagnostic Accuracy of Inflammatory Biomarkers for Salivary Gland Tumours: A Systematic Review and Meta-Analysis

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Abstract

Background: Differentiating benign from malignant salivary gland tumors (SGTs) preoperatively remains a clinical challenge due to overlapping morphological and radiologic features. Systemic inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) have emerged as potential adjuncts reflecting tumor-associated immune dysregulation. This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of these biomarkers for SGTs. **Methods:** A systematic search was conducted in PubMed, SCOPUS, EBSCOhost, and Google Scholar up to September 2025 following the PRISMA-DTA guidelines (PROSPERO registration: CRD420251173943). Studies assessing the diagnostic accuracy of inflammatory biomarkers with histopathology as the reference standard were included. Data on sensitivity, specificity, area under the curve (AUC), and diagnostic odds ratio (DOR) were pooled using a random-effects model, and heterogeneity was assessed using Higgins I^2 statistics. **Results:** Six studies comprising 338 patients met the inclusion criteria. The pooled sensitivity and specificity were 0.71 and 0.81 for NLR, 0.61 and 0.72 for PLR, 0.74 and 0.78 for SII, and 0.71 and 0.73 for SIRI, respectively. Corresponding AUCs ranged from 0.73 to 0.83, indicating moderate-to-excellent diagnostic accuracy. Among the evaluated indices, SIRI showed the highest pooled sensitivity, while SII demonstrated the best discriminative capacity. The integration of SIRI with fine-needle aspiration cytology (FNAC) further improved diagnostic performance (accuracy 81.2%). Heterogeneity across studies was low ($I^2 = 0\%$). **Conclusion:** Inflammatory biomarkers, particularly SII and SIRI, exhibit promising diagnostic value for diagnosing various SGTs and may complement cytological evaluation in indeterminate cases. Prospective multicentric studies with standardized cut-offs are recommended to validate their clinical application.

Keywords: Diagnostic accuracy- Inflammatory biomarkers- Meta-analysis- Salivary gland tumors

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Introduction

Salivary gland tumors (SGTs) represent a rare and heterogeneous group of neoplasms comprising approximately 3–10% of all head and neck tumors, with the parotid gland being the most frequently affected site [1]. The World Health Organization (WHO) 2017 classification recognizes over 30 benign and malignant histopathologic subtypes, highlighting the complexity of their diagnosis and management [1]. While pleomorphic adenoma is the most common benign tumors, mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma are among the prevalent malignant entities [2]. Despite advances in imaging and cytopathological techniques, differentiating between benign and malignant SGTs preoperatively remains a diagnostic challenge due to overlapping morphological and clinical features [2].

The fine-needle aspiration cytology (FNAC) remains the gold standard preoperative diagnostic tool for SGTs, often complemented by ultrasound or magnetic resonance imaging (MRI) [3]. However, its diagnostic accuracy is limited by operator dependency and sampling adequacy. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC), introduced in 2015, has standardized cytological reporting into six diagnostic categories, each with an associated risk of malignancy (ROM) ranging from 10–90% [4-6]. Nonetheless, a significant proportion of cases up to 25% fall into indeterminate categories such as "Atypia of Undetermined Significance" and "Neoplasm of Uncertain Malignant Potential," creating ambiguity in therapeutic decision-making [7]. This uncertainty underscores the need for adjunctive diagnostic tools that can augment cytologic and radiologic findings [8].

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Emerging evidence underscores the intricate relationship between systemic inflammation and tumorigenesis [9]. Chronic inflammatory processes in the tumors microenvironment facilitate angiogenesis, DNA damage, immune evasion, and metastasis through the release of cytokines, chemokines, and growth factors [10]. Peripheral blood–derived inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), have been proposed as cost-effective, easily accessible markers reflecting the host immune response to tumors burden [11]. Elevated NLR and PLR values correlate with poorer prognosis, advanced disease stage, and reduced survival in various malignancies, including oral, laryngeal, and hepatocellular cancers [12].

Although numerous studies have explored the prognostic role of inflammatory biomarkers in head and neck cancers, their diagnostic accuracy in differentiating benign and malignant salivary gland tumors remains less clearly defined [13]. Despite this, the cumulative evidence suggests that inflammatory markers are promising non-invasive adjuncts that could improve early diagnosis and risk stratification of salivary gland neoplasms [14].

Given the rarity and histological heterogeneity of salivary gland tumors, there is a pressing need to identify reliable, low-cost, and easily reproducible diagnostic indicators that can augment existing diagnostic modalities. Inflammatory biomarkers, derived from routine hematological tests, hold immense potential to serve as accessible tools in both primary and tertiary healthcare settings [15]. However, there is no systematic review and meta-analysis that comprehensively evaluates their diagnostic accuracy, predictive thresholds, and heterogeneity across published studies.

Therefore, the present systematic review and meta-analysis aim to quantify the diagnostic accuracy of inflammatory biomarkers (NLR, PLR, SII, and SIRI) for differentiating benign from malignant salivary gland tumors. This review also seeks to address the variability in diagnostic performance, identify optimal cutoff values, and highlight methodological inconsistencies in existing literature. By consolidating current evidence, this study aims to provide evidence-based insights into the potential integration of inflammatory biomarkers into clinical diagnostic algorithms for SGTs.

Materials and Methods

Protocol and Registration

Review was adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analysis – Diagnostic Test Accuracy (PRISMA- DTA) checklist [16] and PROSPERO- CRD420251173943 registration was done. https://www.crd.york.ac.uk/PROSPERO/view/CRD420251173943.

Study Design

Research question in Participants (P), Index test (I), reference standard (R) and target condition (T) format was proposed "What is the diagnostic accuracy of inflammatory biomarkers for salivary gland tumors"?

Eligibility Criteria

Inclusion Criteria

(1) Research Design: studies evaluating the diagnostic or prognostic role of inflammatory biomarkers (NLR, PLR, SII, SIRI) in salivary gland tumors using observational, retrospective, prospective, and cross-sectional methods.

(2) Participants were patients who were 18 years of age or older and diagnosed with salivary gland tumors

(3) Studies comparing benign and malignant histopathological diagnoses.

(4) Studies reporting outcome measurement as sensitivity, specificity, predictive values (PV) and accuracy

(5) English-language publications and as freely available full text articles

(6) Articles published till September 2025

Exclusion Criteria

(1) Animal research, in vitro research, and non-clinical research. Additionally, studies that discussed a single diagnostic instrument were not included.

(2) Research conducted on people under the age of eighteen.

(3) The database does not contain all of the studies.

(4) Articles that just included abstracts were also disqualified.

(5) Research where primary outcomes cannot be computed from the provided raw data, or when primary outcomes of accuracy, sensitivity, and specificity are not reported.

(6) Studies not differentiating benign and malignant SGTs.

(7) Studies including non-salivary gland pathologies or metastatic lesions.

(8) Articles lacking sufficient quantitative or statistical data

Search protocol and study selection

Database search was performed till September 2025 through PubMed, SCOPUS, EBSCOhost and google scholar using key words and Medical Subject Heading (MeSH) terms as shown below (Table 1).

Population: "Salivary gland"[MeSH Terms] AND "salivary gland tumors" [MeSH Terms] OR "malignant transformation" [MeSH Terms] OR "Salivary gland neoplasm"[MeSH Terms] AND "high grade malignant tumors" OR "diagnosis"[MeSH Terms] OR "prognosis" [MeSH Terms]

Index test: "Inflammatory biomarkers"[MeSH Terms] AND "diagnosis" [MeSH Terms] AND "neutrophil-to-lymphocyte ratio" AND "platelet-to-lymphocyte ratio" AND "systemic immune-inflammation index" AND "systemic inflammation response index" AND "diagnostic accuracy" AND "sensitivity"[MeSH Terms] AND "specificity"[MeSH Terms]

Reference standard: "Fine needle aspiration cytology" [MeSH Terms] AND "histopathology" [MeSH Terms] AND "biopsy"[MeSH Terms] AND "Salivary gland cancer" [MeSH Terms] OR "oral tissue" AND ("diagnostic

accuracy" AND "sensitivity" [MeSH Terms] AND "specificity" [MeSH Terms]

Target condition: "Sensitivity AND specificity"[MeSH Terms] AND "salivary gland cancer cancer" [MeSH Terms] OR AND ("diagnostic accuracy") AND "inflammatory biomarkers" [MeSH Terms] AND ("comparative study" AND "randomized controlled trial" [MeSH Terms] AND "cross-sectional study" [MeSH Terms] OR "prospective study".

Screening process

According to the previously established procedure, two review authors conducted the search and screening. There were two stages to the article selection procedure. Two reviewers looked at each paper's abstract and title in phase one. Articles that satisfied the requirements for inclusion were not included. The same reviewers independently assessed and screened a subset of the full papers in Phase 2. Conversation was used to resolve any disputes. A third reviewer was consulted to make the final decision when two reviewers were unable to agree. The final choice was approved by all three authors. The final selection was based on consensus among all three authors, with an inter-reviewer reliability which was assessed using kappa (k) score =0.87.

Data extraction

Authors, study year, sample size (diseased/cases), disease stage, study design, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were the headings under which the information was retrieved. Each study's sensitivity and specificity data were collated, and variables such as true positive, true negative, false positive, and false negatives were manually calculated for the studies using the formulas below in cases where the authors did not supply the data.

a) False positive = (1-specificity) x (1- diseased cases/ total sample)

b) True negative = specificity x (1- diseased cases/ total sample)

c) True positive = sensitivity x diseased cases/ total sample

d) False negative = (1- sensitivity) x diseased cases/ total sample

Assessment of methodological quality

The quality assessment of diagnostic accuracy studies-2 (QUADAS-2) method was used to evaluate the risk of bias through its domains [17] in review manager (RevMan) software version 5.3 for risk of bias summary and applicability.

Statistical analysis

Each index test's explicitness and responsiveness were determined using crude data. Calculation of pooled explicitness with 95% confidence interval (CI), and pooled responsiveness for overall exactness was done through area under the curve (AUC) which is interpreted as follows: >/= 80% regarded as excellent, 70% - 80% as good, between 60% - 69% as fair, and < 60% as poor for a symptomatic test [18].

Data synthesis

Heterogeneity effect was evaluated through Higgins I^2 test which addresses the extent of fluctuation because of heterogeneity only [19]. As per I^2 test measurement the heterogeneity could be low (I^2 <50%) or high (I^2 >50%).

Additional analysis

Additional analysis with positive likelihood ratios (+LR) and negative likelihood ratios (-LR) was performed. When a test is positive, a positive likelihood ratio (+LR) between 2 and 5, 5 and 10, and >10 indicates a small, moderate, and large increase in the probability of disease; when a test is negative, a negative likelihood ratio (-LR) between 0.2 and 0.5, 0.2 and 0.1, and less than 0.1 indicates a small, moderate, and large decrease in the probability of disease [20].

Results

Study Selection

After database search (n=986), duplicates removal (n=75) and after application of eligibility criteria's, six studies were subjected to qualitative analysis and for meta-analysis as shown in Figure 1.

Study Characteristics

Table 2 shows descriptive details from included six studies [21-26] with data analyzed from an aggregate of 338 patients with various salivary gland tumors (Pleomorphic adenoma, Warthin tumors, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma and parotid gland malignancies). Included studies were cross-sectional in nature with retrospective data collection. Among included studies, three studies each were conducted in Turkey [21, 24, 26] and Italy [22, 23, 25]. Index tests evaluated were NLR, PLR, SII and SIRI with histopathology as reference standard. Study outcomes were expressed as sensitivity, specificity, predictive value and area under curve. Inflammatory biomarkers (index test) were compared with the reference standard. NLR had mean sensitivity and specificity of 57.6% and 81.22%. PLR had mean sensitivity and specificity of 58.1% and 67.2%. SII had mean sensitivity and specificity of 60.7% and 76.8% while SIRI had mean sensitivity and specificity of 81.5% and 73.2% respectively (Table 3).

Risk of Bias within Studies

The methodological quality of included studies were largely comparable. Majority of domains were at low risk. Patient selection was the only domain at high risk (consecutive patient selection was avoided) under risk of bias criteria and applicability concerns for Ikinciogullari et al., 2025 [26] as depicted in Figure 2 and 3.

Synthesis of Results/ Meta - analysis

Diagnostic accuracy of inflammatory biomarkers was evaluated as pooled sensitivity, specificity, PLR and NLR, DOR and AUC.

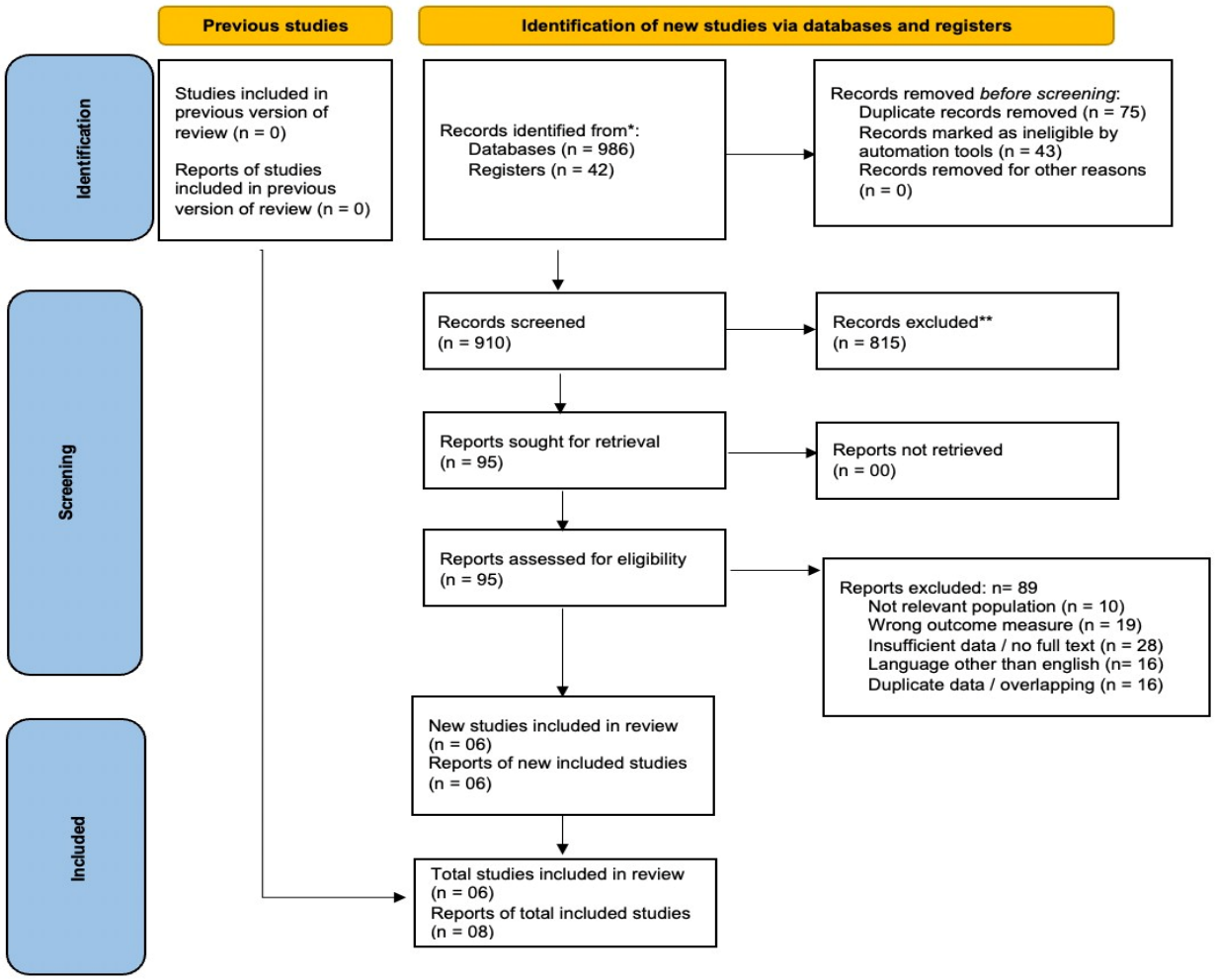

Figure 1. PRISMA Flow Diagram

A) NLR

As shown in Figure 4. (a), (b), data was evaluated from five studies [21,22,24 - 26] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.71 (CI 0.21- 0.98) and pooled specificity was 0.81 (CI 0.21- 1.00) with I^2 being 0%.

As shown in Figure 5. the sensitivity and 1-specificity, with standard error was plotted which showed an AUC of 0.83, signifying an excellent diagnostic efficacy of NLR in identifying intended target disease.

+LR of 3.36 (0.53 – 21.24) and -LR of 0.39 (0.10 – 1.57) was found, as seen in Supplementary Figures 1 (a) & (b), -LR indicated that NLR is 0.39 times more likely to have a negative disease detection than someone without it, pooled +LR showed that -LR is 3.36 times more likely to have a positive detection of the presence of disease than someone with it.

As shown in Supplementary Figure 2, the pooled DOR is 10.72 (0.45 – 254.58) suggesting that overall ability of index test in correctly diagnosing the target condition is

Table 1. Search Strategy

	Strategy
Population	"Salivary gland"[MeSH Terms] AND "salivary gland tumours" [MeSH Terms] OR "malignant transformation" [MeSH Terms] OR "Salivary gland neoplasm"[MeSH Terms] AND "high grade malignant tumours" OR "diagnosis"[MeSH Terms] OR "prognosis" [MeSH Terms]
Index test	"Inflammatory biomarkers"[MeSH Terms] AND "diagnosis" [MeSH Terms] AND "neutrophil-to-lymphocyte ratio" AND "platelet-to-lymphocyte ratio" AND “systemic immune-inflammation index” AND “systemic inflammation response index” AND "diagnostic accuracy" AND "sensitivity"[MeSH Terms] AND "specificity"[MeSH Terms]
Reference standard	“Fine needle aspiration cytology” [MeSH Terms] AND "histopathology" [MeSH Terms] AND "biopsy"[MeSH Terms] AND "Salivary gland cancer" [MeSH Terms] OR "oral tissue" AND ("diagnostic accuracy" AND "sensitivity" [MeSH Terms] AND "specificity" [MeSH Terms]
Target condition	"Sensitivity AND specificity"[MeSH Terms] AND "salivary gland cancer cancer" [MeSH Terms] OR AND ("diagnostic accuracy") AND "inflammatory biomarkers” [MeSH Terms] AND ("comparative study" AND "randomized controlled trial" [MeSH Terms] AND "cross-sectional study" [MeSH Terms] OR "prospective study".

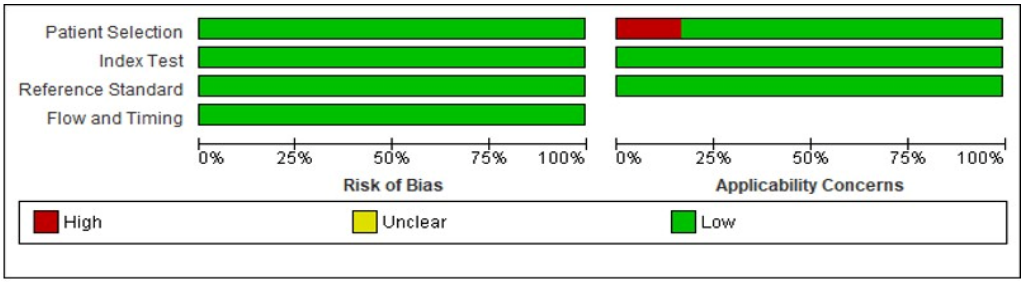

Figure 2. Risk of Bias Graph: as Percentages Across Studies

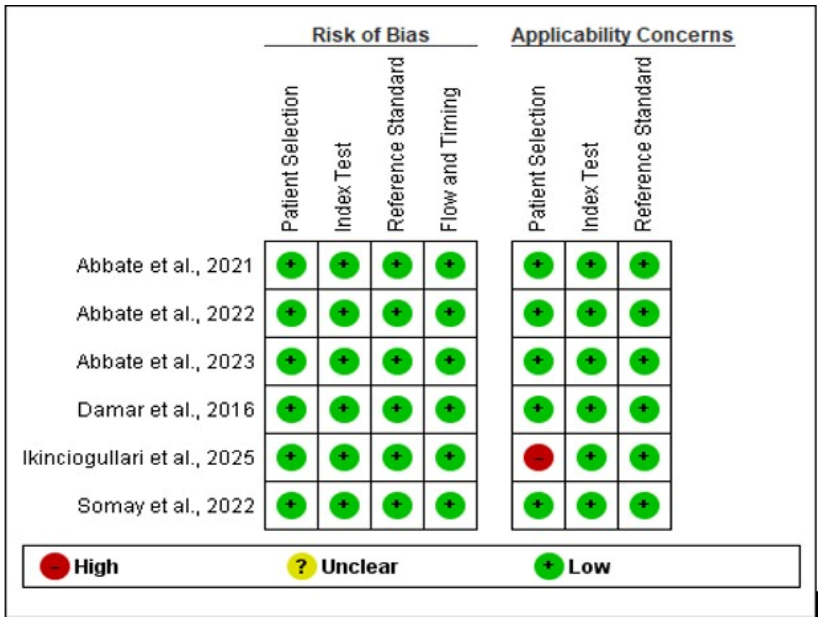

Figure 3. Overall Risk of Bias Summary

moderate to good.

B) PLR

As shown in Supplementary Figure 3, (a), (b), data was evaluated from two studies [22, 25, 26] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.61 (CI 0.07- 0.98) and pooled specificity was 0.72 (CI 0.12- 1.00) with I^2 being 0%.

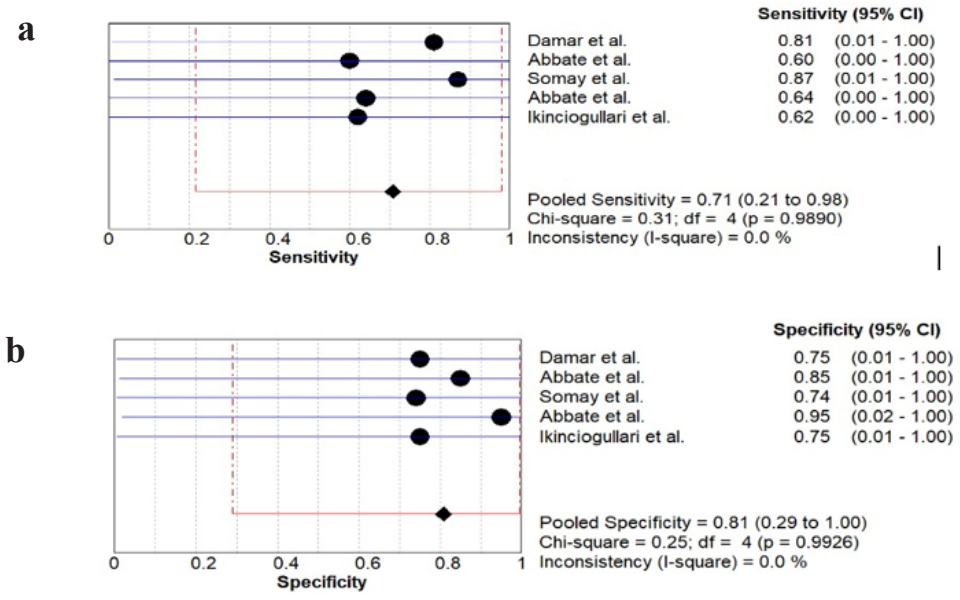

Figure 4. a. Pooled sensitivity of NLR. b, Pooled specificity of NLR

Table 2. Descriptive Study Details of Included Studies

Authors, year of study	Country	Sample size (Diseases/ total)	Patient's age (years)	Study Design	Salivary gland tumours	Index test	Reference Standard	Outcome evaluated	Main findings
Damar et al., 2016 [21]	Turkey	58 / 128	53 (16 – 87)	Retrospective data collection (2010 – 15)	Pleomorphic adenoma, Warthin tumours, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma	NLR	Histopathology	Sensitivity, Specificity, NPV	Preoperative NLR significantly higher in malignant and high-grade tumours
Abbate et al., 2021 [22]	Italy	47 / 191	55	Retrospective design (2016 -2020)	Pleomorphic adenoma, Warthin tumours, mucoepidermoid carcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma	NLR, PLR, SII	Histopathological diagnosis after surgical excision	Sensitivity, Specificity, PPV, NPV, AUC, SROC	SII and NLR significantly higher in malignant than benign tumours; SII had highest diagnostic accuracy among tested markers.
Abbate et al., 2022 [23]	Italy	74	74.5	Retrospective cohort (2011-2018)	Mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, carcinoma ex pleomorphic adenoma	NLR, PLR, SII, SIRI	Histopathological diagnosis	Sensitivity, Specificity, Accuracy	Higher NLR, SII, and SIRI predicted poorer prognosis
Somay et al., 2022 [24]	Turkey	51	52.43 (31 – 75)	Retrospective (2012 -2021)	Parotid gland malignancies	NLR	Histopathology	Sensitivity, Specificity, PPV, NPV	Higher baseline NLR associated with greater risk
Abbate et al., 2023 [25]	Italy	79 / 160	60	Retrospective cohort (2011 -2022)	Mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, carcinoma ex pleomorphic adenoma	SIRI, NLR, PLR	Histopathology	Sensitivity, Specificity, AUC	Combination of all biomarkers improved overall diagnostic accuracy
Ikinciogullari et al., 2025 [26]	Turkey	29 / 177	48.75 (12 – 90)	Retrospective cohort (2019 - 2023)	Pleomorphic adenoma, Warthin tumours, acinic cell carcinoma, mucoepidermoid carcinoma	NLR, PLR, SII, SIRI	Histopathology	Sensitivity, Specificity	SIRI outperformed NLR and PLR for differentiating benign subtypes; diagnostic discrimination moderate for malignancy.

AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value; SII, systemic inflammation response index; SIRI, systemic immune-inflammation index; SROC, summary receiver operating characteristics

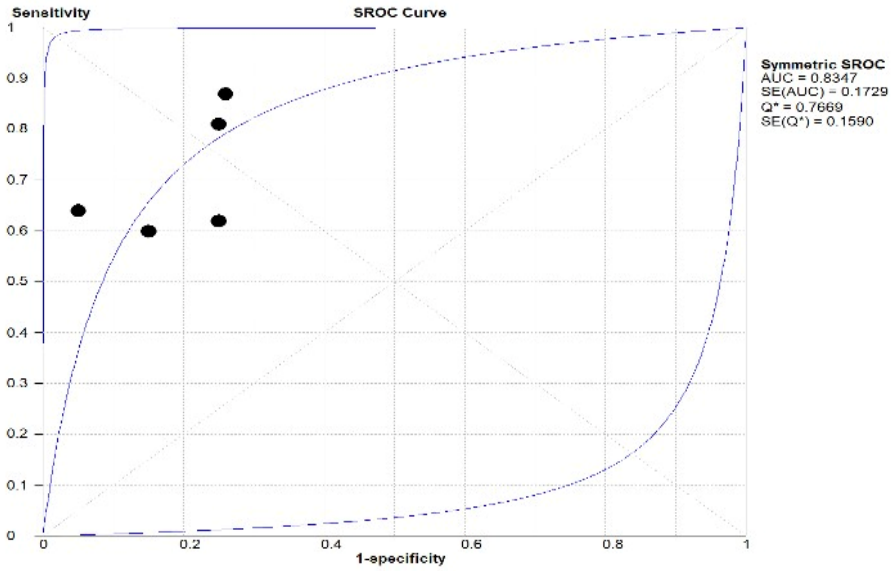

Figure 5. Overall Accuracy of Biomarkers for NLR

As shown in Supplementary Figure 4, the sensitivity and 1-specificity, with standard error was plotted which showed an AUC of 0.73, signifying an excellent diagnostic efficacy of PLR in identifying the intended target disease.

+LR of 2.07 (0.30 – 14.26) and -LR of 0.56 (0.12 – 2.57) was found, as seen in Supplementary Figures 5 (a) & (b), -LR indicated that PLR is 0.56 times more likely to have a negative disease detection than someone without it, pooled PLR showed that +LR is 2.07 times more likely to have a positive detection of the presence of disease than someone with it.

As shown in Supplementary Figure 6, the pooled DOR is 4.41 (0.12 – 164.89) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

C) SII

As shown in Supplementary Figure 7, (a), (b), data was evaluated from three studies [2, 25, 26] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.74 (CI 0.13- 1.00) and pooled specificity was 0.78 (CI 0.14- 1.00) with I^2 being 0%.

As shown in Supplementary Figure 8, the sensitivity and 1-specificity, with standard error was plotted which showed an AUC of 0.79, signifying an excellent diagnostic efficacy of SII in identifying the intended target disease.

Table 3. Diagnostic Accuracy Values of Biomarkers

Authors, year of study	True positive (TP)	True negative (TN)	False positive (FP)	False negative (FN)	Sensitivity (%)	Specificity (%)
			NLR			
Damar et al., 2016 [21]	0.81	0.75	0.25	0.19	81.25	75
Abbate et al., 2021 [22]	0.6	0.85	0.15	0.4	45	86
Somay et al., 2022 [24]	0.87	0.74	0.26	0.13	87.5	74.4
Abbate et al., 2023 [25]	0.64	0.95	0.05	0.36	36.4	95.7
Ikinciogullari et al., 2025 [26]	0.62	0.75	0.25	0.38	38	75
			PLR			
Abbate et al., 2021 [22]	0.55	0.85	0.15	0.45	45	86
Abbate et al., 2023 [25]	0.5	0.73	0.27	0.5	50.5	73.6
Ikinciogullari et al., 2025 [26]	0.79	0.58	0.42	0.21	79	42
			SII			
Abbate et al., 2022 [23]	0.7	0.97	0.03	0.3	30.3	97.9
Abbate et al., 2023 [25]	0.9	0.8	0.2	0.1	90	80.5
Ikinciogullari et al., 2025 [26]	0.62	0.52	0.48	0.38	62	52
			SIRI			
Abbate et al., 2022 [23]	0.9	0.8	0.2	0.1	90	80.5
Abbate et al., 2023 [25]	0.66	0.89	0.11	0.33	66.7	89.3
Ikinciogullari et al., 2025 [26]	0.58	0.5	0.5	0.42	58	50

+LR of 2.22 (0.25 – 20.09) and -LR of 0.39 (0.05 – 2.99) was found, as seen in Supplementary Figures 9 (a) & (b), -LR indicated that SII is 0.39 times more likely to have a negative disease detection than someone without it, pooled +LR showed that SII is 2.22 times more likely to have a positive detection of the presence of disease than someone with it.

As shown in Supplementary Figure 10, the pooled DOR is 7.35 (0.09 – 587.31) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 11(a), (b), data was evaluated from three studies [23,25, 26] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.71 (CI 0.11- 1.00) and pooled specificity was 0.73 (CI 0.12- 1.00) with I^2 being 0%.

As shown in Supplementary Figure 12, the sensitivity and 1-specificity, with standard error was plotted which showed an AUC of 0.76, signifying an excellent diagnostic efficacy of SIRI in identifying the intended target disease.

+LR of 2.02 (0.27 – 15.25) and -LR of 0.47 (0.03 – 3.30) was found, as seen in Supplementary Figures 13 (a) & (b), -LR indicated that SIRI is 0.47 times more likely to have a negative disease detection than someone without it, pooled +LR showed that SIRI is 2.02 times more likely to have a positive detection of the presence of disease than someone with it.

As shown in Supplementary Figure 14, the pooled DOR is 5.71 (0.11 – 289.60) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

Discussion

This systematic review and meta-analysis evaluated the diagnostic accuracy of systemic inflammatory biomarkers neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) for differentiating benign from malignant salivary gland tumors (SGTs). Across six retrospective studies comprising 338 patients, pooled analyses demonstrated moderate diagnostic performance, with AUC values ranging from 0.73 to 0.83 and DORs between 4.41 and 10.72. Collectively, these findings suggest that inflammatory biomarkers provide clinically meaningful, though not definitive, discrimination between benign and malignant SGTs.

Among the evaluated indices, NLR demonstrated the highest pooled AUC (0.83) and DOR (10.72), indicating relatively strong overall discriminative capacity. A pooled sensitivity of 0.71 and specificity of 0.81 suggest that -LR performs better in ruling in malignancy than ruling it out. The +LR (3.36) reflects a small-to-moderate increase in post-test probability when elevated, whereas the -LR (0.39) indicates limited ability to confidently exclude malignancy when values are low.

SII showed balanced sensitivity (0.74) and specificity (0.78), with an AUC of 0.79 and DOR of 7.35. Because SII integrates neutrophil, lymphocyte, and platelet counts, it may better capture the complex interplay between tumor-associated inflammation and host immune response. The inclusion of platelet counts markers of tumor-induced thrombopoiesis and angiogenic stimulation may enhance its biological plausibility in oncologic settings.

SIRI demonstrated pooled sensitivity of 0.71 and specificity of 0.73 (AUC 0.76; DOR 5.71). Although slightly lower in discriminative strength than NLR and SII, SIRI incorporates monocyte counts, which are closely linked to tumor-associated macrophage activity and microenvironment modulation. Interestingly, individual studies suggested SIRI performed particularly well in distinguishing benign subtypes such as pleomorphic adenoma and Warthin tumors, highlighting its potential utility in nuanced differential diagnosis.

PLR demonstrated the lowest overall diagnostic performance (AUC 0.73; DOR 4.41), suggesting that platelet-driven inflammatory response alone may be less discriminatory compared to composite indices.

Importantly, heterogeneity (I^2 = 0%) across pooled analyses was statistically low. However, this likely reflects the small number of studies rather than true clinical homogeneity, as confidence intervals were wide, indicating imprecision.

The findings of this review are consistent with broader oncologic literature in head and neck malignancies, where elevated NLR and SII have been associated with malignancy, aggressive biology, and poor prognosis. Studies in OSCC and laryngeal carcinoma have reported -LR, AUC values ranging from 0.78 to 0.85, closely paralleling the pooled AUC of 0.83 observed in this analysis. This consistency suggests that systemic inflammatory dysregulation may represent a conserved pathophysiological hallmark across epithelial and glandular malignancies of the head and neck region.

Damar et al. [21] first highlighted the diagnostic relevance of NLR in SGTs, demonstrating significantly elevated values in malignant lesions. Subsequent studies by Abbate et al. [22, 23, 25] expanded this concept by incorporating composite indices such as SII and SIRI. Notably, Abbate et al. [25] demonstrated that combining inflammatory biomarkers with fine-needle aspiration cytology (FNAC) improved overall diagnostic accuracy to 81.2%, significantly outperforming FNAC alone. This finding underscores the complementary rather than substitutive role of systemic biomarkers.

Furthermore, the recent scoping review by Migliorelli et al. [27] emphasized the prognostic value of inflammatory markers in salivary gland carcinoma but highlighted the absence of quantitative synthesis regarding diagnostic accuracy. The present meta-analysis fills that gap by providing pooled sensitivity, specificity, and likelihood ratios. While Migliorelli et al. [27] focused primarily on survival and recurrence outcomes, the current review extends the evidence base to preoperative diagnostic discrimination, thereby broadening the clinical applicability of these markers.

However, unlike some prognostic studies that reported stronger associations (particularly for SIRI), the pooled diagnostic metrics in this review demonstrate moderate rather than high accuracy. This discrepancy likely reflects differences in endpoint definition (prognostic vs

diagnostic utility) and threshold selection.

The integration of inflammatory biomarkers into preoperative diagnostic algorithms could be particularly valuable in cases categorized under indeterminate cytological diagnoses within the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). Given that up to 25% of FNAC results fall into ambiguous categories, adjunctive biomarkers may assist in risk stratification and surgical decision-making.

Elevated NLR or SII values may increase clinical suspicion for malignancy, prompting earlier surgical intervention or more extensive imaging. Conversely, low values may support conservative management in selected cases. Importantly, because these indices are derived from routine complete blood counts, they are inexpensive, widely accessible, and easily reproducible—even in resource-limited settings.

Nevertheless, their moderate likelihood ratios indicate that inflammatory biomarkers should not be used as standalone diagnostic tools. Rather, they are best conceptualized as adjunctive risk modifiers within a multimodal diagnostic framework incorporating imaging, cytology, and clinical examination.

The biological basis of these findings aligns with established mechanisms of cancer-related inflammation. Neutrophilia reflects tumor-promoting inflammatory signaling and angiogenesis, while lymphopenia indicates impaired anti-tumor immunity. Platelets facilitate tumor cell survival and metastasis, and monocytes contribute to tumor-associated macrophage differentiation. Composite indices such as SII and SIRI may therefore more comprehensively capture tumor–host immune interactions than single-cell ratios.

However, systemic inflammatory markers are inherently nonspecific and may be influenced by infections, autoimmune conditions, metabolic disorders, and medications—factors inconsistently controlled across included studies.

Limitations

several limitations warrant careful consideration:

1. Retrospective Design: All included studies were retrospective, introducing potential selection and information bias.

2. Small Sample Sizes: The cumulative sample (n=338) remains modest, limiting statistical power and precision.

3. Wide Confidence Intervals: Despite low statistical heterogeneity, pooled estimates demonstrated broad confidence intervals, reflecting imprecision.

4. Variable Cut-off Values: Substantial variability in threshold selection precluded standardization and may have influenced pooled estimates.

5. Geographic Concentration: Studies were limited to Turkey and Italy, potentially limiting ethnic and demographic generalizability.

6. Confounding Factors: Inflammatory comorbidities were not uniformly excluded.

7. Histologic Heterogeneity: Grouping diverse malignant subtypes may obscure subtype-specific inflammatory patterns.

8. Limited Combined Analysis: Only one study evaluated combined biomarker–FNAC models, restricting conclusions regarding synergistic diagnostic performance.

9. Potential Publication Bias: The small number of studies precluded robust publication bias assessment.

Future Recommendations

future research should prioritize:

1. Large-scale, prospective, multicenter diagnostic accuracy trials.

2. Standardization of biomarker cut-off values using uniform ROC methodology.

3. Subgroup analyses stratified by histological subtype and tumor grade.

4. Integration of inflammatory markers with FNAC, radiomics, and molecular profiling.

5. Development of composite predictive algorithms using machine learning approaches.

6. Evaluation of dynamic biomarker changes pre- and post-operatively for recurrence monitoring.

7. Establishment of population-specific reference ranges to enhance external validity.

Prospective validation studies incorporating predefined thresholds and blinded outcome assessment are essential before clinical implementation.

In conclusion, this systematic review and meta-analysis demonstrate that systemic inflammatory biomarkers particularly NLR and SII exhibit moderate diagnostic accuracy in differentiating benign from malignant salivary gland tumors. While not sufficient as standalone diagnostic tools, they represent promising, low-cost adjuncts that may enhance diagnostic confidence, particularly in cytologically indeterminate cases. The current evidence base remains limited by retrospective design and methodological variability; therefore, robust prospective validation is required prior to routine clinical adoption.

Author Contribution Statement

All authors contributed equally in this study.

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Was the study registered in any registration dataset (for clinical trials, guidelines, meta-analysis)

Study registered in PROSPERO database

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