

# Meta-Analysis and Systematic Review of the Relationship between Cervical Lesions, HPV and Vaginal Community State Type

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## ABSTRACT

**Background:** Chronic HPV infection is a precursor of cervical cancer, which is largely caused by dysregulation of vaginal flora and other factors like abnormal H<sub>2</sub>O<sub>2</sub>, neuraminidase and insufficient vaginal hygiene. The relationship between HPV-induced cancer and vaginal microbiota is involved in the viral chronicity and also influences the disease prognosis. A meta-analysis system was used to evaluate the relationship between cervical lesions, HPV and vaginal microenvironment.

**Methods:** PubMed, Web of Science, Cochrane and Embase databases were searched for relevant literature published from 2016 to December 2020. According to the inclusion and exclusion criteria, literature screening, data extraction and quality evaluation were carried out, and stata16 statistical software was used for Meta-analysis and systematic evaluation.

**Results:** The overall relative risk of CST in 95% CI: 0.76-1.4, LSIL group compared with normal cytology group was 0.81. The overall relative risk of CST in the HSIL group and cervical cancer group was 0.77 and 1.26, respectively. It was found that there was publication bias in the HPV positive group (p-value of Begg and Egger were 0.067 and 0.247) and cervical cancer group (p-value of Begg and Egger were 0.677 and 0.457 respectively). There was a significant difference in CST III between HPV positive group and the LSIL group.

**Conclusion:** Cervical lesions and HPV are related to the increase of vaginal microbial diversity, and HPV and LSIL groups are related to CST III, while HSIL and cervical cancer groups are related to CSTIV, which has a certain guiding significance for early clinical diagnosis, but further large-scale studies are needed to confirm our findings.

**Key-words:** Cytology, Cervical lesion, 16S rDNA, HPV, Vaginal microenvironment

## INTRODUCTION

Persistent infection with carcinogenic HPV is necessary for cervical cancer [1-3]. Dysregulated vaginal flora is considered a contributor to persistent HPV-mediated cervical cancer and genital inflammation [4]. In addition to HPV infection, there are other factors that contribute to the development of cervical cancer, with abnormal H<sub>2</sub>O<sub>2</sub>, vaginal cleanliness, β-glucuronidase, and neuraminidase interacting with more lesions [5,6]. As technology has evolved, the study of vaginal microbes

has deepened, and although the bacterial communities that provide these ecosystem services are made up of distinctly different species. They can be clustered into five major community status types (CSTs)- I, II, III, IV, and V [7]. HPV-positive women are at significantly higher risk of precancerous lesions (of any grade) and cancer [3], and the vaginal microbiome of cervical cancer is significantly dysfunctional, and lactobacilli inhibit the reproduction and infection of common vaginal pathogens [8]. The development of HPV-induced cancer is associated with a high diversity of the vaginal microbiota, which is involved in the control of viral persistence and is therefore an indicator of disease prognosis [9].

## MATERIALS AND METHODS

**Retrieval Data Strategy-** Retrieved in uterine cervical neoplasms, papillomavirus infection, parallel mesh, vaginal microbiota, vaginal microbiome, vaginal.

### How to cite this article

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Taken Uterine Cervical Neoplasms, Papillomavirus Infection, Parallel Mesh Search, Vaginal Microbiota, Vaginal Microbiome, Vaginal Microecology, Vaginal Microenvironment, Vaginal environment, vaginal flora as keywords, search PubMed, Web of Science, Cochrane, Embase database search identification records, search time from 2016 to December 2020 published related literature, the preliminary reading of the title and abstract, excluding reviews, systematic reviews, a meta-analysis of studies that are not relevant to the content of this article, full reading of the included literature, excluding the inability to obtain the full text, Literature,

where the original data cannot be obtained, the data is not compliant, and the data cannot be integrated, and finally the literature is included in the evaluation literature.

**Inclusion of Basic information-** According to the Newcastle Ottawa Scale (NOS) independent evaluation of the quality of the included literature, 3 articles were 5 points, 3 articles were 6 points, 1 article was 7 points, and 1 article was 8 points, and the quality of the included literature was relatively high. Its basic characteristics are shows in Table 1.

**Table 1:** Basic features of the included studies

Authors	Age Mean (range)	HPV-negative	HPV-positive	Total No. of study	Type of study	HPV detection techniques s	Vaginal microbial detection technique
Wu <i>et al.</i> [15]	38 (16-50)	14	55	69	Cross-sectional study	HPV genotyping	16S rRNA gene fragment (V3-4)
Chen <i>et al.</i> [13]	HPV(+)47.78 Normal 43.00	/	/	229	Cross-sectional study	HPV genotyping test	16S rRNA sequencing
Klein <i>et al.</i> [25]	/	8	87	144	Cross-sectional gourd study	HPV genotyping	V4 hyper variable region of the 16S rRNA gene
Onywera <i>et al.</i> [14]	34.5 (25.8-39.0)	39	23	62	Roundabout cross-sectional study	Roche linear array HPV genotyping test	16SrRNA (rRNA) gene V4 high-variable region ion spur sequencing
Chao <i>et al.</i> [16]	HPV(+)37.63 (20-65) HPV(-) 38.03 (23-60)	86	65	155	Cross-sectional study	HPV gene detection of cobas 4800 system based on real-time qualitative PCR	16S rDNA gene fragment (V4)
Kwasniewski <i>et al.</i> [9]	/	70	180	250	Cross-sectional study	Polymerase chain reaction (PCR) amplifies the human papillomavirus (HPV) gene sequence	V4 hyper variable region of 16S rRNA
Paola <i>et al.</i> [17]	HPV negative (Mean) 43 HPV positive clearance group 45 HPV positive persistent group 41	17	HPV positive clearance group (n=27) HPV positive persistent group (n=28)	62	Longitudinal cohort study	Hybrid capture 2 assays for HPV DNA detection	V3-V5 hyper variable region of the 16S rRNA gene
Mitra <i>et al.</i> [1]	31 ( 23-45)	24	93	169	Cross-sectional study	HPV DNA testing and 16/18 genotyping	V1-V2 hyper variable region of the 16S rRNA gene

### Inclusion criteria

- **Study type:** Randomized study, retrospective study, cohort study;
- **Research object:** In the eligible articles, the techniques used for species identification in the microbial community include next-generation sequencing, 16S rRNA, high-throughput sequencing, macroscopic gene sequencing, and patients who meet HPV testing.
- Study the diversity of vaginal microbial changes in the HPV-negative or positive group, normal cytology, LSIL, HSIL, and cervical cancer group.

### Exclusion criteria

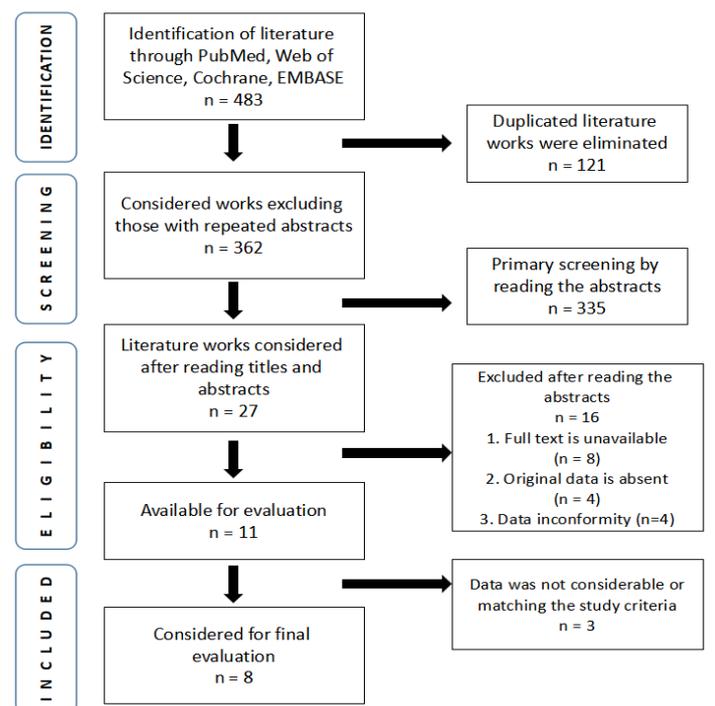
- Abstracts from scientific conferences, editorials, reviews and reviews, and animal studies are not included in studies;
- Documents with incorrect, mutilated or duplicate publications;
- Documents where the original data cannot be obtained, the data cannot be integrated, and the full text cannot be obtained.

**Statistical Analysis-** All statistical analyses were performed using Stata 16 software, using relative risk (RR) and a 95% confidence interval (95% CI). Assessing the effects of various factors, HPV-negative or positive group, normal, LSIL, HSIL, cervical cancer group on CST I, II, III, IV, V, when  $p < 0.1$ , we thought there was statistical significance. Cochrane's Q test and Higgins I<sup>2</sup> were used to assess heterogeneity between studies, with mild heterogeneity considered when  $I^2 < 30\%$ , moderate heterogeneity between  $I^2$  and  $60\%$ , and high heterogeneity in more than  $60\%$ , and  $I^2 < 30\%$  and  $p > 0.1$ , we use a fixed-effects model for data synthesis, otherwise a random-effects model. We assessed the robustness of the results by excluding one study at a time. We used a funnel chart to assess publication bias in the included studies and further calculated the Begg and Egger values for verification, and when the funnel plot symmetry was good and the  $P$ -value of the bag and egger was greater than 0.5, we thought there was no potential publication bias.

## RESULTS

**Literature Screening-** A total of 483 past studies were retrieved. 121 duplicate articles were excluded. Read the titles and abstracts to exclude case reports, reviews, systematic reviews, and non-relevant research content, and the remaining 27 articles were further study based

on the inclusion and exclusion criteria designed for this study, 8 studies were finally included (Fig. 1).



**Fig. 1:** Literature screening method according to PRISMA flowchart

### Meta-Analysis

**HPV-negative/positive group in CST correlation-** As can be seen from Fig. 2, the overall relative risk of CST in the HPV-positive group relative to the HPV-negative group was 0.93 (95% CI: 0.76-1.4); the relative risk of CST I was 0.86 (95% CI: 0.61-1.23), the relative risk of CST II was 1.16 (95% CI: 0.33-4.11), and the relative risk of CST III was 0.76 (95% CI: 0.55-1.05), CST The iv relative risk was 1.28 (95% CI: 0.84-1.95), the relative risk of CST V was 2.50 (95% CI: 0.32-19.46), and the overall heterogeneity was relatively low ( $I^2 = 0\%$ ,  $p = 0.843$ ).

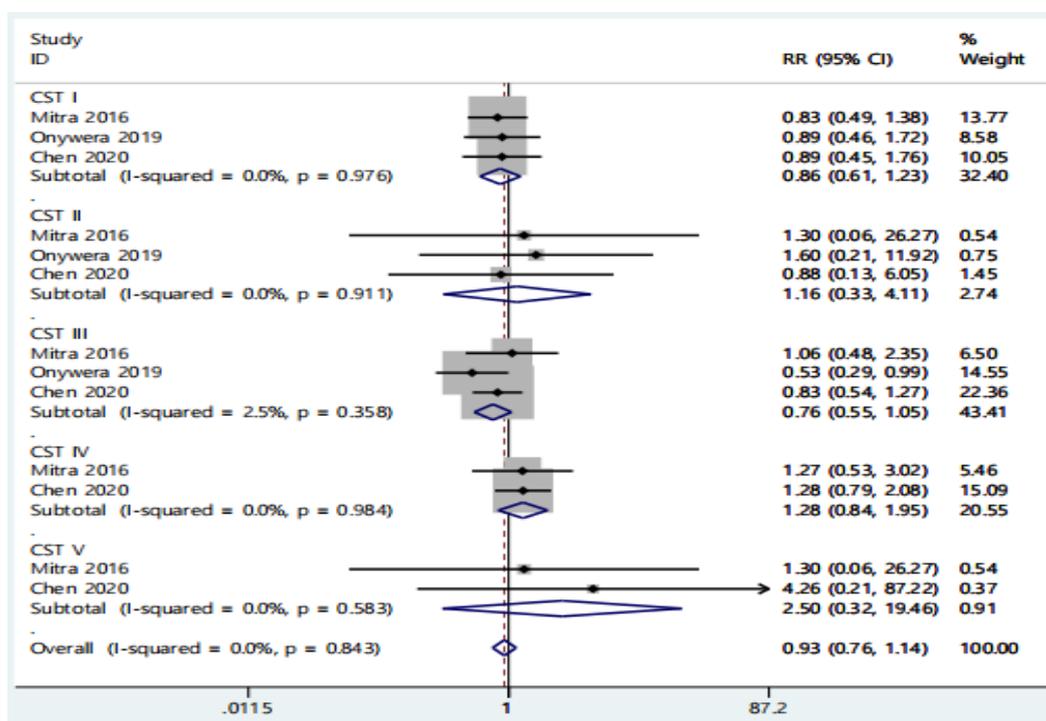
We were specified in the methodology that  $I^2 < 30\%$  and  $p$ -values greater than 0.1 were used in a fixed-effects model, otherwise a random-effects model will be used, so here is a fixed-effects model. Based on the total result of Table 2  $p = 0.466$ , it was not statistically significant, but only the CST III group had statistical significance ( $p = 0.097$ ), and the relative risk (RR) of other groups had a downward trend and had no statistical significance. Fig. 3 shows that the overall results were robust, with no study excluding the overall RR not in the 95% confidence interval. By begg detection and egger detection (Table 3), the  $P$ -value in begg detection was 0.067, and the  $P$ -value in egger detection is 0.247, which may have publication bias, while the funnel chart symmetry is average, and there may also be publication bias, which does not exclude the problem of insufficient sample size (Fig. 4).

**Table 2:** The findings of P-values of HPV, LSIL, HSIL, and cervical cancer in CSTs

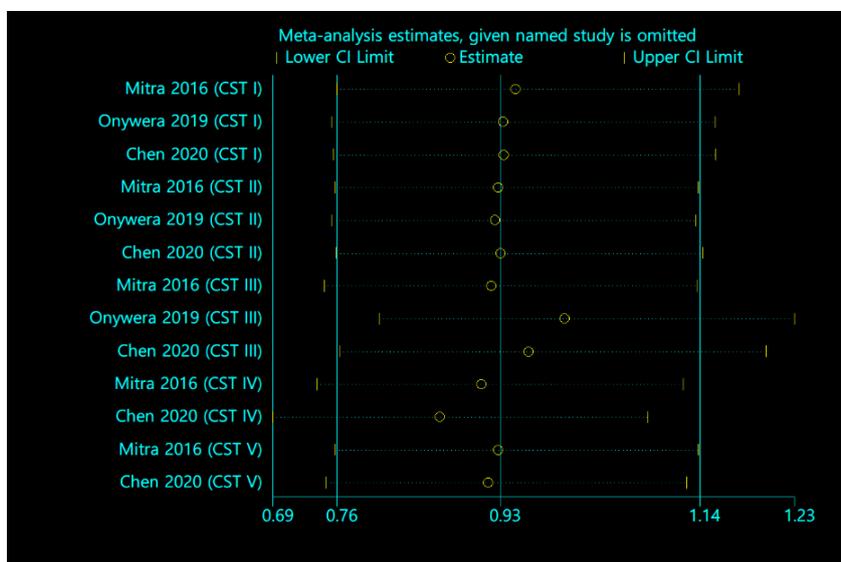
	CST I	CST II	CST III	CST IV	CST V	Overall
HPV(+)	0.414	0.820	0.097	0.258	0.382	0.466
LSIL	0.479	0.623	0.088	0.436	0.177	0.213
HSIL	0.190	0.979	0.140	0.055	0.191	0.316
Cancer	0.268	0.257	0.130	0.011	0.163	0.584

**Table 3:** Publication bias of HPV, LSIL, HSIL, and cervical cancer

Project	HPV(+)	LSIL	HSIL	Cancer
Begg detection	0.067	0.951	1.000	0.677
Egger detection	0.247	0.983	0.536	0.457



**Fig. 2:** Forest diagram of HPV



**Fig. 3:** Sensitivity analysis plot of HPV

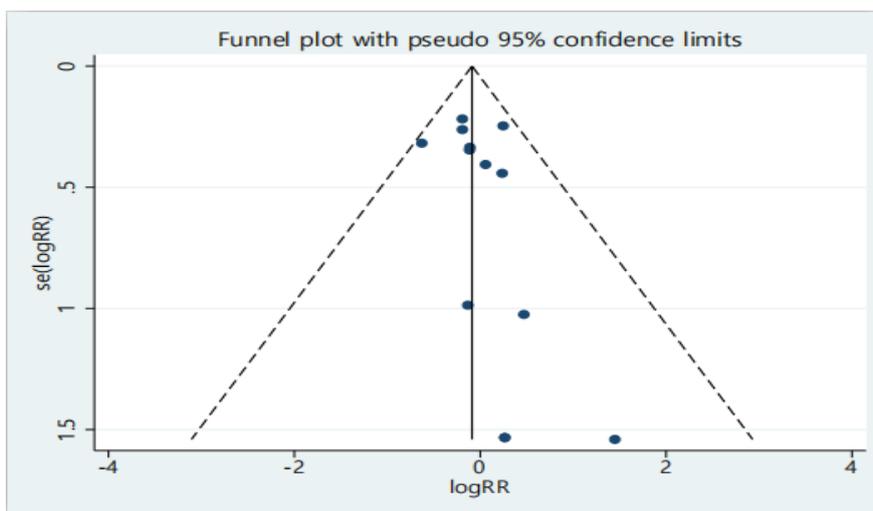


Fig. 4: Funnel diagram of HPV

**LSIL group/normal group in CST correlation-** As can be seen from Fig. 5, the overall relative risk of CST in the LSIL group relative to the normal cytology group was 0.81 (95% CI: 0.58-1.13); the relative risk of CST I was 0.78 (95% CI: 0.40-1.54), the relative risk of CST II was 0.67 (95% CI: 0.14-3.29), and the relative risk of CST III was 0.52 (95% CI: 0.25-1.10), CST The relative risk of IV was 1.23 (95% CI: 0.73-2.06), the relative risk of CST V was 4.29 (95% CI: 0.52-35.60), and there was moderate heterogeneity in the overall heterogeneity ( $I^2=31.9%$ ,  $p=0.128$ ).

In the methodology, we were specified that  $I^2 < 30%$  and  $p$ -value greater than 0.1 were used in a fixed-effects

model, otherwise a random-effects model was used, so here is a random-effects model. Based on the total result of Table 2  $p=0.213$ , it was not statistically significant, but only the CST III group had statistical significance ( $p=0.088$ ), and the relative risk (RR) of other groups had a downward trend and had no statistical significance. Sensitivity analysis shows that the overall results were robust (Fig. 6) and that no single study was excluded from the 95% confidence interval overall. By begg detection and egger detection (Table 3), both  $p$ -values were greater than 0.5, and there was no publication bias, while the funnel diagram symmetry is better, which indicated that there is no publication bias (Fig. 7).

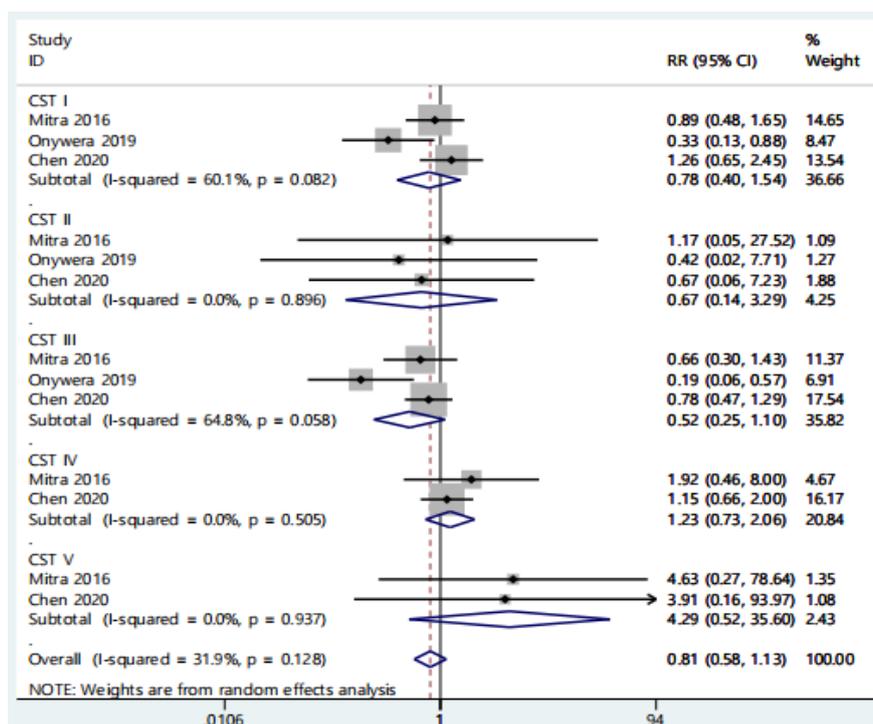


Fig. 5: Forest diagram of LSIL

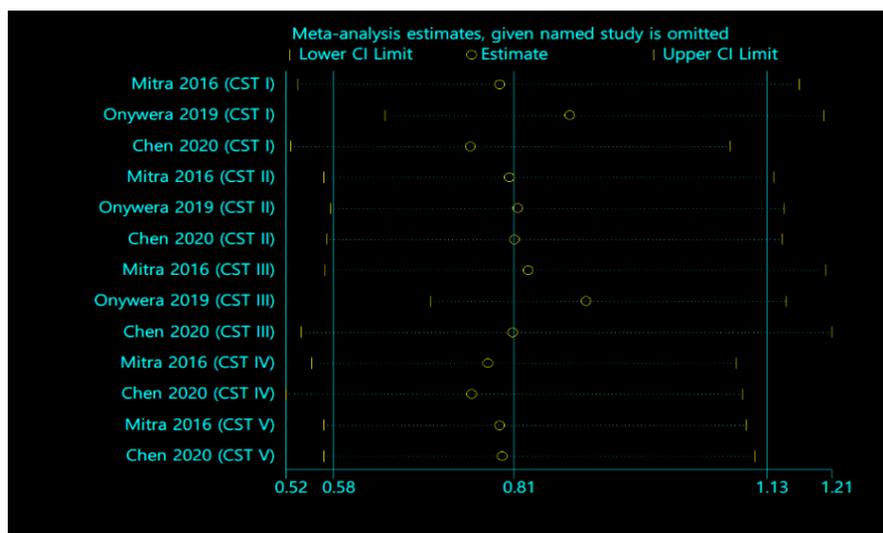


Fig. 6: Sensitivity analysis plot of LSIL

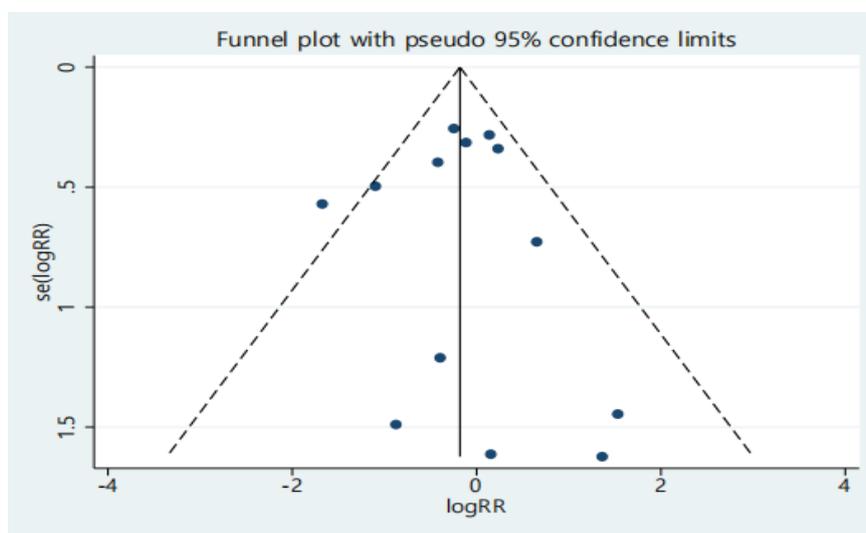


Fig. 7: Funnel diagram of LSIL

**HSIL group/normal group in CST correlation-** As can be seen from Fig. 8, the overall relative risk of CST in the HSIL group relative to the normal cytology group was 0.77 (95% CI: 0.47-1.28); the relative risk of CST I was 0.43 (95% CI: 0.12-1.53), the relative risk of CST II was 0.98 (95% CI: 0.20-4.75), and the relative risk of CST III was 0.50 (95% CI: 0.20-1.25), CST The relative risk of IV was 1.69 (95% CI: 0.99-2.88), the relative risk of CST V was 8.28 (95% CI: 0.35-196.68), the overall heterogeneity was relatively high ( $I^2=53.6%$ ,  $p=0.014$ ), and the heterogeneity was significant in the CST I and CST III groups, 67.7% and 70.2%, respectively, and there was no heterogeneity in the remaining groups. Mitra 2016 in the CST V group was excluded because both the HSIL group and the normal cytology group had 0 positive events, so

it was excluded. In the methodology, we were specified that  $I^2 < 30%$  and a p-value greater than 0.1 was used in a fixed-effects model, otherwise a random-effects model was used, so here is a random-effects model. Based on the total result of (Table 2)  $p=0.316$ , it was not statistically significant, but only the CST IV group had statistical significance ( $p=0.055$ ), and the relative risk (RR) of other groups had a downward trend and had no statistical significance. Fig. 9 shows that the overall results were robust, with no single study excluding the overall RR not in the 95% confidence interval. By Begg detection and Egger detection (Table 3), both p-values are greater than 0.5, and there is no publication bias, while the funnel diagram symmetry is better, which also indicates that there is no publication bias (Fig. 10).

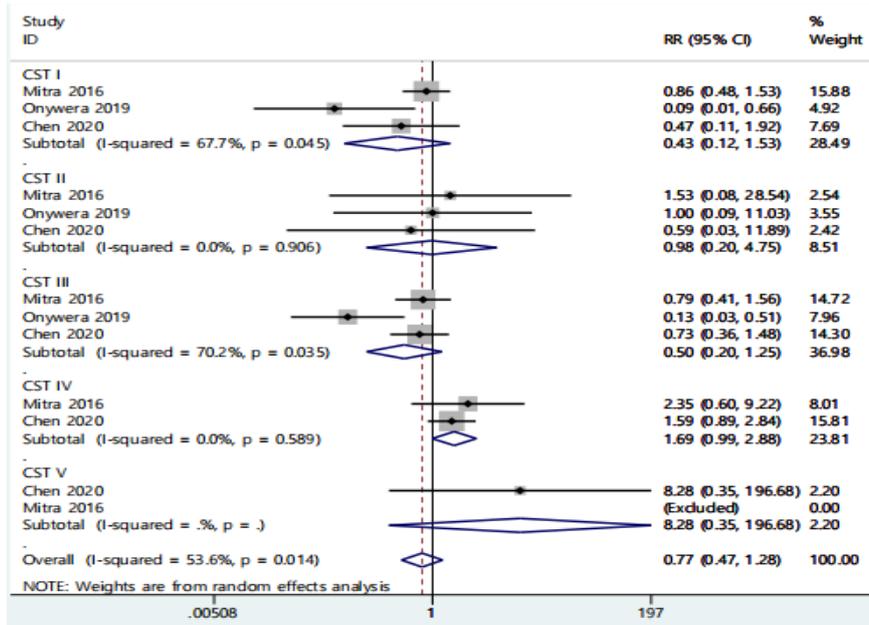


Fig. 8: Forest map of HSIL

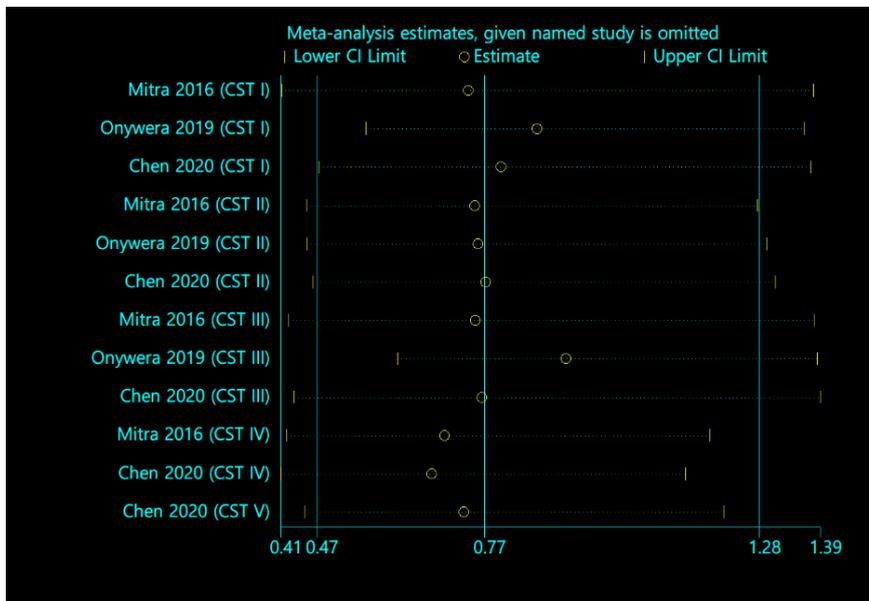


Fig. 9: Sensitivity analysis plot of HSIL

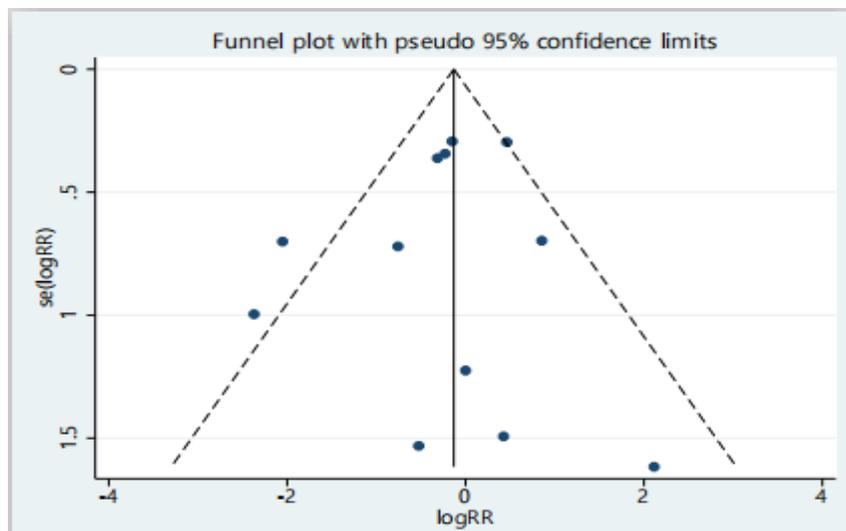


Fig. 10: Funnel diagram of HSIL

**Cervical cancer (Cancer) group/normal cytology group in CST correlation-** As can be seen from Fig. 11, the overall relative risk of CST in the cervical cancer group relative to the normal cytology group was 1.26 (95% CI: 0.55-2.90); the relative risk of CST I was 0.42 (95% CI: 0.09-1.95), the relative risk of CST II was 3.43 (95% CI: 0.41-29.19), and the relative risk of CST III was 0.30 (95% CI: 0.06-1.42), CST The relative risk of IV was 2.17 (95% CI: 1.20-3.95), the relative risk of CST V was 9 (95% CI: 0.41-196.65), there was moderate heterogeneity in the overall heterogeneity ( $I^2=37.0\%$ ,  $p=0.122$ ), and Chen 2020 in the CST V group was excluded because both groups had 0 positive events, so it was excluded. In the methodology, we were specified that  $I^2<30\%$  and a p-value greater than 0.1 were used in a fixed-effects

model, otherwise a random-effects model will be used, so here is a random-effects model. Based on the total result of Table 2,  $p=0.584$ , it was not statistically significant, but only the CST IV group had statistical significance ( $p=0.011$ ), and the other groups had an upward trend and had no statistical significance. Fig. 12 shows that the overall results are relatively robust, and none of the studies has been excluded from the overall RR of 95%, and overall, the sensitivity analyses of these four groups were also relatively robust. By Begg detection and Egger detection (Table 3), the P-value in Begg detection is 0.677, and the P-value in Egger detection is 0.457, there may be publication bias, poor funnel symmetry, and there may also be publication bias (Fig. 13), considering the insufficient sample size.

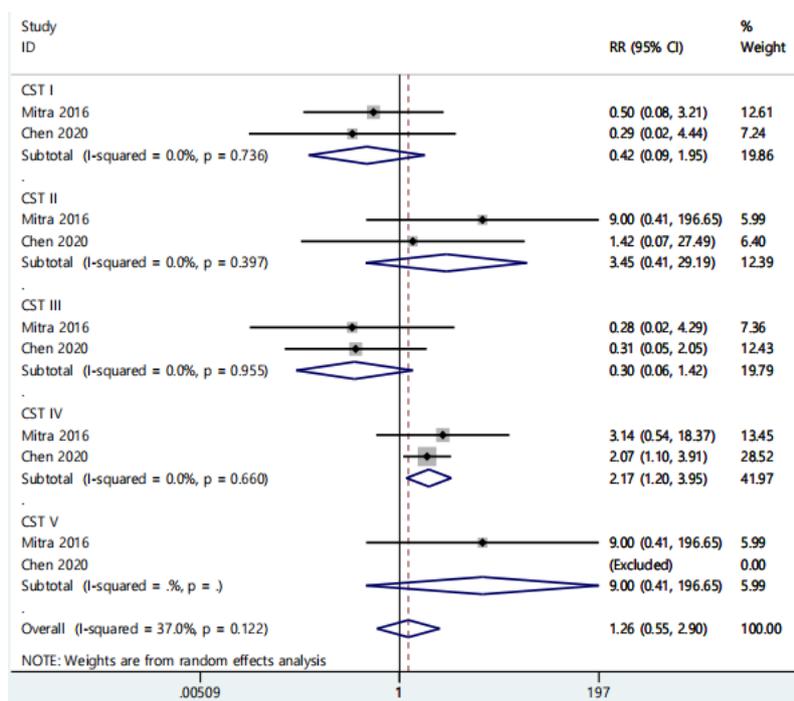


Fig. 11: Forest map of cervical cancer

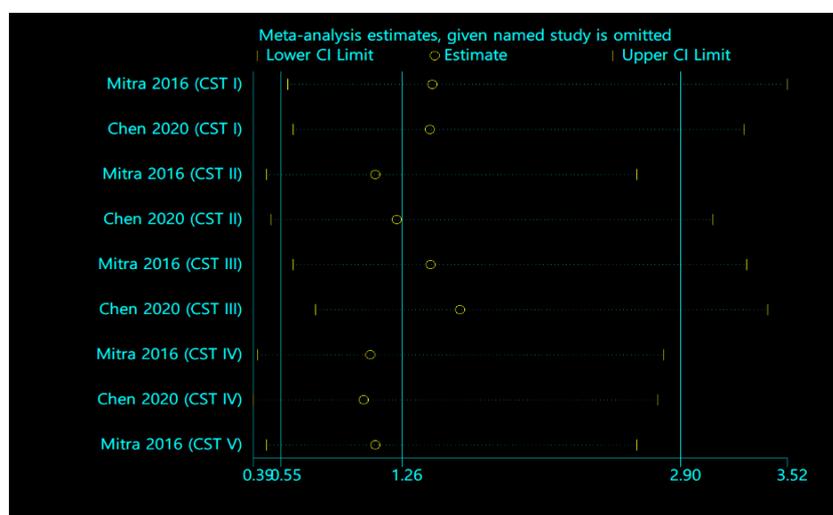
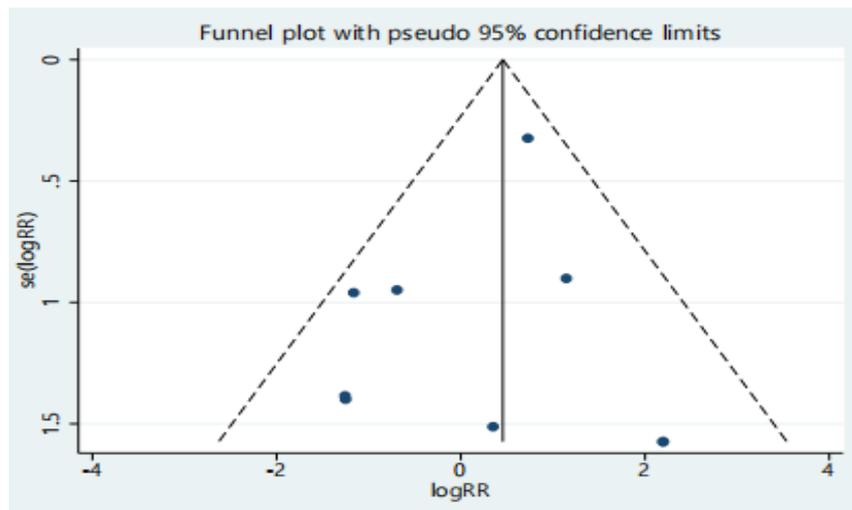


Fig. 12: Sensitivity analysis of cervical cancer



**Fig. 13:** Funnel diagram of cervical cancer

## DISCUSSION

Cervical cancer is caused by the synergistic effects of persistent high-risk HPV infection<sup>[1,10]</sup>. Alterations in the vaginal microbiota are strongly associated with persistent HPV infection, the occurrence of cervical cancer depends on major HPV-related risks such as viral strain and persistence, viral load, and oncogene expression<sup>[11]</sup>, improving the vaginal microbial environment reduces the risk of cervical cancer<sup>[11]</sup>, and the vaginal microbiota plays a functional role in the progression of cervical lesions in women infected with HPV<sup>[12]</sup>, and the development of HPV-induced cancer is associated with a high diversity of the vaginal microbiota<sup>[13]</sup>. The vaginal microbiota is involved in the control of viral persistence and is, therefore, an indicator of disease prognosis<sup>[9]</sup>. A direct result of early HPV infection may be a decrease in levels of probiotics such as *Shuttleworthia*, *Prevotella*, *Lactobacillus*, and *Sneathia*, whereas the most abundant genus in the normal group is *Lactobacillus*<sup>[13,14]</sup>, and *Lactobacillus* is the most dominant genus<sup>[15-17]</sup>, which is considered to represent "health". Cervical-vaginal status, while decreased probiotic levels, can lead to vaginal microbial disorders, and increased levels of other pathogenic bacteria such as *Dispar*, *Streptococcus*, and *Faecalibacterium Prausnitzii*<sup>[10]</sup>, an increase in disease severity associated with a decrease in the relative abundance of *Lactobacilli*<sup>[1]</sup>, maybe a key factor in cancer progression. In addition, KEGG pathway enrichment analysis showed that HPV infection can directly inhibit spore-producing, porphyrin and chlorophyll metabolism, arginine and proline metabolism, isoquinoline alkaloid biosynthesis, ansamycin biosynthesis, etc., resulting in the occurrence

of early symptoms of cervical cancer<sup>[10]</sup>. According to differences in flora composition and relative abundance, the cervical vaginal flora is divided into four main flora<sup>[18]</sup>, and *Lactobacillus crispatus* (*L. aspergillus*) dominates class<sup>[17,18]</sup>; *P. brenneri* (*P. brucellosis*), *P. putida* (*P. malodorous*), *A. vaginae* (*A. vaginalis*), *Burkholderia stagnalis* (*Burkholderia*), *Rhodococcus erythropolis* (*Erythropolis*) and *Prevotella bivia* (*Prevobacterium genitalium*) are the main members of Class II<sup>[18]</sup>, *L. iners*<sup>[17]</sup> is the dominant class III; *B. Stagnalis* (*Staphylococcus*) is the most abundant species in class IV<sup>[18]</sup>. Flora diversity is more pronounced in type II and TYPE IV CST, particularly type II CST<sup>[15]</sup>. Mitra, Di Paola were divided into CST I, II, III, and V by the social community (CST), with *L. crispatus*, *L. gratens* (*L. gasseri*), *L. inert* (*L. iners*), and *L. Jani* (*L. jensenii*) dominating the position<sup>[1,17]</sup>, while lactic acid bacteria depletion was determined to be CST IV<sup>[1,17,18]</sup>, respectively and an increase in the diversity of anaerobic bacteria<sup>[1]</sup>. This is slightly different from the classification above, but it is roughly similar. In our study, LSIL (low-grade squamous intraepithelial lesions), HSIL (high-grade squamous intraepithelial lesions), and cervical cancer groups had no statistically significant overall CST ( $p$ -values= 0.213, 0.316, 0.584, respectively). Wu speculated that the more severe the lesion, the greater the flora diversity, but did not find statistically significant effect<sup>[15]</sup>, which is consistent with the results reported by Mitra<sup>[1]</sup>. Their findings suggest that vaginal microbial diversity is associated with progression in the severity of cervical intraepithelial neoplasia, but not to the point of significance, which is also consistent with our study. However, CST III was statistically significant in the LSIL group, while CST IV in the HSIL and cervical

cancer groups were statistically significant, and HPV infection changed the vaginal bacterial community structure from CST III to CST IV<sup>[13]</sup>, and with the increase in disease severity, the prevalence of microbiota characterized by high diversity and low levels of *Lactobacillus sp.* (CST IV type) also increased<sup>[1,13]</sup>, which was relevant to our study. The normal group was mostly CST III<sup>[13]</sup>, the LSIL group is dominated by CSTIS, but CST IV is less, CST II was more<sup>[15]</sup>, and the LSIL group in our study is associated with CST III, which may be caused by a lack of study numbers, and further research is necessary. Similarly, in the HSIL group, the proportion of CST II increased to 31.2%<sup>[15]</sup>, which was not covered in this study, but the classification of CST and squamous intraepithelial neoplasia was not statistically significant<sup>[15]</sup>, consistent with this study, and the total CST was not statistically significant. In CST in LSIL patients, the predominant bacterial types were *Lactobacillus acidophilus* and *L. iners*, but *Lactobacillus crispatus* was not detected<sup>[9]</sup>, and CST swabs from HSIL showed a large number of vaginal *Gardnerella vaginalis* and *L. acidophilus*, but lack *L. taiwanensis*, *L. iners*, and *L. crispatus*<sup>[9]</sup>. There was an increase in *Prevotella* and *Streptococcus* in the HSIL group<sup>[15]</sup>, but no statistical significance was reported in this study<sup>[15]</sup>. The researchers consider CST IV-BV to be a risk factor for the persistence of HPV<sup>[17]</sup> and suggest that *Atopobium vaginae* and *G. vaginalis* from the vagina are considered potential risk factors for cervical cancer<sup>[17,19]</sup>, with *G. vaginalis* being a high-risk group for CIN 2/3 and cervical cancer<sup>[11]</sup>. At the same time, the former two microbiota (*Atopobium*'s bacteria, *G. vaginalis*) and the silabidase (salivaase gene) genes can be used as microbial markers of HPV persistence and early warning indicators of cervical lesion screening and lesion progression<sup>[6,17]</sup>. The effects of *Gardnerella* are mediated by the direct increase in cervical-vaginal bacterial diversity before the progression of persistent infection to cancer<sup>[20]</sup>, and by monitoring the presence of *Gardnerella* and subsequent elevations in microbial diversity; it can be used to identify the risk of progression in women with persistent high-risk human papillomavirus (HR-HPV) infection<sup>[20]</sup>. The composition of the vaginal microbiota may act as a modifier for high-risk HPV infections<sup>[16]</sup>, changes in lactic acid bacteria reduction and increased microbial diversity promote HPV infection<sup>[17]</sup>, and specific microbiota species may serve as sensors for changes in the cervical

microenvironment associated with high-risk HPV infection<sup>[16]</sup> and may be involved in viral persistence and cancer development<sup>[17]</sup>. *Haemophilus haemolyticus*, *Lachnobacterium bovis*, and *Slackia exigua* can serve as potential indicators of SIL for the detection of a variety of HPV infections<sup>[18]</sup>, while *Delphosia* may be a microbiological marker of cervical precancerous lesions<sup>[15]</sup>. Cervical disease progression is associated with the prevalence of high-risk HPV infection<sup>[15]</sup>, and HPV infection increases the richness and diversity of vaginal bacteria regardless of the status of CINs<sup>[15]</sup>. CST I was the most common CST, followed by CST III, CST IV, CST V, and CST II<sup>[1]</sup>, CST IV was associated with an increase in disease severity<sup>[1,13]</sup>, but there is no difference in the CST IV rates between normal or low-grade squamous intraepithelial lesions HPV-negative and HPV-positive individuals<sup>[1]</sup>, and the total CST is not statistically significant (P-value= 0.466) compared with the HPV-positive and negative groups in our study, but only CST III was statistically significant. The relative risk (RR) of other groups had a downward trend, and there was publication bias in the HPV-positive and negative groups, which was caused by the small sample size. Therefore, it is still believed that the presence of a high diversity of *Lactobacillus* reduced flora may be stronger associated with the presence of clinically significant pre-invasive or invasive disease<sup>[1,13,15]</sup>. HR-HPV-positive infections appear to be more associated with clusters II and III and less prevalent in clusters I and IV<sup>[18]</sup>, which has some relevance to our study. Our study focused on the CST group, and the meta-analysis of the relative abundance of each flora was flawed, so it was systematically evaluated.

Persistent infection with HR-HPV is the leading cause of cervical intraepithelial neoplasia and cervical cancer, with HPV16 being the most common carcinogenic form worldwide, with a detection rate of >60% in patients with cervical cancer<sup>[6]</sup>. On the one hand, the relative abundance of the dominant campylobacter phylum was found to be relatively low, with the phylum Actinomycetes, Clostridium, and virus phylum significantly higher in the positive group of HPV type 16<sup>[21]</sup>, while the composition of *Oribacterium*, *Lachnobacterium*, and *Thermus* in the cervical vaginal microflora was more likely to be related to HPV16<sup>[18]</sup> which indicates that HPV16 or HPV 18. Significant increase in ciliate spp. (*Sneathia*) in patients with infection and cervical cancer<sup>[22]</sup>, alterations in the vaginal

microenvironment and HPV16 infection increase the risk of cervical lesions and interact with cervical intraepithelial neoplasia [6]. Concomitant trichomoniasis vaginitis (TV) infection increases the risk of HPV16 infection in women with CIN2 to 3<sup>[12]</sup>. The composition of Motilibacter in the cervical vaginal microflora is more likely to be related to HPV 52<sup>[18]</sup> while the composition of Litorilina and Paludibaculum in the cervical-vaginal microflora plus a small amount of *L. iners* (*Lactobacillus iners*) in the cervical vaginal microflora is more likely to be related to HPV 58<sup>[18]</sup>.

HPV diversity does not change with cervical dysplasia<sup>[23]</sup>. In the HPV-negative group, Firmicutes are the predominant phylum, accounting for 73.99%<sup>[16]</sup>, while the remaining phyla have a relative abundance of more than 1%, including Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria<sup>[16]</sup>. The relative abundances of women with HR-HPV infection were significantly higher in the families Aerococcaceae, Pseudomonadaceae, and Bifidobacteriaceae<sup>[24]</sup>.

The main defense mechanisms of the cervical vaginal mucosa are antimicrobial peptides, pH values of less than 4.5, and a microbiota dominated by lactic acid bacteria<sup>[25]</sup>. Decrease in lactobacillus<sup>[13]</sup> in HR-HPV infected persons, increased *G. vaginalis*<sup>[13,22,24]</sup>, Atopobium<sup>[13,22,24]</sup>, Prevotella<sup>[24]</sup>, micrococci<sup>[22]</sup>, and increased HPV infection with Prevotella and Bacillus, the relative abundance of Anaerococcus, Sneathia<sup>[24]</sup>, Megasphaera, and Streptococcus<sup>[13]</sup>. Increased bacillus, anaerobes (Anaerococcus), and decreased abundance of *G. vaginalis* may be associated with progression in the severity of CINs<sup>[13]</sup>. The lower genital tract flora may be more closely related to HR-HPV infection<sup>[22]</sup>. In the HPV-positive group, the relative abundance of Actinobacteria, thyrestris<sup>[6]</sup>, and Softderma were higher than in the HPV-negative group<sup>[16]</sup>. In the LR-HPV group, the relative abundance of the dominant thick-walled phylum was low, and the relative abundance of actinomycetes, proteobacteria phylum and *Clostridium* phylum were significantly higher; At the genus level, Gardnerella, Bifidobacterium, Snezia<sup>[6]</sup>, Hydrogenophilus, Burkholderia, and Atroposbacteria are higher<sup>[26]</sup>. Several studies have shown an increase in the number of microorganisms infected with HR-HPV<sup>[11,13,18,22,24]</sup>, and similarly, the microbial diversity of LR-HPV-infected people has also increased significantly<sup>[26]</sup>. Increased microbial diversity in patients with CIN or cervical cancer

infected with HPV<sup>[11]</sup>. In women with CIN disease and cervical cancer, a decrease in *L. curriflatus* and an increase in anaerobic bacteria, such as *G. vaginalis*, anaerobic *P. anaerobius*, and *Porphyromonas uenonis*<sup>[11]</sup> are significantly more common in women with CIN disease and cervical cancer.

## CONCLUSIONS

In summary, cervical lesions, HPV and vaginal microbial diversity increased, and HPV, LSIL group and CST III are related, HSIL, cervical cancer group and CST IV have correlation, which has certain guiding significance for early clinical diagnosis, in addition, the lack of some literature data may lead to results bias.

Therefore, more rigorous controlled studies and increased sample sizes are required to provide a more reliable experimental basis.

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