SYSTEMATIC / NARRATIVE REVIEW ARTICLE

# The diagnostic and prognostic role of miRNA-21 and miRNA-223 in laryngeal squamous cell carcinoma: A systematic review with exploratory meta-analysis

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## ABSTRACT

**Introduction: Laryngeal squamous cell carcinoma (LSCC) is a common head and neck malignancy often diagnosed at advanced stages, resulting in poor prognosis and high recurrence rates. Circulating microRNAs (miRNAs), particularly miR-21 and miR-223, have emerged as promising non-invasive biomarkers because of their stability in body fluids and involvement in tumour biology. This study systematically reviewed the diagnostic and prognostic significance of circulating miR-21 and miR-223 in LSCC and performed an exploratory diagnostic meta-analysis of miR-21 when sufficient quantitative data were available.**

**Materials and Methods: A systematic search was conducted in PubMed, Google Scholar, and SciSpace. Eligible studies evaluated circulating miR-21 and/or miR-223 in serum or plasma samples from LSCC patients and assessed their association with diagnostic or prognostic outcomes. Data regarding expression levels, diagnostic performance, and survival outcomes were synthesized qualitatively. Exploratory diagnostic meta-analysis was performed by pooling Area Under the Curve (AUC) values using the inverse variance method. Heterogeneity was assessed using the $I^2$ statistic, and a random-effects model was applied.**

**Results: Five studies were included in the qualitative synthesis. Elevated miR-21 expression was consistently associated with advanced tumour stage, nodal involvement, recurrence, and poorer survival outcomes. miR-223 demonstrated dynamic changes following treatment and recurrence, suggesting potential utility for disease monitoring. Only two studies were eligible for exploratory diagnostic meta-analysis, yielding an exploratory pooled AUC of 0.77 (95% CI: 0.50–1.04) with substantial heterogeneity ($I^2$ = 83%).**

**Conclusion: Circulating miR-21 and miR-223 show potential clinical utility in LSCC, particularly for prognosis and recurrence monitoring. However, current evidence remains limited and heterogeneous, and the quantitative findings should be interpreted cautiously.**

**KEYWORDS:**
*LSCC; microRNA-21; microRNA-223; prognosis; biomarker*

## INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is the most common malignant tumour of the larynx and remains a major global health problem. Despite advances in surgery, radiotherapy, and chemotherapy, the prognosis of LSCC patients remains suboptimal because many cases are diagnosed at advanced stages and are associated with heterogeneous treatment responses and high recurrence rates. These challenges highlight the urgent need for reliable and minimally invasive biomarkers to improve prognostic assessment, disease monitoring, and post-treatment surveillance.[1-2]

MicroRNAs (miRNAs) are small endogenous non-coding RNAs consisting of approximately 22 nucleotides that regulate gene expression at the post-transcriptional level by promoting messenger RNA degradation or inhibiting translation. miRNAs are involved in multiple biological processes, including cell proliferation, apoptosis, differentiation, invasion, and metastasis. Dysregulated miRNA expression has been widely reported in various human malignancies, including head and neck squamous cell carcinoma (HNSCC), and may reflect underlying tumour biology.[3-4]

Circulating miRNAs detected in serum and plasma have attracted considerable interest as minimally invasive cancer biomarkers because of their relative stability in body fluids. These molecules are protected from RNase degradation through encapsulation within exosomes, microvesicles, or protein complexes, allowing reliable detection in peripheral blood samples.[5-6]

Previous studies in HNSCC have demonstrated that circulating miRNAs may correlate with tumour burden, lymph node metastasis, treatment response, and survival outcomes. Among these, miR-21 is one of the most extensively studied oncomiRs and has been associated with tumour progression and poor prognosis across multiple HNSCC subtypes. In contrast, miR-223 has been implicated in inflammatory regulation and recurrence monitoring, suggesting potential utility in longitudinal disease surveillance.[7-8] However, methodological variability across studies, including differences in specimen processing, normalization controls, detection platforms, and cut-off determination, remains a major challenge for clinical translation.

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A previous systematic review entitled "*Diagnostic and Prognostic Value of microRNAs in Patients with Laryngeal Cancer*" demonstrated the emerging role of miRNAs as potential biomarkers in laryngeal malignancies. However, the review evaluated heterogeneous miRNAs collectively, included both tissue and circulating specimens, and combined diagnostic and prognostic objectives. Consequently, the specific prognostic and monitoring significance of circulating miR-21 and miR-223 in LSCC remains incompletely characterized.[9-12]

Therefore, this study aimed to systematically review the available evidence regarding circulating miR-21 and miR-223 in LSCC, with emphasis on their prognostic and monitoring significance. In addition, an exploratory diagnostic meta-analysis of miR-21 was performed when sufficient quantitative data were available.

## MATERIALS AND METHODS

### Registration

This study was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) checklist. The study protocol has been registered with PROSPERO (registration number: CRD420251246629). As this study is a systematic review, ethical approval and patient consent are not required.

### Search Strategy

A comprehensive literature search was conducted in PubMed, Google Scholar, and SciSpace to identify relevant studies evaluating miR-21 and miR-223 in LSCC. PubMed was selected as the principal biomedical database because it incorporates MEDLINE-indexed literature and provides broad coverage of biomedical publications.

Although EMBASE was not directly searched because of access limitations, supplementary searches using Google Scholar and SciSpace were conducted to maximize retrieval sensitivity and minimise the likelihood of missing relevant studies, as these platforms provide broad coverage of academic publications. Articles were selected based on relevance, availability of full text, and fulfilment of the inclusion criteria. Eligible studies involved human patients, evaluated miR-21 and/or miR-223 expression in serum, plasma, and/or tumour tissue samples, and examined their association with diagnostic or prognostic outcomes in LSCC (3,7). Through this multi-step search strategy, we aimed to ensure a comprehensive literature search and minimise the risk of overlooking relevant studies.

Inclusion criteria included human studies involving patients with LSCC that evaluated miR-21 and/or miR-223 expression in circulating samples and/or tumour tissue and analysed their association with diagnostic or prognostic outcomes, such as survival, tumour stage, or recurrence. Only studies with full text available in English were considered. Exclusion criteria included reviews, editorials, and case reports; in vitro or animal-only studies; studies without diagnostic or prognostic data; and studies with insufficient methodological details or unavailable full text.

1. Search Strategy (PubMed):
   ((miRNA-21[Title/Abstract] OR microRNA-21[Title/Abstract] OR miR-21[Title/Abstract]) OR (miRNA-223[Title/Abstract] OR microRNA-223[Title/Abstract] OR miR-223[Title/Abstract])) AND (laryngeal[Title/Abstract] OR larynx[Title/Abstract]) AND (squamous cell carcinoma[Title/Abstract] OR LSCC[Title/Abstract] OR cancer[Title/Abstract]) AND (prognosis[Title/Abstract] OR survival[Title/Abstract] OR biomarker[Title/Abstract] OR prognostic[Title/Abstract]).
2. Search Strategy (Google Scholar & SciSpace):
   ((miRNA-21[Title/Abstract] OR microRNA-21[Title/Abstract] OR miR-21[Title/Abstract]) OR (miRNA-223[Title/Abstract] OR microRNA-223[Title/Abstract] OR miR-223[Title/Abstract])) AND (laryngeal[Title/Abstract] OR larynx[Title/Abstract]) AND (squamous cell carcinoma[Title/Abstract] OR LSCC[Title/Abstract] OR cancer[Title/Abstract]) AND (prognosis[Title/Abstract] OR survival[Title/Abstract] OR biomarker[Title/Abstract] OR prognostic[Title/Abstract]).

### Data Extraction

Data extraction was performed independently by two reviewers (KA and DA), with verification by a third reviewer (AH) to ensure accuracy and consistency. Extracted information included key study characteristics (first author, year of publication, country, study design prospective or retrospective, cohort or case-control sample size for cases and controls, patient demographics such as age, gender, and TNM stage, as well as follow-up duration). Biomarker-related data were also collected, including the specific miRNAs analysed (miR-21, miR-223, or both), sample type (tissue, serum, or plasma), detection method (qRT-PCR, microarray, or sequencing), normalization controls (U6, GAPDH, or cel-miR-39), and reported expression levels with their corresponding cut-off values. Outcome data encompassed prognostic indicators such as overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), recurrence rates, hazard ratios (HR) with 95% confidence intervals (CI), diagnostic performance metrics including Area Under the Curve (AUC), sensitivity, and specificity, as well as statistical significance values (p-values). Studies were excluded from the quantitative meta-analysis if they did not report AUC, sensitivity, specificity, or sufficient data to calculate SE such as the studies by Hu et al.[4], Falco et al.[6] and Hou et al.[7], and (which evaluated miR-223 instead of miR-21) to ensure the validity of the diagnostic analysis.

### Statistical Analysis

Statistical analysis focused on a meta-analysis of the diagnostic accuracy of circulating miR-21 in laryngeal squamous cell carcinoma (LSCC). This diagnostic meta-analysis was conducted using Area Under the Curve (AUC) values and Standard Errors (SE) derived from the 95% Confidence Intervals (CI) reported in the primary studies. The Inverse Variance method was applied to pool individual AUC estimates from each study. Prior to pooling, statistical heterogeneity among studies was rigorously assessed using the $I^2$ statistic. Heterogeneity was considered substantial if $I^2$ exceeded 50%, in which case a Random-Effects Model was applied to combine the data. A random-effects model was selected because it is more conservative and appropriate

**Table I: Study Overview**

| Author (Year) | miRNA Studied | Objective | Methods | Key Findings | Strengths | Weaknesses |
|---|---|---|---|---|---|---|
| Gao et al.[3] | miR-21 | To assess prognostic value of serum miR-21 in LSCC | Serum qRT-PCR on 236 LSCC patients in a multicenter study | High miR-21 levels were significantly associated with advanced stage and poor 5-year overall survival. AUC for miR-21/10a ratio was 0.896 | Large cohort; multicenter design; includes survival data | No post-treatment monitoring or validation cohort |
| Hu et al.[4] | miR-21 | To evaluate miR-21 expression in tumour tissue and association with prognosis | Tumour tissue qRT-PCR in 46 LSCC patients | miR-21 was significantly overexpressed in tumour tissues and associated with worse 5-year survival. AUC = 0.886 | Clear comparison with adjacent normal tissue; includes survival correlation | Tissue-only analysis; no circulating marker data |
| Re et al.[5] | miR-21-5p | To determine expression of miR-21-5p and its relation to recurrence | Tumour tissue qRT-PCR on 43 LSCC patients | 83.7% of samples showed miR-21-5p overexpression; significantly associated with nodal involvement and recurrence | Targeted marker study; includes clinical-pathological correlation | No blood data; relatively small sample size |
| Falco et al.[6] | miR-223 | To develop a serum diagnostic miRNA signature including miR-223 | Serum qRT-PCR on 130 LSCC patients and healthy controls | miR-223 was part of a high-performing diagnostic panel. Panel AUC = 0.89, sensitivity 88%, specificity 90% | Well-validated diagnostic panel; good control comparison | No survival or longitudinal data; cross-sectional study |
| Hou et al.[7] | miR-21, miR-223 | To examine circulating miRNAs pre- and post-treatment in LSCC | qRT-PCR in plasma and tumour tissue from 25 LSCC patients | miR-223 levels decreased after surgery and increased again with recurrence. miR-21 remained elevated | Shows dynamic behavior of miRNAs; matched tissue and plasma data | Small sample; short follow-up; limited statistical power |

when inter-study variability is substantial. Finally, the test for overall effect was performed using the Z statistic to evaluate the significance of the pooled diagnostic effect, with $p<0.05$ considered indicative of a statistically significant diagnostic role.

### Quality Assessment and Biomarker Measurement

Methodological quality and risk of bias were independently assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Particular attention was given to participant selection, outcome assessment, and biomarker measurement methods, including specimen type, qRT-PCR platform, normalization controls, and cut-off determination. Considerable methodological heterogeneity across studies was identified and taken into account during interpretation of the findings.

## RESULTS

### Study Selection

A total of 566 records were identified through database searching in PubMed, Google Scholar, and SciSpace. After removal of 156 duplicate records, 410 studies underwent title and abstract screening, of which 358 were excluded for irrelevance to the study objective. Subsequently, 52 full-text articles were assessed for eligibility. Of these, 47 studies were excluded because they: (1) evaluated tissue miRNAs without relevant diagnostic or prognostic outcomes related to the objectives of the present review, (2) lacked prognostic or recurrence-related outcomes, (3) did not specifically investigate miR-21 or miR-223, (4) were review or experimental-only studies, or (5) did not provide sufficient quantitative data for meta-analysis. The majority of excluded studies either focused exclusively on tissue-based biomarkers or did not provide sufficient outcome data relevant to the objectives of the present review.

Five studies fulfilled the criteria for qualitative systematic review and were included in the narrative synthesis. However, only two studies (Gao et al.[3] and Re et al.[5]) provided extractable diagnostic parameters, including Area Under the Curve (AUC) values and variance-related measures, suitable for exploratory quantitative pooling. The remaining studies were included only in the qualitative synthesis because they did not provide sufficient statistical parameters required for diagnostic meta-analysis, such as confidence intervals or standard error values for AUC estimates. Therefore, the quantitative synthesis was limited to the two studies with complete diagnostic data and should be interpreted as exploratory rather than confirmatory evidence (Figure 1).

### Study Characteristics

Table I summarizes five studies evaluating the diagnostic and prognostic significance of miR-21 and miR-223 in LSCC using circulating and/or tissue-based specimens. Although the primary focus of this review was circulating biomarkers,

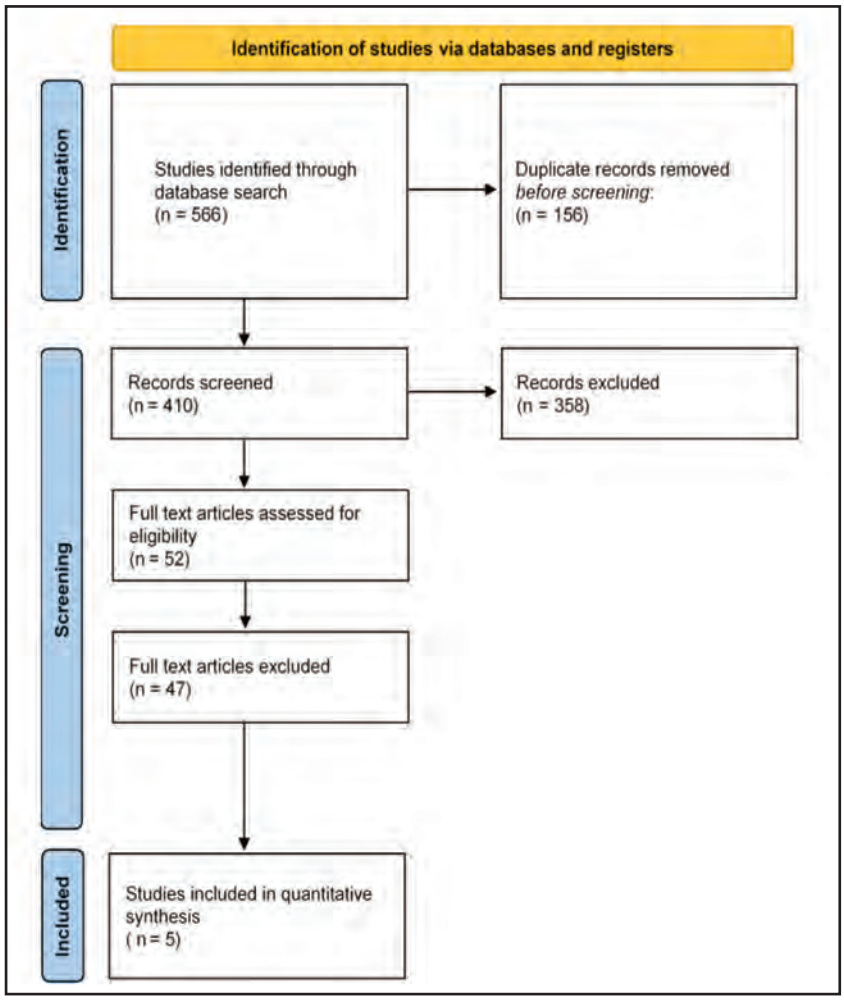


**Fig. 1:** PRISMA flow diagram

**ROBINS-I Risk of Bias Assessment**
**miRNA-21 and miRNA-223 in Laryngeal Squamous Cell Carcinoma Studies**

| Study | Bias due to confounding | Bias in selection of participants | Bias in classification of interventions | Bias due to deviations from intended intervention | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Hu et al. 2014 | Moderate | Moderate | Low | Low | Moderate | Moderate | Moderate | Moderate |
| Re et al. 2017 | Moderate | Moderate | Low | Low | Low | Moderate | Moderate | Moderate |
| Gao et al. 2020 | Moderate | Low | Low | Low | Low | Low | Moderate | Moderate |
| Falco et al. 2024 | Moderate | Low | Low | Low | Low | Low | Moderate | Moderate |
| Hou et al. 2015 | Serious | Moderate | Low | Low | Moderate | Moderate | Moderate | Serious |

**Fig. 2:** Risk of Bias

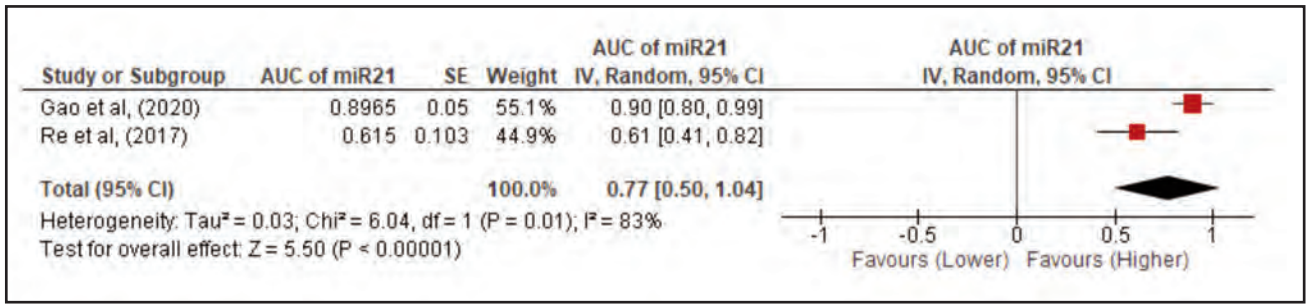


**Fig. 3:** Exploratory diagnostic meta-analysis of miR-21

several eligible studies evaluating tissue-based miRNA expression were also included because they provided clinically relevant prognostic data related to LSCC progression and recurrence.

Gao et al.[3] assessed circulating serum miR-21 and demonstrated strong diagnostic performance (AUC=0.896), along with significant prognostic relevance for five-year survival. Re et al.[5] evaluated miR-21-5p expression in FFPE tissue samples and reported moderate diagnostic accuracy (AUC=0.615), with higher expression significantly associated with advanced tumour stage, nodal involvement, and recurrence. Hu et al.[4] also examined tissue miR-21 expression and reported diagnostic potential (AUC=0.772), although incomplete statistical reporting prevented inclusion in the quantitative meta-analysis.

Falco et al.[6] focused on circulating miR-223 and demonstrated high diagnostic accuracy as part of a serum miRNA panel, while Hou et al.[7] investigated perioperative fluctuations in circulating miR-21 and miR-223 but did not provide AUC values or long-term prognostic metrics. Due to variability in study design and reporting, only two studies (Gao et al.[3]; Re et al.[5]) provided extractable AUC values with variance-related parameters suitable for exploratory quantitative pooling.

**Risk of Bias Assessment**

Based on the ROBINS-I assessment of the five studies evaluating the expression of miR-21 and miR-223 in laryngeal squamous cell carcinoma, the bias due to confounding domain was predominantly rated as *moderate risk*, except for one study (Hou et al.[7]), which showed a *serious risk* due to insufficient control of important confounding factors. In the bias in selection of participants domain, four studies were rated as *moderate risk*, whereas one study (Gao et al.[3]) demonstrated *low risk* because the participant selection process was described more clearly and applied in a more structured manner. For bias in classification of interventions, all studies were assessed as *low risk*, as the classification of miRNA expression was consistently conducted using validated laboratory techniques. The bias due to deviations from intended interventions domain was also rated as *low risk* across all studies, with no indications of deviations that could influence the estimated effect. The bias due to missing data domain showed some variation, with three studies rated as *low risk* and two studies as *moderate risk* due to incomplete reporting of data. In the bias in measurement of outcomes domain, all studies were rated as *moderate risk*, largely because of potential variability in outcome assessment methods and limited information regarding outcome assessor blinding. Meanwhile, in the bias in selection of reported results domain, all studies were judged to have *moderate risk*, as none provided preregistered protocols, and selective reporting could not be ruled out. Overall, four studies were classified as having a *moderate risk* of bias, while one study (Hou et al.[7]) demonstrated a *serious* overall risk. These findings indicate that the overall quality of evidence is moderate and should be interpreted with appropriate caution (Figure 2).

**Exploratory Diagnostic Meta-analysis of miR-21**

The pooled analysis suggested potential clinical discriminatory value of miR-21 in LSCC; however, interpretation remains limited by substantial heterogeneity and the small number of eligible datasets. The pooled AUC was 0.77 (95% CI: 0.50–1.04), suggesting performance above chance level in differentiating LSCC from non-LSCC cases. The overall effect was statistically significant ($Z=5.50$, $p<0.001$). However, several important limitations should be considered. First, the high heterogeneity ($I^2 = 83\%$) indicates substantial variability among studies, justifying the use of a random-effects model and warranting cautious interpretation of the pooled estimate. Second, the wide confidence interval, with the lower bound approaching 0.50, reflects considerable imprecision and uncertainty regarding the true discriminatory performance of miR-21 (Figure 3).

Importantly, although five studies evaluating miR-21 were identified in the systematic review, only two studies provided sufficient extractable quantitative data for meta-analysis. This limitation was primarily due to incomplete reporting of statistical parameters, including missing confidence intervals (Hu et al.[4]), absence of AUC reporting (Hou et al.[7]), or differences in biomarker focus and study endpoints (Falco et al.[6], focusing on miR-223). Furthermore, the included studies varied considerably in terms of clinical objectives, specimen types, laboratory methodologies, normalization controls, and outcome measures. These factors constrained the robustness of the pooled analysis and likely contributed to the substantial heterogeneity observed. Therefore, the findings of this meta-analysis should be interpreted cautiously and considered exploratory and hypothesis-generating rather than definitive evidence of clinical utility.

## DISCUSSION

This systematic review demonstrates the potential clinical value of miR-21 and miR-223 as non-invasive circulating biomarkers in laryngeal squamous cell carcinoma (LSCC). Across all included studies, miR-21 was consistently found to be overregulated in LSCC patients, both in tumour tissue and serum or plasma samples, and strongly correlated with advanced clinical stage, lymph node metastasis, and poor prognosis. In a multicentre study by Gao et al.[3], involving 236 LSCC patients, high serum levels of miR-21 and miR-21/miR-10a ratio were significantly associated with poor survival outcomes, with an AUC of 0.896, supporting its prognostic relevance. Similarly, Hu et al.[4] reported that elevated miR-21 expression in tumour tissues was linked to lower 5-year survival and higher recurrence rates, with an AUC of 0.886 for diagnostic performance. Re et al.[5] further validated the role of miR-21-5p in LSCC, showing that 83.7% of tumour tissue samples expressed high miR-21-5p, which correlated with lymph node involvement and recurrence.[5]

miR-21 functions as an oncomiR that negatively regulates tumour suppressor genes, contributing to cellular proliferation, migration, and invasion in malignancies. Although mechanistic insights were not extensively evaluated in these clinical studies, the observed associations between miR-21 levels and tumour aggressiveness provide strong clinical support for its use as a prognostic tool. Importantly, the fact that miR-21 is measurable in serum or plasma underscores its feasibility for non-invasive clinical applications, such as early diagnosis, risk stratification, and post-treatment surveillance.[3,5]

On the other hand, miR-223 was not studied as widely but showed a distinctly dynamic pattern in relation to treatment response and disease recurrence. Hou et al. found that circulating miR-223 levels declined significantly after surgical resection and increased again in patients who experienced recurrence, suggesting its utility as a real-time biomarker for monitoring LSCC progression or relapse.[7] This behaviour supports its potential role in longitudinal follow-up, particularly in post-operative patients who require sensitive and specific tools for recurrence detection. Furthermore, Falco et al. identified miR-223 as part of a 5-miRNA serum diagnostic signature in 130 LSCC patients. This panel achieved an AUC of 0.89, sensitivity of 88%, and specificity of 90%, indicating strong diagnostic potential, although miR-223 was not analysed independently in that study.[6]

miR-21 is one of the most widely studied oncomiRs across head and neck cancers, including HNSCC broadly and LSCC specifically. Its upregulation has been documented not only in laryngeal carcinoma tissue but also in circulating blood components of HNSCC patients, where miR-21 levels decreased after surgical resection in those with good prognosis but remained high in cases with poor outcome. This supports the relevance of miR-21 as a dynamic circulating biomarker for disease monitoring.[10]

Biologically, miR-21 is known to target tumour suppressor pathways such as PTEN and related downstream signalling, which promotes proliferation and inhibits apoptosis. In LSCC, exosomal miR-21 correlates with reduced PTEN expression, indicating a possible negative regulatory effect on tumour suppressor signalling and contributing to invasive behaviour. This mechanistic insight strengthens its potential utility beyond mere association.[11]

In contrast, miR-223 behaves differently. While many reports of circulating miR-223 in HNSCC suggest that this miRNA can be upregulated in tumour tissues, clinical findings in LSCC serum have shown a decrease in exosomal miR-223 relative to healthy controls.[11] This suggests that miR-223 may play a tumour-suppressive role in the laryngeal carcinoma context, possibly through modulation of the inflammatory tumour microenvironment. Recent data in broader HNSCC research further indicate that dynamic changes in circulating miR-223 post-treatment may correlate with recurrence risk, highlighting its utility in longitudinal surveillance strategies.[10] miR-223 has also shown potential as a non-invasive biomarker in head and neck cancers. In a study by Perdomo et al., low miR-223 expression was associated with an increased risk of metastasis and poor prognosis, although its association was not as strong as that of miR-21. miR-223 is believed to play a role in modulating immune and inflammatory responses through its influence on the NF-κB pathway and the regulation of myeloid cells. The loss of miR-223 regulation may contribute to tumour aggressiveness and resistance to therapy.[2]

Modern research in HNSCC emphasizes the emerging role of circulating miRNAs as part of precision oncology approaches, particularly for real-time monitoring of treatment response and recurrence. A recent *observational prospective study* in HNSCC patients demonstrated that circulating miR-21-5p and other miRNAs strongly associate with tumour burden and stage, supporting their potential as markers for ongoing disease monitoring and tailoring of therapy decisions.[12]

Previous systematic reviews have evaluated the role of multiple microRNAs in laryngeal cancer; however, these studies generally included heterogeneous microRNA targets and broader diagnostic or prognostic objectives. In contrast, the present review specifically focused on circulating miR-21 and miR-223 as prognostic biomarkers in LSCC. Although only a limited number of eligible studies were identified, this reflects the current scarcity of focused evidence on these biomarkers and highlights the need for further standardized large-scale investigations. Despite the limited number of included studies, this focused synthesis remains important to summarize the currently available evidence and identify existing research gaps regarding the prognostic utility of miR-21 and miR-223 in LSCC.

Several limitations of this study should be acknowledged. First, the number of eligible studies was limited, with only five studies included in the systematic review and only two studies providing sufficient diagnostic accuracy data for quantitative synthesis. Second, considerable heterogeneity was observed among the included studies, particularly regarding specimen types, laboratory methodologies, normalization controls, patient populations, and reported clinical outcomes. Third, most included studies were observational in design and had moderate risk of bias, which may affect the robustness and generalizability of the findings. In addition, the small

number of studies precluded subgroup analysis and publication bias assessment. Therefore, the results of this meta-analysis should be interpreted cautiously and considered hypothesis-generating rather than definitive evidence for immediate clinical implementation. Further large-scale, standardized, and prospective studies are needed to validate the prognostic utility of miR-21 and miR-223 in LSCC.

## CONCLUSION

Current evidence suggests that miR-21 is associated with aggressive clinicopathological features and poorer prognosis in LSCC, while miR-223 may have potential utility in recurrence monitoring. Nevertheless, the available evidence remains limited due to the small number of eligible studies, methodological heterogeneity, and incomplete quantitative reporting. Therefore, the findings should be interpreted cautiously, and further large-scale, standardized, and prospective studies are required before these biomarkers can be translated into routine clinical practice.

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## CONFLICT OF INTEREST

None.

## ETHICAL APPROVAL

Not required.

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