eISSN 2255-0569

ORIGINAL

Evaluation of the Sensitivity and Specificity of MicroRNA in the Diagnosis of Cervical Cancer: A Systematic Review and Meta-analysis

Evaluación de la Sensibilidad y Especificidad del MicroRNA en el Diagnóstico del Cáncer Cervical: Una Revisión Sistemática y Meta-análisis

Fatemeh Rabiee[1], Fatemeh Salehi Kahrizsangi[2], Neda Mehralizadeh[3], Somaye Jamali[4]

1. Department of Pharmacology and Pharmaceutical, Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
2. Department of Pathology, Faculty of Medicine, Islamic Azad University, Sari Branch, Sari, Iran
3. Department of Cardiology, Rajayi Heart Center, Iran University of Medical Sciences, Tehran, Iran
4. Department of Internal Medicine, Noor Iranian Polyclinic, Muscat, Oman

Corresponding author
Somaye Jamali
E-mail: dr.somayejamali@yahoo.com
somaye_jamali@yahoo.com

Received: 20 - V - 2023
Accepted: 23 - VI - 2023

doi: 10.3306/AJHS.2023.38.06.26

Abstract

Objectives: New regulatory RNAs called microRNAs are about 22 nucleotides in length. Also, a number of human cancers are also caused by microRNAs; which function both as oncogenes and suppressors. We evaluated the sensitivity and specificity of MicroRNA in diagnosing cervical cancer in the present study.
Methods: A search of the international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase of keywords related to the study objectives was conducted until March 2023. A fixed effect model with the inverse-variance method was used to calculate effect size (95% confidence interval). The meta-analysis was performed using STATA/MP. V17 software.
Results: A meta-analysis was conducted using nine articles in the present study. The sensitivity of microRNA-21 for diagnosis of cervical cancer was 86% (ES: 0.86 [95% CI: 0.70, 1.01]), specificity of microRNA-21 to diagnose cervical cancer was 84% (ES: 0.84 [95% CI: 0.68, 1.00]. The AUC of microRNA-21 on tissue models to diagnose cervical cancer was 85% (ES: 0.85 [95% CI: 0.69, 1.02].
Conclusions: According to the present meta-analysis and the role of microRNA-21 in cervical cancer progression, and considering its relationship with clinic pathological factors, it can be considered a differential marker with high sensitivity and specificity.

Key words: Diagnosis, Neoplasms, Sensitivity and Specificity, Uterine Cervical Neoplasms.

Resumen

Objetivos: Los nuevos ARN reguladores denominados microARN tienen una longitud de unos 22 nucleótidos. Además, varios tipos de cáncer humano también son causados por microARN; que funcionan tanto como oncogenes como supresores. Evaluamos la sensibilidad y especificidad de MicroRNA en el diagnóstico de cáncer de cuello uterino en el presente estudio.
Métodos: Se realizó una búsqueda en las bases de datos internacionales PubMed, Scopus, Science Direct, ISI, Web of Knowledge y Embase de palabras clave relacionadas con los objetivos del estudio hasta marzo de 2023. Se utilizó un modelo de efectos fijos con el método de la varianza inversa para calcular tamaño del efecto (intervalo de confianza del 95%). El metanálisis se realizó con STATA/MP. programa V17.
Resultados: Se realizó un metanálisis utilizando nueve artículos en el presente estudio. La sensibilidad del microARN-21 para el diagnóstico de cáncer de cuello uterino fue del 86 % (ES: 0,86 [IC del 95 %: 0,70, 1,01]), la especificidad del microARN-21 para el diagnóstico del cáncer de cuello uterino fue del 84 % (ES: 0,84 [IC del 95 %: 0,68, 1,00]. El AUC de microARN-21 en modelos de tejido para diagnosticar cáncer de cuello uterino fue del 85 % (ES: 0,85 [IC del 95 %: 0,69, 1,02].
Conclusiones: De acuerdo con el presente metaanálisis y el papel del microARN-21 en la progresión del cáncer de cérvix, y considerando su relación con factores clínico patológicos, puede considerarse un marcador diferencial con alta sensibilidad y especificidad.

Palabras clave: Diagnóstico, Neoplasias, Sensibilidad y Especificidad, Neoplasias del Cuello Uterino.

Cite as: Rabiee F, Kahrizsangi FS, Mehralizadeh N, Ja S. Evaluation of the Sensitivity and Specificity of MicroRNA in the Diagnosis of Cervical Cancer: A Systematic Review and Meta-analysis. *Academic Journal of Health Sciences 2023*; 38 (6):26-31 doi: 10.3306/AJHS.2023.38.06.26

Introduction

The fourth most common cancer among women is cervical cancer. In 2018, 570,000 new cases occurred, which is 7.5% of all women's deaths from cancer, and annually more than 311,000 deaths from cervical cancer occur worldwide, more than 85% of which occur in less developed societies[1]. The World Health Organization has estimated that in 2030, this cancer will kill about 474,000 women annually, and low- and middle-income countries will suffer 95% of these deaths[2]. Cervical cancer screening (Pap smear test) by detecting abnormal changes in cervical cells that may lead to cervical cancer if not treated, and also by detecting the presence of certain types of human papillomavirus (HPV) that cause fundamental changes in the Cervix and eventually lead to cancer, it prevents cancer[3,4]. HPV 16 and HPV 18 strains cause approximately 70% of cervical carcinoma cases[5,6]. The findings of the studies have shown that, in addition to the mentioned cases, personal and sexual health, having several sexual partners, poverty, a history of sexually transmitted infections, smoking, immune deficiency, contraceptive pills, and early initiation of sexual intercourse can cause the disease, help people with cervical cancer[7-11].

Based on the available evidence, microRNAs can also play a role in cervical carcinogenesis[12]. MicroRNAs are a large subgroup of 18-25 nucleotide non-coding RNAs that are evolutionarily conserved. Several studies have determined that microRNAs play a critical role in cancer initiation and progression[13]. Depending on the type of mRNAs they inhibit, microRNAs can suppress tumors or inhibit oncogenesis[14]. Proliferation and invasion of cells are stimulated by microRNA-21, while the process of apoptosis is inhibited[15]. Growth, programmed death, differentiation, and cell proliferation are all regulated by microRNA interactions with target genes, and microRNAs have been directly implicated in cancer development[16]. Cancer samples show abnormal expression of many microRNAs based on their structure and function[17].

The expression of microRNAs is also associated with functional differences between tumor types and stages of cancer[18]. The expression of miRNA is associated with clinical and biological characteristics of tumors, such as tissue type, differentiation, invasion, and response to treatment[19]. Human serum or plasma can be studied to identify cancer miRNAs and tumor cells without the use of invasive methods. miRNAs can be used as diagnostic markers by examining human serum or plasma. Malignant cells are easily available, except for leukemia[20,21]. Early diagnosis of cancer can be enhanced by using miRNAs closely related to malignant phenotypes as diagnostic markers[22]. As most common cancer screening methods are not able to detect the disease early, a key aspect of the timely diagnosis of cancer is the identification of tumor miRNAs in the bloodstream during the gradual progression of the disease. Many studies have indicated that microRNA-21 plays an oncogenic and anti-apoptotic role[23]. Based on the findings of studies in patients with cervical cancer, the level of microRNA-21 increases, which can effectively diagnose cervical cancer as a diagnostic biomarker[24-26]. In many studies, increased expression of microRNA-21 has been investigated in all types of cancers, especially cervical cancer; However, the findings of the studies are not consistent, and there are many challenges; Therefore, in the present study, an attempt has been made to investigate the results of microRNA increased expression studies as a diagnostic and prognostic method in cervical cancer in order to provide stronger evidence. Therefore, MicroRNA was evaluated to determine its sensitivity and specificity for the diagnosis of cervical cancer in the current study.

Methods

Search strategy

The present study was conducted using the PRISMA 2020 checklist[27]. Searches were conducted in the international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase using keywords related to the study objectives; all articles were reviewed until March 2023. The PICO strategy (Population, Intervention, Comparison, and Outcomes) is summarized in **table I**. Keywords and the Mesh terms:

(((((("Neoplasms"[Mesh] OR "Early Detection of Cancer"[Mesh]) OR "Neoplasms/diagnosis"[Mesh]) OR "Uterine Cervical Neoplasms "[Mesh]) AND "MicroRNAs"[Mesh]) OR ("Biomarkers"[Mesh] OR "Biomarkers, Tumor"[Mesh])) AND "Diagnosis"[Mesh]) AND "Sensitivity and Specificity"[Mesh].

Table I: PICO strategy.

PICO strategy	Description
P	Population: Patients with cervical cancer
I	Intervention: microRNA-21
C	Comparison: healthy controls
O	Outcome: Sensitivity and Specificity

Data collection

First, a checklist including the author's name, publication year, study design, sample size, Cancer stage, and MicroRNA was prepared. The study data were entered in this checklist and summarized in Table II. The sensitivity and diagnostic specificity data of the studies were extracted and used for meta-analysis. Two independent, blinded reviewers screened each record, and a third person retrieved each report. The selection of articles was based on inclusion and exclusion criteria.

Inclusion and Exclusion criteria

Only articles published in English, prospective and retrospective studies, case–control studies, miRNA

models based on qRT-PCR data, and reported diagnostic performance data were included. Case studies, case reports, and review articles; studies without access to the full text were excluded from the study.

Risk assessment

The quality of studies was measured using Diagnostic Accuracy Studies (QUADAS-2)[28]. In this tool, four areas of patient selection, index test, reference standard, and schedule are examined; Assessment of bias is rated as "high," "low," and "uncertain."

Data analysis

I2 coefficients were used to estimate potential heterogeneity between studies. Low heterogeneity is defined as values less than 50%, moderate heterogeneity is defined as values between 50% and 75%, and high heterogeneity is defined as values greater than 75%. A fixed effect model with the inverse-variance method was used to calculate the effect size (95% confidence interval). STATA/MP. Meta-analysis was conducted using V17 software.

Results

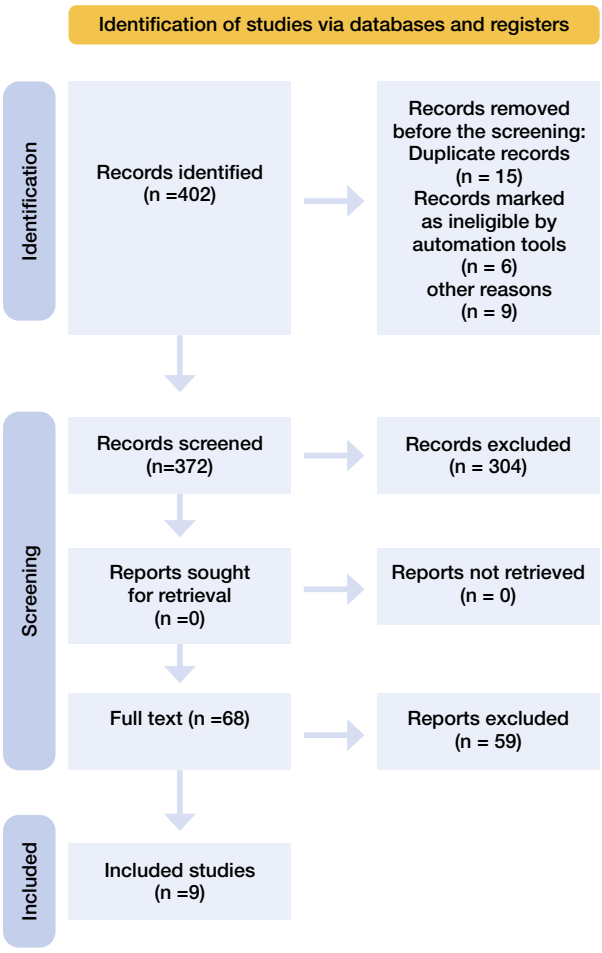
Study selection

402 articles were found utilizing keywords in the initial search, and they were all entered into EndNote X8 software; Duplicate articles, articles with inappropriate and inconsistent titles, and other reasons were removed, then the abstracts of 372 articles were reviewed, 304 articles were removed (based on the inclusion and exclusion criteria). The full text of 68 articles was reviewed. Articles whose full text was incomplete had incomplete data, articles that were not in line with the objectives of the study were excluded, and finally, nine articles were selected (**Figure 1**). All the steps of searching and reviewing the articles were done by two blind observers and evaluated by a third observer.

Study characteristics

One prospective study and eight case-control were selected and included in the present meta-analysis. A total of 1324 patients (Experimental: 707; Control: 617); **table II** shows a summary of the data extracted.

Figure 1: PRISMA 2020 Checklist.



Risk assessment

All studies had high quality (low risk of bias).

Diagnostic accuracy

Subgroup meta-analysis

The AUC of MicroRNA to diagnose cervical cancer was 82% (ES: 0.82 [95% CI: 0.75, 0.88], (I^2=0%; p =0.98; low heterogeneity) (**Figure 2**). According to subgroup meta-analysis AUC of microRNA-21 to diagnose cervical cancer was 84% (ES: 0.84 [95% CI: 0.74, 0.93], (I^2=0%; p =0.86; low heterogeneity).

Table II: Full-text demographic data extracted from selected studies.

n	Study. Years	Study Design	Source of MiRNAs	Number of Patients		Cancer Stage	MicroRNA
				Cancer Group	Control Group		
1	Aftab et al., 2021[29]	Prospective	Tissue	40	30	I-IV	miR-21, miR-199a, and miR-155-5p
2	Du et al., 2020[30]	Case-control	Serum	140	140	I-II	miRNA-29a, miRNA25, miRNA-486-5p
3	Ruan et al., 2020[31]	Case-control	Serum	68	57	NR	microRNA-21 and microRNA-124
4	Zamani et al., 2020[32]	Case-control	Tissue	50	46	NR	miR-21 and miR29-a
5	Qiu et al., 2020[24]	Case-control	Serum	112	90	I-IIA	miR-21
6	Ma et al., 2019[33]	Case-control	Plasma	97	87	I-II	miR-21
7	Zhu et al., 2018[34]	Case-control	Tissue	25	23	NR	miR-21-5p, miR-34a
8	Park et al., 2017[35]	Case-control	Tissue	Serum	50	I-IIA	MiR-9, miR-21, and miR-155
9	Jia et al., 2015[36]	Case-control	Serum	123	94	III	miR-21, -29a, -25, -200a and -486-5p

Figure 2: AUC of MicroRNA to diagnose cervical cancer.

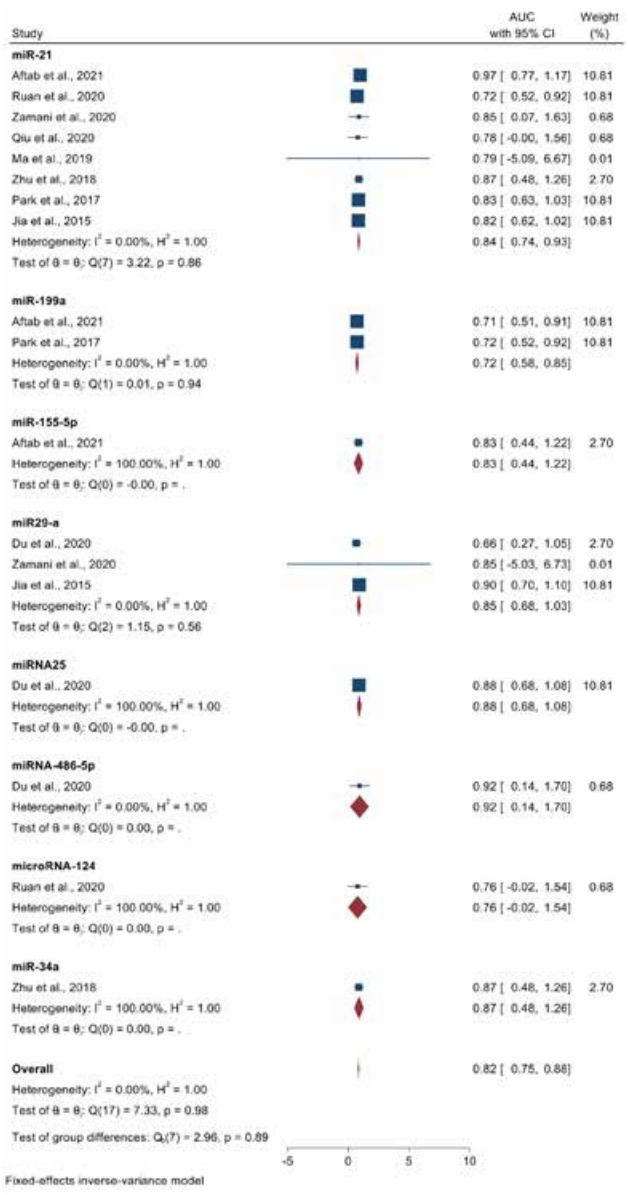


Figure 3: AUC of MicroRNA to diagnose cervical cancer.

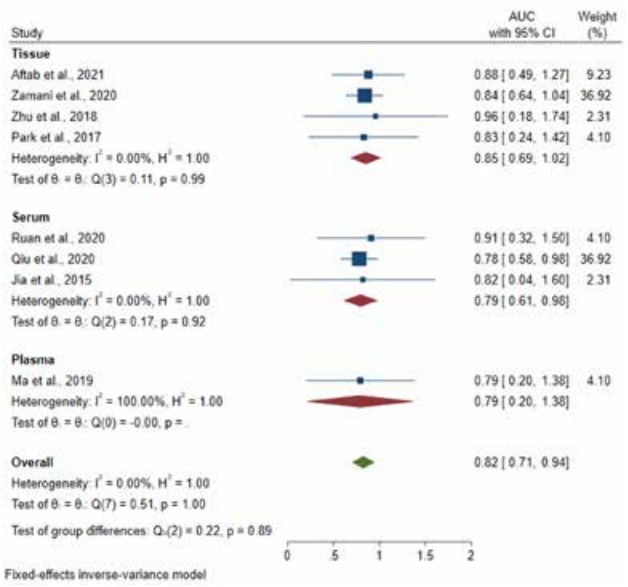


Figure 4: Sensitivity of microRNA-21 to diagnose cervical cancer.

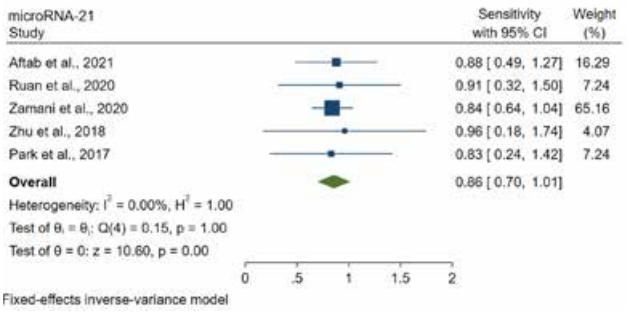
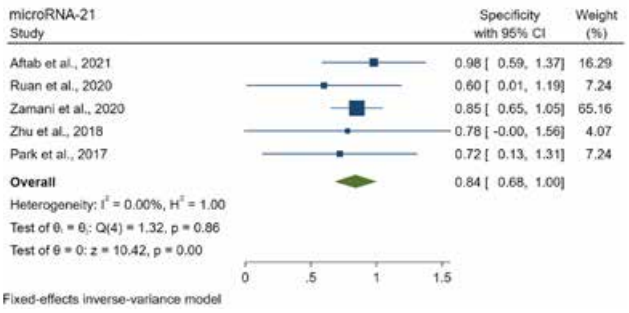


Figure 5: Specificity of microRNA-21 to diagnose cervical cancer.



The AUC of microRNA-21 on tissue models to diagnose cervical cancer was 85% (ES: 0.85 [95% CI: 0.69, 1.02], (I^2=0%; p =0.99; low heterogeneity) (**Figure 3**). AUC of microRNA-21 on serum models to diagnose cervical cancer was 79% (ES: 0.79 [95% CI: 0.61, 0.98], (I^2=0%; p =0.92; low heterogeneity) (**Figure 3**). AUC of microRNA-21 on plasma models to diagnose cervical cancer was 79% (ES: 0.79 [95% CI: 020, 1.38], (I^2=0%; p =0.92; low heterogeneity) (**Figure 3**).

Sensitivity and specificity

The sensitivity of microRNA-21 to diagnose cervical cancer was 86% (ES: 0.86 [95% CI: 0.70, 1.01], (I^2=0%; p =1.00; low heterogeneity) (**Figure 4**). Specificity of microRNA-21 to diagnose cervical cancer was 84% (ES: 0.84 [95% CI: 0.68, 1.00], (I^2=0%; p =0.86; low heterogeneity) (**Figure 5**).

Discussion

In patients with cervical cancer, the expression of microRNA-21 may act as a diagnostic marker. An increase in microRNA-21 results in a reduction in tumor suppressor protein expression and an increase in oncogenic protein expression[35,37,38]. Considering these roles, microRNA-21 can be a suitable option for investigating cancer and metastasis development. The increased expression of microRNA-21 in cancer tissues makes it useful for early

metastasis detection and follow-up. Because oncogenic and apoptotic properties of this microRNA affect tumor cells, it causes a disturbance in the apoptosis pathway, which favors the survival of cancer cells[39].

In the present study, subgroup meta-analysis showed that the diagnostic accuracy of microRNAs in cervical cancer diagnosis is acceptable. Also, microRNA-21 was used in articles more than other microRNAs; for this reason, its sensitivity and specificity were investigated. Became; Meta-analysis showed that the sensitivity and specificity of microRNA-21 in cervical cancer diagnosis is high. Also, subgroup meta-analysis showed that the AUC of microRNA-21 on tissue models to diagnose cervical cancer is higher than serum and plasma models. There was low heterogeneity between studies, so the present study provides strong evidence, and the selected studies were of high quality. One of the weaknesses of the present study was that only one prospective study was investigated, and no randomized clinical trial study was found. The present study observed that microRNAs are potential cancer biomarkers, and the diagnostic importance of microRNA-21 in cervical cancer was well-defined. Also, other studies have shown that microRNA-21 has high sensitivity and specificity in diagnosing other cancers[40-42]. Changes in the expression levels of miRNAs can be stably and easily measured in tumor tissues, plasma, serum, and urine samples[29]. Meta-analysis studies have shown that in patients with all types of cancers, microRNA-21 is an important and independent prognostic biomarker for patient survival[43,44]. It has been well studied that MicroRNA-21 is one of the most well-known microRNAs. On the other hand, this microRNA plays an oncogenic role by turning off a series of essential genes that lead to cancerous cells. This microRNA is found in a variety of cancers[45].

Conclusion

Considering the results of the present meta-analysis and the low heterogeneity between studies, the present study provides strong evidence. Based on the present meta-analysis and the role of microRNA-21 in the progression of cervical cancer, and considering its relationship with clinicopathological factors, it can be considered a differential marker with high sensitivity and specificity. Also, cervical cancer patients can benefit from this non-invasive method for early diagnosis. MicroRNA-21 has an oncogenic role, and by measuring its amount in patients' tissue, it is possible to check the progress of cancer.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. World Health Organization. WHO recommendations on self-care interventions: human papillomavirus (HPV) self-sampling as part of cervical cancer screening. World Health Organization; 2020.

2. Steben M. Political Considerations. Canada's Role in Accelerating Global Elimination of Cervical Cancer. 2019.

3. Arora A, Tripathi A, Bhan A. Classification of cervical cancer detection using machine learning algorithms. In2021 6th International conference on inventive computation technologies (ICICT) 2021;827-35. https://doi.org/10.1109/ICICT50816.2021.9358570.

4. Savira M, Putra AE, Donel S, Mutia L, Ovinita S, Lipoeto NI. L1 Gene Molecular Variation of Human Papilloma Virus Type 16 from Cervical Cancer Patient.2020. https://doi.org/10.21203/rs.3.rs-32572/v1.

5. Oyouni AA. Human papillomavirus in cancer: Infection, disease transmission, and progress in vaccines. Journal of Infection and Public Health. 2023;16(4):626-31. https://doi.org/10.1016/j.jiph.2023.02.014.

6. Dinita Devi N, Chyrmang D, Baidya K, Sobita Devi Y. Askin tumor: a case report of a rare tumor. International Journal of Scientific Research in Dental and Medical Sciences. 2021 Sep 19;3(3):153-5. https://doi.org/10.30485/ijsrdms.2021.300418.1183.

7. Chen Y, Sun B, Marcella C. Evaluation of the Diagnostic Accuracy of Superparamagnetic Iron Oxide Nanoparticles on Breast Cancer: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2023;5(1):27-34. https://doi.org/10.30485/ijsrdms.2023.386797.1445.

8. Gravitt PE, Winer RL. Natural history of HPV infection across the lifespan: role of viral latency. Viruses. 2017;9(10):267. https://doi.org/10.3390/v9100267.

9. Small Jr W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: a global health crisis. Cancer. 2017;123(13):2404-12. https://doi.org/10.1002/cncr.30667.

10. Temesgen MM, Alemu T, Shiferaw B, Legesse S, Zeru T, Haile M, et al. Prevalence of oncogenic human papillomavirus (HPV 16/18) infection, cervical lesions and its associated factors among women aged 21–49 years in Amhara region, Northern Ethiopia. Plos one. 2021;16(3):e0248949. https://doi.org/10.1371/journal.pone.0248949.

11. Zena D, Elfu B, Mulatu K. Prevalence and Associated Factors of Precancerous Cervical Lesions among Women in Ethiopia: A Systematic Review and Meta-Analysis. Ethiopian Journal of Health Sciences. 2021;31(1):189-200. https://doi.org/10.4314/ejhs.v31i1.20.

12. Rokos T, Kudela E, Pribulova T, Kozubik E, Holubekova V, Biringer K. miR-21–A Novel Marker for Cervical Cancer?. Actual Gynecology & Obstetrics/Aktuální Gynekologie a Porodnictví. 2021;13:48-56.

13. Prakash P, Widjaja J, Marcella C, Sun B. Evaluation of the Sensitivity and Specificity of Circulating MicroRNAs to Diagnose Breast Cancer: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2023;5(1):35-47. https://doi.org/10.30485/ijsrdms.2023.389124.1460.

14. Tornesello ML, Faraonio R, Buonaguro L, Annunziata C, Starita N, Cerasuolo A, et al. The role of microRNAs, long non-coding RNAs, and circular RNAs in cervical cancer. Frontiers in oncology. 2020;10:150. https://doi.org/10.3389/fonc.2020.00150.

15. Lu JM, Zhang ZZ, Ma X, Fang SF, Qin XH. Repression of microRNA-21 inhibits retinal vascular endothelial cell growth and angiogenesis via PTEN dependent-PI3K/Akt/VEGF signaling pathway in diabetic retinopathy. Experimental Eye Research. 2020;190:107886. https://doi.

org/10.1016/j.exer.2019.107886.

16. Far BF, Vakili K, Fathi M, Yaghoobpoor S, Bhia M, Jamal MR. The role of microRNA-21 (miR-21) in pathogenesis, diagnosis, and prognosis of gastrointestinal cancers: A review. Life Sciences. 2022:121340. https://doi.org/10.1016/j.lfs.2022.121340.

17. Naeli P, Yousefi F, Ghasemi Y, Savardashtaki A, Mirzaei H. The role of MicroRNAs in lung cancer: implications for diagnosis and therapy. Current molecular medicine. 2020;20(2):90-101. https://doi.org/10.2174/1566524019666191001113511.

18. He L, Zhou Y. Evaluation of increased microRNA-21 in the serum of patients with cardia cancer. Cellular and Molecular Biology. 2022;68(4):60-5.

19. Babaei K, Shams S, Keymoradzadeh A, Vahidi S, Hamami P, Khaksar R, et al. An insight of microRNAs performance in carcinogenesis and tumorigenesis; an overview of cancer therapy. Life sciences. 2020;240:117077. https://doi.org/10.1016/j.lfs.2019.117077.

20. Han W, Cui H, Liang J, Su X. Role of MicroRNA-30c in cancer progression. Journal of Cancer. 2020;11(9):2593-2601. https://doi.org/10.7150%2Fjca.38449.

21. Negrini M, Nicoloso MS, Calin GA. MicroRNAs and cancer—new paradigms in molecular oncology. Current opinion in cell biology. 2009;21(3):470-9. https://doi.org/10.1016/j.ceb.2009.03.002.

22. Li C, Zhou T, Chen J, Li R, Chen H, Luo S, et al. The role of Exosomal miRNAs in cancer. Journal of translational medicine. 2022;20(1):1-5. https://doi.org/10.1186/s12967-021-03215-4.

23. Schaefer A, Jung M, Kristiansen G, Lein M, Schrader M, Miller K, et al. MicroRNAs and cancer: current state and future perspectives in urologic oncology. InUrologic Oncology: Seminars and Original Investigations 2010;28(1):4-13. https://doi.org/10.1016/j.urolonc.2008.10.021.

24. Qiu H, Liang D, Liu L, Xiang Q, Yi Z, Ji Y. A novel circulating miRNA-based signature for the diagnosis and prognosis prediction of early-stage cervical cancer. Technology in Cancer Research & Treatment. 2020;19:1533033820970667. https://doi.org/10.1177/1533033820970667.

25. Khalili M, Ebrahimi M, Fazlzadeh A, Moradkhani A, Jamali S. Evaluation of the Survival Rate and Clinical Outcome of Nanodrug Administration for the Treatment of Lung Cancer: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2022;4(3):140-7. https://doi.org/10.30485/ijsrdms.2022.359947.1363.

26. Han Y, Xu GX, Lu H, Yu DH, Ren Y, Wang L, et al. Dysregulation of miRNA-21 and their potential as biomarkers for the diagnosis of cervical cancer. International journal of clinical and experimental pathology. 2015;8(6):7131-39.

27. Jamali S, Nouhravesh M. Evaluation of the Clinical Outcome of Carbon Nanoparticles on Thyroid Cancer: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2023;5(1):48-56. https://doi.org/10.30485/ijsrdms.2023.389580.1464.

28. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.

29. Aftab M, Poojary SS, Seshan V, Kumar S, Agarwal P, Tandon S, et al. Urine miRNA signature as a potential non-invasive diagnostic and prognostic biomarker in cervical cancer. Scientific reports. 2021;11(1):1-3. https://doi.org/10.1038/s41598-021-89388-w.

30. Du S, Zhao Y, Lv C, Wei M, Gao Z, Meng X. Applying serum proteins and microRNA as novel biomarkers for early-stage cervical cancer detection. Scientific Reports. 2020;10(1):1-8. https://doi.org/10.1038/s41598-020-65850-z.

31. Ruan F, Wang YF, Chai Y. Diagnostic values of miR-21, miR-124, and M-CSF in patients with early cervical cancer. Technology in Cancer Research & Treatment. 2020;19:1-8. https://doi.org/10.1177/1533033820914983.

32. Zamani S, Hosseini SM, Sohrabi A. miR-21 and miR29-a: potential molecular biomarkers for HPV genotypes and cervical cancer detection. Microrna. 2020;9(4):271-5. https://doi.org/10.2174/2211536609666191115110015.

33. Ma G, Song G, Zou X, Shan X, Liu Q, Xia T, et al. Circulating plasma microRNA signature for the diagnosis of cervical cancer. Cancer Biomarkers. 2019;26(4):491-500. https://doi.org/10.3233/CBM-190256.

34. Zhu Y, Han Y, Tian T, Su P, Jin G, Chen J, et al. MiR-21-5p, miR-34a, and human telomerase RNA component as surrogate markers for cervical cancer progression. Pathology-Research and Practice. 2018;214(3):374-9. https://doi.org/10.1016/j.prp.2018.01.001.

35. Park S, Eom K, Kim J, Bang H, Wang HY, Ahn S, et al. MiR-9, miR-21, and miR-155 as potential biomarkers for HPV positive and negative cervical cancer. BMC cancer. 2017;17:1-8. https://doi.org/10.1186/s12885-017-3642-5.

36. Jia W, Wu Y, Zhang Q, Gao GE, Zhang C, Xiang Y. Expression profile of circulating microRNAs as a promising fingerprint for cervical cancer diagnosis and monitoring. Molecular and clinical oncology. 2015;3(4):851-8. https://doi.org/10.3892/mco.2015.560.

37. Liu J, Sun H, Wang X, Yu Q, Li S, Yu X, et al. Increased exosomal microRNA-21 and microRNA-146a levels in the cervicovaginal lavage specimens of patients with cervical cancer. International journal of molecular sciences. 2014;15(1):758-73. https://doi.org/10.3390/ijms15010758.

38. Yang HS, Jansen AP, Komar AA, Zheng X, Merrick WC, Costes S, et al. The transformation suppressor Pdcd4 is a novel eukaryotic translation initiation factor 4A binding protein that inhibits translation. Molecular and cellular biology. 2003;23(1):26-37. https://doi.org/10.1128/MCB.23.1.26-37.2003.

39. Büssing I, Slack FJ, Großhans H. let-7 microRNAs in development, stem cells and cancer. Trends in molecular medicine. 2008;14(9):400-9. https://doi.org/10.1016/j.molmed.2008.07.001.

40. Gokhale MV, Agarwal P, Biswas DA. Does Fat Distribution Play a Role in Obesity-Associated Iron Deficiency Anemia? An Anthropometry-based Analysis in Young Women. International Journal of Scientific Research in Dental and Medical Sciences. 2022;4(3):119-26. https://doi.org/10.30485/ijsrdms.2022.351785.1335.

41. Wilting SM, Snijders PJ, Verlaat W, Jaspers AV, Van De Wiel MA, Van Wieringen WN, et al. Altered microRNA expression associated with chromosomal changes contributes to cervical carcinogenesis. Oncogene. 2013;32(1):106-16. https://doi.org/10.1038/onc.2012.20.

42. Zeng K, Zheng W, Mo X, Liu F, Li M, Liu Z, et al. Dysregulated microRNAs involved in the progression of cervical neoplasm. Archives of gynecology and obstetrics. 2015;292:905-13. https://doi.org/10.1007/s00404-015-3702-5.

43. Jiang G, Mu J, Liu X, Peng X, Zhong F, Yuan W, et al. Prognostic value of miR-21 in gliomas: comprehensive study based on meta-analysis and TCGA dataset validation. Scientific reports. 2020;10(1):4220. https://doi.org/10.1038/s41598-020-61155-3.

44. Irimie-Aghiorghiesei AI, Pop-Bica C, Pintea S, Braicu C, Cojocneanu R, Zimța AA, et al. Prognostic value of MiR-21: an updated meta-analysis in Head and Neck Squamous Cell Carcinoma (HNSCC). Journal of clinical medicine. 2019;8(12):2041. https://doi.org/10.3390/jcm8122041.

45. Parto P, Masoudian N. The expansion of Micro-RNA 21 (miR-21) in the serum of patients with gastric cancer. 2016.