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Serum and salivary microRNA-31 in early detection of head and neck squamous cell carcinoma: A systematic review and meta-analysis

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Abstract

Background: Oral cancer is the sixth most common cancer in the world and the third most common cancer in developing countries. Early detection of oral cancer can reduce mortality in several ways. The aim of the present study was to combine the quantitative results of various studies concerning serum and salivary microRNAs for early diagnosis of head and neck squamous cell carcinoma (HNSCC).

Methods: This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guideline. We searched all the relevant english studies in international databases of PubMed/Medline, Scopus, Web of Science, Cochrane, ProQuest, Embase, and Wiley until February 2022. A random-effects model was used to estimate the pooled odds ratio (OR) and its corresponding 95% confidence interval (CI) for each study. A total of 672 articles were found. After screening, 93 articles were approved for systematic review. Finally, five completely relevant articles were examined in the meta-analysis.

Results: Considering all studies regarding miRNAs, the combined results indicated that AUC = 0.73, with a sensitivity of 71.68% and a specificity of 69.95%, could be used for HNSCC diagnosis. Due to the moderate sensitivity and specificity of miRNAs, they may be able to confirm or exclude suspected cases of this disease, enhancing their utility as clinical diagnostic indicators.

Conclusion: The available data provide evidence that miRNAs, especially MiR-31 expression in the saliva, serum, or plasma, can be used as a diagnostic biomarker for HNSCC patients. However, controlled clinical trials with large sample sizes are needed to validate different miRNAs.

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Highlights

What is current knowledge?
Current knowledge indicates that early detection of head and neck squamous cell carcinoma (HNSCC) can reduce mortality. The study aimed to combine results from various research studies on serum and salivary microRNAs for early HNSCC diagnosis. The systematic review and meta-analysis identified miRNAs, especially MiR-31, as potential diagnostic biomarkers for HNSCC patients.

What is new here?
The study's findings suggest that miRNAs, specifically MiR-31, could serve as diagnostic indicators for HNSCC, potentially confirming or excluding suspected cases and enhancing their clinical diagnostic utility. However, controlled clinical trials with large sample sizes are needed to validate different miRNAs as diagnostic biomarkers for HNSCC.

Introduction

Among all cancers, oral cancer is the sixth most common cancer in the world, coming in third among developing countries (1). The most common type of oral cancer is squamous cell carcinoma (OSCC), which accounts for 90% of all oral cancers and is estimated to affect more than 500,000 people annually (2, 3).

According to recent statistics on cancer deaths among people, early detection is one of the most effective ways to reduce mortality (3). If OSCC is detected in the early stages of cancer (T1), survival chances increase to 80%, and when it is detected later in the cancer course (T3-4), survival rates drop to 20-30% (4).

The diagnostic method of oral cancer is basically based on histopathology (5). Early diagnosis can be made in different ways such as imaging and optical technologies, staining living tissues with toluidine blue, oral preparation of cytology with the help of computer from brush biopsy samples, saliva samples, molecular analysis, and biomarkers including mRNA, miRNA, and proteins (5).

MicroRNAs are short, non-coding RNAs that regulate the translation and degradation of mRNAs and mediate post-transcriptional gene expression. Aberrant microRNA can disrupt normal cell growth cycles and cause malignancy. In general, microRNAs act either as oncogenes or as tumor suppressors in cancers, including oral cancer (6).

Many articles related to microRNA in saliva, serum, and plasma have been reviewed in different types of cancers, including OSCC, stating that this biomarker can be used as a non-invasive method in the diagnosis and prognosis of human cancers (7).

The aim of the present study was to combine the quantitative results of various studies concerning serum and salivary microRNAs for early diagnosis of head and neck squamous cell carcinoma (HNSCC) using the meta-analysis method.

Methods

1. Search strategy and study selection

A literature search was conducted for English language case-control articles that investigated various types of miRNAs in serum and saliva for the diagnosis of HNSCC during the years 2000 to 2022, which were indexed and eligible for meta-analysis in databases such as PubMed, Scopus, Web of Science, Central Cochrane, ProQuest, Embase, and Wiley (Table 1). The articles were scored based on the criteria of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist and the results of risk of bias assessment were determined. For each analyzed category, a judgment with titles of low risk, high risk, or unclear risk was expressed in a report after evaluation by 2 authors.

2. Protocol and registration

The present study is based on the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-analyses).
Based on a systematic search of databases and registered articles, all eligible articles were identified, and the desired values were extracted (Figure 1). Searching in the titles and abstracts of the studies was done using logical combinations of keywords. Geographical limitations and language limitations were not considered.
The present study has also been registered in the PROSPERO database for possible protocols (CRD42021227449 reference No.).

3. Selection criteria

3.1. Inclusion criteria

1. Articles related to the topic
2. Case-control articles
3. Articles where the samples were from saliva, serum, or plasma

Table 1. Syntax used in databases

Database	Syntax	No. of results
PubMed	("HNSCC"[Title/Abstract] OR "Squamous Cell Carcinoma of Head and Neck"[MeSH Terms] OR "carcinoma squamous cell of head and neck"[Title/Abstract] OR "Head and Neck Squamous Cell Carcinoma"[Title/Abstract] "oral squamous cell carcinoma"[Title/Abstract] OR "oral squamous cell carcinomas"[Title/Abstract] OR "OSCC"[Title/Abstract] OR "OSCCs"[Title/Abstract] OR "oral cancer"[Title/Abstract] OR "oral cancers"[Title/Abstract] OR "oral carcinoma"[Title/Abstract] OR "oral carcinomas"[Title/Abstract] OR "Mouth Neoplasms"[MeSH Terms] OR "mouth neoplasm"[Title/Abstract] OR "mouth squamous cell carcinoma"[Title/Abstract] OR "mouth cancer"[Title/Abstract] OR "Mouth Neoplasms"[MeSH Terms] OR "mouth tumor"[Title/Abstract]) AND ("micro rna"[Title/Abstract] OR "micro rnas"[Title/Abstract] OR "microrna"[Title/Abstract] OR "MicroRNAs"[MeSH Terms] OR "mirna"[Title/Abstract] OR "mirnas"[Title/Abstract]) AND ("Plasma"[MeSH Terms] OR "plasmas"[Title/Abstract] OR "Serum"[MeSH Terms] OR "serums"[Title/Abstract] OR "Blood"[MeSH Terms] OR "bloods"[Title/Abstract] OR "Saliva"[MeSH Terms] OR "salivas"[Title/Abstract] OR "salivae"[Title/Abstract] OR "salivary"[Title/Abstract] OR "secretory"[Title/Abstract] OR "hematic"[Title/Abstract] OR "hematics"[Title/Abstract] OR "hemic"[Title/Abstract] OR "haemic"[Title/Abstract])	**134**
Scopus	(TITLE-ABS-KEY ("Squamous Cell Carcinoma of Head and Neck" OR "HNSCC" OR "squamous cell carcinoma head and neck" OR "carcinoma squamous cell of head and neck" OR "Head and Neck Squamous Cell Carcinoma" OR "oral squamous cell carcinoma" OR "oral squamous cell carcinomas" OR OSCC OR OSCCs OR "oral cancer" OR "oral cancers" OR "oral carcinoma" OR "oral carcinomas" OR "mouth neoplasms" OR "mouth neoplasm" OR "mouth squamous cell carcinoma" OR "mouth cancer" OR "mouth carcinoma" OR "mouth tumor")) AND (TITLE-ABS-KEY ("micro rna" OR "micro rnas" OR "microrna" OR "micrornas" OR "mirna" OR "mirnas")) AND (TITLE-ABS-KEY ("plasma" OR "plasmas" OR "serum" OR "serums" OR "blood" OR "bloods" OR "saliva" OR "salivas" OR "salivae" OR "salivary" OR "secretory" OR "salivation" OR "hematic" OR "hematics" OR "hemic" OR "haemic" OR "blood level" OR "blood and hemopoietic system"))	**295**
Web of Science	TOPIC: ((((((((((((((("head and neck Squamous Cell Carcinoma*" OR "Squamous Cell Carcinoma* of head and neck") OR "oral Squamous Cell Carcinoma*") OR HNSCC) OR "oral Carcimona*") OR "oral neoplas*") OR "oral tumor*") OR "oral malignan*") OR OSCC) OR OSCCs) OR "mouth Carcimona*") OR "mouth neoplas*") OR "mouth tumor*") OR "mouth malignan*") AND ((((MicroRNA OR miRNA*) OR Micro RNA) OR stRNA) OR Small RNA)) AND (((((((((Blood OR hemato*) OR haemato*) OR Serum) OR plasma*) OR haemin) OR hemic) OR hematic*) OR Saliva*) OR secretory)). Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	**244**
Central Cochrane	plasma OR plasmas OR serum OR serums OR blood OR bloods OR saliva OR salivas OR salivae OR salivary OR secretory OR salivation OR hematic OR hematics OR hemic OR haemic OR blood level OR blood and hemopoietic system in Title Abstract Keyword AND Squamous Cell Carcinoma of Head and Neck OR HNSCC OR squamous cell carcinoma head and neck" OR "carcinoma squamous cell of head and neck" OR "Head and Neck Squamous Cell Carcinoma" OR "oral squamous cell carcinoma" OR "oral squamous cell carcinomas" OR OSCC OR OSCCs OR "oral cancer" OR "oral cancers" OR "oral carcinoma" OR "oral carcinomas" OR "mouth neoplasms" OR "mouth neoplasm" OR "mouth squamous cell carcinoma" OR mouth cancer" OR "mouth carcinoma" OR "mouth tumor" in Title Abstract Keyword AND micro rna OR micro rnas OR microrna OR micrornas OR mirna OR mirnas in Title Abstract Keyword - (Word variations have been searched)	**581**
ProQuest	(ab("oral squamous cell carcinoma" OR "oral squamous cell carcinomas" OR OSCC OR OSCCs OR "oral cancer" OR "oral cancers" OR "oral carcinoma" OR "oral carcinomas" OR "mouth neoplasms" OR "mouth neoplasm" OR "mouth squamous cell carcinoma" OR "mouth cancer" OR "mouth carcinoma" OR "mouth tumor" OR "Squamous Cell Carcinoma of Head and Neck" OR "squamous cell carcinoma head and neck" OR "carcinoma squamous cell of head and neck" OR "Head and Neck Squamous Cell Carcinoma" OR "HNSCC") AND ab("micro rna" OR "micro rnas" OR "microrna" OR "micrornas" OR "mirna" OR "mirnas") AND ab("plasma" OR "plasmas" OR "serum" OR "serums" OR "blood" OR "bloods" OR "saliva" OR "salivas" OR "salivae" OR "salivary" OR "secretory" OR "salivation" OR "hematic" OR "hematics" OR "hemic" OR "haemic" OR "blood level" OR "blood and hemopoietic system")) OR (su("oral squamous cell carcinoma" OR "oral squamous cell carcinomas" OR OSCC OR OSCCs OR "oral cancer" OR "oral cancers" OR "oral carcinoma" OR "oral carcinomas" OR "mouth neoplasm" OR "mouth squamous cell carcinoma" OR "mouth cancer" OR "mouth carcinoma" OR "mouth tumor" OR "Head and Neck Neoplasms" OR "neoplasms head and neck" OR "Cancer of Head and Neck" OR "Head and Neck Cancer" OR "Squamous Cell Carcinoma of Head and Neck" OR "squamous cell carcinoma head and neck" OR "carcinoma squamous cell of head and neck" OR "Head and Neck Squamous Cell Carcinoma" OR "HNSCC") AND su("micro rna" OR "micro rnas" OR "microrna" OR "micrornas" OR "mirna" OR "mirnas") AND su("plasma" OR "plasmas" OR "serum" OR "serums" OR "blood" OR "bloods" OR "saliva" OR "salivas" OR "salivae" OR "salivary" OR "secretory" OR "salivation" OR "hematic" OR "hematics" OR "hemic" OR "haemic" OR "blood level" OR "blood and hemopoietic system"))	**50**
Embase	) ((head:ti,ab,kw AND 'neck squamous cell carcinoma*': ti,ab,kw OR 'squamous cell carcinoma* of head': ti,ab,kw) AND neck:ti,ab,kw OR oral squamous cell carcinoma*': ti,ab,kw OR hnscc:ti,ab,kw OR 'oral carcinoma*': ti,ab,kw OR 'oral neoplasia *': ti,ab,kw OR 'oral tumor': ti,ab,kw OR 'oral malignancy *': ti,ab,kw OR OSCC:ti,ab,kw OR OSCCs:ti,ab,kw OR 'mouth carcinoma*': ti,ab,kw OR 'mouth neoplasia * ' ': ti,ab,kw OR 'mouth tumor*': ti,ab,kw OR 'mouth disease *': ti,ab,kw) AND (microrna:ti,ab,kw OR mirna *: ti,ab,kw OR 'micro rna ': ti,ab,kw OR strna:ti,ab,kw OR 'small rna ': ti,ab,kw) AND (blood:ti,ab,kw OR hemato *: ti,ab,kw OR haemato *: ti,ab,kw OR serum:ti,ab,kw OR plasma*: ti,ab,kw OR haemic:ti,ab,kw OR hemic:ti,ab,kw OR hematic*: ti,ab,kw OR saliva*: ti,ab,kw OR secretory:ti,ab,kw) OR 'head and neck squamous cell carcinoma' / exp OR 'oral squamous cell carcinoma cell line' / exp OR 'mouth cancer'/ exp OR 'mouth tumor'/ exp)	**432**
Wiley	"Squamous Cell Carcinoma of Head and Neck" OR "HNSCC" OR "squamous cell carcinoma head and neck" OR "carcinoma squamous cell of head and neck" OR "Head and Neck Squamous Cell Carcinoma" OR "oral squamous cell carcinoma" OR "oral squamous cell carcinomas" OR OSCC OR OSCCs OR "oral cancer" OR "oral cancers" OR "oral carcinoma" OR "oral carcinomas" OR "mouth neoplasms" OR "mouth neoplasm" OR "mouth squamous cell carcinoma" OR mouth cancer" OR "mouth carcinoma" OR "mouth tumor" in Abstract and "micro rna" OR "micro rnas" OR "microrna" OR "micrornas" OR "mirna" OR "mirnas" in Abstract and "plasma" OR "plasmas" OR "serum" OR "serums" OR "blood" OR "bloods" OR "saliva" OR "salivas" OR "salivae" OR "salivary" OR "secretory" OR "salivation" OR "hematic" OR "hematics" OR "hemic" OR "haemic" OR "blood level" OR "blood and hemopoietic system" in Abstract	**20**
	Total = 1746, Duplicates = 1020, After deleting duplicated reference = 726	

3.2. Exclusion criteria

1. Absence of the full text of the article
2. Articles with tissue samples
3. Studies other than case-control ones

A total of 672 articles were found after removing duplicates with Endnote X9 software, as shown in Table 2. After screening and reviewing them carefully, 93 articles were approved after being removed based on various reasons, including irrelevance in terms of study type, method, type of cancer, metastasis, or the lack of the full text of the articles. To avoid bias, 2 researchers performed the search independently. The cases of disagreement between the 2 reviewers were decided by a third person. After the selection process, 2 reviewers independently extracted the data from the studies. Finally, 5 completely related articles with small amounts of sensitivity, specificity, and area under the curve (AUC) in relation to MiR-31 were examined in the meta-analysis.

The lack of access to some scientific databases, the unavailability of the full text of a study, the lack of required results in the studies, and publication biases are the limitations of this study.

4. Statistical analysis

1. Using a funnel plot to detect the distribution bias of primary studies before and after sensitivity analysis
2. Using Cochran's Q test to determine the degree of heterogeneity in the results of primary studies
3. Due to the confirmation of heterogeneity between studies, the model with random effects was used.
4. As the necessary assumptions were established, a cumulative meta-analysis was used.
5. The meta-regression method was also used to determine the cause of heterogeneity, and Stata v. 12 software was used for data analysis.

5. Quality assessment of individual studies

The quality assessment of the studies was scored based on the criteria of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist. The results of the risk of bias assessment are shown in detail in Table 3. For each analyzed category, a judgment with titles of low risk, high risk, or unclear risk was expressed in a report after evaluation by 2 authors. Studies with low risk were considered as good quality studies.

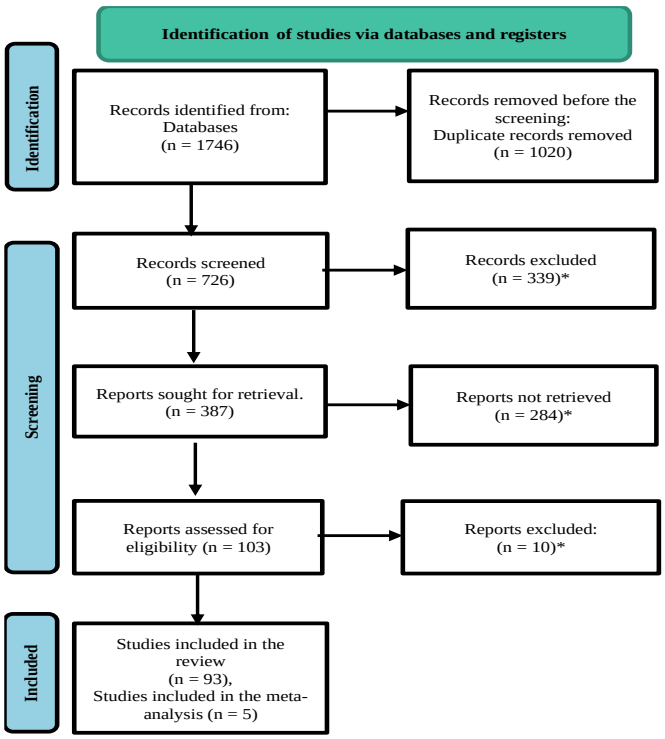

Figure 1. PRISMA flow diagram
*The reasons for removing the articles are stated in Table 2

Table 2. Articles divided by databases and reasons for removing them

Database	Reasons						Total
	Irrelevant study (book chapter/SR/ Meta/Conf. p.) *	Irrelevant subject	Malignant other than OSCC & PML *	Metastasis	No full text	Accepted	
1. Scopus	97	109	37	9	1	77	330
	36.6%	45.6%	37.8%	42.9%	10%	82.7%	45.5%
2. PubMed	17	25	39	0	0	2	83
	6.4%	10.5%	39.8%	0%	0%	2.2%	11.4%
3. Web of Science	23	28	12	1	4	2	70
	8.7%	11.7%	12.2%	4.8%	40%	2.2%	9.6%
4. ProQuest	5	14	6	0	0	2	27
	1.9%	5.9%	6.1%	0%	0%	2.2%	3.7%
5. Embase	123	63	4	11	5	10	216
	46.4%	26.4%	4.1%	52.4%	50%	10.7%	29.7%
6. Cochrane	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
7. Wiley	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Total	265	239	98	21	10	93	726
	100.0%	100.0%	100.0%	100.0%	100.0 %	100.0%	100.0%

*SR = Systematic Review, Meta = Meta-analysis, Conf. p. = Conference paper, PML = Premalignant Lesions; OSCC: Oral Squamous Cell Carcinoma

The reason for the large number of articles in Scopus compared to the other databases is the removal of duplicate articles in Scopus from other search databases

Table 3. Qualitative evaluation of diagnostic studies based on QUADAS-2

Study	Risk of bias				Applicability concerns		
	Patient selection	Index Test	Reference standard	Flow and timing	Flow and timing	Patient selection	Reference standard
1. Scholtz et al. 2022 (16)	L	L	L	L	L	L	L
2. Lu et al. 2019 (22)	L	U	L	L	L	LL	L
3. Wang et al. 2018 (14)	L	L	L	L	L	L	L
4. Liu et al.2012 (6)	L	L	L	L	L	L	L
5. Liu et al. 2010 (15)	L	L	L	L	L	L	L

* L = Low risk, H = High risk, U = Unclear risk

Results

3.1. Systematic review results

In this study, a search was conducted in PubMed, Scopus, Embase, Web of Science, ProQuest, Wiley, and Central Cochrane databases using the described search strategy (Figure 1).

In reviewing the articles, it can be concluded that in patients with HNSCC, miRNA expression may either be elevated or decreased. The miR-21, miR-31, miR-24, miR-494, and miR-155 levels increased, while miR-200, miR-125, and miR-146 levels decreased.

A total of 245 miRNAs were investigated in these studies, of which 8 types of miRNAs were repeated in more than 4 articles. Investigations showed that miR-21, miR-31, and miR-200 had the most repetitions, respectively.

According to Table 4, the investigation of miR-21 in 14 studies showed that this biomarker was prepared by qRT-PCR, TaqMan MiR assays, dSCORE, and NGS from saliva, serum, and plasma samples drawn from the mouth, larynx, and neck regions. MiR-21 increased in 12 articles, and in the articles of Ishinaga (2019) (8) with a sample size of 115 (86 sick people and 29 healthy people) and Yap (2019) (9) with a sample size of 116 (53 sick people and 63 healthy people), a decrease in the amount of this biomarker has been reported.

The investigation of miR-31 in 8 studies showed that this biomarker was prepared from saliva, serum, and plasma samples by qRT-PCR, NGS, and ISAR/Cas12a-dmStrip methods and was examined in the mouth and neck areas. In all studies, an increase in the amount of this biomarker has been reported and was evaluated in the present meta-analysis according to the reported values of sensitivity, specificity, and AUC.

The investigation of miR-200 in 6 studies showed that this biomarker was prepared by RT-qPCR and electrochemical methods from saliva, serum, and plasma samples and was examined only in the oral region. In the article of Wiklund (2011) (10), with a sample size of 32 (25 patients and 7 healthy people), an increase in the amount of this biomarker has been reported. A decrease in the level of this biomarker has been reported in other studies.

The investigation of miR-24 in 4 studies showed that this biomarker was prepared from saliva and serum samples by RT-qPCR, miRNA microarray, and dSCORE methods and was investigated only in the oral region. According to 3 articles, this biomarker has increased, and in the article of Yap et al. (2019) (9) with a sample size of 116 (53 sick people and 63 healthy people), a decrease in the amount of this biomarker has been reported.

The investigation of miR-125 in 4 studies showed that this biomarker was prepared by RT-qPCR, NGS, and electrochemical methods and exclusively from saliva samples and was investigated only in the mouth area. A decrease in this biomarker has been reported in all studies.

The investigation of miR-146 in 5 studies showed that this biomarker was prepared by RT-qPCR, PCR-RFLP, and PCR arrays from saliva and blood samples and was investigated in the mouth and neck area. MiR-146 decreased in 3 articles, and in articles of Yilmaz et al. (2020) (11) with a sample size of 142 (42 sick people and 100 healthy people) and Hung et al. (2013) (12) with a sample size of 63 (51 sick people and 12 healthy people), a rise in the amount of this biomarker has been reported.

The investigation of miR-494 in 4 studies showed that this biomarker was analyzed by RT-qPCR and miRNA microarray methods and exclusively from blood samples and only in the oral region. An increase in the level of this biomarker has been reported in all studies.

The investigation of miR-155 in 4 studies showed that this biomarker was prepared by qRT-PCR, Microarrays, and TaqMan MiR assays from saliva and plasma samples and examined in the mouth and neck areas. In 3 articles, the level of the biomarker has been elevated, and in the article of Lerner et al. (2015) (13) with a sample size of 68 (56 patients and 12 healthy people), a decrease in the amount of this biomarker was reported.

3.2. Meta-analysis results

To perform the meta-analysis, we evaluated MiR-31 for its sensitivity, specificity, and AUC values in 5 validated articles (Table 5, 6). In Figure 2, the information of all 5 studies and their weights based on the fixed model for the feature index can be seen. The meta-analysis estimation of the feature index based on a random model is also reported. The highest weight was assigned to the study of Wang (2018) (14), which is equal to 21.88%. The study by Liu (2010) (15) had the lowest weight (18.16%).

As shown in Figure 3, the information of all 5 studies and their weights based on the fixed model for the AUC index can be seen. The meta-analysis estimation of the AUC index based on a random model is also reported. The highest weight was assigned to the study by Wang (2018) (14), which is equal to 27.69%. Scholtz's study (2022) (16) had the lowest weight (16.54%).

3.2.1 Charts related to publication bias

Begg's test and a funnel plot were used to check publication bias. Due to the symmetrical funnel plot in Figure 4, no heterogeneity is apparent between the studies. On the other hand, the P-value for the sensitivity index using Begg's test was equal to 0.212, which indicates the absence of publication bias.

It can be concluded from Figure 5 that there is no heterogeneity between studies since the funnel plot is symmetrical. On the other hand, the P-value for the feature index using Begg's test was equal to 0.325, which indicates the absence of publication bias.

Figure 6 shows that the funnel diagrams are symmetrical, suggesting no heterogeneity between the studies. On the other hand, the P-value for the AUC index using Begg's test was equal to 0.090, which indicates the absence of publication bias.

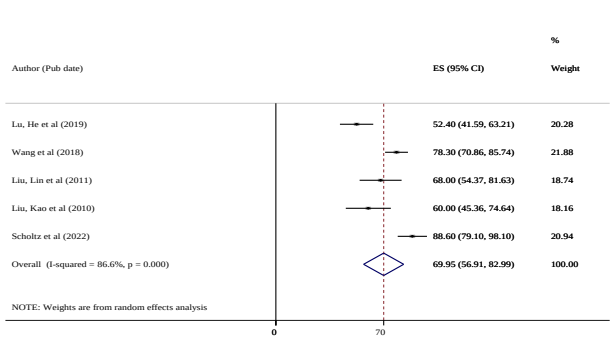

Figure 2. Forest plot showing specificity and 95% confidence interval (CI) for each of the 4 studies on miR-31 in head and neck squamous cell carcinoma (HNSCC) patients, with pooled specificity (random-effects model)

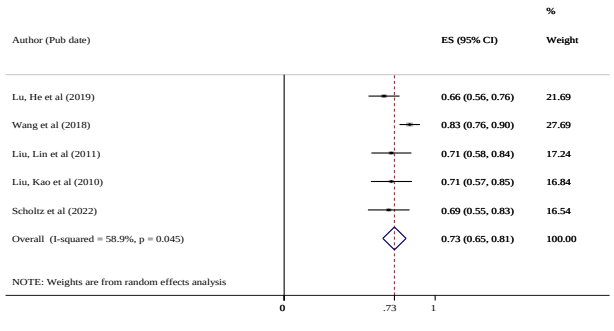

Figure 3. Forest plot showing area under the curve (AUC) and 95% confidence interval (CI) for each of the 4 studies of miR-31 in head and neck squamous cell carcinoma (HNSCC) patients, with pooled AUC (random-effects model)

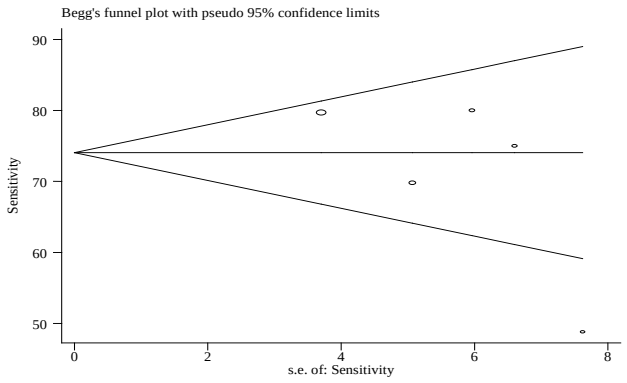

Figure 4. Funnel plot of sensitivity for each of the 5 miR-31 studies (P-value = 0.212)

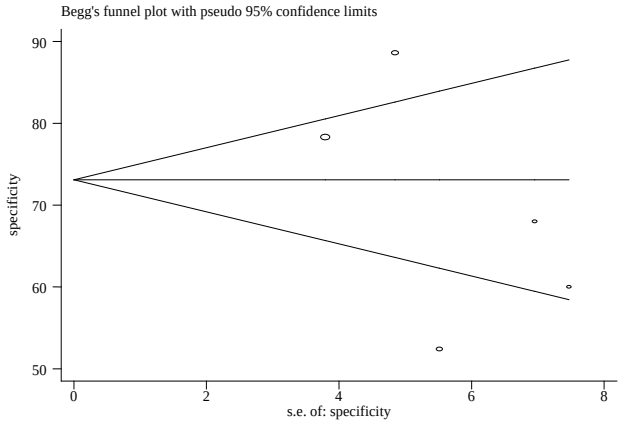

Figure 5. Funnel plot of specificity for each of the 5 miR-31 studies (P-value = 0.325)

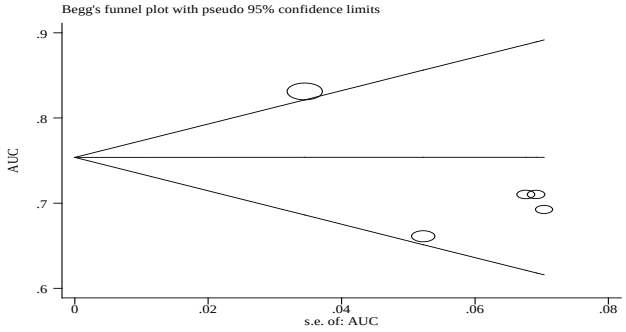

Figure 6. Funnel plot of area under the curve (AUC) for each of the 5 miR-31 studies (P-value = 0.090)

3.2.2. Sensitivity analysis

In the sensitivity analysis, the contribution of each study to the overall outcome of the studied index was evaluated. Table 7 shows a sensitivity value of 71.68%, a specificity value of 69.95%, and an AUC value of 0.73. This table shows what the total amount would be if the studies were removed one by one. Figures 7-9 show how each indicator is affected by removing each study.

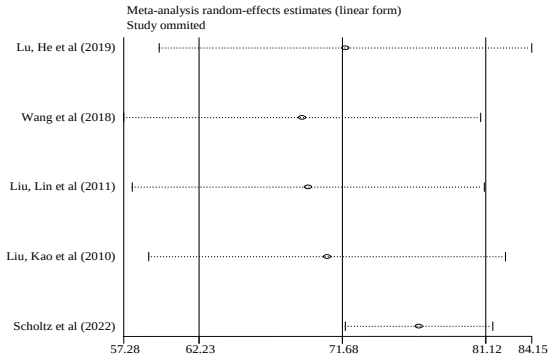

Figure 7. Sensitivity analysis of sensitivity for each of the 5 studies of miR-31 in head and neck squamous cell carcinoma (HNSCC) patients

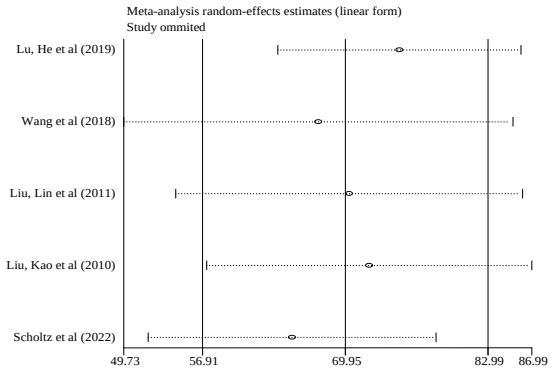

Figure 8. Sensitivity analysis of specificity for each of the 5 studies of miR-31 in head and neck squamous cell carcinoma (HNSCC) patients

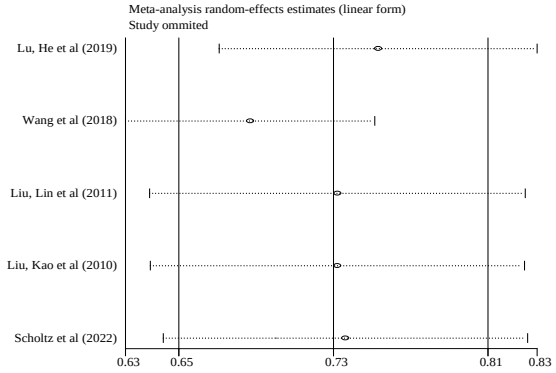

Figure 9. Sensitivity analysis of area under the curve (AUC) for each of the 5 studies of miR-31 in head and neck squamous cell carcinoma (HNSCC) patients

Table 4. Data extracted from final studies with more than 4 microRNA replicates

ID	Type of MicroRNA	Author (y)	Sample	Location of the carcinoma	Case/Control	Sensitivity	Specificity	AUC	Up/down regulation	Method of detection
1	**miR-21**	B Karimi et al. (2020) (7)	Serum	Oral	20 / 20	95%	95%	-	↑	RT-PCR
		Ishinaga et al. (2019) (8)	Plasma	HNSCC	86 / 29	60.3%	50.0%	0.756	↓	qRT-PCR
		Mahmood et al. (2019) (23)	Plasma	Oral	100 / 100	90%	90%	0.829	↑	qRT-PCR
		Yap et al. (2019) (9)	Saliva	Oral	53 / 63	86.8%	81.5%	0.8676	↓	dSCORE + RT-qPCR
		Mehdipour et al. (2018) (24)	Saliva	Oral	30 / 15	-	-	-	↑	qRT-PCR
		Momen heravi et al. (2018) (25)	Plasma	Oral	10 / 10	-	-	-	↑	TaqMan MiR assays + qRT-PCR
		Singh et al. (2018) (26)	Serum	Oral	20 / 40	-	-	-	↑	qRT-PC
		Yap et al. (2018) (27)	Saliva	Oral	30 / 30	97.9%	96.7%	0.95	↑	NGS + RT-qPCR
		Wei et al. (2016) (28)	Plasma	Laryngeal	22 / 19	80%	60%	0.6723	↑	ddPCR + RT-PCR
		Yan et al. (2016) (29)	Plasma	Oral	8 / 3	-	-	-	↑	qRT-PCR
		Zahran et al. (2015) (30)	Saliva	Oral	20 / 20	65%	65%	0.73	↑	qRT-PCR
		Ren et al. (2014) (31)	Blood	Oral	58 / 32	patient:62.1%, healthy:84.5%	patient:90.6%, healthy:62.5%	patient:0.788, healthy:0.774	↑	qRT-PCR
		Hsu et al. (2012) (32)	Plasma	HNSCC	50 / 17	83.3%	51.9%	0.741	↑	RT-PCR
		Jung et al. (2012) (33)	Serum	Oral	17 / 17	-	-	-	↑	qRT-PCR
2	**miR-31**	Scholtz et al. (2022) (16) *Meta	Saliva	Saliva	43 / 44	48%	88%	0.69	↑	RT-qPCR
		Chen et al. (2020) (34)	Saliva	Oral	5 / 3	-	-	-	↑	ISAR/Cas12a-dmStrip
		Lu, He et al. * (2019) (22)	Serum	Oral	82 / 53	76.8%	73.6%	0.776	↑	qRT-PCR
		Mehdipour et al. (2018) (24)	Saliva	Oral	30 / 15	-	-	-	↑	qRT-PCR
		Wang et al. * (2018) (14)	Serum	HNSCC	118 / 60	79.7%	78.3%	0.831	↑	RT- PCR
		Yap et al.(2018) (27)	Saliva	Oral	30 / 30	-	-	-	↑	NGS + RT-qPCR
		Liu et al.*(2012) (6)	Saliva	Orally	45 / 24	80%	68%	0.71	↑	qRT-PCR
		Liu, Kao et al.* (2010) (15)	Plasma	Orally	43 / 21	75%	60%	0.71	↑	RT-PCR
3	**miR-200**	Mehdipour et al. (2018) (24)	Saliva	Orally	30 / 15	-	-	-	↓	qRT-PCR
		Yan et al. (2018) (35)	Serum	Oral	87 / 40	98%	75%	0.9481	↓	qRT-PCR
		Sun, Cao et al. (2017) (36)	Plasma	Oral	80 / 80	90.0%	88.75%	0.9173	↓	qRT-PCR
		Wang, Zhang et al. (2013) (37)	Saliva	Oral	5 / 5	-	-	-	-	Electrochemical + RT-qPCR
		Wiklund et al. (2011) (10)	Saliva	Oral	25 / 7	-	-	-	↑	qRT-PCR
		Park et al. (2009) (2)	Saliva	Oral	50 / 50	-	-	0.54	↓	RT-qPCR
4	**miR-24**	Karimi et al. (2020) (7)	Serum	Oral	20 / 20	80%	70%	-	↑	RT-PCR
		He L et al. (2020) (38)	Saliva	Oral	49 / 14	64.4%	80%	0.738	↑	miRNA microarray+ qRT-PCR
		Yap et al. (2019) (9)	Saliva	Oral	53 / 63	86.8%	81.5%	0.8676	↓	dSCORE + RT-qPCR
		Lin et al. (2010) (39)	Blood	Oral	33 / 10	70%	92%	0.82	↑	qRT-PCR
5	**miR-125**	Mehdipour et al. (2018) (24)	Saliva	Oral	30 / 15	-	-	-	↓	qRT-PCR
		Yap et al. (2018) (27)	Saliva	Oral	30 / 30	97.9%	96.7%	0.95	↓	NGS + RT-qPCR
		Wang, Zhang et al. (2013) (37)	Saliva	Oral	5 / 5	-	-	-	-	Electrochemical + RT-qPCR
		Park et al. (2009) (2)	Saliva	Oral	50 / 50	-	-	0.53	↓	RT-qPCR
6	**miR-146**	Yilmaz et al. (2020) (11)	Blood	Oral	42 / 100	_-	_-	_-	↑	PCR-RFLP
		Salazar et al. (2018) (40)	Saliva	HNSCC	108 / 108	-	-	0.66	↓	PCRArrays
		Min et al. (2017) (41)	Blood / Saliva	Oral	51 / 10	Blood: 78%, Saliva: 95%	Blood: 80%, Saliva: 82%	Blood: 0.8033, Saliva: 0.9004	↓	RT-qPCR
		Lerner et al. (2015) (13)	Blood	HNSCC	56 / 12	-	-	-	↓	Microarrays+ RT-PCR
		Hung et al. (2013) (12)	Plasma	Oral	51 / 12	79%	92%	0.86	↑	qRT-PCR
7	**miR-494**	Emami et al. (2020) (42)	Blood	Oral	50 / -	-	-	-	↑	RT-PCR
		Ries, Baran et al. (2017) (43)	Blood	Oral	54 / -	71.4%	76.2%	0.78	↑	RT-qPCR
		Ries, Agaimy et al (2014) (44)	Blood	Oral	57 / -	50%	85%	0.715	↑	miRNA microarray + qRT -PCR
		Ries, Vairactors et al. (2014) (45)	Blood	Oral	50 / -	75%	85%	0.72	↑	miRNA microarray + qRT -PCR
8	**miR-155**	Emami et al. (2020) (42)	Blood	Oral	50 / -	-	-	-	↑	RT-PCR
		Narimani et al. (2019) (46)	Blood	Oral	30 / 30	-	-	-	↑	qRT-PCR
		Moment Heravi et al. (2018) (25)	Plasma	Oral	10 / 10	-	-	-	↑	TaqMan MiR assays + qRT-PCR
		Lerner et al. (2015) (13)	Blood	HNSCC	12/56	-	-	-	↓	Microarrays + RT-PCR

HNSCC: Head and Neck Squamous Cell Carcinoma; AUC: Area Under the Curve

Table 5. Data extracted from the articles included in the meta-analysis

ID	First author (Year, Reference)	Place of study	Type of sample	Location of carcinoma	Method of detection	Case sample size	Control sample size	Sensitivity (%)	Specificity (%)	AUC
1	Scholt Z (2022) (16)	Hungary	Saliva	Oral	qRT -PCR	43	44	48.00	88.00	0.69
2	Lu (2019) (22)	China	Serum	Oral	qRT -PCR	82	53	69.80	52.4	0.661
3	Wang (2018) (14)	China	Serum	HNSCC	RTPCR	118	60	79.70	78.3	0.831
4	Liu (2012) (6)	Taiwan	Saliva	Oral	qRT-PCR	45	24	80.00	68.0	0.710
5	Liu (2010) (15)	Taiwan	Plasma	Oral	RT-PCR	43	21	75.00	60.0	0.710

AUC: Area Under the Curve; HNSCC: Head and Neck Squamous Cell Carcinoma

Table 6. The estimated sensitivity (%), specificity (%), and AUC of mir-31 in preoperative patients and their 95% confidence intervals [a]

Index	N	Random-effects model (95% confidence interval)	Heterogeneity test1	
			I-squared (%)	P-value
Sensitivity (%)	5	71.68 (62.23, 81.12)	73.4	0.005
Specificity (%)	5	69.95 (56.91, 82.99)	86.6	< 0.001
AUC	5	0.73 (0.65, 0.81)	58.9	0.045
Weight (16.49%)				

AUC: Area Under the Curve
[a] Estimation was performed based on fixed and random effects models.

Table 7. Sensitivity analysis of specificity, sensitivity, and AUC for each of 5 studies of miR-31 in head and neck squamous cell carcinoma (HNSCC) patients

Omitted study	Coefficient (95% confidence interval)		
	Sensitivity	Specificity	AUC
Scholtz (2022) (16)	76.72 (71.87, 81.58)	65.96 (51.96, 78.24)	0.74 (0.65, 0.83)
Lu (2019) (22)	71.88 (59.61, 84.15)	74.89 (63.80, 85.99)	0.75 (0.67, 0.83)
Wang (2018) (14)	69.04 (57.28, 80.79)	67.50 (49.73, 85.26)	0.69 (0.63, 0.75)
Liu (2012) (6)	69.43 (57.83, 81.02)	70.31 (54.47, 86.14)	0.73 (0.64, 0.83)
Liu (2010) (15)	70.67 (58.92, 82.43)	72.14 (57.29, 86.99)	0.73 (0.64, 0.83)
Combined	71.68 (62.23, 81.12)	69.95 (56.91, 82.99)	0.73 (0.65, 0.81)
Random-effects model			

AUC: Area Under the Curve

Discussion

Early detection of oral cancer is essential to have a better prognosis, and studies demonstrated that miRNAs can act as biomarkers for the detection of cancer in its early stage (17).

Specific miRNA expression patterns can not only differentiate cancer cells from normal cells but can also identify the tissue in which the primary tumor originated and can be an early diagnostic marker of HNSCC (18-20).

Our meta-analysis included 5 completely related articles with small amounts of sensitivity, specificity, and AUC in relation to MiR-31. Considering all studies regarding miRNAs, the combined results indicated that AUC = 0.73, with a sensitivity of 71.68% and a specificity of 69.95%, could be used for HNSCC diagnosis. Due to the moderate sensitivity and specificity of miRNAs, they may be able to confirm or exclude suspected cases of this disease, enhancing their utility as clinical diagnostic indicators.

In a meta-analysis by Tian et al., which included 23 studies, combined results indicated that sensitivity, specificity, and AUC were 0.759, 0.773, and 0.832, respectively, indicating a relatively high diagnostic accuracy of miRNAs in differentiating OSCC patients from healthy controls (3).

Another meta-analysis reported that the combined sensitivity and specificity of blood and salivary miRNAs in the diagnosis of OSCC were 0.78 and 0.82, respectively. The overall AUC was 0.91. This study also only included the results of miRNAs in the saliva and blood of patients with OSCC (21).

As a result, miRNAs, especially MiR-31 expression in saliva, serum, or plasma, have the ability to discriminate HNSCC from healthy controls, suggesting that miRNAs are promising molecular markers for the early identification of HNSCC. Since heterogeneity often exists in meta-analyses of diagnostic accuracy data, possible causes that could contribute to the inconsistency in accuracy estimates across the study were investigated, and a random-effect model was used. Interestingly, the funnel plot asymmetry test showed no evidence of publication bias (P-value = 0.325).

Our meta-analysis has a few limitations. First, since all the studies we included were case-control studies, it is unclear how much risk bias might have influenced the quality assessment. Second, when combining the findings of the included articles, we might have overlooked other factors such as different patient stages, HNSCC subtype, HPV (human papillomavirus) status, miRNA normalization methods, and cut-offs.

Therefore, additional studies are needed to compare the diagnostic effect of multiple miRNAs and individual miRNAs on HNSCC. The precise role of miRNAs in the carcinogenesis of tumors remains unknown despite the excellent diagnostic performance achieved by miRNAs in most studies.

Conclusion

The available data provide evidence that miRNAs, especially MiR-31 expression in saliva, serum, or plasma, can be used as a diagnostic biomarker for HNSCC patients. However, controlled clinical trials with large samples are needed to validate different miRNAs.

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Ethical statement

This research was conducted according to ethical guidelines approved by the Ethics Committee of the Golestan University of Medical Sciences (Ethics approval code: IR.GOUMS.REC.1399.368).

Conflicts of interest

The authors declare that there is no conflict of interest.

Author contributions

The authors confirm contribution to the paper as follows: Study conception and design: MN, BN, MM, MS, AF; Bibliographic search and data extraction: MN, AF, MM; Analysis and interpretation of results: BN, MN, AF; Manuscript preparation: AF, MN, BN. All the authors have revised and approved the final version of the manuscript.

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