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The diagnostic accuracy of serum and plasma microRNAs in detection of cervical intraepithelial neoplasia and cervical cancer: A systematic review and *meta*-analysis

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ABSTRACT

Studies suggest a need for new diagnostic approaches for cervical cancer including microRNA technology. In this review, we assessed the diagnostic accuracy of microRNAs in detecting cervical cancer and Cervical Intraepithelial Neoplasia (CIN).

We performed a systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline for protocols (PRISMA-P). We searched for all articles in online databases and grey literature from 01st January 2012 to 16th August 2022. We used the quality assessment of diagnostic accuracy studies tool (QUADAS-2) to assess the risk of bias of included studies and then conducted a Random Effects Meta-analysis.

We identified 297 articles and eventually extracted data from 24 studies. Serum/plasma concentration miR-205, miR-21, miR-192, and miR-9 showed highest diagnostic accuracy (AUC of 0.750, 0.689, 0.980, and 0.900, respectively) for detecting CIN from healthy controls. MicroRNA panels (miR-21, miR-125b and miR-370) and (miR-9, miR-10a, miR-20a and miR-196a and miR-16–2) had AUC values of 0.897 and 0.886 respectively for detecting CIN from healthy controls. For detection of cervical cancer from healthy controls, the most promising microRNAs were miR-21, miR-205, miR-192 and miR-9 (AUC values of 0.723, 0.960, 1.00, and 0.99 respectively).

Abbreviations: CIN, Cervical Intraepithelial Neoplasia; microRNA, micro Ribonucleic Acid; Pap, Papanicolaou test; PCR, Polymerase Chain Reaction; VIA, Visual Inspection with Acetic acid; WHO, World Health Organisation.

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We report higher diagnostic accuracy of upregulated microRNAs, especially miR-205, miR-9, miR-192, and miR-21. This highlights their potential as stand-alone screening or diagnostic tests, either with others, in a new algorithm, or together with other biomarkers for purposes of detecting cervical lesions. Future studies could standardize quantification methods, and also study microRNAs in higher prevalence populations like in sub-Saharan Africa and South Asia.

Our review protocol was registered in PROSPERO (CRD42022313275).

1. Background

Worldwide, there were 770,828 estimated incident cervical cancer cases in 2020 (Sung et al., 2021). Cervical cancer is the second most common cancer among women aged 15 to 44 years worldwide (Sung et al., 2021; Bruni et al., 2019). Cervical cancer accounts for more than 270 000 deaths annually, 85 % of which occur in developing countries (WHO, 2020), especially in sub-Saharan Africa (Anorlu, 2008). Cervical Cancer stands at 43/100,000 cancer cases in East Africa (WHO, 2021), and in Uganda, there is a reported age standardized cervical cancer incidence higher than the global average at 56.2 per 100,000 women (WHO, 2021).

A well-proven way to prevent cervical cancer is to screen and detect pre-cancerous lesions before they transform into invasive cancer (WHO, 2020). In addition, cervical cancer is treatable when diagnosed in its early stages (Sankaranarayanan, 2014). However, only 5 % of women in low and middle-income countries undergo cervical cancer screening (Sibiya, 2012). The current approaches to cervical cancer screening and diagnosis include visual inspection with acetic acid, Pap smear cytology, colposcopy, and histology. However, Pap smear, the most widely used screening method, is limited by its low diagnostic accuracy, compared to newer DNA-based methods, especially in identifying cancer in dysplastic squamous and glandular cells of the cervix (WHO, 2020; Anorlu, 2008; Sankaranarayanan, 2014; Botha et al., 2010). Also, the current cervical cancer screening methods suffer cultural and religious drawbacks as well as social barriers related with women's willingness to take up cervical cancer screening and other barriers in similar contexts (Ndejjo et al., 2017). Therefore, new methods that are both sensitive and specific for significant pre-cancerous lesions or cancer, while being affordable, non–invasive and user-friendly, are urgently needed to screen for cervical cancer in developing countries (Sibiya, 2012). Any screening test must be able to detect almost all people with the disease especially in its preclinical stage, should be safe to administer, should carry along a reasonable cost and hence affordable, it should lead to improved health outcomes and also widely available to the population (Wilson et al., 1968). Though MicroRNAs require expensive equipment and complicated techniques for their measurement, efforts are being undertaken to not only standardize their detection methods but also to design MicroRNA based point of care devices that could be cheaper and easy to use.

1.1. The research gap

There are several circulating biomarkers of cervical cancer or cervical intraepithelial neoplasia that have been studied. However, their diagnostic value requires further investigation. MicroRNAs belong to a novel category of small non-coding RNA molecules that regulate a wide variety of pathophysiological processes (Farazi et al., 2013; Dai et al., 2016; Palanichamy and Rao, 2014). MicroRNAs were previously thought to exclusively exist in tumor cells, but currently it is known that they can exist in body fluids, especially blood (Turchinovich et al., 2011). Recent evidence suggests that exosomal microRNAs in blood have the potential to improve prognostic and diagnostic workup in cancer (Preethi et al., 2022). Moreover, they could easily be quantified in blood, based on standardized laboratory methods.

Specifically, for cervical cancer, earlier studies by Allegra, Alonci (Allegra et al., 2012) and Anindo and Yaqinuddin (Anindo and Yaqinuddin, 2012) revealed that microRNAs are expressed both in cancerous tissues and in serum. As a result, serum concentrations of micro RNAs have been proposed as diagnostic and prognostic monitoring tools for cancer (Wittmann and Jäck, 2010). Evidence strongly points to blood concentrations of micro RNAs being of prognostic value for cervical cancer (Ma et al., 2014; He et al., 2014; Liang et al., 2014; Luo et al., 2013; Luo et al., 2019; Cheung et al., 2012; Wang and Jiang, 2015; Wang et al., 2014; Park et al., 2014; Yang and Zhang, 2019; Yang et al., 2014). This indicates the potential role of microRNAs in cervical cancer screening, diagnosis, and prognostic monitoring. Several studies on premalignant lesions indicate that microRNAs are involved at every stage during the development of invasive cervical cancer (Rao et al., 2012; Pedroza-Torres et al., 2014; Ribeiro and Sousa, 2014; Sharma et al., 2014). Multiple studies have shown that a number of microRNAs are upregulated during the progression to cervical cancer (Gao et al., 2018). For instance, miR-10a has been shown to have an increased expression during the development of cervical cancer (Cheung et al., 2012; Wilting et al., 2013) as well as miR-20b (Cheung et al., 2012; Wilting et al., 2013), miR-9 (Cheung et al., 2012; Wilting et al., 2013; Zeng et al., 2015), miR-16 (Wilting et al., 2013; Li et al., 2011) and miR-106a (Wilting et al., 2013; Li et al., 2011). From a systematic review by Gao et al (Gao et al., 2018), miR-16, miR-106a, and miR-21 are equally upregulated and are associated with progression from intermediate stages to cervical cancer. miR-21 has specifically been shown by several studies to be upregulated during cervical carcinogenesis (Wilting et al., 2013; Zeng et al., 2015; Bumrungthai et al., 2015; Shishodia et al., 2015).

The first steps in microRNA analysis involve extraction and stabilization. MicroRNA detection in serum/plasma is done using quantitative reverse transcription Polymerase chain reaction (qRT-PCR). This normally employs miR-1228-3p as an internal control and a single microRNA-specific stem-loop RT-primer (Lyu et al., 2019; 2019.). The relative expression levels for each microRNAs are then calculated using the $2^{-\Delta\Delta Ct}$ method (Cao et al., 2021).

Different authors, however, report different sensitivity and specificity values for different microRNAs in respect to cervical cancer detection. In view of having new non-invasive, user-friendly, accurate, and a standardizable test, it is crucial to conduct this systematic review to compute the diagnostic accuracy of different serum microRNAs in the detection of cervical neoplasms. Specifically, our review determined the diagnostic accuracy of serum microRNAs in detecting cervical intraepithelial neoplasia and cervical cancer in women of reproductive age globally.

2. Materials and methods

Overall, we followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Diagnostic Test Accuracy (PRISMADTA) (Shamseer et al., 2015; McInnes et al., 2018; Salameh et al., 2020). We prepared a protocol for this review and registered it in PROSPERO database, number CRD42022313275, before publishing it in an open access peer reviewed journal (Ssedyabane et al., 2023).

2.1. Eligibility criteria

2.1.1. Study eligibility criteria

We included all original articles from prospective and retrospective

cohorts, cross-sectional, and case control studies that reported diagnostic accuracy or up/down regulation of individual or panels of serum or plasma microRNAs in the detection of cervical intraepithelial neoplasia or cervical cancer, in women aged 20 years and above, using histology as a gold standard. We also specified studies carried out from 01st January 2012 to 16th August 2022. We excluded all studies done on nonhuman participants, those that quantified microRNAs from specimens other than serum or plasma, those studies that never reported measures of diagnostic accuracy, studies that never used quantitative methods for microRNAs, and conference presentations as well as duplicate studies from the multiple databases searched. Fig. 1.

2.2. Search strategy

2.2.1. Data sources

Our data sources included databases, institutional websites, grey literature, and contacting authors from 01st January 2012 to 16th August 2022. To identify all the studies, we searched MEDLINE through PubMed platform, Web of Science, Embase through Ovid platform, CINAHL, as well as Scopus. We also searched for grey literature such as conference papers, technical reports, theses and dissertations in Google Scholar, Google, OpenGrey, ProQuest as well as British Library EThos. We screened through reference lists of included studies for additional eligible studies that could have been missed by the search.

2.2.2. Electronic search

The electronic search explored the combinations of the keywords covering the PICOS elements, and combining them by using Bollean logic operators "AND", "OR" or "NOT". The population component included the words "Uterine cervical neoplasms*" [Mesh] OR "Cervical cancer*" [tw] OR "Human uterine cancer*" [tw] OR "SCC" [tw] OR "Cancer of the cervix*" [tw] OR "Cervical intraepithelial neoplasia*" [tw] OR "CIN" [tw].

The intervention component included: "Circulating MicroRNA"

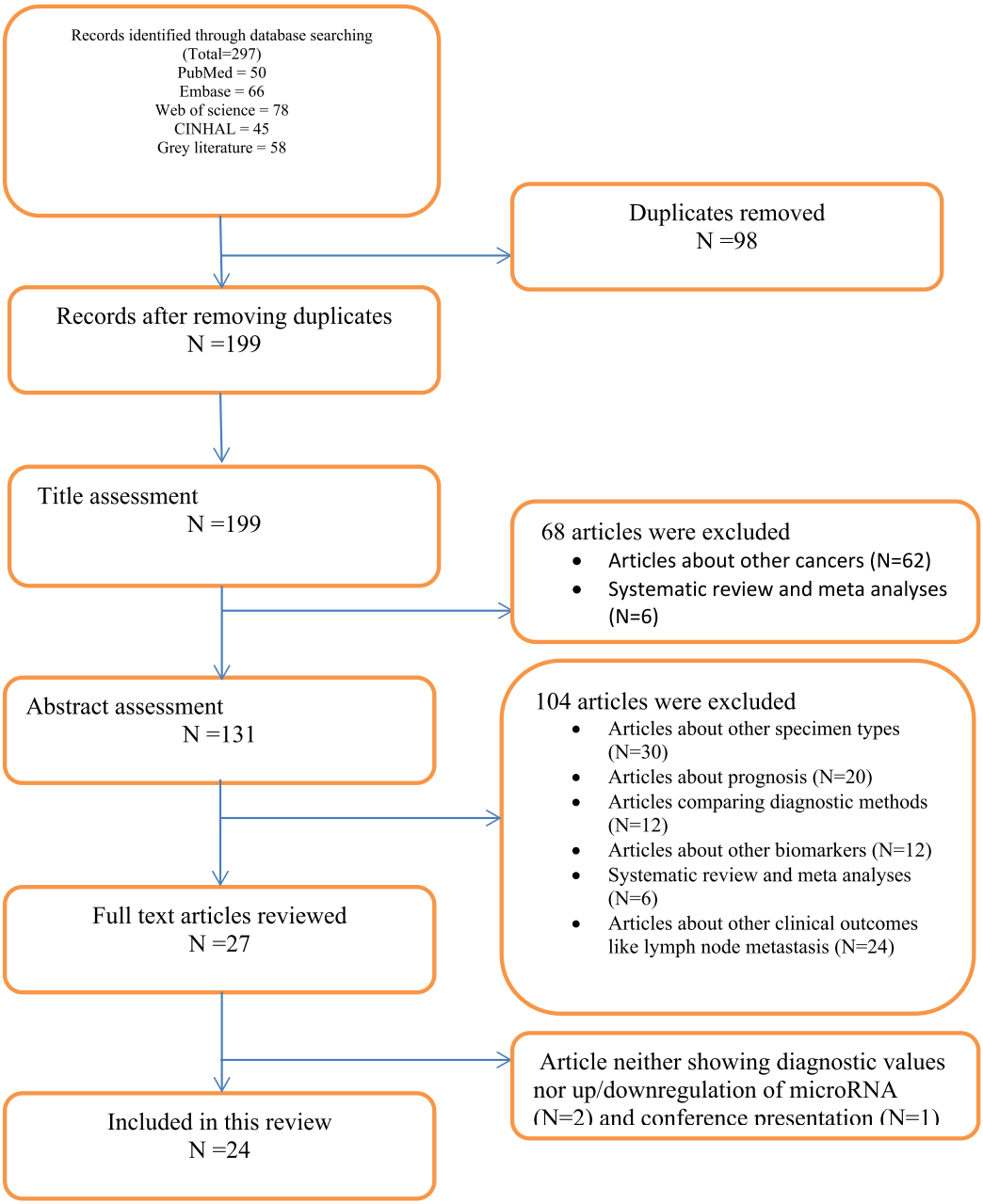

Fig. 1. Prisma Flow Chart.

[Mesh] OR "Circulating micro RNA" [tw] OR "microRNAs*" [tw] OR "Circulating miRNAs" [tw] OR "Circulating serum micro RNA" [tw] OR "microRNAs*"[tw] OR "Circulating serum miRNAs*"[tw] OR "Serum micro RNA" [tw] OR "microRNAs*"[tw] OR "Serum miRNAs*"[tw] OR "Biomarkers*"[tw] OR "Blood*"[tw] OR "micro RNA" [tw] OR "microRNAs*"[tw].

The outcome component included the words "Early Detection of Cancer*"[Mesh] OR Diagnosis*[tw] OR "Diagnostic value*" [tw] OR "Diagnostic utility*" [tw] OR Sensitivity* [tw] OR Specificity*[tw] OR Specific*[tw] OR Sensitive*[tw] OR "up regulated*" [tw] OR "Down regulated*" [tw] OR "increased*" [tw] OR "Decreased*" [tw] OR "positive predictive value*" [tw]. OR "Negative predictive value*" [tw].

For the comparator, there were no specific terms since they were already considered in the description of the population. Also, we did not include specific study designs in the search. We instead applied this in the eligibility criteria. The full search string is available in Table 2.

We combined keywords, medical subject headings terms (MESH) and their synonyms, and these were divided into three components. All the search components were combined with the Boolean operators "AND" while the keywords within each component were combined with "OR." There were no language restrictions for this review. We re-ran the searches just before the final analyses to retrieve the most recent studies eligible for inclusion.

2.2.3. Selection of studies and data extraction

Two reviewers (FS and ATK) performed duplicate and independent data extraction. The screening was a two-step process with initial title/abstract screening followed by retrieval of full texts and their screening. We have provided a list of excluded full-text articles with reasons for exclusion as an appendix of the final report.

We developed a data extraction form, and this was piloted initially to achieve a good level of agreement between the data extractors. Two reviewers (FS and ATK) independently extracted data from all eligible articles. The following data was extracted along the following headings:

Study characteristics: Author, year of publication, country, study design, sample size, and number of participants in each study group (control, CIN and cancer).

Laboratory test information: Index testing method, type of sample (e.g. whole blood, serum or plasma), and units of measurement. Type of individual microRNA(s) or panel of microRNA studied.

Gold standard: Histological confirmation or rule out of cancer.

Outcomes of interest: sensitivity, up up-regulated, down- regulated, increased, decreased, normal, specificity, predictive value of positivity and negativity as well as area under the curve.

2.2.4. Quality assessment

Two researchers (JNN and ATK) independently assessed articles for risk of bias and methodological quality using the quality assessment of diagnostic accuracy studies 2 tool (QUADAS-2) (Whiting et al., 2011). QUADAS-2 is widely recognized for diagnostic test accuracy research across four domains including: patient selection, index test, reference standard, and flow and timing. Application of this tool involved summarizing the review question, tailoring the tool to the review, generating review-specific guidelines, constructing a flow diagram for each primary study, and finally assessing the risk of bias and other concerns regarding applicability.

2.2.5. Minimizing publication bias, selection bias and bias during extraction of data from included studies

A third reviewer (JNN) validated the electronic search by performing a second and independent search in PubMed. The third reviewer also screened all articles that had been excluded by the initial reviewers. We resolved any disagreements among reviewers during screening, selection, abstraction, and risk of bias assessment through consensus where the need arose. By including both published and unpublished data from multiple sources in our search, we were able to minimize publication bias.

2.2.6. Statistical analyses and evidence synthesis

An overview of the available studies has been summarised in a flow chart and tabulated. We described data from eligible studies in a structured narrative synthesis. It is in this narrative synthesis that we summarised data as article author, year of publication, setting, study designs, sample size and population, type of laboratory index and reference tests, and diagnostic test accuracy outcomes.

We used the Lehmann model bivariate approach for the *meta*-analysis (Van Houwelingen et al., 1993). We also grouped microRNAs basing on up or downregulation. It is along these groupings that we further performed a *meta*-analysis. We derived pooled sensitivity as well as specificity for upregulated and downregulated microRNAs.

2.2.7. Handling of missing data

For variables that were needed but found either missing or not reported, we labeled them as not reported, "NR". Thereafter, we sought clarification from the authors on a case-by-case basis. We did not apply any secondary analyses on such missing data.

3. Results

3.1. Differences between the published protocol and the actual systematic review conduct

We did not find any single microRNA with measures of diagnostic accuracy being reported by more than two studies. Therefore, we did not perform a *meta*-analysis for individual microRNAs as proposed in the protocol. We instead performed a *meta*-analysis for groups of up-regulated and down-regulated microRNAs.

3.2. Systematic review flow, screening, and inclusion

As presented in the flow chart (Fig. 1), our first search identified 297 articles, from which 98 duplicates were removed. The remaining 199 articles were subjected to the title and abstract screening phase. At this stage, 172 articles did not meet the inclusion criteria. The remaining 27 articles were then submitted for full-text screening phase. Three (WHO, 2020) articles were excluded as they lacked information about diagnostic values of serum microRNA, did not show "up" or "down regulation", or were in abstract form only. Thus 24 studies met our criteria and were finally included in data extraction and analysis for this systematic review. We assessed these studies according to the PRISMA guidelines.

3.3. Characteristics of included studies

We present the characteristics of all included studies in Table 1. From a total of 24 studies, 20 were from China, 2 were from Japan and 2 from Iran. There was no single study from sub-Saharan Africa. Twenty one (Liang et al., 2014) studies were case control, while three (3) studies were cohort studies. For all included studies, the control groups included healthy women with a mean sample size of 83 (range 12–193), and totaling 1,441 people. The cervical intraepithelial neoplasia (CIN) groups included women with cervical intraepithelial neoplasia with a mean sample size of 92.5 (range 18–186), while the cervical cancer (CC) groups included women with cervical cancer with a mean sample size of 94 (range 18–184), and altogether giving 1487 participants.

21 Studies reported microRNAs in serum while three (WHO, 2020) studies reported to have evaluated microRNAs in plasma specimens. There were no other specimen types reported in any of the included studies that were evaluated for microRNAs. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was the method used to quantify microRNAs in all included studies

Table 1
Characteristics of included studies.

						Control Group		CIN Group		Cervical Cancer Group	
Author	**Year**	**Country**	**Study design**	**Specimen type**	**Detection method**	**N**	**Mean age**	**N**	**Mean age**	**N**	**mean age**
Zheng, Hou (Zheng et al., 2019)	2019	China	Case control	plasma	qRT-PCR	121	50	NI	NI	NI	NI
Kong, Tang (Kong et al., 2017)	2017	China	Case control	serum	qRT-PCR	NI	NI	NI	NI	NI	NI
Nagamitsu, Nishi (Nagamitsu et al., 2016)	2016	Japan	Case control	serum	qRT-PCR	31	39.0 ± 11.2	55	34.3	45	49.0 ± 14.1
Qiu et al. (Qiu et al., 2020)	2020	China	Case control	serum	qRT-PCR	90	NI	45	NI	112	NI
Xin et al. (Xin et al., 2016)	2016	China	cohort	serum	qRT-PCR	60	37.0 ± 8.4	126	36.0 ± 5.8	NI	NI
Liu et al. (Liu et al., 2015)	2015	China	Case control	serum	qRT-PCR	50	NI	86	NI	105	NI
Wei et al. (Wei et al., 2017)	2017	China	Case control	plasma	qRT-PCR	120	NI	120	NI	120	NI
Zhang et al. (Zhang et al., 2015)	2015	China	cohort	serum	qRT-PCR	193	NI	186	NI	184	NI
Yamanaka et al. (Yamanaka et al., 2021)	2021	Japan	Case control	serum	qRT-PCR	34	NI	64	NI	46	NI
Du et al. (Du et al., 2020)	2020	China	cohort	serum	qRT-PCR	NI	NI	NI	NI	NI	NI
Ruan et al. (Ruan et al., 2020)	2020	Iran	Case control	serum	qRT-PCR	57	48.39 + 10.17	NI	NI	64	47.57 + 8.19
Farzanehpour et al. (Farzanehpour et al., 2019)	2019	Iran	Case control	serum	qRT-PCR	36	36	18	47	18	61
Luo et al. (Luo et al., 2019)	2019	China	Case control	serum	qRT-PCR	NI	NI	NI	NI	NI	NI
Jia et al. (Jia et al., 2015)	2015	China	cohort	serum	qRT-PCR	94	NI	NI	NI	123	NI
Zhu et al. (Zhu et al., 2021)	2021	China	Case control	serum	qRT-PCR	30	NI	NI	NI	30	NI
Cao et al. (Cao et al., 2021)	2021	China	Case control	serum	qRT-PCR	119	NI	NI	NI	124	NI
Li et al. (Li et al., 2018)	2018	China	Case control	serum	qRT-PCR	21	NI	NI	NI	21	NI
Cao et al. (Cao et al., 2021)	2021	China	Case control	serum	qRT-PCR	18	NI	NI	NI	18	NI
Cao et al. (Cao et al., 2021)	2021	China	Case control	serum	qRT-PCR	60	NI	NI	NI	60	NI
Lv et al. (Lv et al., 2021)	2021	China	Case control	serum	qRT-PCR	22	NI	NI	NI	38	NI
Zhang et al. (Zhang et al., 2021)	2021	China	Case control	serum	qRT-PCR	191	NI	NI	NI	107	NI
Yang and Zhang. (Yang and Zhang, 2019)	2019	China	Case control	plasma	qRT-PCR	50	NI	50	NI	50	NI
Sun et al (Sun et al., 2017)	2017	China	Case control	serum	qRT-PCR	32	NI	NI	NI	40	NI
Jiang et al (Jiang et al., 2017)	2017	China	Case control	serum	qRT-PCR	12	NI	NI	NI	182	53 ± 9

3.4. Findings on outcomes of interest

3.4.1. Dysregulated microRNAs in CIN

In this review, a total of 40 microRNAs were represented as "Normal", "Up-regulated" or "Down-regulated" in cervical cancer or CIN compared to healthy controls. Table 2 shows that four microRNAs miR-100 (Yamanaka et al., 2021) miR-125b (Qiu et al., 2020), miR-145 (Wei et al., 2017) and miR-370 (Yamanaka et al., 2021; Qiu et al., 2020; Wei et al., 2017) were down regulated in serum or plasma of CIN groups compared to healthy controls. Three microRNAs, miR-16–2, miR-195 and miR-497 (Zhang et al., 2015) showed no alteration in their serum or plasma expression in the CIN groups compared to healthy controls.

3.4.2. Dysregulated microRNAs in cervical cancer

For cervical cancer groups, a total of 38 microRNAs were either differentially expressed or non-altered in serum or plasma. Eleven microRNAs including miR-370 (Qiu et al., 2020), miR-101 (Jiang et al., 2017), miR-375-3p (Cao et al., 2021), miR-651 (Zhu et al., 2021), miR-100 (Yamanaka et al., 2021), miR-125a-5p (Lv et al., 2021), miR-125b (Qiu et al., 2020), miR-145 (Wei et al., 2017), miR-18a, miR-195 and miR-2861 (Zhang et al., 2021) were down regulated in the serum or plasma of cervical cancer groups compared to healthy controls. One microRNA, miR-218 (You et al., 2015), showed no difference in serum or plasma expression in the cervical cancer group compared to healthy controls. Another 26 microRNAs, as shown in Table 2, were up regulated in serum or plasma of cervical cancer groups compared to healthy controls. MicroRNAs miR-205, miR-21 and miR-486-5p were reported as up regulated in serum or plasma of cervical cancer groups compared to healthy controls by two studies each (Qiu et al., 2020; You et al., 2015; Farzanehpour et al., 2019; Ruan et al., 2020; Du et al., 2020; Jia et al., 2015).

3.4.3. Diagnostic accuracy of serum/plasma microRNAs

3.4.3.1. Diagnostic accuracy of microRNAs in detection of CIN. In this review, we included studies that evaluated the diagnostic accuracy of serum or plasma microRNAs for the diagnosis of cervical cancer or cervical intraepithelial neoplasia. 40 individual microRNAs and seven

Table 2
Dysregulation of serum or plasma microRNAs in CIN and cervical cancer.

CIN			Cervical cancer		
Down regulated	**No difference**	**Up regulated**	**Down regulated**	**No difference**	**Up regulated**
miR-100 (Yamanaka et al., 2021)	miR-16–2 (Xin et al., 2016)	miR-152 (Yang and Zhang, 2019)	miR-370 (Qiu et al., 2020)	miR-218 (You et al., 2015)	miR-16–2 (Jia et al., 2015)
miR-125b (Qiu et al., 2020)	miR-195 (Du et al., 2020)	hsa-mir-92a (Kong et al., 2017)	miR-101 (Jiang et al., 2017)		SNHG17 (Cao et al., 2021)
miR-145 (Wei et al., 2017)	miR-497 (Du et al., 2020)	miR-1290 (Zheng et al., 2019)	miR-375-3p (Cao et al., 2021)		miR-192 (Qiu et al., 2020)
miR-370 (Yamanaka et al., 2021; Qiu et al., 2020; Wei et al., 2017)		miR-192 (Farzanehpour et al., 2019)	miR-651 (Zhu et al., 2021)		miR-124 (Ruan et al., 2020)
		miR-196a (Liu et al., 2015)	miR-100 (Yamanaka et al., 2021)		miR-152 (Yang and Zhang, 2019)
		miR-205 (Qiu et al., 2020)	miR-125a-5p (Lv et al., 2021)		miR-21 (Ruan et al., 2020)
		miR-21 (Qiu et al., 2020)	miR-125b (Qiu et al., 2020)		miR-196a (Liu et al., 2015)
		miR-9 (Farzanehpour et al., 2019)	miR-145 (Wei et al., 2017)		miR-425-5p (Sun et al., 2017)
			miR-18a (Zhang et al., 2021)		miR-200a (Jia et al., 2015)
			miR-195 (Zhang et al., 2021)		hsa-mir-92a (Kong et al., 2017)
			miR-2861 (Zhang et al., 2021)		miR-205 (You et al., 2015)
					miR-122-5P (Cao et al., 2021)
					miR-20a-5p (Cao et al., 2021)
					miR-21 (Ruan et al., 2020)
					miR-127 (You et al., 2015)
					miR-1290 (Nagamitsu et al., 2016)
					miR-133a-3p (Nagamitsu et al., 2016)
					miR-25 (Nagamitsu et al., 2016)
					miR-29a (Nagamitsu et al., 2016)
					miR-3142 (Luo et al., 2019)
					miR-486-5p (Du et al., 2020; Li et al., 2018)
					miR-497 (Du et al., 2020)
					miR-9 (You et al., 2015)
					miRNA-25 (Du et al., 2020)
					miRNA-29a (Du et al., 2020)

panels of microRNAs were evaluated for their diagnostic accuracy for the detection of cervical cancer or CIN as shown in Table 3.

3.4.3.2. Area under the curve for individual serum/plasma microRNAs in detection of CIN. We present a total of 9 individual microRNAs that were evaluated for their diagnostic accuracy in detection of CIN compared to healthy controls. miR-192 (Farzanehpour et al., 2019) had the highest AUC (0.980, 95 % CI 0.95–1.00) while miR-21 (Qiu et al., 2020) had the lowest AUC (0.689) as shown in Table 3.

3.4.3.3. Sensitivity of individual serum/plasma microRNAs in detection of CIN. Only four individual serum/plasma microRNAs had sensitivity values reported in detection of CIN compared to healthy controls. And the reported microRNAs included miR-145 (Wei et al., 2017), miR-9 miR-192 and miR-205 (Farzanehpour et al., 2019), with sensitivities of 91.7 % (95 % CI 75–89), 77.8 %, 83.3 % and 66.7 % respectively.

3.4.3.4. Specificity of individual serum/plasma microRNAs in detection of CIN. We report specificity values for four individual serum/plasma microRNAs in detection of CIN compared to healthy controls. These microRNAs included miR-145 (Wei et al., 2017), miR-9, miR-192 and miR-205 (Farzanehpour et al., 2019) with specificities of 54.2 % (95 % CI 55–72), 94.4 %, 94.4 % and 88.9 % respectively.

3.4.3.5. Area under the curve for serum/plasma microRNA panels in detection of CIN. We found three panels of microRNAs that were evaluated for diagnostic accuracy to detect CIN compared to healthy controls. These included the first panel (miR-21, miR-125b and miR-370) (Qiu et al., 2020) showing the highest AUC value (0.897), the second panel (miR-9, miR-10a, miR-20a and miR-196a and miR-16–2) (Xin et al., 2016) with the AUC value of 0.886 and the third panel (miR-195, miR-2861 and miR-497) with the lowest AUC value of 0.734 (95 % CI 0.683–0.784).

3.4.3.6. Sensitivity and specificity of serum/plasma microRNAs panels in detection of CIN. The only panel whose sensitivity and specificity were reported was "miR-16–2, miR-195, miR-2861 and miR-497", and its reported values were 62.6 % and 88.9 %, respectively.

3.4.4. Diagnostic accuracy of microRNAs in detection of Cervical Cancer.

3.4.4.1. Area under the curve for serum/plasma individual microRNAs in detection of cervical cancer.. There were a total of 32 microRNAs which were evaluated for diagnostic accuracy in the detection of cervical cancer compared to healthy controls. The majority of them had their AUC above 0.700 as shown in Table 3. Notable miR-192 had the highest AUC value (1.000, 95 % CI 1–1) followed by miR-9 with the AUC value of 0.999 (95 % CI 0.99–1), followed by miR-205 with the AUC value of 0.960 (95 % CI 0.89–1) and miR-21 having the lowest AUC value 0f

Table 3
Diagnostic accuracy of serum or plasma individual microRNAs and panels of microRNAs for detection of CIN and cervical cancer.

			CIN					Cervical Cancer			
Author	**MicroRNA Studied**	**MicroRNA Panel**	**Up/Down Regulated**	**AUC**	**SENS**	**SPEC**	**Up/Down Regulated**	**AUC**	**SENS**	**SPEC**
Zheng et al. (Zheng et al., 2019)		let-7a-3p, let-7d-3p, miR-30d-5p, miR-144-5p, miR-182-5p, miR-183-5p, miR-215-5p, and miR-4443		NI	NI	NI		0.992	NI	NI
Zheng et al. (Zheng et al., 2019)		miR-30d-5p and let-7d-3p		NI	NI	NI		0.922	NI	NI
Kong et al. (Kong et al., 2017)	hsa-miR-92a		up regulated	NI	NI	NI	up regulated	0.83	69.60 % [58.0–81.0)	80.40 % [70.0–91.0)
Nagamitsu et al. (Nagamitsu et al., 2016)	miR-1290		up regulated	NI	NI	NI	up regulated	0.7957	90.30 % [84.0–97.0)	62.20 % [51.0–73.0)
Qiu et al. (Qiu et al., 2020)	miR-21		up regulated	0.689	NI	NI	up regulated	0.783	NI	NI
Qiu et al. (Qiu et al., 2020)	miR-125b		down regulated	0.735	NI	NI	down regulated	0.642	NI	NI
Qiu et al. (Qiu et al., 2020)	miR-370		down regulated	0.821	NI	NI	down regulated	0.822	NI	NI
Qiu et al. (Qiu et al., 2020)		miR-21, miR-125b and miR-370		0.897	NI	NI		0.912	NI	NI
Xin et al. (Xin et al., 2016)		miR-9, miR-10a, miR-20a and miR-196a		0.886	NI	NI		NI	NI	NI
Liu et al. (Liu et al., 2015)	miR-196a		up regulated	NI	NI	NI	up regulated	NI	NI	NI
Wei et al. (Wei et al., 2017)	miR-145		down regulated	0.828 [0.779–0.878)	91.70 %	54.20 %	down regulated	0.848 [0.802–0.894)	81.70 % [75.0–89.0)	63.30 % [55.0–72.0)
Zhang et al. (Zhang et al., 2015)	miR-16–2		Normal	NI	NI	NI	up regulated	NI	NI	NI
Zhang et al. (Zhang et al., 2015)	miR-195		Normal	NI	NI	NI	down regulated	NI	NI	NI
Zhang et al. (Zhang et al., 2015)	miR-497		Normal	NI	NI	NI	up regulated	NI	NI	NI
Zhang et al. (Zhang et al., 2015)	miR-2861		NI	NI	NI	NI	down regulated	NI	NI	NI
Zhang et al. (Zhang et al., 2015)		miR-16–2, miR-195, miR-2861 and miR-497		0.73 (0.68–0.78)	62.60 %	88.90 %		0.849	73.10 %	88.40 %
Yamanaka et al. (Yamanaka et al., 2021)	miR-100		down regulated	0.879	NI	NI	down regulated	0.879	NI	NI

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Table 3 (*continued*)

			CIN				Cervical Cancer			
Du et al. (Du et al., 2020)	miRNA-29a			NI	NI	NI	up regulated	0.72	NI	NI
Du et al. (Du et al., 2020)	miRNA-25			NI	NI	NI	up regulated	0.74	NI	NI
Du et al. (Du et al., 2020)	miRNA-486-5p			NI	NI	NI	up regulated	0.87	NI	NI
Du et al. (60]		miRNA-29a, miRNA-25 and miRNA-486-5p		NI	NI	NI		0.9	87.10 %	89.30 %
Ruan et al. (Ruan et al., 2020)	miR-21			NI	NI	NI	up regulated	0.723 (0.63–0.82)	91.23 % (86.0–96.0)	58.82 % (50.0–67.0)
Ruan et al. (Ruan et al., 2020)	miR-124			NI	NI	NI	up regulated	0.766	57.89 % (49.0–67.0)	94.12 % (90.0–98.0)
Farzanehpour et al. (Farzanehpour et al., 2019)	miR-9		up regulated	0.9	77.8	94.4	up regulated	0.99(99–1)	100	94.4
Farzanehpour et al. (Farzanehpour et al., 2019)	miR-192		up regulated	0.98	83.3	94.4	up regulated	1(1–1)	100	94.4
Farzanehpour et al. (Farzanehpour et al., 2019)	miR-205		up regulated	0.75	66.7	88.9	up regulated	0.96(0.89–1)	88.2	88.9
Luo et al. (Luo et al., 2019)	miR-3142			NI	NI	NI	up regulated	NI	NI	NI
You et al. (You et al., 2015)	miR-127			NI	NI	NI	up regulated	0.82	75.51 % [68.0–83.0)	83.82 % (77.0–90.0)
You et al. (You et al., 2015)	miR-205			NI	NI	NI	up regulated	0.843	72.00 % (64.0–80.0)	82.35 % (75.0–89.0]
You et al. (You et al., 2015)	miR-218			NI	NI	NI	no difference	NI	NI	NI
Jia et al. (Jia et al., 2015)	miR-21			NI	NI	NI	up regulated	0.819	NI	NI
Jia et al. (Jia et al., 2015)	miR-29a			NI	NI	NI	up regulated	0.819	NI	NI
Jia et al. (Jia et al., 2015)	miR-25			NI	NI	NI	up regulated	0.726	NI	NI
Jia et al. (Jia et al., 2015)	miR-200a			NI	NI	NI	up regulated	0.658	NI	NI
Jia et al. (Jia et al., 2015)	miR-486-5p			NI	NI	NI	up regulated	0.685	NI	NI
Jia et al. (Jia et al., 2015)		miR-486-5p, miR-200a, miR-25, miR-29a and miR-21		NI	NI	NI		0.908	NI	NI
Zhu et al. (Zhu et al., 2021)	miR-651			NI	NI	NI	down regulated	0:905	NI	NI
Cao et al. (Cao et al., 2021)	SNHG17			NI	NI	NI	up regulated	0.863	84.70 % (76.0–94.0)	78.20 % (68.0–89.0)
Cao et al. (Cao et al., 2021)	miR-375-3p			NI	NI	NI	down regulated	0.869	75.80 % (65.0–87.0)	86.60 % (78.0–95.0)
Li et al. (Li et al., 2018)	miR-486-5p			NI	NI	NI	up regulated	0.9	NI	NI
Cao et al. (Cao et al., 2021)		miR-122-5p, miR20a-5p, and miR-133a-3p		NI	NI	NI		0.808	74.60 %	72.50 %
Cao et al. (Cao et al., 2021)	miR-122-5P			NI	NI	NI	up regulated	0.672	67.50 % (56.0–79.0)	64.50 % (52.0–77.0)
Cao et al. (Cao et al., 2021)	miR-20a-5p			NI	NI	NI	up regulated	0.681	62.00 % (50.0–74.0)	79.50 % (69.0–90.0)
Cao et al. (Cao et al., 2021)	miR-133a-3p			NI	NI	NI	up regulated	0.666	68.90 % (57.0–81.0)	69.30 % (58.0–81.0)
Lv et al. (Lv et al., 2021)	miR-125a-5p			NI	NI	NI	down regulated	0.7129	59.10 % (47.0–72.0)	84.20 % (75.0–93.0)
Zhang et al. (Zhang et al., 2021)	miR-18a			NI	NI	NI	down regulated	0.856	95.00 % (93.0–97.0)	76.00 % (71.0–81.0)

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Table 3 (*continued*)

		CIN				Cervical Cancer			
Yang and Zhang, (Yang and Zhang, 2019)	miR-152	up regulated	0.831	NI	NI	up regulated	0.935	NI	NI
Sun et al. (Sun et al., 2017)	miR-425-5p		NI	NI	NI	up regulated	NI	NI	NI
Jiang et al. (Jiang et al., 2017)	miR-101		NI	NI	NI	down regulated	NI	NI	NI

0.723 (95 % CI 0.631–0.815).

3.4.4.2. Sensitivity of serum/plasma individual microRNAs in detection of cervical cancer.. Sensitivity values for the detection of cervical cancer were reported for only 17 out of 32 microRNAs. And out of the 17, only 11 had sensitivities above 70 % as shown in Table 3. Of note were miR-192 (Qiu et al., 2020), miR-9 (Farzanehpour et al., 2019) each having a sensitivity of 100 %. The lowest sensitivity value was reported for miR-205 (Farzanehpour et al., 2019) and it was 72.0 %.

3.4.4.3. Specificity of serum/plasma individual microRNAs in detection of cervical cancer.. Specificity values for detecting cervical cancer were reported on 17 out of 32 microRNAs but only 9 were above 80 % as shown in Table 3. Highest specificities were reported for miR-192 and miR-9 (Farzanehpour et al., 2019) with each having a specificity value of 94.4 %. The lowest specificity value of 82.35 % was reported for miR-205.

3.4.4.4. Area under the curve for serum/plasma microRNA panels in detection of cervical cancer.. There were 7 panels of microRNAs that were evaluated for diagnostic accuracy for the detection cervical cancer compared to healthy controls as shown in Table 3. These panels included one with eight microRNAs (let-7a-3p, let-7d-3p, miR-30d-5p, miR-144-5p, miR-182-5p, miR-183-5p, miR-215-5p, and miR-4443) and it showed the highest AUC value of 0.992. The second panel contained two micro RNAs (miR-30d-5p and let-7d-3p) and this had an equally high AUC of 0.922. Other microRNA panels were (miR-21, miR-125b and miR-370) (Qiu et al., 2020), (miR-16–2, miR-195, miR-2861 and miR-497), (miR-29a, miR-25 and miR-486-5p) (Du et al., 2020), (miR-486-5p, miR-200a, miR-25, miR-29a and miR-21) and (miR-122-5p, miR20a-5p, and miR-133a-3p) (Cao et al., 2021) having AUC values of 0.912, 0.849 (95 % CI 0.813–0.886), 0.900, 0.908 (95 % CI 0.686–0.948) and 0.808 respectively.

3.4.4.5. Sensitivity of serum/plasma microRNA panels in detection of cervical cancer.. The only panels with reported sensitivities were two i.e. (miRNA-29a, miRNA-25 and miRNA-486-5p) (Du et al., 2020) and (miR-122-5p, miR20a-5p, and miR-133a-3p) (Cao et al., 2021). Their sensitivity values for the detection of cervical cancer compared with healthy controls were 91.23 % and 74.60 %, respectively.

3.4.4.6. Specificity of serum/plasma microRNA panels in detection of cervical cancer.. Our review reports relatively low specificity values for microRNA panels i.e. (miRNA-29a, miRNA-25 and miRNA-486-5p) (Du et al., 2020) and (miR-122-5p, miR20a-5p, and miR-133a-3p) (Cao et al., 2021). Their specificity values for the detection of cervical cancer compared with healthy controls were 58.82 % and 72.50 %, respectively.

3.4.4.7. Meta-analyzed sensitivity and specificity of up-regulated and down-regulated microRNAs in detection of cervical cancer.. We report a *meta*-analyzed sensitivity and specificity of serum/plasma microRNAs for both upregulated and downregulated. The *meta*-analyzed sensitivity and specificity of upregulated microRNAs for detection of cervical cancer were 86.0 % (95 % CI 85.0–88.0) (Fig. 2) and 80.0 % (95 % CI 78.0–82.0) (Fig. 4) respectively. The *meta*-analyzed sensitivity and specificity of downregulated microRNAs for detection of cervical cancer were 92.0 % (95 % CI 89.0–94.0) (Fig. 3) and 77.0 % (95 % CI 73.0–80.0) (Fig. 5) respectively.

3.4.4.8. Methodological quality assessment.. Two reviewers (FS and ATK) assessed the quality of all the 24 included articles using the QUADAS-2 tool. This tool assesses quality of studies in terms of patient selection, index test, reference standard and flow and timing for risk if bias domain, and of patient selection, index test and reference standard for the domain of applicability concerns. Using this tool, the quality assessment revealed an overall good quality. However, we observed a potential bias in our review. We found a high risk of bias in 21 studies in the patient selection domain of the QUADAS-2 tool. The risk of bias and applicability concerns for studies included in this review are presented in Table 4.

4. Discussion

Cervical cancer is a public health problem predominantly in low- and middle-income countries. It is important to note that cervical cancer can be effectively treated once diagnosed at the stage of cervical intra-epithelial neoplasia (CIN). This requires new, accurate and user-friendly diagnostic methods with high uptake and acceptability by both patients and health care providers. MicroRNAs are biomolecules that can be easily detected and quantified in different body fluids, especially serum and plasma. Numerous research studies have attempted to demonstrate the diagnostic utility of different microRNAs for detecting cervical cancer or CIN.

4.1. Principal findings

Two microRNAs had high AUC values for the detection of CIN compared to healthy controls, and these were miR-192 (0.980) and miR-9 (0.900). The same microRNAs had high values for sensitivity (77.8 % and 83.3 % respectively) as well as high specificity (94.4 % and 94.4 % respectively). There was a reported high specificity value for miR-205 (88.9 %) and high sensitivity value for miR-145 (91.7 %).

For the detection of cervical cancer in comparison with healthy controls, several microRNAs were reported with high diagnostic accuracy values. For instance, high AUC values were reported for miR-205 (0.900), miR-192 (1.000) and miR-9 (0.999). High specificity values were equally reported for miR-192 (100 %), miR-9 (100 %), miR-21 (91.23 %). Specificity values of 88.9 %, 94.4 %, 94.4 % and 94.12 % were also reported for miR-205, miR-194, miR-9, and miR-124, respectively. In this review, we take note of the reported high diagnostic accuracy (sensitivity, specificity and AUC) of miR-205, miR-9, miR-192 and miR-21 for detection of CIN or cervical cancer in comparison with healthy controls.

We report that 8 microRNAs (miR-152, hsa-mir-92a, miR-1290, miR-192, miR-196a, miR-205, miR-21 and miR-9) are up regulated in CIN. We also report that 25 microRNAs (miR-16–2, SNHG17, miR-192, miR-

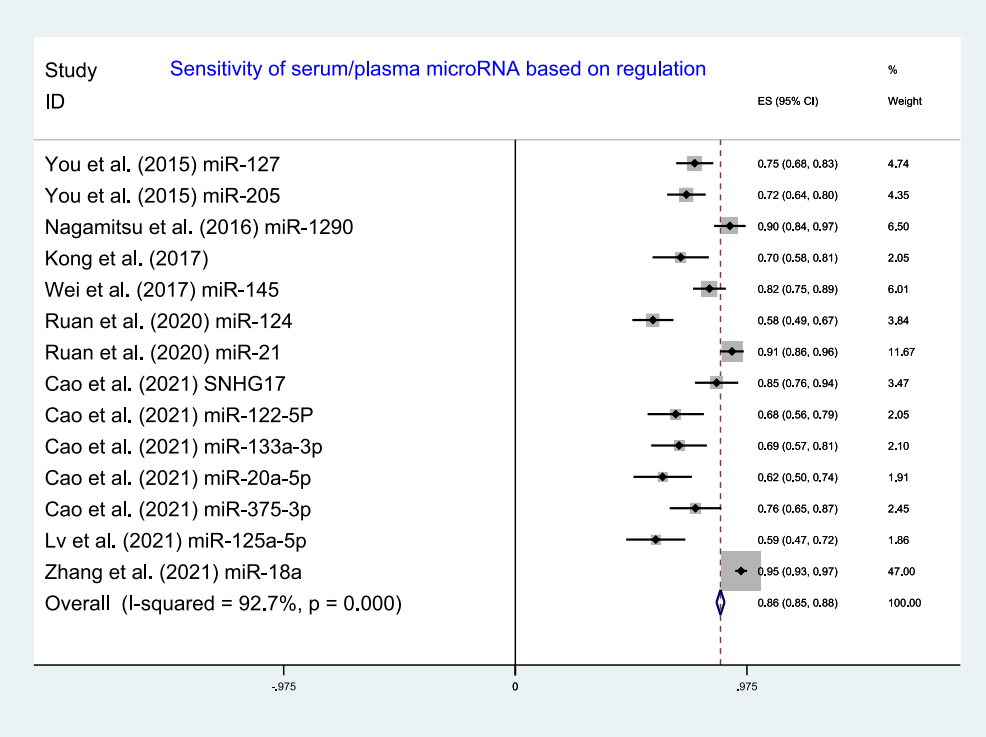

Fig. 2. Sensitivity of upregulated serum/pasma microRNAs in detection of cervical cancer.

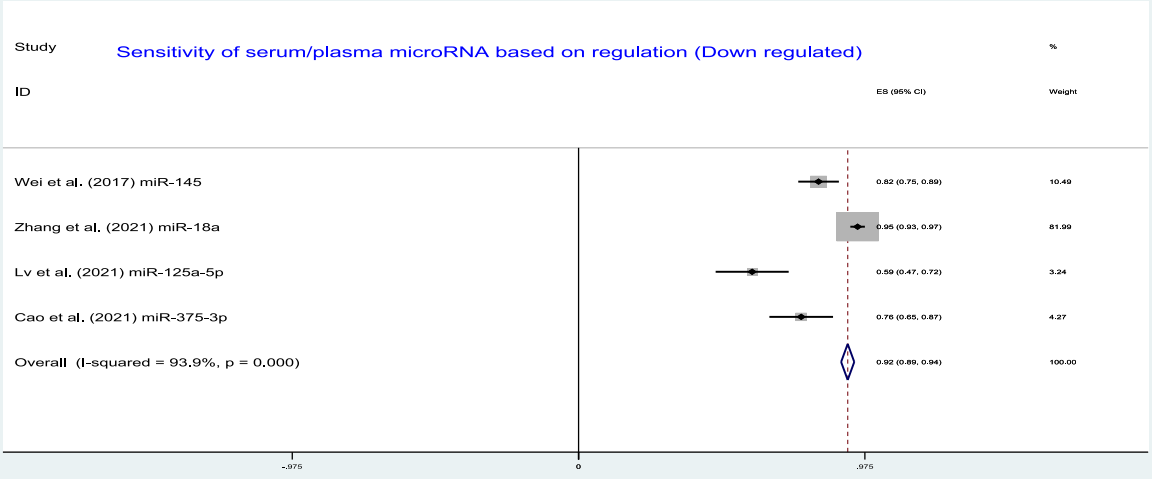

Fig. 3. Sensitivity of downregulated serum/pasma microRNAs in detection of cervical cancer.

124, miR-152, miR-21, miR-196a, miR-425-5p, miR-200a, hsa-mir-92a, miR-205, miR-122-5P, miR-20a-5p, miR-127, miR-1290, miR-133a-3p, miR-25, miR-29a, miR-3142, miR-486-5p, miR-497, miR-9, miRNA-25, miRNA-486-5p and miRNA-29a) are up regulated in cervical cancer.

4.2. General findings

In this review, we present an assessment of serum or plasma expression of several microRNAs in CIN and cervical cancer. We also present the diagnostic accuracy of individual microRNAs or microRNA panels for detection of CIN or cervical cancer compared to healthy controls. Through a literature search, we identified 24 studies, mostly from Chinese and Asian populations, a similar observation from previous reviews (Nagandla et al., 2021; Causin, 2021), which studied the accuracy of serum or plasma microRNAs in detection of CIN or cervical cancer.

All reviewed studies reported to have quantified microRNAs using quantitative reverse transcription polymerase chain reaction (qRT-PCR). However, there were in-depth specific methodological differences in the exact application of qRT-PCR, especially in normalisation. We note that results from microRNA quantification can be greatly affected by normalisation methods (Kroh et al., 2010). Apart from the principles of qRT-PCR, we identified no universal procedure for quantitative assessment of serum or plasma microRNAs. This relates to the fact that there is no standard reference microRNA, as it is for many other techniques for laboratory measurement of other biomolecules.

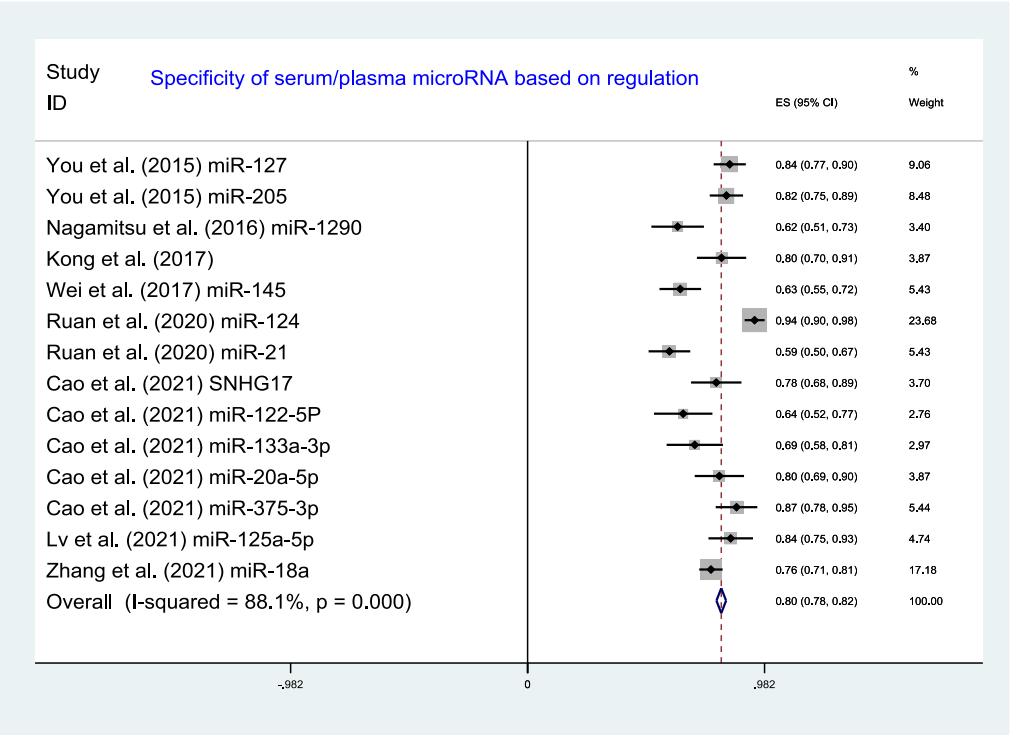

Fig. 4. Specificity of upregulated serum/pasma microRNAs in detection of invassive cervical cancer.

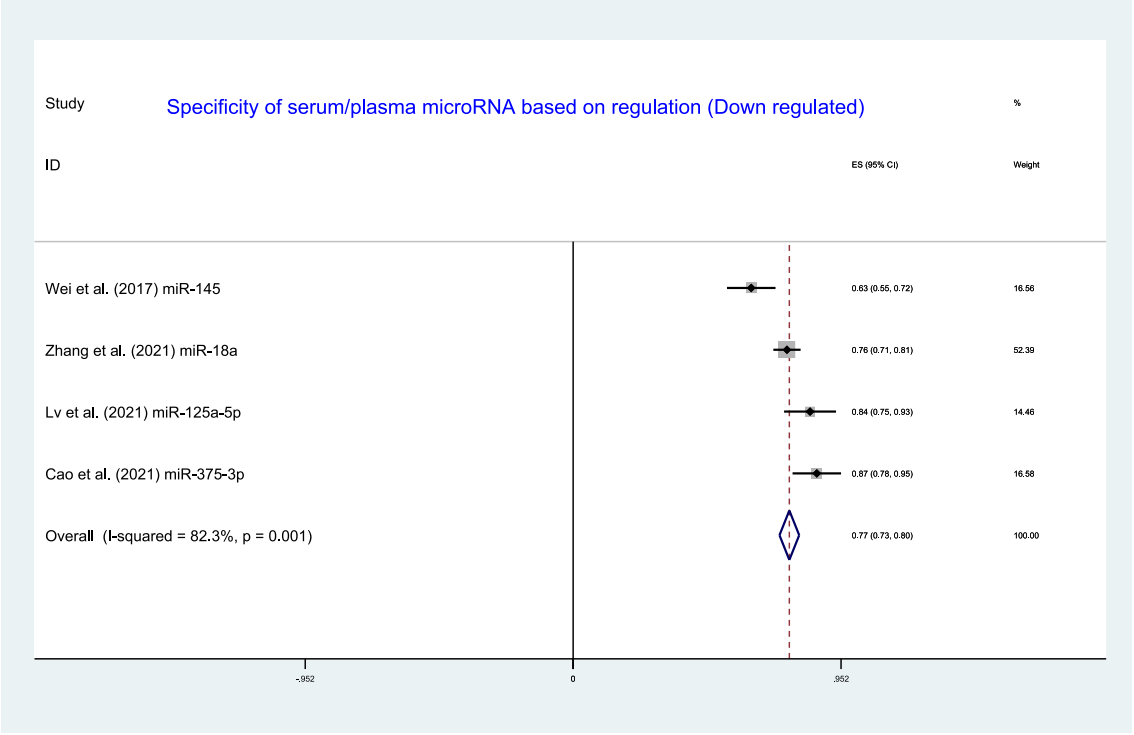

Fig. 5. Specificity of downregulated serum/pasma microRNAs in detection of invassive cervical cancer.

4.3. Findings in relation to other systematic reviews.

Our review identified several microRNAs with high diagnostic accuracy for CIN or cervical cancer. Many of these microRNAs, specifically miR-9, miR-192, and miR-21 had been earlier identified in a systematic review by Nascimento et al (Nascimento et al., 2022). From our review, we documented that in addition to miR-9, miR-192 and miR-21, miR-205 had a high diagnostic accuracy in detecting CIN or cervical cancer. In a systematic review by Nagandla et al (Nagandla et al., 2021), the authors emphasized a higher sensitivity value of miR-205 for detection of high grade squamous intraepithelial lesions. However, this review reported results of miR-205 expression in exfoliated cervical cells. We

Table 4
Assessment of bias and quality of included articles.

	Risk of Bias				Applicability Concerns		
Author	Patient Selection	Index test	Reference Standard	Flow and Timing	Patient Selection	Index test	Reference Standard
Zheng, et al. (Zheng et al., 2019)	HR	LR	LR	LR	LR	LR	LR
Kong et al. (Kong et al., 2017)	HR	LR	LR	LR	LR	LR	LR
Nagamitsu et al (Nagamitsu et al., 2016)	HR	LR	LR	LR	LR	LR	LR
Qiu et al. (Qiu et al., 2020)	HR	LR	LR	LR	LR	LR	LR
Xin et al. (Xin et al., 2016)	HR	LR	LR	LR	LR	LR	LR
Liu et al. (Liu et al., 2015)	HR	LR	LR	LR	LR	LR	LR
Wei et al. (Wei et al., 2017)	HR	LR	LR	LR	LR	LR	LR
Zhang et al. (Zhang et al., 2015)	LR	LR	LR	LR	LR	LR	LR
Yamanaka et al. (Yamanaka et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Du et al. (Du et al., 2020)	LR	LR	LR	LR	LR	LR	LR
Ruan et al. (Ruan et al., 2020)	HR	LR	LR	LR	LR	LR	LR
Farzanehpour et al. (Farzanehpour et al., 2019)	HR	LR	LR	LR	LR	LR	LR
Luo et al. (Luo et al., 2019)	HR	LR	LR	LR	LR	LR	LR
Jia et al. (Jia et al., 2015)	LR	LR	LR	LR	LR	LR	LR
Zhu et al. (Zhu et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Cao et al. (Cao et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Li et al. (Li et al., 2018)	HR	LR	LR	LR	LR	LR	LR
Cao et al. (Cao et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Cao et al. (Cao et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Lv et al. (Lv et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Zhang et al. (Zhang et al., 2021)	HR	LR	LR	LR	LR	LR	LR
Yang and Zhang (Yang and Zhang, 2019)	HR	UC	UC	UC	LR	LR	LR
Sun et al (Sun et al., 2017)	HR	LR	LR	LR	LR	LR	LR
Jiang et al. (Jiang et al., 2017)	HR	LR	LR	LR	LR	LR	LR

HR = High risk, LR = Low risk, UC = Unclear.

also highlight that these microRNAs can be quantified not only in serum as presented by Nascimento et al (Nascimento et al., 2022), but also in plasma. A high diagnostic accuracy of miR-9 for CIN and cervical cancer was also reported by Onyango et al (Onyango et al., 2020) though mostly in cervical tissue samples.

Our review found out a number of microRNAs that are either down regulated or up regulated in CIN or cervical cancer. We report many more microRNAs that are down regulated in CIN or cervical cancer compared to a previous systematic review by Nagandla et al (Nagandla et al., 2021) who reported only five microRNAs (miR-34, miR-7, miR-203, miR-29 and miR-375) as down regulated in CIN and cervical cancer. In their systematic review, Pardini et al (Pardini et al., 2018) indicated miR-125b, miR-375, miR-100 and miR-145 as down regulated. Notable is the up regulation of miR-21 as reported by Nagandla et al (Nagandla et al., 2021) though in exfoliated cervical cells. Also, in a previous systematic review by Pardini et al (Pardini et al., 2018) the notable microRNAs that were indicated as up regulated included miR-9, miR-196a and miR-21.

In our review, we observed more down regulated microRNAs including miR-370, miR-101, miR-651 and miR125a while up regulated microRNAs included the notable miR-205 among others. These results further represent the usefulness of some microRNAs in the detection of CIN and cervical cancer.

5. Systematic review strengths and limitations

This is the first review documenting the diagnostic accuracy of both serum and plasma microRNAs for detecting CIN and cervical cancer. We have employed robust, validated, and internationally accepted methods and tools, bearing in mind the sizeable number of studies included compared with previous reviews.

However, we were unable to find a single serum or plasma microRNA whose diagnostic accuracy was reported by more than two studies and were unable to perform a *meta*-analysis. This could be explained by the fact there are so many incompletely validated microRNAs that are being reported frequently and by different researchers, suggesting the need for a consensus among communities of practice for which our review provides a starting point. We also report a limitation concerning completeness of data. Many studies never reported all the measures of diagnostic accuracy. For instance, most studies reported AUC without sensitivity and specificity values. Another limitation was the fact that we did not fully explore grey literature, largely because of insufficiency of time, this being an academic (PhD) research project. We searched for articles published from 2012 to 2022 based on our preliminary search results in PubMed as published in our protocol (Ssedyabane et al., 2023). There could have been some articles published before 2012 and after 2022 considering the fact that there is increasing interest in microRNA research. Many primary studies reported smaller sample sizes and most never reported confidence intervals for point estimates. This has a serious impact on statistical power. Another major limitation to our review is the fact that most of the retrieved studies were from China and the remaining few mostly from Iran and Japan. This poses a big limitation on generalizability of findings to other geographical regions of the world, especially sub-Saharan Africa.

Noteworthy, a good number of studies did not provide an adequate description of participants in either of the study groups (control, CIN and cervical cancer). For instance, we could hardly identify the mean age of participants in many study groups in several studies. Good enough, all included studies indicated that the gold standard, histology, was used to confirm lesion types and grades and hence adequately categorize participants in respective groups.

Also, we note that none of the included articles in this review resulted from prospective studies. This could have had significant shortcomings in statistical reporting since data on some variables might have been missed while calculating diagnostic accuracy.

6. Implications for future research and next steps.

We take note that microRNAs have a huge potential as diagnostic biomarkers of CIN and cervical cancer screening and/or diagnosis. The few cohort studies that exist had smaller sample sizes and this limits the derivation of conclusions on the exact potential of serum or plasma

microRNAs in the detection of CIN or cervical cancer. We therefore propose prospective cohort studies, with adequate sample sizes that are multicentred to cover different geographical regions and broader populations. Policymakers should prioritize investment in microRNA research for cervical cancer. Investment could be in terms of infrastructure and training, and these could reduce the rather high costs associated with microRNA testing. It is these costs that currently render microRNA testing not feasible in low and middle income countries.

Apart from their huge potential as diagnostic biomarkers of CIN and cervical cancer screening and/or diagnosis, we acknowledge the fact that integration of microRNAs into clinical laboratory practices often requires standardized and reproducible laboratory measurements. These procedures are currently challenging for circulating miRNAs compared to the already existing HPV DNA. Factors such as the low RNA concentration in plasma/serum, the presence of endogenous inhibitors in clinical samples, and variables like sample quality and storage significantly often affect microRNA measurement and hence profiling. This calls for specific approaches for standardization and reproducibility of laboratory measurements of circulating microRNAs.

World over, self-sampling is now being encouraged as a means of improving uptake of cervical cancer screening. Considering the observed accuracy of microRNAs in detection of CIN and cervical cancer, there exists a potential of a microRNA based point of care device once technical challenges of microRNA detection and quantification are addressed.

7. Conclusion

In conclusion, from this systematic review, we report that serum or plasma concentration of microRNAs, especially miR-205, miR-9, miR-192 and miR-21, have high diagnostic accuracy for the detection of CIN and cervical cancer and hence promising biomarkers poised for broader exploration. This shows their potential as stand-alone screening or diagnostic tests, or in conjunction with others, in a new algorithm, or together with the already existing biomarkers for purposes of diagnosing CIN or cervical cancer. However, due to limited number of studies, it is challenging for us to objectively make conclusions about usage of miR-205, miR-9, miR-192 and miR-21. Future studies should be directed towards standardizing quantification methods and studying cost implication of microRNAs applications in populations underserved by current cervical cancer screening, such as in sub Saharan Africa and South Asia.

CRediT authorship contribution statement

Frank Ssedyabane: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ekwaro A. Obuku:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Eve Namisango:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Joseph Ngonzi:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Cesar M. Castro:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Hakho Lee:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Thomas C. Randall:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Moses Ocan:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Robert Apunyo:** Writing – review & editing, Resources, Project administration, Methodology, Data curation. **Alison Annet Kinengyere:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Rogers Kajabwangu:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Aziza Tahirah Kisawe:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization. **Josephine Nambi Najjuma:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Deusdedit Tusubira:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Nixon Niyonzima:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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All the data used for this review is available from the corresponding author upon meaningful request.

Ethics approval and consent to participate

Ethics approval is not required for this systematic review manuscript. However, this being part of a doctoral research project, approval was sought from the Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) (MUST-2022-612).

Consent for publication

Not applicable.

Competing interests

We, the authors declare that we do not have any competing interests.

Author contribution

The first and corresponding author, FS, conceived the idea and developed the first drafts of the protocol and the review manuscript. AAK and FS developed the search strategy. Co-authors, JNN and ATK participated in independent and duplicate data searching, data retrieval and synthesis, quality assessment and risk of bias assessment. Co-authors MO, EN, RA, NN, JN, DT, SC, RK, CMC, HL, TCR and EAO refined protocol and the review manuscript, provided overall guidance in the entire write up and approved the final version prior to submission. All authors are accountable to all aspects of this manuscript.

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