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Evaluation of the Sensitivity and Specificity of MiRNAs in Discriminating Oral Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Approximately 90% of all oral malignant tumors are squamous cell carcinomas. This study aims to evaluate the sensitivity and specificity of miRNAs in discriminating oral squamous cell carcinoma. **Material and methods:** There are many international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, Embase, and many other databases in oral squamous cell carcinoma searched until May 2023. Data analysis using STATA/MP. V17 software was done in 95% confidence intervals. Effect size (sensitivity and specificity) were calculated using a fixed effect model with an inverse-variance method**.** **Results:** The full text of 25 studies was reviewed; finally, 17 studies were selected according to the objectives of the present study and included in the meta-analysis. The sensitivity and specificity of miRNAs in diagnosing OSCC were 77% (ES, 77% CI; 70%, 84%; p<0.01) and 80% (ES, 80% CI; 73%, 87%; p<0.01), respectively. Test of group differences showed no significant difference between sensitivity and specificity of the salivary, blood, and serum miRNAs in diagnosing oral squamous cell carcinoma (OSCC) (p>0.05). **Conclusions:** Based on the meta-analysis of the present study, the diagnostic accuracy of miRNAs for the diagnosis of OSCC is high; Blood, saliva, and serum miRNAs had similar sensitivity and specificity.

1. Introduction

Cancer is a disease that occurs due to uncontrollable cell division caused by environmental factors and genetic disorders.[1] Squamous cell cancer of the head and neck is characterized by a heterogeneous group of malignancies affecting the oral cavity, nasal cavity, paranasal sinuses, larynx, pharynx, and salivary glands.[2] The most common type of squamous cell cancer of the head and neck is oral cancer, also known as oral squamous cell carcinoma (OSCC).[3] More than 90% of oral cancers are OSCCs, the most common malignant neoplasms of the oral cavity. Gene changes affecting the appearance of proteins have been implicated in the development of oral cancer, and this protein dysregulation can lead to uncontrolled cell proliferation, tissue invasion, and metastasis.[4] There is a less than 50% five-year survival rate for OSCC patients despite recent advances in diagnosis and treatment methods.[5, 6] Most oral cancers are diagnosed in advanced stages. These lesions are discovered when they have led to the appearance of clinical symptoms as a result of much progress, and this has caused the prognosis of oral cancer to be poor in most parts of the world.[7] This cancer accounts for 5% of all cancer cases in men and 2% in women. The factors that increase this disease in old age are carcinogenic factors such as cigarettes, alcohol, and tobacco, with an increase in DNA damage, as well as viruses and other microbial factors and their effects on the oral mucosa.[8, 9] Biological markers are molecules in the blood, body fluids, and tissues, indicating normal or abnormal processes, diseases, or conditions.[10] Examining several biomarkers together can provide the medical staff with more accurate and reliable results for the diagnosis of cancers.[11] MicroRNAs (miRNAs) are a large subgroup of 18-25 nucleotide non-coding RNAs that are evolutionarily conserved.[12] These molecules control gene expression after transcription by inhibiting the translation of messenger RNA (mRNA) or inducing its degradation.[13, 14] Many recent studies show the potential role of miRNAs in the development of oral cancer.[15, 16] Studies have investigated the use of miRNAs in diagnosing OSCC. However, the clinical value of miRNAs in diagnosing OSCC is unclear, and more comprehensive studies are needed. Therefore, in

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the present study, an attempt has been made to present the accuracy of miRNA detection in the diagnosis of OSCC with strong evidence by examining the results of the studies. Therefore, this study aims to evaluate the sensitivity and specificity of miRNAs in discriminating oral squamous cell carcinoma.

2. Material and methods

Search strategy

In the present study, Systematic Review and Meta-analysis methods were used to answer the question, "What is the sensitivity and specificity of miRNAs in diagnosing oral squamous cell carcinoma." Systematic Review and Meta-analysis is an evidence-based approach that provides an accurate and reliable report of previous research findings using the PRISMA 2020 checklist[17] as a standard tool and a systematic review of all empirical evidence with appropriate criteria to answer the question. Researches, identifies and collects. The current study uses the PICO strategy to construct the research question specified in Table 1. The four elements of the PICO model include patient/population, intervention, comparison, and outcome; The PICO process begins with a case scenario from which a question related to the case is constructed and phrased to facilitate finding an answer.

Table 1. PICO strategy.

PICO Strategy	Description
P	Population: OSCC Patients
I	Intervention: miRNAs
C	Comparison: healthy controls
O	Outcome: sensitivity and specificity

All international databases of PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase and databases in the field of oral squamous cell carcinoma using keywords ((((((((("Squamous Cell Carcinoma of Head and Neck"[Mesh]) OR ("Squamous Cell Carcinoma of Head and Neck/mortality"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/prevention and control"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/surgery"[Mesh] OR "Squamous Cell Carcinoma of Head and Neck/therapy"[Mesh])) AND "MicroRNAs"[Mesh]) OR ("MicroRNAs/blood"[Mesh] OR "MicroRNAs/classification"[Mesh] OR "MicroRNAs/standards"[Mesh] OR "MicroRNAs/therapeutic use"[Mesh])) OR "Serum"[Mesh]) OR "Saliva"[Mesh]) OR "Blood"[Mesh]) AND "Area Under Curve"[Mesh]) OR "Sensitivity and Specificity"[Mesh]) OR ("False Negative Reactions"[Mesh] OR "Predictive Value of Tests"[Mesh])) OR "False Positive Reactions"[Mesh] were searched until May 2023.

Study selection criteria

Inclusion criteria included all studies that investigated the diagnostic value of miRNAs in blood, plasma, and saliva in OSCC; studies with a control group (healthy people); reporting the sensitivity and specificity of miRNAs in OSCC; access to the full text of the study; and the language of publication was English. The exclusion criteria included studies with incomplete methodology and case studies, case reports, in-vitro and in-vivo studies, and review articles.

Data collection

A checklist was prepared by two independent and blind authors related to the data of the studies as a data collection tool. Then both checklists were checked by a third independent and blind author, duplicate items were removed, and each three income authors approved the final checklist. Two authors did data extraction independently, and the information was recorded in the checklist. In case there is no agreement on a specific issue, the opinion of the third referee was considered as a criterion. This checklist had two parts. The first part included the demographic and clinical data, including the name of the author, the year of publication of the article, the sample size, the number of patients in the intervention and control groups, the gender and average age of the participating patients, the type of sample obtained, and the type of miRNA. Moreover, the second part was the data related to the diagnostic accuracy used in the meta-analysis.

Risk assessment

The quality of the selected studies was measured using Diagnostic Accuracy Studies (QUADAS2) criteria.[18] This tool has four key domains which are:

- Patient selection
- Index test
- Reference standard
- Flow and timing

Each domain is assessed for risk of bias, and the first three are for applicability concerns. Signaling questions are included to help judge the risk of bias.

Data analysis

Data analysis using STATA/MP. V17 software was done in 95% confidence intervals. Effect size (sensitivity and specificity) were calculated using a fixed effect model with an inverse-variance method. In addition, the chi-square test was used to check the heterogeneity between the studies. The I^2 coefficient value is less than 50% as low heterogeneity; between 50 and 75% was considered moderate heterogeneity, and above 75% was high heterogeneity.

3. Results

Study selection

First, a search was conducted using keywords in international databases, and 194 articles were found, all of which were entered into End.Note.X8 software; Duplicate articles and records marked as ineligible by automation tools and for other reasons were removed. The abstracts of 113 articles were reviewed, and according to the inclusion and exclusion criteria, 88 studies were excluded, and the full text of 25 studies was reviewed; finally, 17 studies were selected according to the objectives of the present study and included in the meta-analysis (Fig. 1).

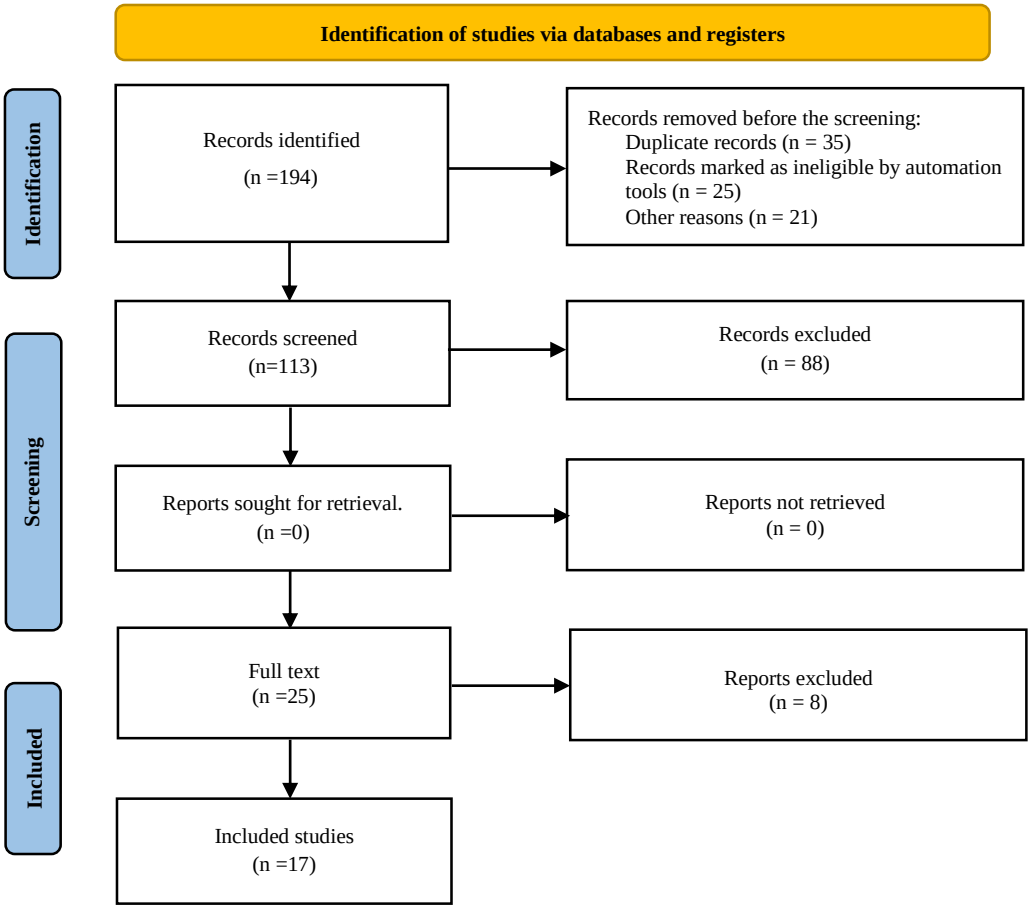

Fig. 1. PRISMA 2020 Checklist.

Study characteristics

In the present study, OSCC patients were compared with healthy people (control group); 606 men and 320 women participated in the OSCC group, and 432 men and 289 women participated in the control group. The average age of participants in both groups is reported in Table 2. In six studies, the sample type was serum; in three studies, it was blood; and in eight studies, it was saliva. The types of miRNAs under investigation are summarized in Table 2.

Table 2. Data extracted from included studies.

No	Study. Years	Number of Patients				Mean of Age		Sample Type	MiRNA	Bias Assessment
		OSCC		Control						
		Male	Female	Male	Female	OSCC	Control			
1	Mazumder et al., 2023[19]	32	15	28	14	57	57	Serum	miR-31–5p, miR-483–5p, miR-486–5p, miR30e-5p	Low
2	Ukey et al., 2023[20]	22	12	22	7	47	33	Blood	miR-221-3p, miR-133a-3p, and miR-9-5p	Low
3	Scholtz et al., 2022[21]	28	15	16	28	57.9	57.6	Saliva	miR-31-5p, miR-345-3p, and miR-424-3p	Low
4	Kiran et al., 2022[22]	44	24	46	16	48.6	48.6	Saliva	miR-21	Low
5	Karimi et al., 2020[23]	14	6	14	6	46.4	47	Serum	miR-21, miR-24, miR-29a	Low
6	Emami et al., 2020[24]	26	24	28	22	44.1	45.4	Blood	miR-155	Mod
7	He et al., 2020[25]	30	19	8	6	NR	NR	Saliva	miR-24-3p	Mod

8	Chang et al., 2018[26]	111	3	68	2	53.3	52.6	Plasma	miR-150-5p, miR-423-5p, miR423-5p	Mod
9	Chen et al., 2018[27]	73	48	27	28	NR	NR	Serum	miR-99a	Low
10	Sun et al., 2018[28]	35	45	36	44	54	53	Serum	miR-200b-3p	Mod
11	Wan et al., 2017[29]	34	13	59	54	NR	NR	Saliva	miR9, miR127, miR134, miR191, miR222, miR-455	Low
12	Duz et al., 2016[30]	19	6	21	4	54	46.9	Saliva	miR-139-5p	Low
13	Tachibana et al., 2016[31]	20	11	16	15	75	75	Serum	miR-233	Low
14	Zahran et al., 2015[32]	50	50	9	11	51	51	Saliva	miR-21, miR-145, miR-184	Mod
15	Momen-Heravi et al., 2014[33]	8	1	5	3	60	60	Saliva	miR-27b, miR-136	Low
16	Ren et al., 2014[34]	39	19	16	16	61	61	Blood	miR-21	Low
17	MacLellan et al., 2012[35]	21	9	13	13	62	62	Serum	miR-338-3p, miR-29a, miR-223, miR-16	Low

Risk of bias assessment

According to QUADAS2, 12 studies were of high quality, and five were of moderate quality.

Meta-analysis

Table 3 shows a meta-analysis of the area under the curve (AUC), false negative, false positive, true positive, and true negative. The AUC value was 74% (ES, 0.74 CI; 0.68, 0.80; p<0.01) (Table 3).

Table 3. Diagnostic value.

Study. Years	Area Under Curve	False Negative	False Positive	True Positive	True Negative
Mazumder et al., 2023[19]	0.80	-----	-----	-----	-----
	0.78	-----	-----	-----	-----
	0.90	-----	-----	-----	-----
Ukey et al., 2023[20]	0.80	-----	-----	-----	-----
Scholtz et al., 2022[21]	0.77	-----	-----	-----	-----
Kiran et al., 2022[22]	0.73	1	1	6	8
Karimi et al., 2020[23]	-----	1	1	19	19
	-----	6	6	16	14
	-----	0	0	20	20
Emami et al., 2020[24]	-----	11	8	39	42
	-----	14	10	36	40
	-----	16	7	34	43
He et al., 2020[25]	0.74	17	3	32	11
Chang et al., 2018[26]	0.70	45	16	69	54
	0.68	47	19	67	51

	0.75	33	29	82	51
Chen et al., 2018[27]	-----	24	9	97	46
Sun et al., 2018[28]	0.92	8	9	72	71
Wan et al., 2017[29]	0.82	19	7	28	106
Duz et al., 2016[30]	0.81	7	4	18	21
Tachibana et al., 2016[31]	0.70	10	12	21	19
Zahran et al., 2015[32]	0.73	35	7	65	13
	0.68	40	6	60	14
	0.86	20	5	80	15
Momen-Heravi et al., 2014[33]	0.96	1	0	8	8
Ren et al., 2014[34]	-----	22	3	36	29
MacLellan et al., 2012[35]	0.82	6	5	24	21
	0.82	7	6	23	20
	0.81	1	10	29	16
	0.84	12	2	18	24
Meta-analysis	0.74 (0.68, 0.80)	21.53 (21.48, 21.59)	7.58 (7.52, 7.64)	41.11 (41.05, 41.17)	25.93 (25.87, 25.99)

Sensitivity and specificity of miRNAs in diagnosing OSCC

The sensitivity of miRNAs in diagnosed OSCC was 77% (ES, 77% CI; 70%, 84%; p<0.01) with low heterogeneity (I^2=0%; P=0.99) (Fig. 2). Specificity of miRNAs in diagnosed OSCC was 80% (ES, 80% CI; 73%, 87%; p<0.01) with low heterogeneity (I^2=0%; P =0.98) (Fig. 3).

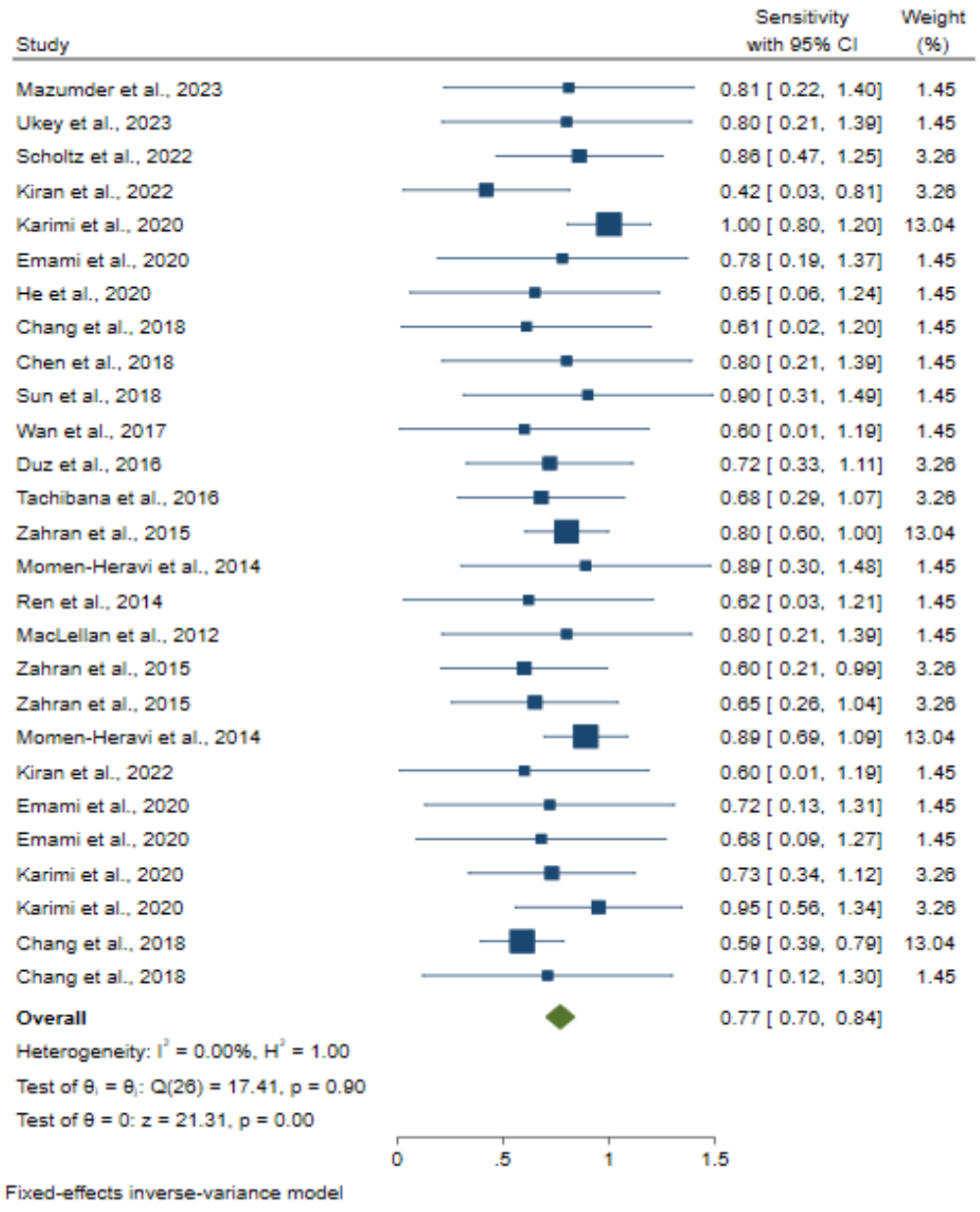

Fig. 2. The forest plot showed a sensitivity of miRNAs in diagnosing OSCC.

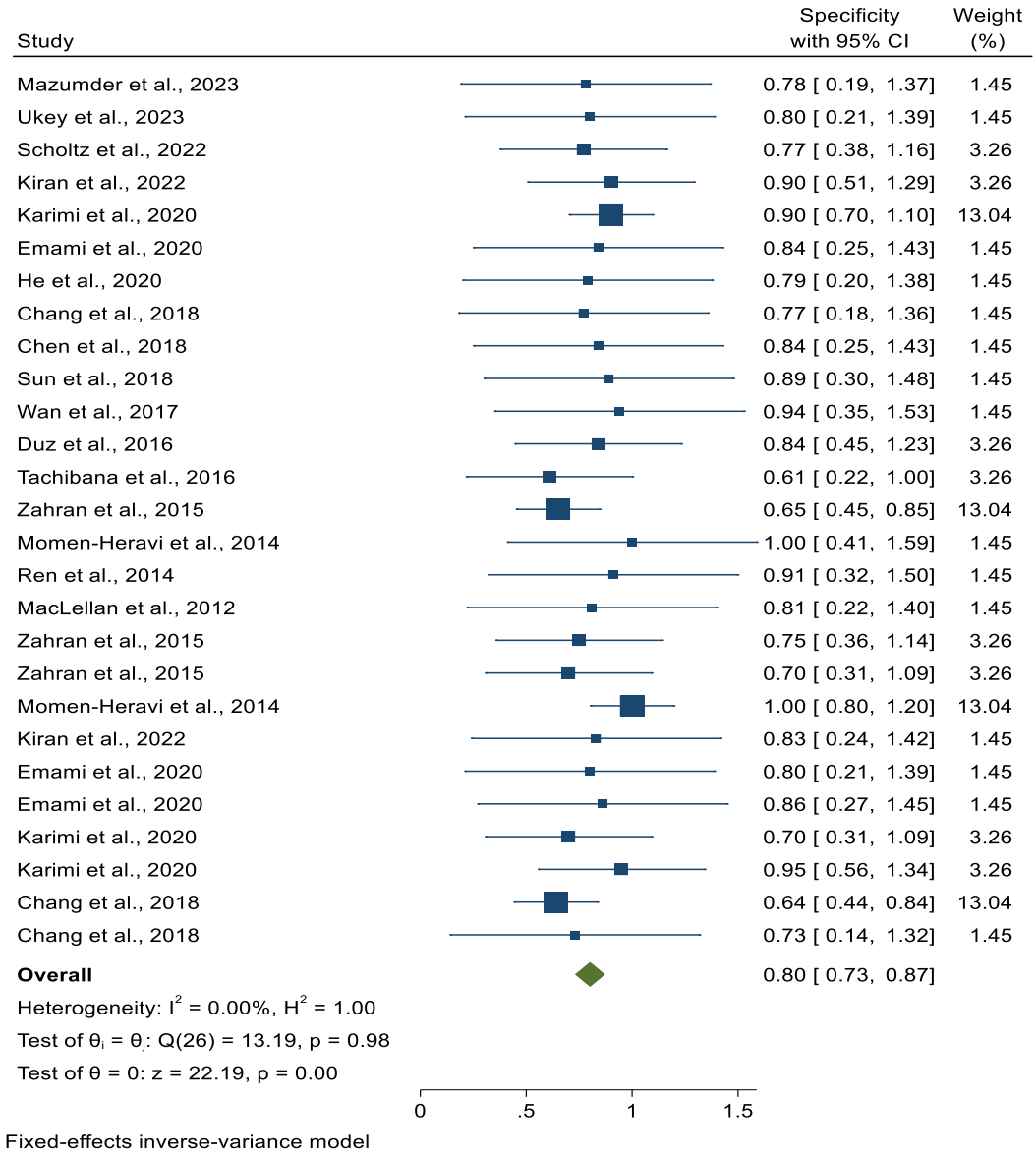

Fig. 3. The forest plot showed a specificity of miRNAs in diagnosing OSCC.

Subgroup meta-analysis

The sensitivity of salivary miRNAs in diagnosed OSCC was 76% (95% CI: 0.66–0.86) with low heterogeneity (I^2=0%; P =0.74), the sensitivity of blood miRNAs in diagnosed OSCC was 73% (95% CI: 0.53–0.94) with low heterogeneity (I^2=0%; P =1.00), and sensitivity of serum miRNAs in diagnose OSCC was 79% (95% CI: 0.68–0.91) with low heterogeneity (I^2=16.44%; P =0.30). Test of group differences showed no significant difference between the sensitivity of the salivary, blood, and serum miRNAs in diagnosing OSCC (p=0.84) (Fig. 4).

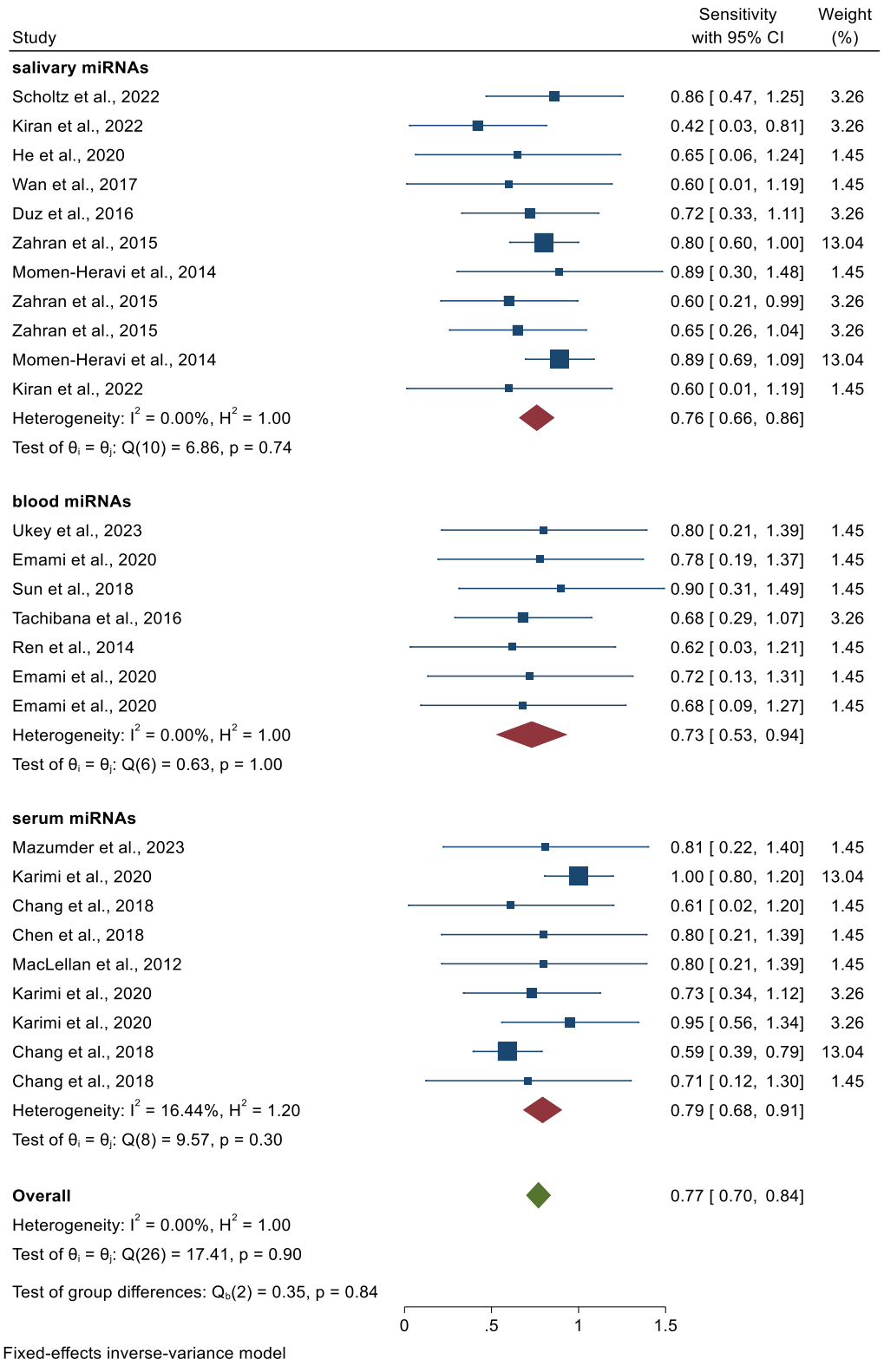

Fig. 4. The forest plots showed a sensitivity of salivary, blood, and serum miRNAs in diagnosing OSCC.

The specificity of salivary miRNAs in diagnosed OSCC was 82% (95% CI: 0.72–0.92) with low heterogeneity (I^2=0%; P =0.69), specificity of blood miRNAs in diagnosed OSCC was 78% (95% CI: 0.58–0.99) with low heterogeneity (I^2=0%; P =0.98) and specificity of serum miRNAs in diagnose OSCC was 78% (95% CI: 0.67–0.89) with low heterogeneity (I^2=0%; P =0.82). Test of group differences showed no significant difference between the specificity of the salivary, blood, and serum miRNAs in diagnosing OSCC (p=0.86) (Fig. 5).

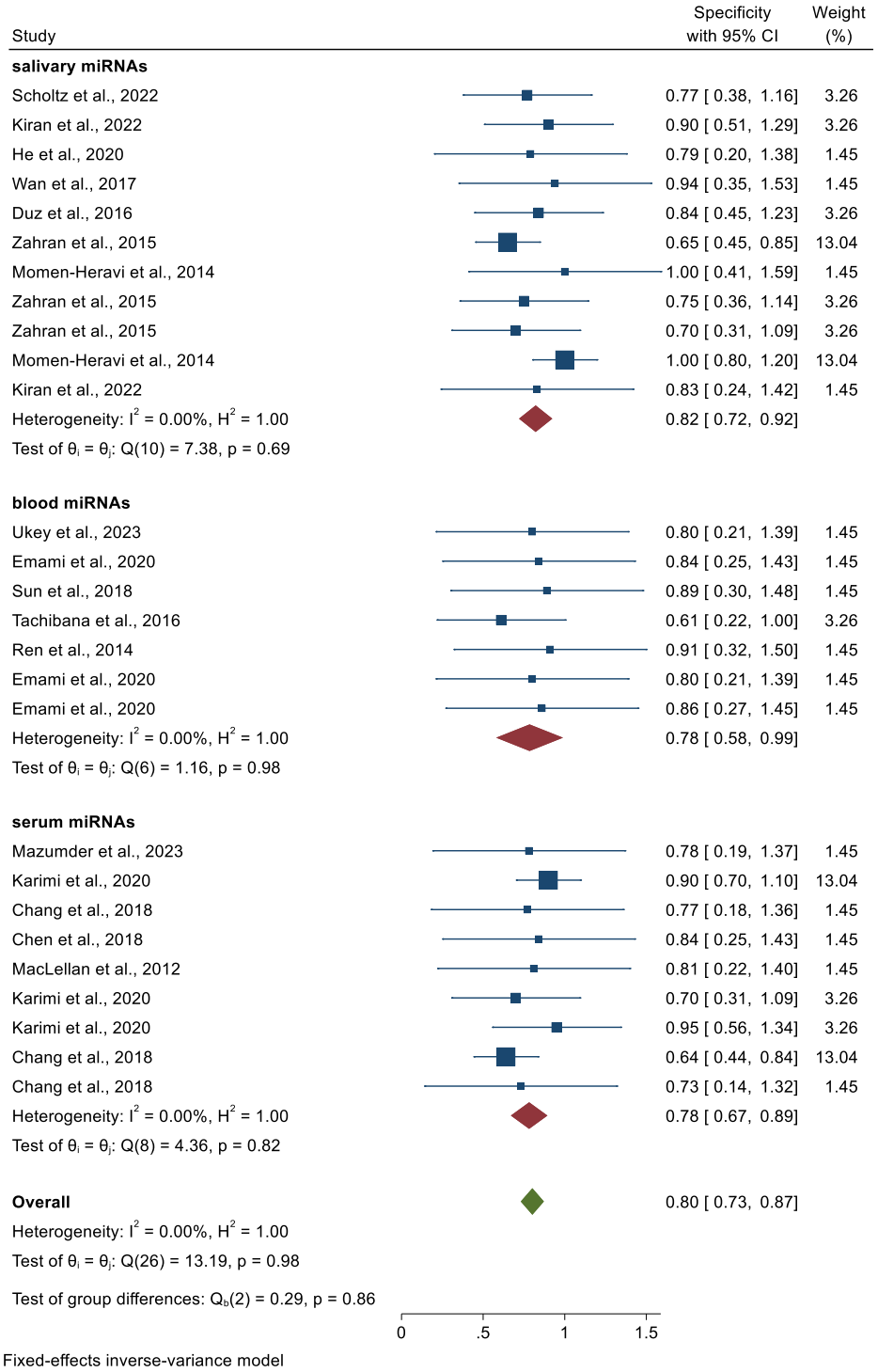

Fig. 5. The forest plots showed a specificity of salivary, blood, and serum miRNAs in diagnosing OSCC.

Funnel plots are a visual tool for investigating publication and other biases in meta-analysis and show the relationship between a study's effect size and its precision. Based on Figures 6 and 7, no significant emission bias was observed.

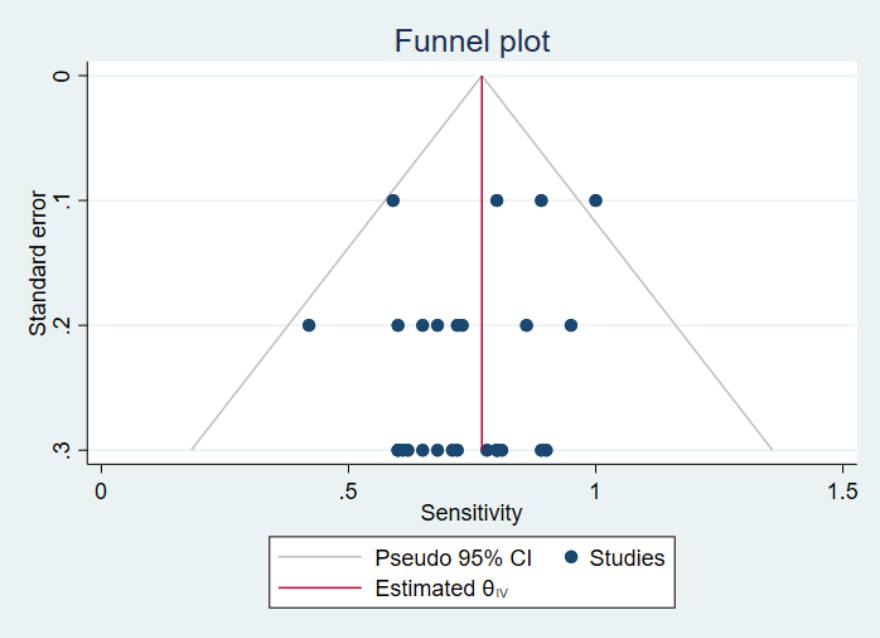

Fig. 6. Funnel plots for publication bias of sensitivity.

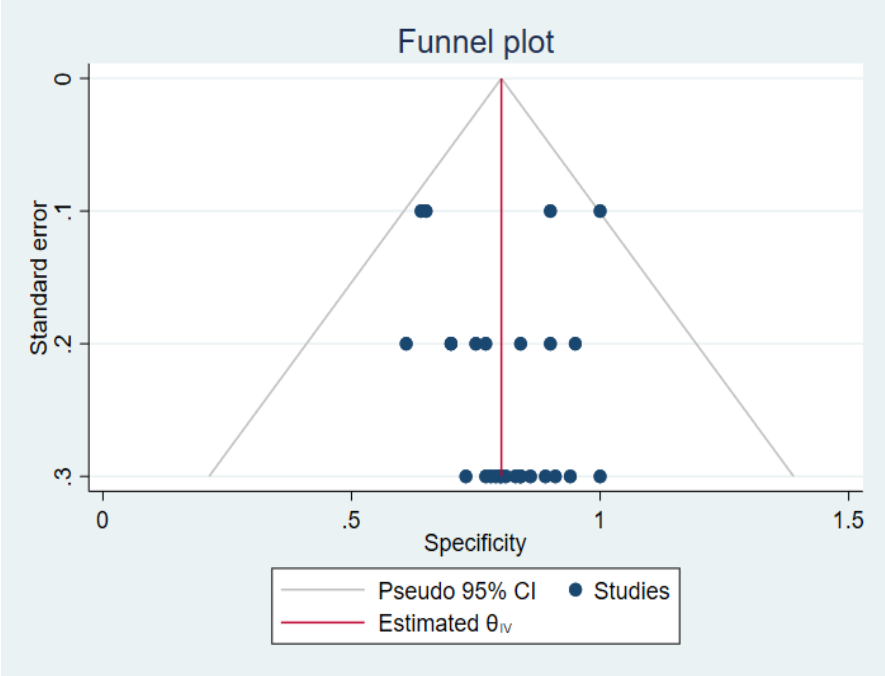

Fig. 7. Funnel plots for publication bias of specificity.

4. Discussion

Squamous cell cancer of the head and neck is characterized by a heterogeneous group of malignancies affecting the oral cavity, nasal cavity, paranasal sinuses, larynx, pharynx, and salivary glands.[36] According to the studies, several levels of regulatory molecules (mRNA, miRNA, and protein) are involved in developing and maintaining cancer phenotypes.[37] In addition to the key biological function of miRNA in OSCC tumor genesis, it has been shown that the expression levels of some miRNAs are related to clinical pathology variables and have diagnostic and prognostic value in OSCC.[38] miRNAs are effectively present in bodily fluids such as blood, saliva, urine, and breathing. Therefore, they can be made available by non-invasive methods.[39] The survival rate for patients with OSCC is five years; Despite the advances in treatment methods, the survival rate in these patients has not increased and has remained almost unchanged.[40] Usually, these patients are diagnosed in the final stages of the disease, and the analysis of the biopsy sample taken is long. Therefore, invasive diagnostic methods should replace faster diagnostic methods.[41] Therefore, investigating minimally invasive diagnostic methods is very important; in the present study, the diagnostic value of miRNAs in diagnosing OSCC was measured. The selected studies were of high quality, and few were of medium quality; as seen in the meta-analysis, there is low heterogeneity between studies, which indicates that the findings of the present study can provide good and sufficient evidence. In this

meta-analysis, miRNAs showed high and acceptable sensitivity and specificity for OSCC diagnosis. Also, by subgroup meta-analysis, it was observed that the diagnostic value of miRNAs in blood, saliva, and serum is almost the same. Statistically, no significant difference was observed between the three groups. The findings of the present study confirm the evidence that miRNAs are a potential diagnostic biomarker in patients with OSCC. Based on the sample size of the studies, it can be seen that the sensitivity and specificity are higher in the studies with a smaller sample size; therefore, it is necessary to conduct studies with a higher sample size because the diagnostic efficiency may have been exaggerated in studies with a small sample size. Also, higher sensitivity and specificity were reported in studies with medium quality compared to studies with high quality. Therefore, the diagnostic efficiency may be overestimated in medium-quality studies; it is necessary to confirm the finding of the present study. Obedience should be done with a similar cognitive method and higher quality. Most of the studies were done on saliva samples, which shows that using saliva samples instead of blood and serum can have good diagnostic efficiency. In the selected studies, different types of miRNAs were used to check the diagnostic accuracy of OSCC. However, due to the high dispersion between the miRNAs used, a subgroup meta-analysis was performed; the findings show that the combined use of several miRNAs can play an important role in diagnosing OSCC. Also, a subgroup meta-analysis was impossible due to the scattering of published data in studies such as smoking habits and alcohol consumption. Future studies need to investigate the effect of these two parameters.

5. Conclusion

Meta-analysis of the present study shows that miRNAs can be used to diagnose OSCC with high accuracy is high; Blood, saliva, and serum miRNAs had similar sensitivity and specificity and did not have significant differences in OSCC diagnosis. The present study provides good evidence for the diagnostic value of miRNAs in OSCC. However, studies with a higher sample size and standard cognitive methodology must confirm the evidence.

Conflict of Interest

The authors declared that there is no conflict of interest.

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