Diagnostic value of HPV E6/E7 mRNA in screening for cervical intraepithelial neoplasia grade 2 or worse: A systematic review and meta-analysis

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Abstract. Histology is considered the gold standard for diagnosing the pathological progress of cervical cancer development, while cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) is the cutoff for intervention in clinical practice. The diagnostic value of human papillomavirus (HPV) E6/E7 mRNA in screening for CIN2+ has not been systematically summarized. A meta-analysis was conducted as part of the present study conducted to explore the diagnostic value of HPV E6/E7 mRNA in screening for CIN2+, aiming to provide a new marker for earlier clinical diagnosis of cervical cancer. The PubMed, Embase and Cochrane Library databases were searched from inception to May 2023. Studies reporting the true positive, false positive, true negative and false negative values in differentiating between CIN2+ and CIN2- were included, while duplicate publications, studies without full text, incomplete information or inability to conduct data extraction, animal experiments, reviews and systematic reviews were excluded. STATA software was used to analyze the data. A total of 2,224 patients were included of whom there were 1,274 patients with CIN2+ and 950 patients with CIN2-. The pooled sensitivity and specificity of the studies overall were 0.89 (95% CI, 0.84-0.92) and 0.59 (95% CI, 0.46-0.71), respectively; the positive likelihood ratio (LR) and the negative LR of the studies overall were 2.31 (95% CI, 1.61-3.32) and 0.21 (95% CI, 0.14-0.30), respectively. The pooled diagnostic odds ratio of the studies overall was 11.53 (95% CI, 6.85-19.36). Additionally, the area under the curve was 0.88. The analysis indicated that HPV E6/E7 mRNA has high diagnostic efficacy for CIN2+. HPV E6/E7 mRNA is highly sensitive in the diagnosis of CIN2+, which helps to reduce the rate of missed diagnoses. However, lower specificity may lead to a higher number of misdiagnoses in healthy patients.

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Introduction

Cervical cancer is one of the most common malignant tumors in the world that can affect the physical and mental health of women (1). Globally, there are ~530,000 new cervical cancer cases and 275,000 cervical cancer-related deaths each year, and incidence has indicated steadily/gradually declining patient age at the time of diagnosis (2). Cervical intraepithelial neoplasia (CIN) is a precancerous lesion of cervical invasive carcinoma, which can be divided into three grades, namely CIN1, 2 and 3; the higher the grade of CIN, the greater the probability of cervical invasive carcinoma development (3). Histology is considered the gold standard for diagnosing the pathological progress of cervical cancer development, while CIN2 or worse (CIN2+) is the cutoff for intervention in clinical practice (4). Additionally, international expert consensus recommendations require demonstration of high intra- and inter-laboratory reproducibility, and non-inferior sensitivity and specificity for the outcome of CIN2+ compared with pathological testing (5).

Persistent or repeated infection with high-risk human papillomavirus (HPV) is the main cause of cervical cancer, which can be prevented and treated (6,7). The progress from precancerous cervical lesions to cancer diagnosis requires 5-12 years. Therefore, early screening and treatment of precancerous cervical lesions are of great significance (8). The E6 and E7 proteins are oncoproteins produced by high-risk HPV types such as HPV-16 and HPV-18. HPV types are classified as low-risk or high-risk based on their association with the development of certain health conditions, particularly cervical cancer. The classification is primarily determined by the potential of the virus to cause malignant transformation in cells. Low-Risk HPV types are less likely to lead to the

development of cancer. High-risk HPV types are more likely to cause persistent infections that can lead to the development of cancer (9). These proteins play a pivotal role in the initiation and progression of cervical cancer. E6 and E7 are known for their ability to interact with cellular proteins, disrupting normal regulatory pathways in infected cells. Understanding the significance of E6 and E7 proteins is crucial in the context of cervical cancer diagnosis (9). HPV E6/E7 mRNA plays a role in the transcription and expression of oncogenes and can be used as an early marker for the development of cervical cancer lesions (10,11). The detection of HPV E6/E7 mRNA can serve as a biomarker for identifying infections with high-risk HPV types and assessing the risk of cervical cancer development. Although a previous systematic review investigated HPV E6/E7 mRNA for the detection of CIN2+, it is noteworthy that systematic reviews are only qualitative analyses of the literature. Therefore, the diagnostic value of HPV E6/E7 mRNA in screening for CIN2+ still lacks a more objective meta-quantitative analysis (12). A meta-analysis was conducted as part of the present study to explore the diagnostic value including sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), diagnostic odds ratio (DOR) and area under curve (AUC) of HPV E6/E7 mRNA in screening for CIN2+, aiming to provide a new marker for the clinical diagnosis of cervical cancer.

Materials and methods

Literature inclusion and exclusion criteria. Inclusion criteria: i) Retrospective or prospective studies evaluating the diagnostic value of E6/E7 mRNA in differentiating between CIN2+ and CIN2-; ii) histopathology as the gold standard; and iii) true positive (TP), true negative (TN), false positive (FP) and false negative (FN) values can be directly or indirectly extracted from the retrieved literature. Exclusion criteria: i) Animal studies, case reports and conference papers; ii) no available data; and iii) duplicate reports or studies based on the same data.

Search strategy. The PubMed, Embase and Cochrane Library databases were searched from inception to May 2023. The search terms included: '((((diagnosis[Title/Abstract]) OR (diagnostic[Title/Abstract])) OR (sensitivity[Title/Abstract])) OR (specificity[Title/Abstract])) AND ((((((((((((((Human Papillomavirus Virus[Title/Abstract]) OR (Papillomavirus Virus, Human[Title/Abstract])) OR (Virus, Human Papillomavirus[Title/Abstract])) OR (Human Papillomaviruses[Title/Abstract])) OR (HPV, Human Papillomavirus Viruses[Title/Abstract])) OR (Human Papilloma Virus[Title/Abstract])) OR (Human Papilloma Viruses[Title/Abstract])) OR (Papilloma Virus, Human[Title/Abstract])) OR (Virus, Human Papilloma[Title/Abstract])) OR (HPV Human Papillomavirus[Title/Abstract])) OR (HPV Human Papillomaviruses[Title/Abstract])) OR (Human Papillomavirus, HPV[Title/Abstract])) OR (Human Papillomaviruses, HPV[Title/Abstract])) AND ((Messenger RNA[Title/Abstract]) OR (mRNA[Title/Abstract]))) AND ((E6[Title/Abstract]) OR (E7[Title/Abstract])))'.

Literature screening and data extraction. Literature search, screening and extraction of relevant material was carried out by

Table I. Baseline characteristics of the included studies.

First author(s), year	Sample size, n		Age, years		TP	FP	FN	TN	Sensitivity, %	Specificity, %	(Refs.)
	CIN 2+	CIN 2-	CIN 2+	CIN 2-							
Andersson *et al*, 2011	87	68	32 (21-79)		79	22	8	46	91.0	68.0	(14)
Waldstrom and Ornskov, 2011	126	67	30 (16-65)		117	41	9	26	92.5	38.2	(15)
Liu *et al*, 2013	57	35	N/A	N/A	41	9	16	26	71.9	74.3	(16)
Shi *et al*, 2017	348	102	39.7±8.9	42.2±9.7	248	33	100	69	71.3	67.6	(17)
Camus *et al*, 2018	10	10	N/A	N/A	9	5	1	5	90.0	50.0	(18)
Fan and Shen, 2018	95	97	N/A	N/A	87	18	8	79	91.5	81.4	(19)
Han *et al*, 2018	101	96	48.8±12.5	42.8±10.3	86	32	15	64	85.1	66.7	(20)
Pan *et al*, 2019	92	209	45.46 (20-89)		85	140	7	69	92.4	33.0	(21)
Zhang *et al*, 2020	328	209	43.9±11.1		308	44	20	165	93.8	79.0	(22)
Sun *et al*, 2021	30	57	35.4±6.5		26	29	4	28	86.7	49.1	(23)

Data are shown as mean ± SD or median (quartiles); N/A, not applicable; TP, true-positive; FP, false-positive; FN, false-negative; TN, true-negative; CIN, cervical intraepithelial neoplasia.

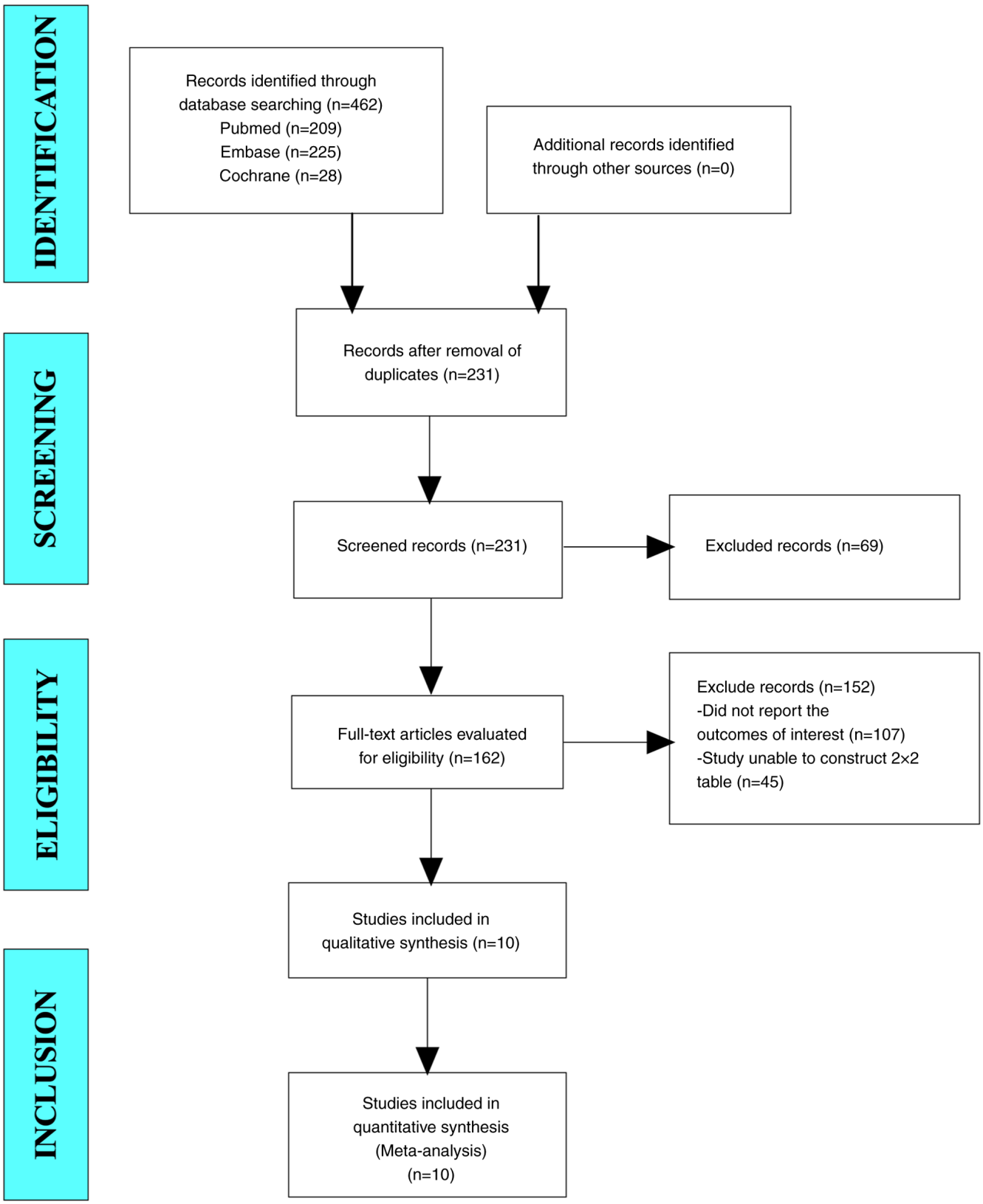

Figure 1. Flow diagram for selection of studies.

two researchers. When there were questions or disagreements, a third researcher was consulted before making a decision. The data extraction content included: Author, year of publication, sample size, sex, age and the values of TP, FP, TN and FN. If no TP, FP, TN and FN values were reported, data such as sensitivity, specificity, positive predictive value and negative predictive value were used to reverse the extrapolation.

Literature quality assessment. The QUADAS-2 tool (www.quadas.org) was separately used by two academics

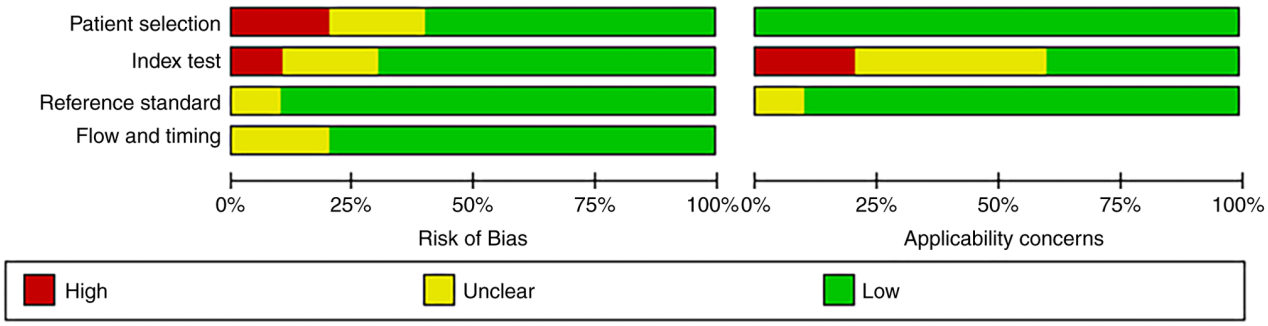

Figure 2. Methodological quality graph.

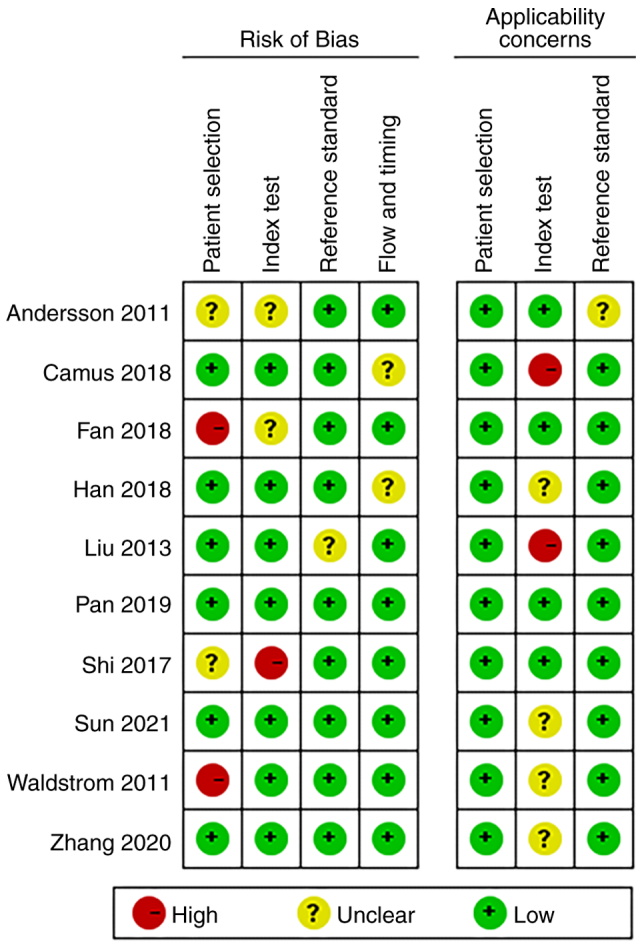

Figure 3. Methodological quality summary.

for evaluating the quality of published literature (13), and RevMan (version 5.3) (https://training.cochrane.org/online-learning/core-software/revman) was used to draw a quality evaluation map.

Data synthesis and statistical analysis. Bivariate model or hierarchical summary receiver operating characteristic (SROC) model was used to combine sensitivity and specificity. The I^2 value was used to evaluate the heterogeneity caused by non-threshold effects. If I^2>50%, the random effects model was used, otherwise, the fixed effects model was used. When I^2 is 25-50%, heterogeneity is low. When I^2 is 50-75%, heterogeneity is at a moderate level, and when I^2>75%, there is a high degree of heterogeneity. Subgroup analysis was performed to explore the causes of heterogeneity among the included studies. All analyses were performed with STATA (version 15.1; StataCorp LP). All statistical tests were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Results of literature search. In the current study, a total of 462 studies were retrieved from the aforementioned databases. After eliminating duplicate studies, 231 studies were obtained. After browsing titles and abstracts, 162 studies were obtained. Finally, 10 articles were included in the present meta-analysis through full-text reading (Fig. 1).

Baseline characteristics and quality assessment of the included studies

Baseline characteristics of the included studies. The present meta-analysis comprised 10 publications. A total of 2,224 patients were included, of whom there were 1,274 patients with CIN2+ and 950 patients with CIN2-. The age range the CIN2+ group was 30.0-48.8 years, while the age range of the CIN2- group was 30.0-45.46 years, which was comparable (Table I) (14-23).

Quality assessment of the included studies. 'Risk of bias' mainly includes four aspects: 'Patient selection', 'index test', 'reference standard', and 'flow and timing' (13). Of the 'patient selection' assessment, only two studies were high risk (patients employing selection methods that did not meet the aforementioned criteria, potentially introducing selection bias), and the rest were low risk (patients that adhered to the criteria for random or sequential selection). There was only one study in 'index test' showing high risk. Nine studies with regard to the aspect 'reference standard' were low-risk and 8 studies with regard to the aspect 'flow and timing' were low-risk. Additionally, 'applicability concerns' mainly includes three aspects (13): Patient selection, index test and reference standard. For 'index test', there was also one study that showed high-risk, and the rest were low risk. Overall, the quality of the literature included in the present review was acceptable (Figs. 2 and 3).

Results of meta-analysis. Since the I^2 for sensitivity (91.71%), specificity (93.95%), LR+ (94.7%), LR- (89.3%) and DOR (84.2%) were >50%, representing a high level of inconsistency

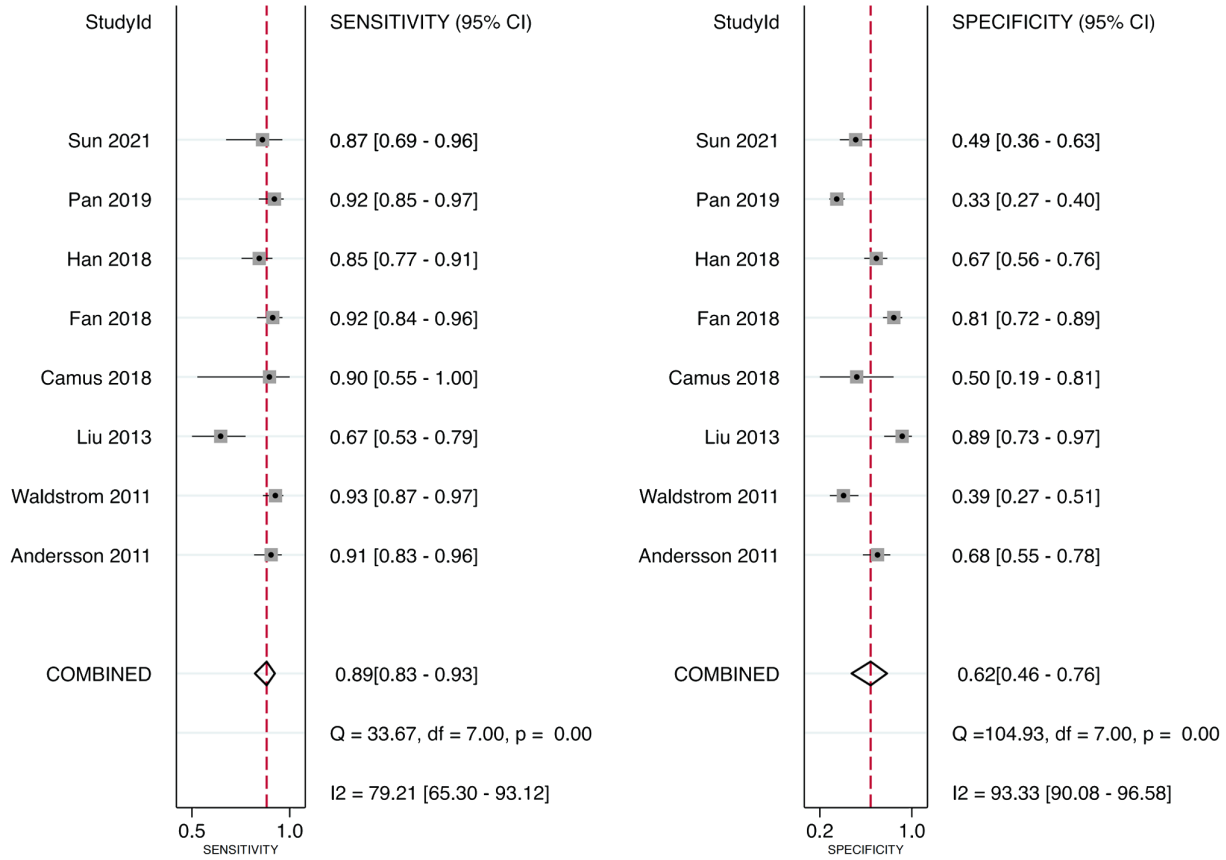

Figure 4. Forest plot of sensitivity and specificity of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus.

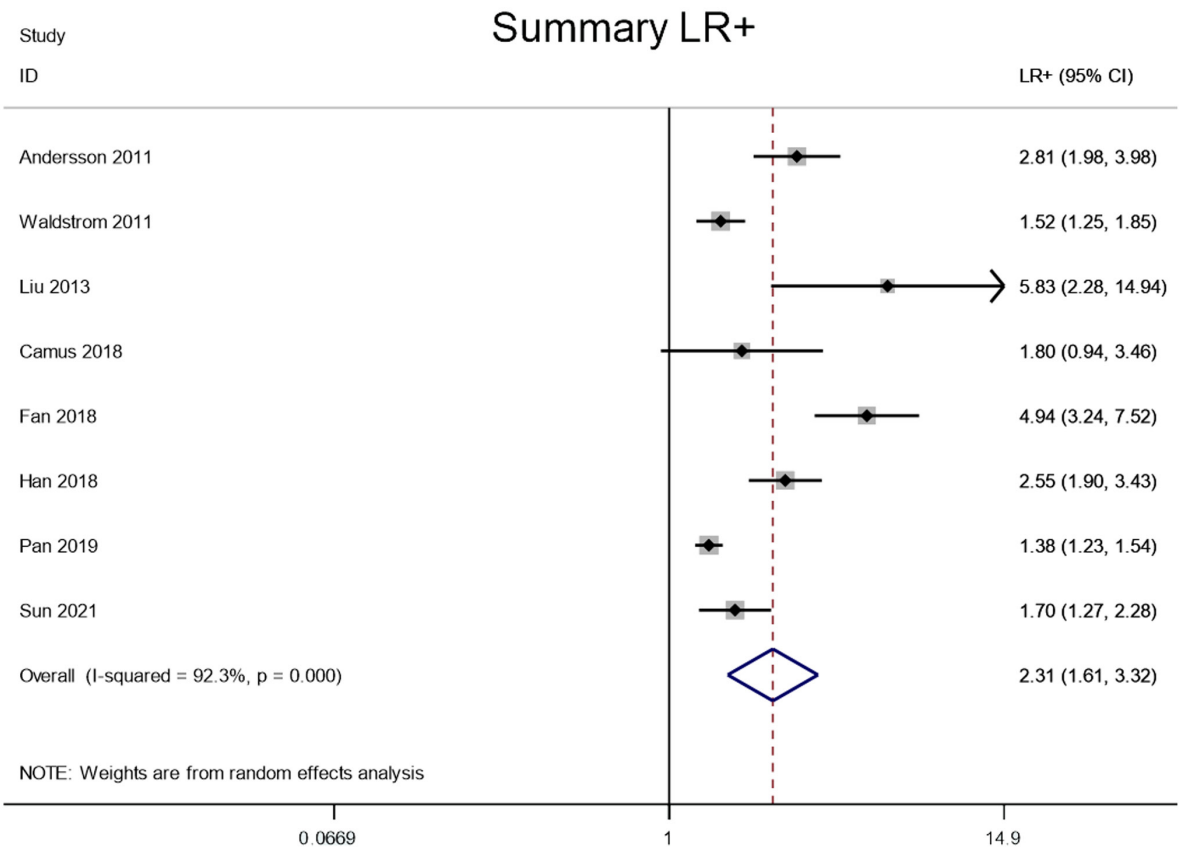

Figure 5. Forest plot of the LR+ of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; LR+, positive likelihood ratio; HPV, human papillomavirus.

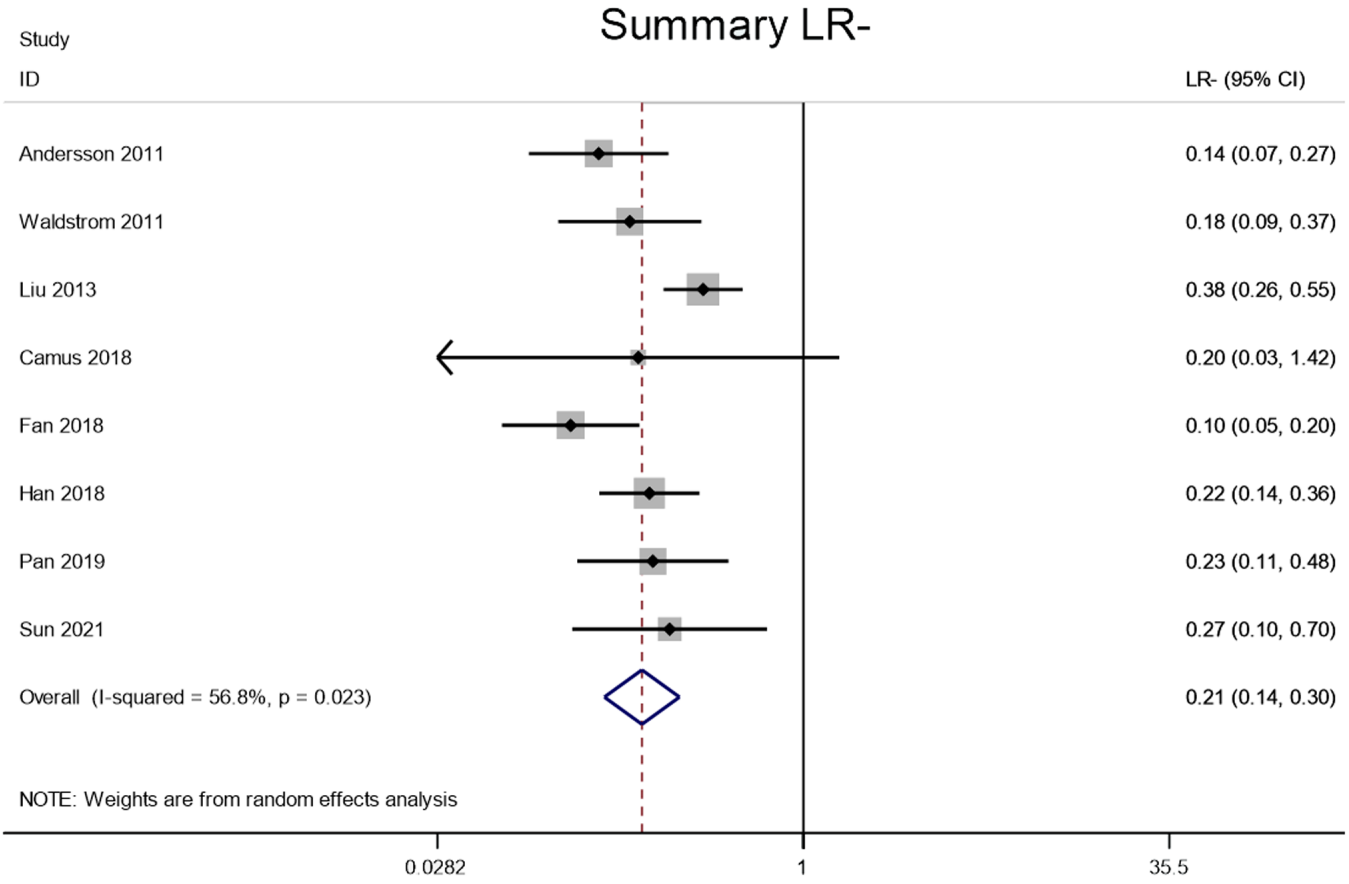

Figure 6. Forest plot of the LR- of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; LR-, negative likelihood ratio; HPV, human papillomavirus.

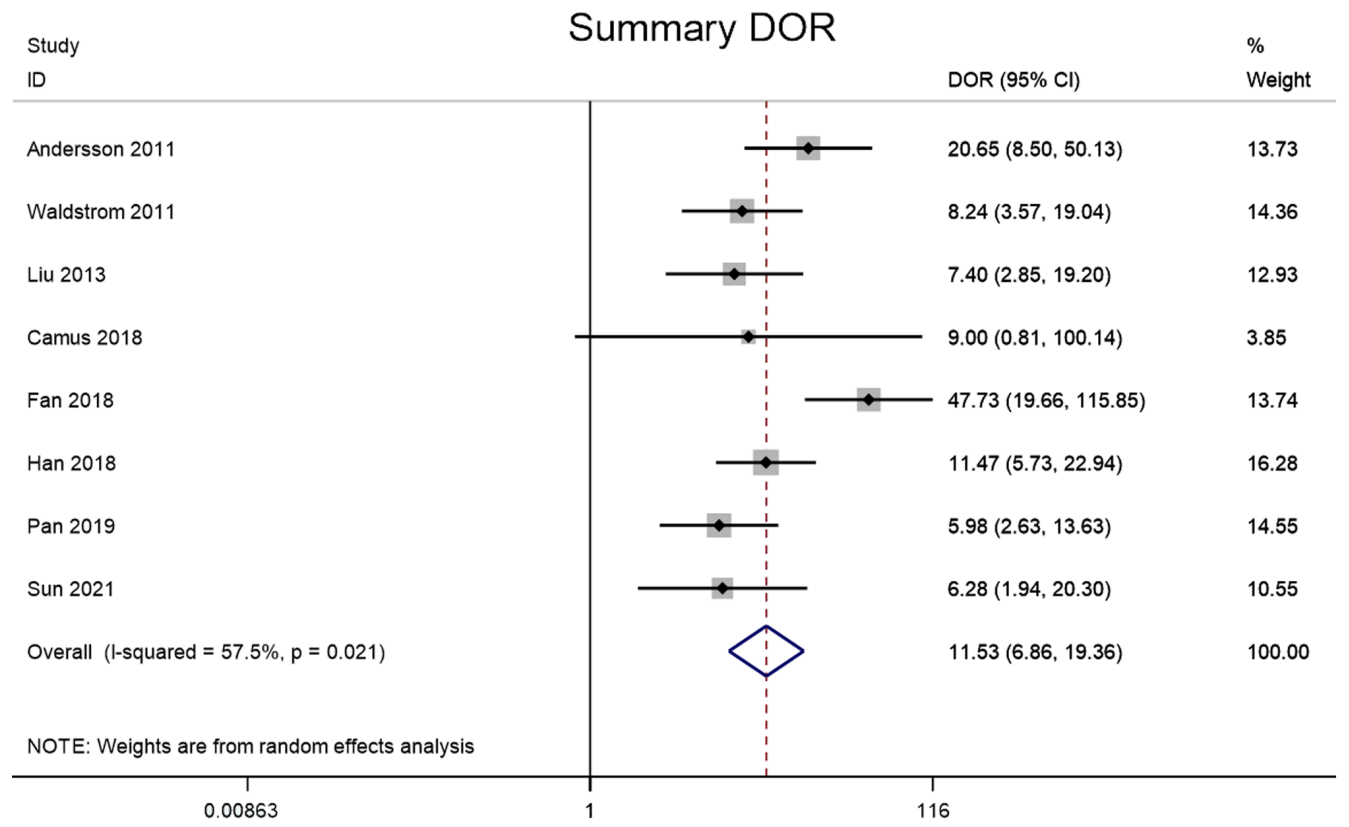

Figure 7. Forest plot of the DOR of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; DOR, diagnostics odd ratio; HPV, human papillomavirus.

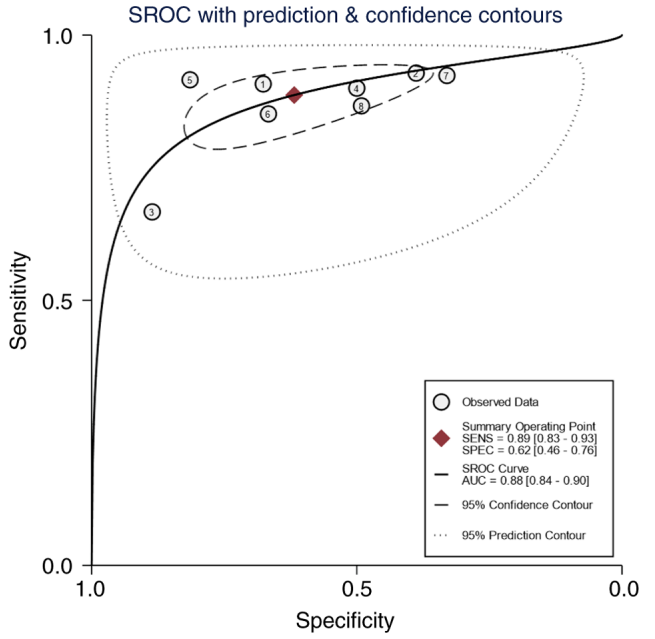

Figure 8. SROC curve of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; SROC, summary receiver operating characteristic; HPV, human papillomavirus; AUC, area under the curve; sens, sensitivity; spec, specificity.

among studies, a sensitivity analysis was conducted to find sources of heterogeneity (Figs. S1-4). The results showed that the two studies by Shi *et al* (17) and Zhang *et al* (22) had a greater impact on the results. Both studies were excluded and tested for heterogeneity again. The results of the repeated heterogeneity test showed that the heterogeneity was significantly reduced.

Sensitivity and specificity. Meta-analysis was performed through a random-effect model due to heterogeneity in sensitivity (I^2=79.21%) and specificity (I^2=93.33%). The pooled sensitivity and specificity of the studies overall were 0.89 (95% CI, 0.83-0.93) and 0.62 (95% CI, 0.46-0.76), respectively (Fig. 4).

LR+ and LR-. Meta-analysis was performed through a random-effect model due to lower heterogeneity in LR+ (I^2=92.3%) and LR- (I^2=56.8%). The pooled LR+ and LR- of the studies overall were 2.31 (95% CI, 1.61-3.32) and 0.21 (95% CI, 0.14-0.30), respectively (Figs. 5 and 6).

DOR. Meta-analysis was performed through a random-effect model due to lower heterogeneity in DOR (I^2=57.5%). The pooled DOR of the studies overall was 11.53 (95% CI, 6.86-19.36; Fig. 7).

ROC analysis. When the AUC value is 0.5-0.6, it is considered that the diagnostic tool is ineffective, 0.6-0.7 is poor, 0.7-0.8 is average, 0.8-0.9 is good and 0.9-1.0 is excellent (24). The SROC curve of the present study shows that AUC was 0.88 (95% CI, 0.84-0.90), indicating that E6/E7 mRNA has good diagnostic value for cervical cancer screening (Fig. 8).

Sensitivity analysis. Sensitivity analysis was carried out by iteratively excluding each included study individually, followed by re-conducting the meta-analysis with the remaining studies. The results of this sensitivity analysis were then compared to the original analysis to evaluate the influence of each study on the meta-analysis outcomes. Notably, after the exclusion of

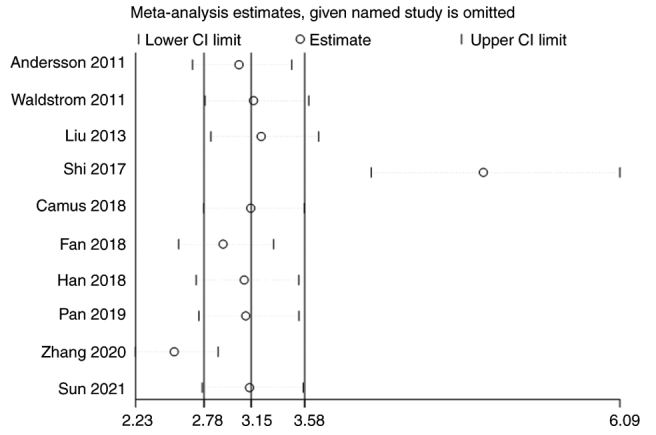

Figure 9. Sensitivity analysis of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus.

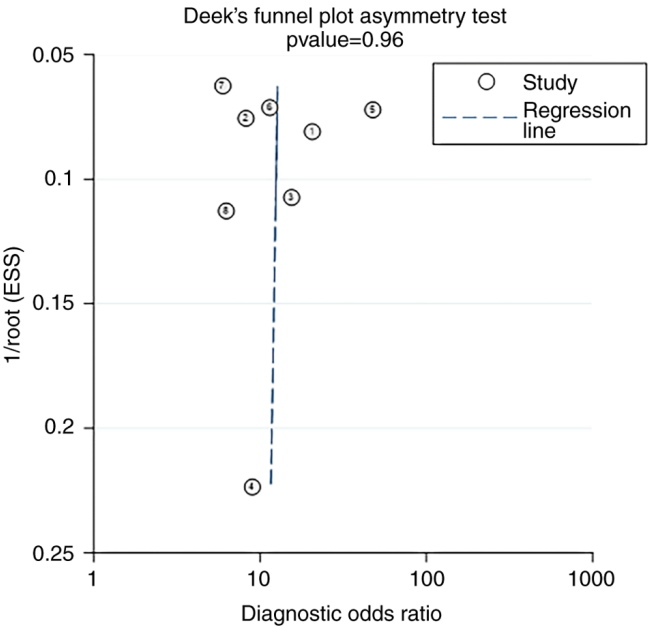

Figure 10. Deek's Funnel plot of HPV E6/E7 mRNA to distinguish between CIN2+ and CIN2-. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; ESS, effective sample size.

the studies conducted by Shi *et al* (17) and Zhang *et al* (22), the subsequent meta-analysis exhibited considerable changes compared with the original analysis. Therefore, it can be inferred that these two studies had a pronounced impact on the overall results (Fig. 9).

Publication bias. The P-value of the Deek's funnel plot of HPV E6/E7 mRNA for distinguishing between CIN2+ and CIN2 was 0.96, indicating that there was no obvious publication bias in the current study (Fig. 10).

Discussion

It is now clear that the occurrence and development of cervical cancer and CIN are mainly caused by the continuous infection with high-risk HPV. HPV DNA testing is primarily

a way to check if a patient is infected with HPV. Although it has a high sensitivity, its specificity is relatively low, and it cannot evaluate the infection stage of cervical HPV and the activity of viral oncogenes (25). HPV circular DNA is free in the nucleus of the host, and viral nucleic acid is generally integrated in the genome of the host normal cell, which can cause the inactivation or loss of E2 gene fragment, and then lead to the mRNA transcription of viral E6 and E7 oncogenes (19). Basu *et al* (26) reported that HPV E6/E7 proteins could bind to p53 and pRb, the key tumor suppressor proteins in cervical epithelial cells, respectively, and lead to their inactivity, resulting in abnormal cell cycle regulation and increasing the risk of malignant degeneration of CIN. An increasing number of studies have revealed that the expression level of HPV E6/E7 mRNA is positively associated with the severity of cervical lesions, and the higher the expression level, the greater the risk of high-grade CIN progressing to cervical cancer (27,28). Therefore, the present meta-analysis explored the diagnostic value of HPV E6/E7 mRNA in screening for CIN2+, aiming to provide a new marker for clinical diagnosis of cervical cancer.

Firstly, the pooled sensitivity and specificity of the studies overall were 0.89 (95% CI, 0.84-0.92) and 0.59 (95% CI, 0.46-0.71), respectively. This indicates that HPV E6/E7 mRNA is highly sensitive in the diagnosis of CIN2+, which helps to reduce the rate of missed diagnosis. However, lower specificity may lead to higher misdiagnosis in healthy patients. Additionally, the pooled DOR of the studies overall was 11.53 (95% CI, 6.85-19.36), suggesting that HPV E6/E7 mRNA had high diagnostic efficacy. Notably, the SROC curve of the current study showed that the AUC of 0.88 (95% CI, 0.84-0.90) indicates that E6/E7 mRNA has good diagnostic value for cervical cancer screening. In a study by Camus *et al* (18), the sensitivity of HPV DNA for CIN2+ diagnosis was 80%, while the AUC was 0.76. In addition, Zhang *et al* (29) reported an HPV DNA sensitivity of 86.5% and an AUC of 0.865. This suggests that the sensitivity and diagnostic accuracy of HPV E6/E7 mRNA may be higher than that of HPV DNA. When HPV E6/E7 mRNA detection is positive, cervical cancer histopathological examination should be performed for early diagnosis and early intervention.

However, the present study also has certain limitations. First, most of the included studies were retrospective, thus potentially introducing selection bias and limiting the generalizability of the findings to broader populations or screening settings. Further large-scale randomized controlled trials are needed to validate the findings. Second, most of the included studies were single-center, retrospective studies. Third, while the current study reported no obvious publication bias based on Deek's funnel plot, publication bias can be challenging to detect, especially when the number of included studies is limited. Fourth, the study primarily focused on diagnostic accuracy measures. However, it does not directly assess clinical outcomes, such as the impact of HPV E6/E7 mRNA testing on patient management or the reduction in cervical cancer incidence or mortality. Fifth, the study does not directly compare HPV E6/E7 mRNA testing with other screening methods, making it challenging to evaluate whether this biomarker offers advantages over existing diagnostic approaches.

HPV E6/E7 mRNA testing has high diagnostic efficacy for CIN2+. HPV E6/E7 mRNA is highly sensitive in the diagnosis of CIN2+, which helps to reduce the rate of missed diagnoses. However, lower specificity may lead to more misdiagnoses in healthy patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FSX and TFR made substantial contributions in conceving and drafting the manuscript. QGW and RRP made substantial contributions to acquisition of data. SZC and JL made substantial contributions to analysis and interpretation of data. FSX and JL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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