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ORIGINAL ARTICLE

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Evaluation of the multiple HPV-based "screen and triage" algorithms in real-world settings of rural China

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ABSTRACT

Objective: Drawbacks of human papillomavirus (HPV) primary screening, including high referral rates and low specificity, highlight the necessity for triage strategies to balance the screening benefits with potential harms.

Methods: A cross-sectional, population-based diagnostic study was conducted in rural Xinjiang, China involving 8,638 women ≥ 25 years of age who participated in organized cervical cancer screening between 2023 and 2024. The study evaluated the accuracy and efficiency of multiple HPV-based "screen-triage" strategies. Histologically confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+ and CIN3+) served as disease outcomes.

Results: Among single-step triage strategies, only extended genotyping for the seven most carcinogenic HPV types (HPV16/18/31/33/45/52/58) maintained sensitivity for CIN2+ comparable to HPV screening without triage (90.0% *vs.* 92.5%, P = 0.50) but significantly improved specificity (94.7% *vs*. 90.8%, $P < 0.001$). This approach led to a 38% reduction in colposcopy referrals (relative rate, 0.62; 95% CI: 0.59–0.65). Two-step triage algorithms (HPV16/18 with reflex ASC-US+ or methylation) showed slightly lower but non-significant sensitivity (87.5%, P = 0.13/89.6%, P =0.50) than HPV primary screening without triage, yet achieved significantly increased specificity (> 95%, $P < 0.001$) and reduced colposcopy referral by ~50% (relative rate, 0.5; $P < 0.001$). If negative for cytology or methylation, women positive for 12 high-risk HPV types (excluding HPV16/18) had a < 2% risk of CIN2+ (CIN3+ risk < 1%), indicating delayed follow-up.

Conclusions: Focusing on the seven high-risk HPV types within a one-step "screen-triage" framework effectively balances minimal sensitivity loss with significant gains in specificity, reducing unnecessary referrals and treatments, especially valuable in resource-limited settings. Integrating HPV genotyping with methylation results improves the accurate identification of women requiring immediate referral, which is advisable when resources allow.

KEYWORDS Cervical cancer screening; human papillomavirus (HPV); triage; HPV genotyping; methylation

Introduction

Cervical cancer is currently one of the most preventable cancers *via* human papillomavirus (HPV) vaccination, screening, and early treatment of precancerous lesions. Many countries are working towards the WHO initiative to eliminate cervical cancer with the following 2030 targets: 90% HPV vaccine coverage for girls by 15 years of age; 70% screening coverage for women between 35 and 45 years of age; and 90% treatment for women identified with cervical disease[1]. Among these targets, achieving 70% screening coverage with high-performance tests is particularly challenging due to the complexity of screening procedures and the difficulty in quality assurance, particularly in low-health resource settings.

Prevention of cervical cancer through screening involves a multistep process that includes primary screening, triage of positive screening results, colposcopy and biopsy confirmation, and treatment of precancerous lesions[2]. Over the years,

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HPV primary screening has been extensively validated as the most effective first-line method for cervical cancer screening and is recommended by the WHO[3]. However, concerns remain regarding the low specificity, which leads to many false-positive results. Moreover, the potential harms of false-positive results include unnecessary referrals and consequent overtreatment[4], as well as psychological impacts, such as anxiety, distress, fear of cancer, and even stigma related to a positive HPV test result[5]. Therefore, how to manage HPV-positive women has become a critical public health issue worldwide.

Several biomarkers show potential for triaging HPV-positive women with different performance characteristics; some biomarkers have superior sensitivity, while some biomarkers have superior specificity. Current triage options mainly include cytology, HPV16/18 genotyping, p16/Ki67 dual staining, visual inspection with acetic acid (VIA), methylation testing, and combinations of these methods[6]. There is limited evidence evaluating these biomarkers concurrently within the same population and most studies have focused on the subsets of HPV-positive individuals rather than assessing triage efficacy in full-programmatic contexts. Moreover, implementing triage workflows introduce systematic complexities, such as the need for specialized laboratory equipment, a robust health information system, and additional technical staff, that are disproportionally challenging in settings with low health resources where infrastructure gaps erode screening effectiveness. This situation highlights the urgent need for context-adapted triage strategies that balance accuracy with operational feasibility in HPV-based screening programs in settings with low health resources.

Therefore, we conducted a population-based HPV primary screening study in rural Xinjiang to evaluate the performance of different "screen-triage" combinations across the entire screened population. The assessed algorithms include PCR-based HPV primary screening with subsequent triage of high-risk (hr)HPV-positive women using cytology, genotyping, and methylation markers. The current study aimed to provide practical insights into the real-world application of these algorithms, especially with a focus on the feasible "screen-triage" algorithms suitable to settings with low health resources.

Materials and methods

Study population

The detailed methods used in this study have been described previously[7]. In brief, a population-based, cross-sectional study consecutively recruited 8,638 women ≥ 25 years of age from 2 counties [Bachu and Moyu (Xinjiang, China)] between March 2023 and November 2024 (**Figure 1**). Eligibility criteria included age > 25 years, residency in 1 of the 2 counties, mental capacity to understand the screening process, and signed informed consent. Exclusions were pregnant women, treatment for cervical lesions within 3 y, a hysterectomy, or severe medical conditions. Local healthcare personnel obtained informed consent from participants after explaining the study procedure. Then, every participant completed a confidential questionnaire covering demographic, gynecologic, obstetric, and sexual history. Each participant then underwent a pelvic examination, during which cervical samples were collected for various screening tests, as detailed below. Laboratory tests were performed blinded to other screening results.

Liquid-based cytology (LBC)

Cytology specimens collected using ThinPrep (Hologic, Bedford, MA, USA) or an LBP cell preservation solution (Guangzhou LBP Medicine Science & Technology Co, Ltd., Guangzhou, China) were firstly used to prepare a slide for LBC, which was classified according to the Bethesda 2014 classification system. Cytology results were interpreted by experienced cytologists blinded to other screening results. Atypical squamous cells of undetermined significance or worse (ASC-US+) were considered abnormal.

SureX® HPV DNA genotyping test

The SureX® HPV 25X Genotyping Kit (Health Gene Tech, Ningbo, China) is a multiplex PCR test targeting the E6/E7 DNA regions of the HPV genome. The SureX® HPV 25X Genotyping Kit provides individual genotyping information for 25 HPV types, including 14 hrHPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), and 11 non-hrHPV types (HPV6, 11, 26, 42, 43, 44, 53, 73, 81, 82, and 83). The SureX® HPV 25X Genotyping Kit has been evaluated previously[8]. In the current study 2 mL residual liquid of the ThinPrep sample was used for SureX® HPV testing. Samples that were positive for ≥ 1 of the 14 hrHPV types were considered hrHPV-positive.

Hybrid capture-based HPV DNA tests

As detailed previously, two hybrid capture-based HPV assays were utilized in this study. Specifically, among the 8,638

participants, 2,188 and 6,450 were evaluated using the DH2 (Delton, Hangzhou, China) and careHPV tests (careLYFE, Suzhou, China), respectively. The DH2 and careHPV tests are nucleic acid hybridization assays with signal amplification using microplate chemiluminescence for the detection of 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in bulk without genotyping.

careMe DNA methylation test

The careMe methylation test kit, which is based on methylation-specific real-time PCR techniques for the qualitative detection of the methylation status of one human gene (EPB41L3) and two viral genes (HPV16L1/HPV18L2), was performed for all hrHPV-positive women using the residuals of the ThinPrep or careHPV samples according to the instructions for use (careLYFE, Suzhou, China). The details of the test procedure have been described previously[9]. In brief, the cervical samples were vortexed for 2 min in 600 μL of lysis buffer, then DNA was extracted using the Magnetic DNA Puri Kit (careLYFE). Then, the 40-μL eluted and purified DNA was used for the bisulfite conversion reactions using the Magnetic DNA Methylation Kit (careLYFE). Then, PCR was carried out according to the manufacturer's instructions (careLYFE). A risk value was calculated from Ct values and normalized using internal controls. A risk value (R-value) for each sample was calculated from the Ct value of each gene based on the results of the EPB41L3 and HPV16L1/HPV18L2 PCR assays, then normalized by each internal control gene. According to the test instructions, a cut-off R-value of ≥ 1.8 was regarded as a positive methylation result.

Colposcopy and histology examination

Women with a hrHPV-positive or cytology-positive (ASC-US+) results were referred for colposcopy within 3 months, which was performed by a senior colposcopy specialist from a provincial cancer hospital. The following biopsy protocol was followed: 1) if the colposcopy impression was satisfactory and indicated abnormalities, targeted biopsies were obtained from the suspected areas; 2) if colposcopy was unsatisfactory or in the case of HPV16/18 or a high-grade squamous intraepithelial lesion (HSIL) + LBC, then 4 random biopsies at the 3, 6, 9, and 12 o'clock positions were obtained; and 3) due to ethical considerations, those with satisfactory and normal colposcopy impressions and no evidence of HPV16/18 and cytology < HSIL were not biopsied and considered free of disease [< cervical intraepithelial neoplasia grade 2 (CIN2)].

All biopsy tissues were sent to the Pathology Department of the provincial cancer hospital for diagnosis by senior pathologists specializing in gynecologic oncology. A second senior pathologist was consulted for an additional independent evaluation in cases with ambiguous findings. p16 immunohistochemical staining was performed on specimens with ambiguous findings based on the pathologists' recommendations. The histologic findings were classified as follows: no dysplasia; CIN1, CIN2, CIN3, or cancer. CIN2+ and CIN3+ were used as disease endpoints.

Statistical analysis

Descriptive statistics summarized the demographic characteristics. All analyses on the diagnostic performance of multiple "screen-triage" strategies (**Table 1**) were based solely on the SureX HPV test results to ensure assay consistency for algorithm evaluation, which were available for all enrolled women. Sensitivity, specificity, and 95% confidence intervals (CIs) were calculated for CIN2+ and CIN3+ endpoints. Pairwise comparisons of colposcopy referral rates, sensitivity, and specificity were performed using McNemar's test. *P*-values were corrected using the Bonferroni method to adjust for multiple comparisons across eight algorithms. In this context, statistical significance

Table 1 Evaluated algorithms

Index	Description of evaluated "screen-triage" algorithms
1	hrHPV primary screening without triage
2	hrHPV with LBC (ASC-US+) triage of hrHPV+ women
3	hrHPV with HPV16/18 triage of hrHPV+ women
4	hrHPV with 5 hrHPV (HPV16/18/31/33/45) triage of hrHPV+ women
5	hrHPV with 7 hrHPV (HPV16/18/31/33/45/52/58) triage of hrHPV+ women
6	hrHPV with careMe methylation triage of hrHPV+ women *Target genes by careMe: human gene, EPB41LE, and HPV16/18 viral genes in the L1/L2 regions*
7	HPV16/18 genotyping with reflex LBC (ASC-US+) for other 12 hrHPV+ women
8	HPV16/18 genotyping with reflex careMe methylation for other 12 hrHPV+ women

Each algorithm was evaluated separately for the detection of CIN2+ and CIN3+, respectively.

was determined by an adjusted alpha level ($\alpha = 0.05/n$) rather than the conventional alpha level ($\alpha = 0.05$), where n represents the number of comparisons. Furthermore, the relative ratios of colposcopy referral rates, sensitivities, and specificities between different triage strategies were computed with 95% CIs to further demonstrate the increase or reduction in specific indicators.

Statistical significance was evaluated by verifying whether the 95% CI included unity. Efficiency was assessed by comparing colposcopy referral rates and computing the number of colposcopies needed to detect one CIN2+/CIN3+ case (NNR). The immediate risk of CIN2+/CIN3+ was evaluated to reveal the clinical utility of different test results using the thresholds recommended by European experts[10] and American guidelines[11]. Statistical analyses were performed using Stata (version 15.1; StataCorp, TX, USA). Statistical significance was defined as a $P < 0.05$ (two-sided) for primary comparisons without multiplicity adjustment unless otherwise specified. Significance thresholds were adjusted for analyses involving multiple comparisons, as detailed above.

Ethical statement

The study protocol was approved by the Ethics Committee of The Affiliated Tumor Hospital of Xinjiang Medical University (Approval No. K-2021064). All recruited women provided written informed consent to participate in this study.

Results

Study population

Of the 8,638 participating women, 11.2% (963/8,578) were hrHPV-positive based on the PCR-based HPV test (**Figure 1**). Overall, 80 CIN2+ cases were detected, of which 39 were CIN3+ cases, including two cancer cases. The demographic characteristics of the women are presented in **Table 2**. The median age of the participants was 49 y [interquartile range (IQR), 43–55 y] and 1,710 (19.9%) underwent cervical cancer screening within the previous 3 years.

Biomarker positivity among hrHPV-positive women by histologic endpoints

Biomarker positivity increased with the severity of cervical lesions among hrHPV-positive women (**Figure 2 and Table S1**). The careMe methylation test demonstrated 26.0% in normal lesions, 46.9% in CIN1, as well as 64.3% and 97.1% among CIN2 and CIN3+ lesions, respectively. The cytologic evaluation revealed lower positive rates than other biomarkers among all lesions.

Accuracy of different "screen-triage" algorithms for CIN2+/CIN3+ detection

Applying any triage method significantly decreased the colposcopy referral rates and increased the specificity compared to HPV screening alone without triage, as shown in **Figure 3 and Table 3**.

Seven hrHPV genotyping (HPV16/18/31/33/45/52/58) alone achieved slightly but not significantly lower sensitivity for CIN2+ detection than hrHPV screening without triage (90.0% *vs*. 92.5%, relative sensitivity at 0.97, 95% CI: 0.94–1.01) among single-step triage methods (algorithms 1–6), while other single-triage methods significantly decreased the sensitivity of HPV screening [relative sensitivity and upper confidence limits (UCLs) < 1 for all others].

Both two-step triage algorithms (7 & 8) achieved similar sensitivities compared to hrHPV primary screening alone (with a relative sensitivity between 0.95 and 0.97 with 95% CIs, including 1 for both).

All analyses were repeated using CIN3+ as the outcome and similar patterns were observed (**Figure S1 and Table S2**).

Immediate risk of CIN2+/CIN3+ among hrHPV-positive women predicted by different biomarkers

Among hrHPV-positive women, most carcinogenic 5- and 7-hrHPV genotype screening had intermediate risks (17.0% and 14.0%), respectively, falling within the yellow zone according to the European threshold for CIN2+ risk (2% and 20%)[10], indicating the need for further follow-up or triage (**Figure 4A**). Of note, methylation-positive results and cytology ASC-US+ results among hrHPV+ women were associated with >20% of CIN2+ risk, warranting immediate colposcopy. If cytology tested negative or was methylation-negative among the other 12 hrHPV-positive women, the immediate CIN2+ risk was 0.96% and 0.65%, respectively, falling in the green zone and indicating delayed follow-up (**Figure 4A**).

The same risk evaluation was performed using CIN3+ as the outcome (**Figure 4B**). If the hrHPV-positive women were

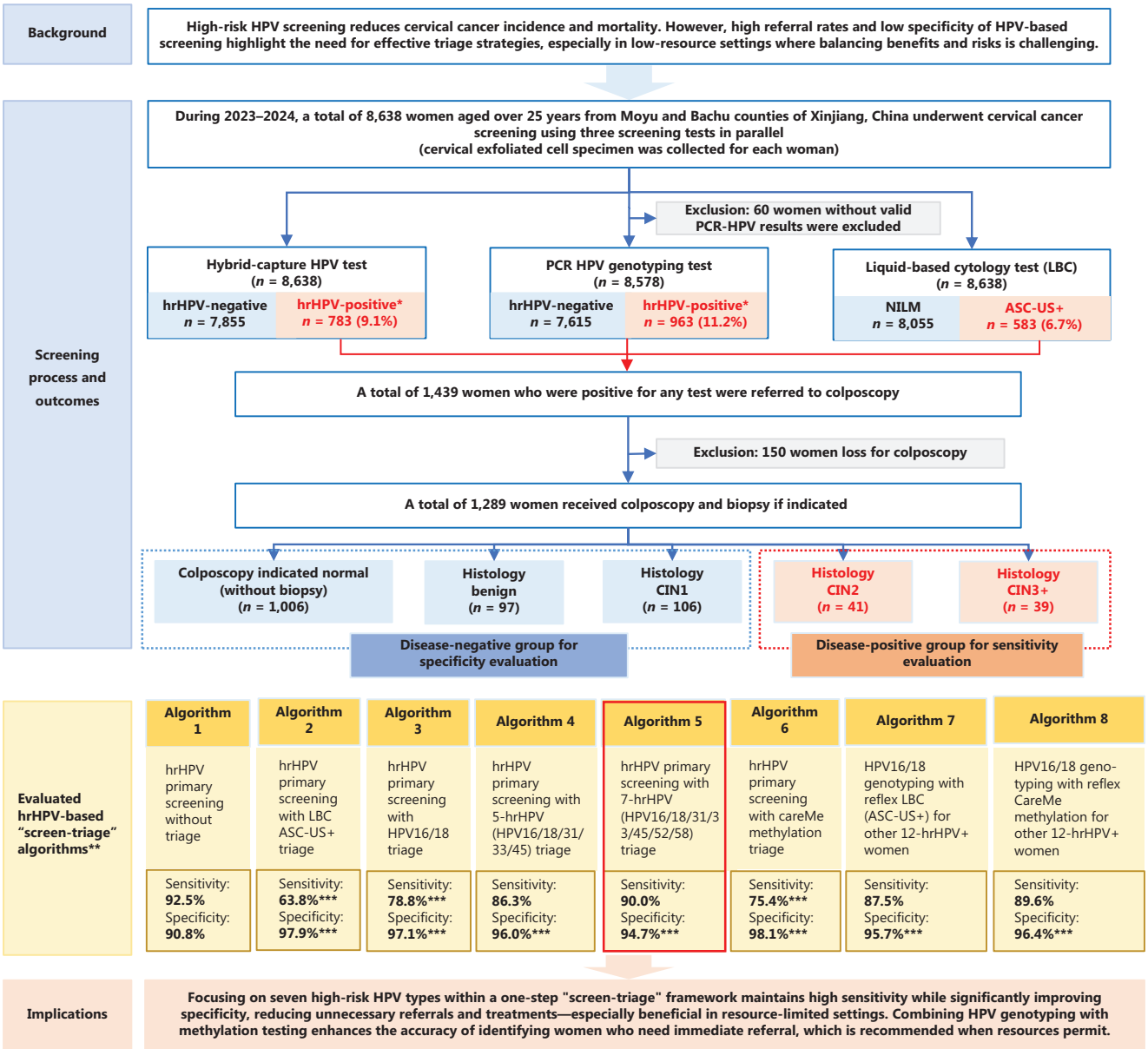


Figure 1 Study flowchart for the concurrent evaluation of triage strategies following primary HPV screening in rural China. This population-based study was conducted in Moyu and Bachu counties (Xinjiang, China) between 2023 and 2024. A total of 8,638 women > 25 years of age were enrolled and received primary screening using two HPV tests (hybrid capture HPV & PCR-based HPV test) and liquid-based cytology. Follow-up and outcomes: Women who screened positive for any test were referred for colposcopy and biopsy if indicated. A total of 1,289 women completed the diagnostic process with valid colposcopy and histologic outcomes. The final histologic distribution was as follows: 1,006 with normal findings; 97 with benign changes; 106 with CIN1; 41 with CIN2; and 39 with CIN3+. The sensitivity, specificity, and predictive values of each triage strategy for detecting CIN2+ were calculated and compared to hrHPV primary screening without triage. *Furthermore, all hrHPV-positive women had the careMe methylation test, which targets the human gene, *EPB41LE*, and HPV16/18 viral genes in the L1/L2 regions. **All analyses on the diagnostic performance of multiple "screen-triage" strategies were based solely on the PCR-based HPV test results to ensure assay consistency for algorithm evaluation, which provided individual genotype information. "Screen-Triage" Strategy Evaluation: We concurrently evaluated eight "screen-triage" algorithms (hrHPV primary screening with the triage of cytology/genotyping/methylation) to identify optimal approaches suitable for low-resource settings. The performance of each algorithm was evaluated against the histologic gold standard. *** indicates that the difference in sensitivity or specificity was statistically significant compared to that of hrHPV without triage (Algorithm 1). The statistical significance was determined using an adjusted alpha level (α = 0.05/7 = 0.00714) according to

the Bonferroni method, rather than the conventional alpha level (α = 0.05). Clinical Implications: The study demonstrate that focusing on 7 hrHPV types within a one-step "screen-triage" framework maintains high sensitivity comparable to hrHPV primary screening without triage while significantly improving specificity for CIN2+, potentially reducing unnecessary colposcopy referrals in low-resource settings. The findings provide critical evidence for designing efficient, context-appropriate cervical screening programs that balance accuracy with operational feasibility. ASC-US+, atypical squamous cells of undetermined significance or worse; CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology.

Table 2 Demographic characteristics of study population

Characteristics	Women, No. (n = 8,573)[a]	No. of hrHPV-positive women (n = 963)[b]	Prevalence of hrHPV[b]	P value
Age, y				< 0.001
Median (IQR)	49 (43–55)	51 (44–57)	–	
25–34	471	48	10.2%	
35–44	2,377	231	9.7%	
45–54	3,657	386	10.6%	
55–64	1,689	232	13.7%	
≥ 65	379	66	17.4%	
Marital status				< 0.001
Married	7,364	760	10.3%	
Divorced	214	41	19.2%	
Widowed	852	144	16.9%	
Other	143	18	12.6%	
Education				0.092
Uneducated	775	108	13.9%	
Primary school	5,318	599	11.3%	
Junior high school	1,774	180	10.1%	
High school	322	34	10.6%	
College or above	384	42	10.9%	
Residence				0.053
Bachu	3,827	458	12.0%	
Moyu	4,746	505	10.6%	
Age of sexual debut, y				0.003
Median (IQR)				
< 18	4,468	546	12.2%	
≥ 18	4,105	417	10.2%	
Lifetime sexual partners, No.				0.101
Median (IQR)	17 (16–18)	17 (16–18)		
1	5,852	635	10.9%	

Table 2 Continued

Characteristics	Women, No. (n = 8,573)[a]	No. of hrHPV-positive women (n = 963)[b]	Prevalence of hrHPV[b]	P value
≥ 2	2,721	328	12.1%	
Pregnancies, No.				0.425
Median (IQR)	4 (3–6)	4 (3–6)		
0	95	14	14.7%	
1–3	2,360	276	11.7%	
4–6	4,773	516	10.8%	
≥ 7	1,345	157	11.7%	
Age at first delivery, y				0.131
Median (IQR)	19 (18–21)	19 (18–21)		
< 18	1,738	213	12.3%	
≥ 18	6,835	750	11.0%	
Contraception				< 0.001
Yes	4,252	402	9.5%	
No	4,321	561	13.0%	
Family history of cancer				0.002
Yes	7,890	862	10.9%	
No	683	101	14.8%	
Cervical cancer screening history in recent 3 years				0.148
Yes	1,710	209	12.2%	
No	6,863	754	11.0%	

[a]Of the 8,638 participants, 60 missed the PCR HPV test results and 5 had invalid questionnaires, leaving 8,573 women included in this table; [b]hrHPV-positive results based on PCR HPV genotyping test. HPV, human papillomavirus; IQR, interquartile range; NA, not applicable.

shown to be positive for HPV16/18, cytologic evaluation revealed ASC-US+, or the methylation test was positive, the immediate risks for CIN3+ were 10.5%, 12.6%, and 16.8%, respectively, based on the European risk thresholds for CIN3+ (1% and 10%)[10], indicating the need for immediate colposcopy. The following findings warrant immediate colposcopy according to the latest ASCCP thresholds[11] with the immediate risk for CIN3+ exceeding 4%: 5 hrHPV+ (HPV16/18/31/33/45); 7 hrHPV+ (HPV16/18/31/33/45/52/58); cytologic evaluation revealing ASC-US+; and methylation-positive (**Figure 4B**).

Notably, HPV35/39/51/56/59/66/68-positivity without co-detection of other hrHPV types was associated with a CIN2/3+ risk < 2%, even when methylation or cytology results were positive.

Discussion

How to manage a large number of HPV screened-positive women is the most crucial issue to realize the effective implementation of HPV-based screening programs worldwide. Thus, the screening performance of several biomarkers was assessed, including extended genotyping and different methylation biomarkers as the triage methods of a novel PCR-based HPV primary screening among the general population, which provides essential real-world evidence for directly comparing the multiple "screen-triage" scenarios. Although the concept of triage using HPV genotyping and methylation has been evaluated in many studies, the real-world implementation in resource-limited settings, like rural China where healthcare

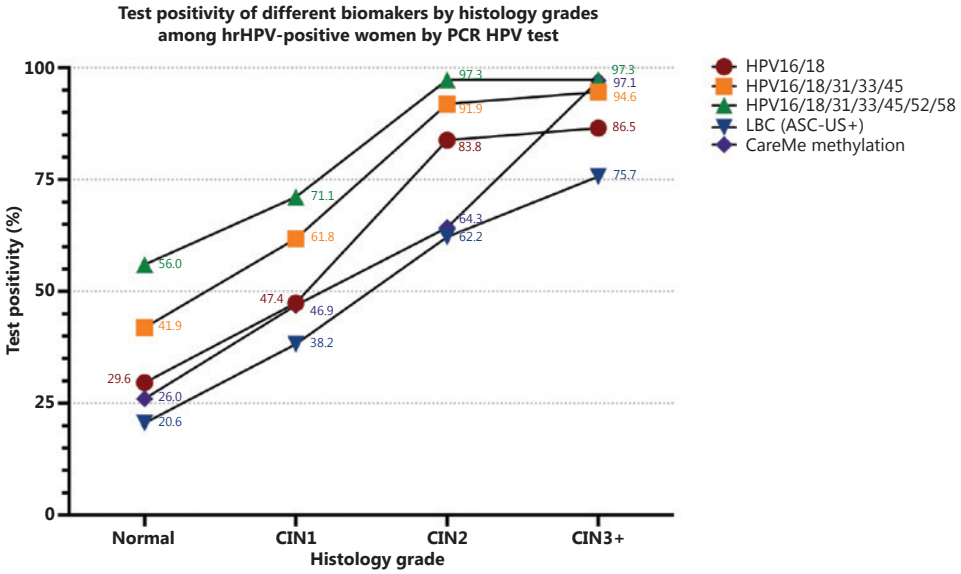


Figure 2 Test positivity of different biomarkers in different histology grades among hrHPV-positive women by the PCR HPV test. Red circles indicate HPV16/18-positivity in different histology grades, orange blocks represent HPV16/18/31/33/45-positivity, green triangles represent HPV16/18/31/33/45/52/58-positivity, blue triangles correspond to cytology ASC-US+-positivity, and purple diamonds illustrates careMe methylation-positivity in different grades, where the methylation test targets one human gene (EPB41L3) and two viral genes (HPV16L1/HPV18L2). ASC-US+, atypical squamous cells of undetermined significance or worse; CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; LSIL+, low-grade squamous intraepithelial lesion or worse.

infrastructure gaps, different HPV distribution characteristics, and socioeconomic barriers intersect, remains underexplored and operationally complex. This study directly addressed this translational gap by evaluating multiple triage algorithms within the population from one of the most remote areas of China, which can overcome local constraints while maintaining effectiveness.

The current study revealed that applying any triage test could significantly increase the specificity and decrease the colposcopy referral rates of HPV-based screening without any triage. Still, it is difficult to maintain high sensitivity by applying single-step triage, in which only the extended genotyping with 7 hrHPV types (HPV16/18/31/33/45/52/58) had comparable sensitivity and significantly improved specificity with a significant reduction (38%) in colposcopy referral rates. Both two-step triage strategies (targeting HPV16/18 in the first step and sequentially applying cytology/methylation for other hrHPV type-positive women) achieved comparable sensitivity with HPV primary screening alone.

HPV primary screening with cytology triage is the most frequently used screening algorithm in most countries and is recommended by many guidelines. While such an algorithm provided a small benefit (sensitivity only at 63.8%) in the current study, the algorithm remarkably hampered the high sensitivity of HPV primary screening. The sensitivity of cytology varied greatly among studies, ranging from 43%–73% in ATHENA study sites and 32%–88% in ESTAMPA study centers[12,13], which highlights the challenge in ensuring consistent high-quality cytology on a global scale, despite decades of investment. The shortages of trained cytopathologists and delayed result reporting in rural clinics render complex triage workflows less practical. Therefore, it is imperative to find alternative triage methods.

HPV types differ significantly in prevalence and oncogenicity[14]. Although many studies have explored partial or extended genotyping for triage of HPV-positive women, limited evidence exists for 7 hrHPV types. The primary rationale for focusing on these types is derived from a recent global systematic review, which concluded that HPV16 (61.7%), followed by HPV18 (15.3%), HPV45 (4.8%), HPV33 (3.8%), HPV58 (3.5%), HPV31 (2.8%), and HPV52 (2.8%) contributed to 94.7% of invasive cervical cancer, while the remaining HPV types (HPV35, 59, 39, 56, 51, 68, 73, 26, 69, and 82) contributed a mere 5.3%[15]. In addition, Swedish nationwide data revealed that the number of women needed to screen (NNS) and the number of women needing follow-up (NNF) were

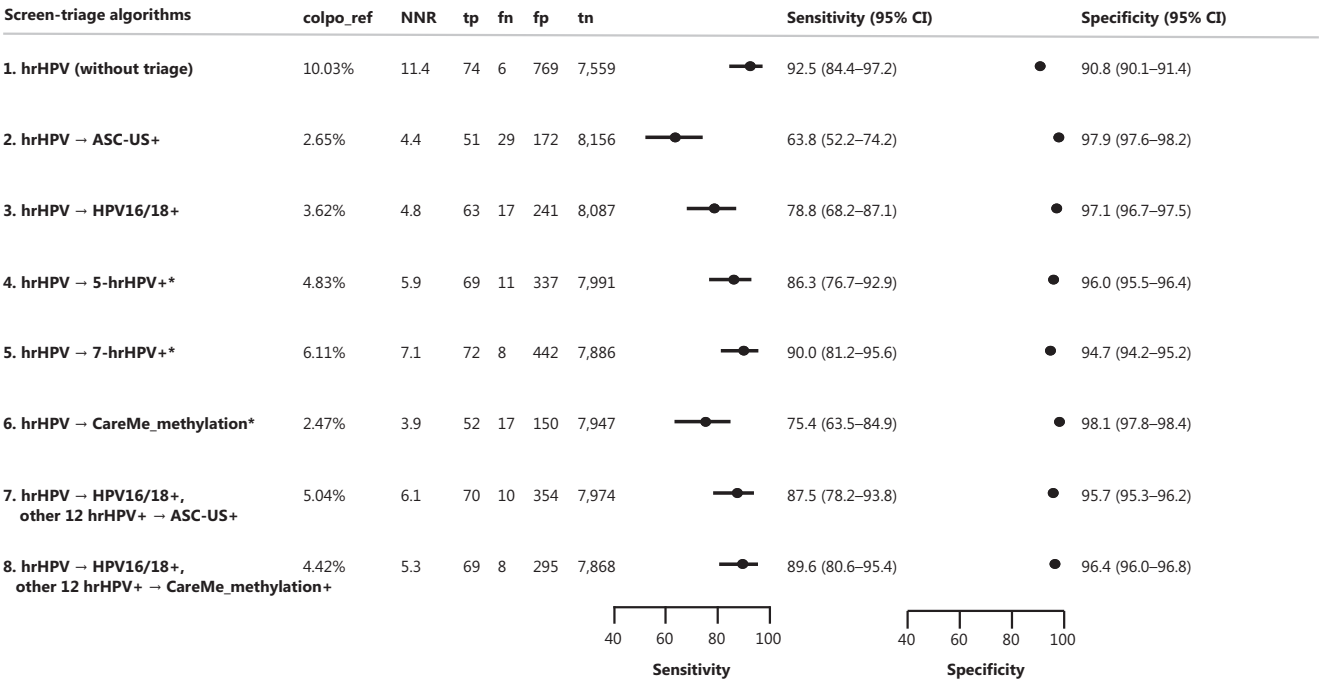


Figure 3 Forest plots depicting the clinical performance of different "screen-triage" algorithms for CIN2+ detection. Clinical performance of different tests were evaluated by calculating colposcopy referral rates, as follows: (tp + fp)/total screened population; number needed to referral to detect per CIN2+ (NNR) = (tp + fp)/tp; sensitivity = tp/total CIN2+; and specificity = tn/total women without CIN2+. The total number of CIN2+ cases was 80 in this study. The variation in the number of total CIN2+ cases evaluated in specific triage strategies (Strategies 6 & 8) was due to an insufficient residual sample volume for the methylation test in a small subset of hrHPV-positive women. *5 hrHPV+, positive for one or more types of HPV16, 18, 31, 33, or 45; 7 hrHPV+, positive for one or more types of HPV16, 18, 31, 33, 45, 52, or 58; careMe_meth+, positive for careMe methylation test targeting the human gene, *EPB41L3*, and viral genes, *HPV16L1/HPV18L2*; ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse, including CIN2, CIN3, and cancer cases; colpo-ref, colposcopy referral rates; fn, false negative; fp, false positive; hrHPV, high-risk human papillomavirus; tp, true positive; tn, true negative.

40~500 times higher for hrHPV types commonly screened for with lower oncogenic potential (HPV35, 39, 51, 56, 59, 66, and 68)[16]. The current study provided real-world evidence supporting the importance of prioritizing HPV16, 18, 31, 33, 45, 52, and 58 in screening because these types offer favorable sensitivity and specificity in one-step triage as HPV testing becomes the primary screening method and more and more qualified HPV genotyping assays become available[17]. Furthermore, the 7 hrHPV genotyping triage strategy requires only a single PCR-based test, which reduces reliance on cytology expertise and cuts colposcopy referrals by 38%, making the 7 hrHPV genotyping triage strategy feasible for decentralized clinics. In addition, by demonstrating that women with 7 hrHPV-negativity have a low CIN2+ risk (0.61%), delayed follow-up was an acceptable option instead of immediate colposcopy, which is aligned with the WHO-recommended 'see-and-treat' approaches for low-resource settings. A critical consideration is the inherent reliability of the HPV testing method itself when using a genotyping-based triage strategy. It is noteworthy that while > 200 commercial HPV tests are available, only approximately 10 have been rigorously validated according to international guidelines, such as the Meijer criteria, for primary cervical cancer screening[17]. Although the SureX HPV test used in this study was not prospectively validated per the Meijer guidelines, a post-hoc analysis demonstrated non-inferior performance compared to internationally validated assays (careHPV and DH2) for detection of CIN2+ and CIN3+, which fulfilled contemporary validation benchmarks as detailed in our recent comparative study[7]. Methylation biomarkers targeting different genes have shown promise in cervical cancer screening and are included as one of the future tests in the latest WHO guideline[3] but the

Table 3 Relative sensitivity and specificity of PCR HPV-based "screen-triage" algorithms for CIN2+ detection

PCR HPV-based algorithms		Relative colpo_ref	*P*	Relative sensitivity (95% CI)	*P*	Relative specificity (95% CI)	*P*
1	hrHPV	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
2	hrHPV → Ascus+	0.25 (0.23–0.28)	**< 0.001**	0.69 (0.59–0.80)	**< 0.001**	1.08 (1.07–1.09)	**< 0.001**
3	hrHPV → HPV16/18+	0.37 (0.34–0.40)	**< 0.001**	0.85 (0.77–0.94)	**0.001**	1.07 (1.06–1.08)	**< 0.001**
4	hrHPV → 5 hrHPV+*	0.50 (0.47–0.530)	**< 0.001**	0.93 (0.88–0.99)	0.063	1.06 (1.05–1.06)	**< 0.001**
5	hrHPV → 7 hrHPV+*	0.62 (0.59–0.65)	**< 0.001**	0.97 (0.94–1.01)	0.500	1.04 (1.04–1.05)	**< 0.001**
6	hrHPV → careMe methylation+*	0.33 (0.30–0.37)	**< 0.001**	0.83 (0.74–0.92)	**0.001**	1.05 (1.05–1.06)	**< 0.001**
7	hrHPV → HPV16/18+, other 12 hrHPV+ → ASC-US+	0.50 (0.47–0.53)	**< 0.001**	0.95 (0.90–1.00)	0.125	1.06 (1.05–1.06)	**< 0.001**
8	hrHPV → HPV16/18+, other 12 hrHPV+ → CareMe methylation*	0.54 (0.51–0.58)	**< 0.001**	0.97 (0.93–1.01)	0.500	1.04 (1.04–1.05)	**< 0.001**

*****5 hrHPV+: positive for one or more types of HPV16, 18, 31, 33, or 45; 7 hrHPV+: positive for one or more types of HPV16, 18, 31, 33, 45, 52, or 58; careMe_methylation triage targeting one human gene (*EPB41L3*) and two viral genes (*HPV16L1/HPV18L2*). colpo-ref, colposcopy referral rate; CI, confidence interval. Pairwise comparisons of colposcopy referral rates, sensitivity, and specificity were performed using McNemar's test. To adjust for multiple comparisons across eight algorithms, *P*-values were corrected using the Bonferroni method. In this context, statistical significance was determined by an adjusted alpha level ($\alpha = 0.05/7 = 0.00714$) instead of the conventional alpha level ($\alpha = 0.05$).

performance requires further validation before clinical recommendation and use. The latest systematic review reported the pooled sensitivity and specificity for methylation at 68% and 75%, respectively, for detecting CIN2+ in hrHPV-positive women[18]. An earlier systematic review reported comparable values of 68.6% and 71.1%, respectively[19]. Both reviews highlight challenges in translating existing evidence into clinical practice due to variations in methylation target genes, study populations, and designs. Another significant study evaluated the WID-qCIN methylation test (targeting *DPP6*, *RALYL*, and *GSX1* genes) in a large real-life cohort, demonstrating a sensitivity of 77% for CIN2+ and 90.9% for cancer. When combined with HPV16/18, the sensitivity increased to 85.9% for CIN2+ and 100.0% for cancer[20]. Despite the different target genes, the overall performance of the methylation test used in the current study aligns with the abovementioned and previous studies[21-25]. By including a sizeable unvaccinated screening population, the current study strengthens the existing body of evidence. Beyond test accuracy, economic viability and operational feasibility are paramount considerations for implementing screening strategies in low-resource settings. Current methylation tests requiring for specialized laboratory equipment, stable cold chain transportation, and higher unit cost present significant barriers to implementation in primary care settings. Future advances in point-of-care methylation testing and automated mass production could potentially overcome these economic and logistical challenges, enabling more versatile application in the future.

Several national guidelines have adopted multistep screen-triage algorithms to maintain the high sensitivity of HPV-based screening and enhance specificity[26,27]. Indeed, most guidelines recommend triaging hrHPV-positive women using HPV16/18 genotyping with reflex cytology. The same approach was simulated and extended to another combination (HPV16/18 genotyping followed by methylation), which has rarely been assessed previously. These algorithms demonstrated similar sensitivity and improved specificity by reducing colposcopy referrals compared to hrHPV screening alone. However, the logistic complexity of such algorithms (the requirement for second test and related resources) must be considered because the quality of screening procedures, compliance of screened populations, and even the healthcare providers, particularly in low- and middle-income countries (LMICs), are affected.

In recent years management of abnormal screening results has shifted from a result-based to a risk-based framework[28]. The risk thresholds proposed by Arbyn et al.[10] and ASCCP 2019[11] were adopted given the absence of a Chinese

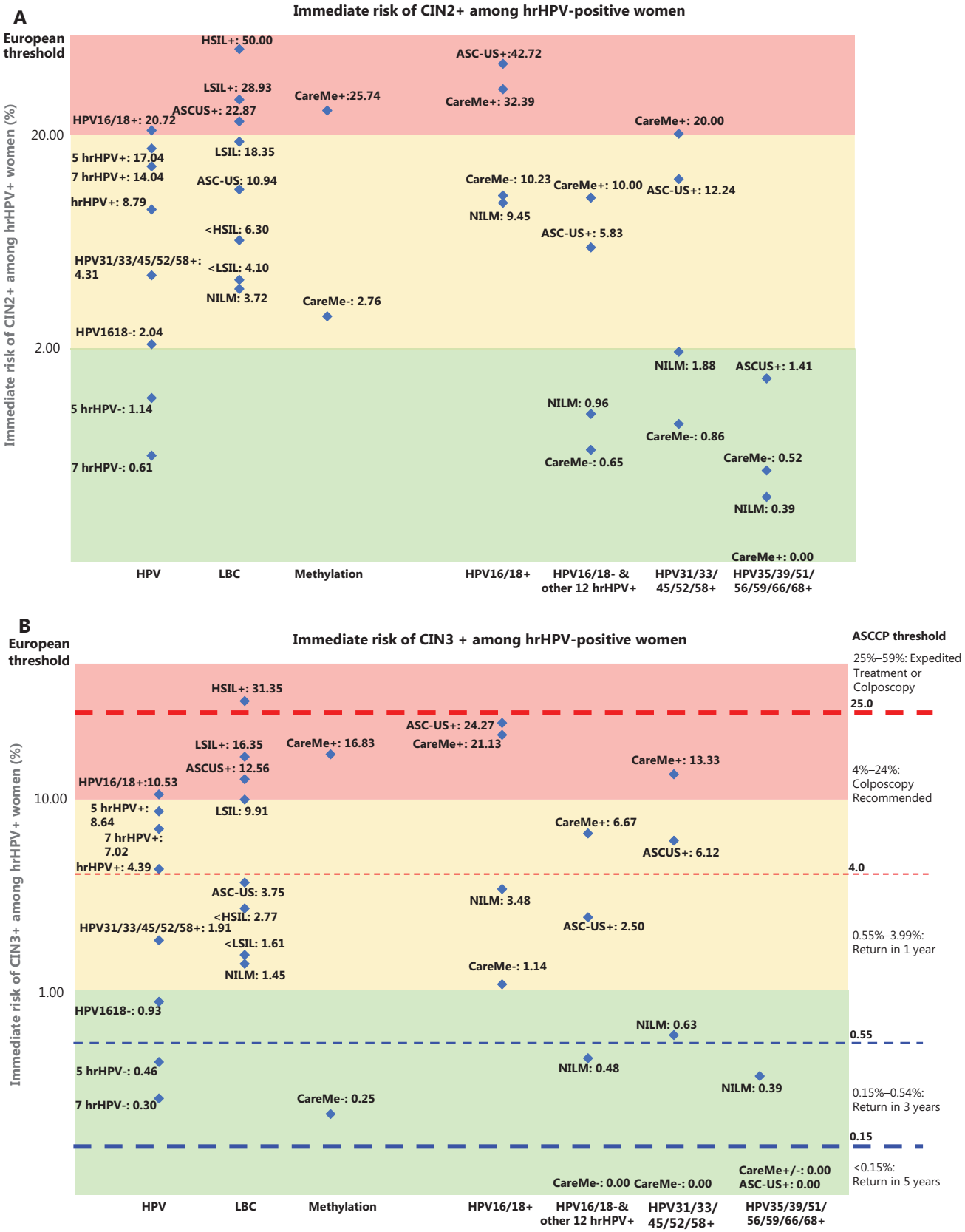

A
Immediate risk of CIN2+ among hrHPV-positive women
European threshold
Immediate risk of CIN2+ among hrHPV+ women (%)
20.00
2.00
HSIL+: 50.00
LSIL+: 28.93
ASCUS+: 22.87
HPV16/18+: 20.72
5 hrHPV+: 17.04
7 hrHPV+: 14.04
hrHPV+: 8.79
HPV31/33/45/52/58+: 4.31
HPV1618-: 2.04
5 hrHPV-: 1.14
7 hrHPV-: 0.61
LSIL: 18.35
ASC-US: 10.94
<HSIL: 6.30
<LSIL: 4.10
NILM: 3.72
CareMe+:25.74
CareMe-: 2.76
ASC-US+:42.72
CareMe+: 32.39
CareMe-: 10.23
NILM: 9.45
CareMe+: 10.00
ASC-US+: 5.83
CareMe+: 20.00
ASC-US+: 12.24
NILM: 1.88
ASCUS+: 1.41
NILM: 0.96
CareMe-: 0.65
CareMe-: 0.86
CareMe-: 0.52
NILM: 0.39
CareMe+: 0.00
HPV
LBC
Methylation
HPV16/18+
HPV16/18- & other 12 hrHPV+
HPV31/33/45/52/58+
HPV35/39/51/56/59/66/68+
B
Immediate risk of CIN3 + among hrHPV-positive women
European threshold
ASCCP threshold
Immediate risk of CIN3+ among hrHPV+ women (%)
10.00
1.00
HSIL+: 31.35
LSIL+: 16.35
ASCUS+: 12.56
HPV16/18+:10.53
5 hrHPV+: 8.64
7 hrHPV+: 7.02
hrHPV+: 4.39
HPV31/33/45/52/58+: 1.91
HPV1618-: 0.93
5 hrHPV-: 0.46
7 hrHPV-: 0.30
LSIL: 9.91
ASC-US: 3.75
<HSIL: 2.77
<LSIL: 1.61
NILM: 1.45
CareMe+: 16.83
CareMe-: 0.25
ASC-US+: 24.27
CareMe+: 21.13
CareMe+: 6.67
NILM: 3.48
CareMe-: 1.14
CareMe+: 13.33
ASCUS+: 6.12
ASC-US+: 2.50
NILM: 0.63
NILM: 0.48
NILM: 0.39
CareMe-: 0.00
CareMe-: 0.00
CareMe+/-: 0.00
ASC-US+: 0.00
25.0
4.0
0.55
0.15
25%–59%: Expedited Treatment or Colposcopy
4%–24%: Colposcopy Recommended
0.55%–3.99%: Return in 1 year
0.15%–0.54%: Return in 3 years
<0.15%: Return in 5 years
HPV
LBC
Methylation
HPV16/18+
HPV16/18-& other 12 hrHPV+
HPV31/33/45/52/58+
HPV35/39/51/56/59/66/68+

Figure 4 The immediate risk of CIN2+ and CIN3+ predicted by test results and the combination. (A) women with a CIN2+ risk < 2% (green area) can return to routine screening, according to the CIN2+ risk categories proposed by Arbyn et al.[10]. Those with a risk > 20% (red area) should have immediate colposcopy. Women with intermediate risks (2%–20%, yellow area) may be advised to repeat testing after 1 y. (B) Two threshold systems are shown For CIN3+ outcomes. The 1% and 10% thresholds (left axis) were determined according to Arbyn et al.[10], which means that women with a CIN3+ risk < 1% (green area) can return to routine screening. Women with a risk > 10% (red area) should have immediate colposcopy. Women with intermediate risks (1%–10%, yellow area) may be advised to repeat testing after 1 y. According to the ASCCP Risk-based Management Consensus[11] (right axis), women with an immediate CIN3+ risk < 0.15% can wait 5 y for the next round screening. Women with a CIN3+ risk between 0.15% and 0.54% should return in 3 y. Women with a CIN3+ risk between 0.55% and 3.99% should return in 1 y. Women with a CIN3+ risk between 4.0% and 24.9% should have immediate colposcopy. Women with a ≥ 25% CIN3+ risk may be considered for immediate treatment. ASC-US+, atypical squamous cells of undetermined significance or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or worse, including CIN2, CIN3, and cancer cases; CIN3+, cervical intraepithelial neoplasia grade 3 or worse, including CIN3 and cancer cases; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL+, low-grade squamous intraepithelial lesion or worse; NILM, negative for intraepithelial lesion or malignancy.

benchmark. The analysis showed that the combination of HPV genotyping with cytology or methylation tests improves the precise risk stratification of hrHPV-positive women. Women positive for HPV35/39/51/56/59/66/68 without other hrHPV infections have a low risk (< 2%) of CIN2+/CIN3+ and may be scheduled for delayed follow-up. Given the different resource availability and the average risk of cervical (pre)cancer among the local population, different regions/countries still need to determine the appropriate risk threshold.

No international consensus on minimum sensitivity thresholds for triage tests has been established. Based on the results herein and the imperative to preserve the benefit of highly sensitive primary HPV screening, strategies that substantially reduce sensitivity, such as the use of standalone cytology (63.8%) or methylation testing (75.4%), are not recommended for triage because these strategies result in unacceptable missed case rates. The choice between a one-step (7 hrHPV) and a two-step (genotyping with reflex methylation) strategy should be guided by local priorities and infrastructure. The one-step approach prioritizes maximizing sensitivity and is suited for regions with high attrition rates, whereas the two-step approach maximizes specificity and is optimal for settings in which the colposcopy capacity is the absolute limiting constraint. Defining a universally applicable and safe long-term risk threshold for triage-negative women remains a critical goal for future research.

The findings herein offer direct, actionable evidence for advancing the China' national elimination strategy and global WHO guidelines. The 7 hrHPV genotyping strategy provides an immediately scalable pathway for China by drastically reducing colposcopy referrals (38%) and associated costs, making organized screening logistically and financially feasible for rural clinics. This approach aligns with the "Accelerated Elimination Action Plan's" goal of equitable coverage. The data herein from a real-world, low-resource setting strongly supports expanding the WHO recommended triage options beyond HPV16/18 genotyping plus cytology. HPV16/18/31/33/45/52/58 in a one-step genotyping strategy achieved high sensitivity without cytology, a critical advantage when high-quality cytology is unavailable. Furthermore, defining a very low-risk threshold (< 2% CIN2+) for 7 hrHPV-negative women provides a validated benchmark for implementing the WHO' recommended risk-based management and delayed follow-up in similar populations.

The main limitations of the current study include the fact that only cross-sectional data was available because further follow-up is ongoing. Consequently, we cannot provide recommendations for retesting intervals based on different screening results, but this will be of interest in a corollary study. Second, partial verification bias may arise from assuming disease-free status in women with hrHPV- and ASC-US-negative results who were not referred to colposcopy, as well as women with normal colposcopy without a biopsy. While this limitation remains inherent to population-based screening studies and reflects real-world screening constraints, where universal biopsies of low-risk women is ethically and logistically untenable. Our triple-testing design (two HPV assays and cytology screening in parallel) minimized false-negatives at the primary screening level. Crucially, because colposcopy has imperfect sensitivity, particularly for absolute disease detection, the relative sensitivity comparisons inherently mitigate this bias. Third, the limited number of CIN3+ cases (n = 39) restricted the statistical power for subgroup comparisons. Because CIN2+ endpoints provided robust evidence for

our primary conclusions, analyses involving CIN3+ outcomes should be interpreted with caution due to wide confidence intervals and encouraged to be validated in larger cohorts. Finally, the restriction of our cohort to rural areas of Xinjiang may limit the immediate generalizability of the findings due to regional variations in HPV epidemiology. Specifically, while the overall prevalence of hrHPV was lower in this region, the proportion of HPV16 infection (33.7%) was significantly higher compared to other provinces in China[29-31]. In addition, the population is predominantly composed of Uyghur women and the region faces unique healthcare challenges. However, through localized HPV profiling and resource modeling, this tiered framework supports the equitable implementation of the cervical cancer elimination strategy in China beyond the northwestern regions.

Conclusions

The current study offers valuable insights into HPV-based cervical cancer screening. Focusing on HPV16, 18, 31, 33, 45, 52, and 58 in HPV-based screening optimizes the accuracy and efficiency of "screen-triage" algorithms while simplifying logistics, which could be achieved by a one-step strategy when a PCR-based HPV genotyping assay is used and is particularly practical for areas with limited healthcare resources. Women positive only for HPV35/39/51/56/59/66/68 have a relatively low risk of CIN2+/CIN3+, suggesting delayed referral. Methylation-positivity among hrHPV+ women indicate the significantly high immediate risk for CIN2+/CIN3+, necessitating prompt colposcopy. Further research is encouraged to evaluate the long-term clinical and cost-effectiveness of these findings.

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Conflict of interest statement

RR received free reagents from Dalton China for independent research. Sciensano, the employer of MA, received funding from the European Society of Gynaecological Oncology (ESGO), the World Health Organization (Geneva, Switzerland, *via* the Agreement for Performance of Work for guidelines on Screening and Treatment of Pre-Invasive Cervical Disease), the European Commission Initiative on Cervical Cancer (EC-CvC), and the VALGENT network. The funders had no role in the study design, data analysis, data interpretation, or report writing. The other authors report no conflicts of interest.

Author contributions

Conceived and designed the analysis: Remila Rezhake, Guzhalinuer Abulizi.

Collected the data: Guzhanuer Abuduxikuer, Guligeina Abudurexiti, Tangnuer Abulimiti, Kadeliya Muhetaer, Qian Zhuo, Yumei Ouyang, Jing Yang, Gulixian Tuerxun, Wenyun Li.

Analyzed and interpretated the data: Remila Rezhake, Kadeliya Muhetaer, Yumei Ouyang, Marc Arbyn.

Wrote the paper: Remila Rezhake, Guzhalinuer Abulizi contributed to writing the original draft of the manuscript.

Revised the paper: Marc Arbyn, Fanghui Zhao.

Obtained the funding: Remila Rezhake, Guzhalinuer Abuliz.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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