Significant specificity of TruScreen in cervical cytology of ASC and LSIL women with incomplete cervical transformation zone type during COVID-19 post-pandemic in China: a prospective study

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Abstract

Objective: To evaluate the efficacy of TruScreen (TS) detecting cervical intraepithelial neoplasia (CIN) in cytology of atypical squamous cells (ASC) and low-grade squamous intraepithelial lesion (LSIL) women during COVID-19 post-pandemic. Design: Prospective, single-center study. Setting: Changsha, China. Population: ASC and LSIL women from December 2020 to May 2021. Methods: Participants underwent TS, colposcopy examination and biopsy in turn. Diagnostic value of TS, high-risk human papillomavirus (hrHPV) and TS combined with hrHPV were compared. Differences of TS regarding cervical transformation zone (TZ) type and menopause, correlations between TS and p16, Ki-67 were assessed. Main outcome measures: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) for diagnostic value. Spearman coefficient for correlation. Results: A total of 483 patients were enrolled. Specificity of TS detecting CIN1+, CIN2+, CIN3+ were 77.1% (95% CI, 70.4%-82.7%), 66.7% (95% CI, 61.5%-71.5%), 62.7% (95% CI, 57.8%-67.4%) and all were significantly higher than hrHPV test ($P<0.001$). TS had a high sensitivity (68.0% vs 52.0%, $P>0.05$) and significantly higher specificity (70.0% vs 48.5%, $P<0.05$) and NPV (89.6% vs 73.3%, $P<0.05$) in women with incomplete cervical TZ type (II and III) than TZ type I in detection of CIN2+. Conclusion: TS is an effective triage screening method for cervical cytology of ASC and LSIL women during COVID-19 post-pandemic, especially for incomplete cervical TZ type women. Funding: Supported by National Natural Science Foundation Project of China (81771546) and Hunan Science and Technology Innovation Project (2020SK53404). Keywords: TruScreen; Cervical cancer screening; Cervical transformation zone; CIN; COVID-19.

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Running title: Significant specificity of TruScreen

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Methods: Participants underwent TS, colposcopy examination and biopsy in turn. Diagnostic value of TS, high-risk human papillomavirus (hrHPV) and TS combined with hrHPV were compared. Differences of TS regarding cervical transformation zone (TZ) type and menopause, correlations between TS and p16, Ki-67 were assessed.

Main outcome measures: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC) for diagnostic value. Spearman coefficient for correlation.

Results: A total of 483 patients were enrolled. Specificity of TS detecting CIN1+, CIN2+, CIN3+ were 77.1% (95% CI, 70.4%-82.7%), 66.7% (95% CI, 61.5%-71.5%), 62.7% (95% CI, 57.8%-67.4%) and all were significantly higher than hrHPV test (P<0.001). TS had a high sensitivity (68.0% vs 52.0%, P>0.05) and significantly higher specificity (70.0% vs 48.5%, P<0.05) and NPV (89.6% vs 73.3%, P<0.05) in women with incomplete cervical TZ type (II and III) than TZ type I in detection of CIN2+.

Conclusion: TS is an effective triage screening method for cervical cytology of ASC and LSIL women during COVID-19 post-pandemic, especially for incomplete cervical TZ type women.

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Tweetable abstract

TruScreen detection is a triage cervical cancer screening method with higher specificity in cervical cytology ASC and LSIL women, especially whom with incomplete cervical transformation zone type.

Introduction

Cervical cancer ranked the fourth for both incidence and mortality of gynecological cancers globally in 2020 [1]. In China, there were approximately 110,000 newly diagnosed cases and 60,000 deaths reported in 2020 [1]. Prevention and treatment of cervical cancer is still a serious problem in the world. In fact, cervical intraepithelial neoplasia (CIN) progresses slowly to cervical cancer, it provides gynecologists with chances to detect and treat CIN or cervical cancer under appropriate screening approaches [2, 3].

Currently, the high-risk human papillomavirus (hrHPV) testing and cervical cytology either alone or in combination (co-testing) are recommended as primary cervical screening strategies [4, 5]. HPV-based testing

alone has been proven efficacious worldwide, it demonstrated a superior sensitivity over cytology but with a lower specificity [6, 7]. Most HPV infections are transient and can be eliminated by hosts within 1-2 years especially in young women [8]. Thus, positive HPV testing results may cause over-referral colposcopy and patients' psychological burden [9]. On the contrary, cytology alone has a relatively low sensitivity owing to sampling quality, technic, and intra/inter-observer errors during cytological morphological assessment [10]. Sensitivities of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) were 34%-96% and 18%-89% for detecting CIN2+ [11]. Moreover, when transferring to colposcopy and biopsy, patients with cervical transformation zone (TZ) type III, often postmenopausal women, cannot be assessed comprehensively due to the unseen cervical squamocolumnar junction (SCJ). Thus, endocervical curettage (ECC) is applied [12]. Therefore, incorporation of additional screening methods is necessary.

TruScreen (TS) is a non-invasive diagnostic method for CIN with immediate and automatically generated results [13]. Briefly, it detects and analyzes cervical tissues through optoelectronic signals emitted from the tip of the device. Up to date, TS has been studied in several studies in different population worldwide [13-19]. According to a meta-analysis, the pooled sensitivity, specificity and area under curve (AUC) of TS were 76%, 69%, 0.7859 respectively, the author thus concluded that TS had a moderately good diagnostic accuracy [20].

Since the coronavirus disease 2019 (COVID-19) has been declared a global pandemic in January 2020 [21], challenges for cervical screening emerged and still exists now during COVID -19 post-pandemic. Gynecologists are seeking for a better method to decrease cervical specimen contact during screening session, meanwhile reducing colposcopy and biopsy. The non-invasiveness and immediacy of reports make TS a suitable choice for this purpose.

Our objective is to evaluate efficacy of TS detecting ASC and LSIL patients and explore any feasibility of TS as one of the cervical cancer screening methods in China.

Methods

Study design and population

This prospective, single-center study was conducted in the Second Xiangya hospital, Hunan, China from December 2020 to May 2021 (known as COVID-19 post-pandemic). Patients who attended gynecological outpatient department or were transferred to colposcopy examination, both with abnormal cytology results of ASCUS, LSIL or atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H) within three months were enrolled in our study. The exclusion criteria were elucidated in Figure1. Informed written consents were obtained from all the participants. Age, menstruation status, present medical history and HPV results of each patient were collected. Pathological results were referred as the golden standard.

Cervical cytology examination

ThinPrep cytologic test (TCT, Hologic, Marlborough, MA, USA) was used to determine the cervical cytology. The TCT report format referred to the Bethesda Report System of Cervical Cytology in 2014. We accepted TCT reports from our hospital and other qualified hospitals or medical centers.

HPV genotyping

We used Hologic Aptima HPV test for testing 14 types hrHPV E6/E7 mRNA (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and Hybribio Rapid GenoArray to determine the 21 specific HPV types including 13 high-risk types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), 6 low-risk types (types 6, 11, 42, 43, 44, and CP8304 [81]) and 2 probable high-risk types (types 53 and 66). The tests were carried out and reported according to manufacturer's instructions. It should be noted that we included patients who had completed primary cervical cancer screening not only in our hospital but also in other hospitals, therefore, the HPV testing kits were various (mainly Roche Cobas 4800 HPV test and Qiagen

Digene HC2 HPV DNA test). As such, the HPV testing could not be uniformed. The HPV results were recorded as hrHPV+ and hrHPV-.

TruScreen (TS) detection

The TS detection (TS01, TruScreen Limited, London, United Kingdom) was performed by a trained physician at outpatient department or colposcopy room ahead of any examination. The patients lied down in lithotomy position, and then the physician inserted a speculum and placed the TS handpiece with its single-use sensor into patients' vagina until the tip of probe clinging to the surface of cervix. The detection path was set in a certain pattern according to the manufacturers' instruction, 31 points at maximum of cervix surface were probed. After the whole process was completed, the TS results were printed out as 'normal' or 'abnormal'. 'Normal' was defined as normal squamous or columnar epithelial, physiological metaplasia or HPV-related changes, while 'abnormal' was defined as CIN1, CIN2, CIN3 and cervical cancer We recorded 'normal' TS results as 'negative', while 'abnormal' as 'positive'.

Colposcopy and histology

All the participants underwent colposcopy examination (3ML LED, Leisegang, Berlin, German) performed by a qualified gynecologist after TS detection finished. 5% acetic acid and 5% Lugol's iodine solution were applied in turn onto the cervix to visualize cervical lesions. Cervical biopsies were obtained at the suspicious lesion area. If no suspicious lesion spotted, random biopsies of four quadrants were then obtained. In cervix of incomplete cervical TZ (type II or III), ECC was performed. Finally, pathological investigations for the collected specimens were performed by two expertized pathologists. Reports of pathological diagnosis according to CIN reporting system were referred as the gold standard. Status of p16 and Ki-67 immunohistochemistry (IHC) staining were recorded.

Statistical analysis

Statistical analysis was performed by IBM SPSS Statistics 26. CIN1+, CIN2+ and CIN3+ were used as the observation endpoints, respectively. The sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV) and area under curve (AUC) were calculated to validate the efficacy of TS either alone or in combination with HPV test. McNemar's exact test was used to compare these indicators between TS, hrHPV and TS combined with hrHPV. Chi-square test and Fisher exact test was used to evaluate the differences between different groups regarding TZ type and menstruation status. Spearman correlation analysis was used to verify the association between TS and p16, Ki-67. For all the statistical tests, two-sided p-value less than 0.05 was considered statistically significant.

Results

Participants' characteristics and main clinical outcomes

A total of 483 patients were enrolled, among whom 71.6% were ASCUS, 24.8% were LSIL and 3.5% were ASC-H (Figure 1, Table S1). 18 patients were excluded for pathological analysis (reasons shown in Figure 1). The overall mean age was 43.5 years (range 15-71 years) with no difference among the three TCT groups. Generally, 70.6% women were non-menopausal. The overall positive rates of TS and hrHPV were 40.2%, 71.6%, respectively. Of 472 participants who completed colposcopy examination, 20.1% were cervical TZ type I, 29.2% were TZ type II and 49.8% were TZ type III. In total pathological investigations of 465 participants, there were 41.3% no CIN or worse reported, 36.1% CIN1, 11.4% CIN2, 9.9% CIN3 and 1.3% cervical cancer. Significant differences were observed among the three TCT groups regarding menstruation status, positive rate of TS and hrHPV, TZ type and pathological results (all $P<0.001$).

Overall performance of different screening tests for detecting CIN1+, CIN2+ and CIN3+

The sensitivity, specificity, PPV, NPV and AUC of the three screening methods (TS alone, hrHPV alone, TS in combination with hrHPV) for detecting CIN1+, CIN2+ and CIN3+ were summarized in Table S2, Table 1 and Table S3, respectively. Generally, single hrHPV test had the highest sensitivity and NPV in all settings compared with the other two methods. The overall sensitivity of TS for detecting CIN1+, CIN2+

and CIN3+ were 53.1%, 65.7%, 67.3%, respectively, while hrHPV had the corresponding significantly higher sensitivity of 82.7%, 96.2%, 96.2% (all P<0.001). The highest sensitivity of TS was 92.3% observed in ASC-H group for detecting CIN2+.

Oppositely, TS alone and TS in combination with hrHPV had significantly higher specificitiy (77.1% vs 82.8% vs 43.2% for CIN1+, 66.7% vs 73.3% vs 35.1% for CIN2+, 62.7% vs 68.4% vs 31.1% for CIN3+, all P<0.001) and PPV (76.7% vs 79.9% vs 67.4% for CIN1+, 36.5% vs 41.5% vs 30.2% for CIN2+, 18.5% vs 20.7% vs 15.0% for CIN3+, all P<0.001) than hrHPV in overall population. TS in combined with hrHPV detecting CIN1+ in ASCUS patients had the highest specificity (83.7%) in all settings.

When comparing TS alone with TS in combination with hrHPV, only in detecting overall CIN1+ patients (P<0.001) and ASCUS CIN1+ patients (P=0.004) did the two methods showed significant differences. The top three AUC were allocated to TS in combination with hrHPV in detecting overall CIN2+ patients (0.690), LSIL CIN2+ patients (0.678) and LSIL CIN3+ patients (0.677).

TS showed significantly higher specificity and NPV in incomplete cervical TZ type than TZ type I

Incomplete cervical TZ type compromises type II and III. Table 2 and Table S4 showed the general TS detecting performance in participants grouped by TZ type. For detecting CIN1+, TS demonstrated significantly higher specificity in incomplete cervical TZ type than TZ type I in ASCUS, LSIL and overall CIN1+ patients (83.1% vs 62.1%, 74.3% vs 25.0%, 81.1% vs. 57.6%, respectively. All P<0.05).

For overall CIN2+ patients, TS showed significantly higher specificity and NPV in incomplete cervical TZ type than TZ type I (70.0% vs 48.5%, 89.6% vs 27.1%, both P<0.05). Of all CIN2+ patients, TS had a higher specificity in ASCUS group (73.1% vs 53.3%, P<0.05) and a higher NPV in LSIL group (85.2% vs 26.7%, P<0.05) in incomplete cervical TZ type than TZ type I.

For detecting CIN3+, TS in both ASCUS group and LSIL group demonstrated a higher specificity in incomplete cervical TZ type than TZ type I (69.4% vs 53.0%, 63.0% vs. 23.5%, both P<0.05). In addition, CIN3+ LSIL group had a significantly higher NPV (94.4% in incomplete cervical TZ type vs 13.3% in TZ type I) and the highest AUC (0.715). In overall CIN3+ population, specificity (66.9% vs 46.4%, P<0.05), PPV (19.9% vs 6.3%, P<0.05) and NPV (95.2% vs 86.7%, P<0.05) of TS all presented higher in incomplete cervical TZ type than TZ type I.

Moreover, sensitivities of TS detecting CIN2+ and CIN3+ in all settings were all higher in incomplete cervical TZ type than TZ type I, even though no statistical significancy observed.

TS demonstrated a better clinical performance in non-menopausal patients than post-menopausal patients for detecting CIN1+

Overall detecting cases of TS in patients with TZ type III grouped by menopausal status was shown in Table S4. For detecting CIN1+, TS showed a significant difference between non-menopause group and post-menopause group (P=0.006 for ASCUS, P=0.006 for LSIL and P<0.001 for overall CIN1+ population). Moreover, the overall sensitivity for detecting CIN1+ and CIN3+ was significantly higher in non-menopausal group than post-menopausal group (45.8% vs 28.1% for CIN1+, 85.7% vs 33.3% for CIN3+, both P<0.05) (Table S5). Noteworthily, TS detecting in non-menopausal LISL group showed AUC of 0.714 (CIN1+), 0.824 (CIN2+) and 0.923 (CIN3+). For overall non-menopausal CIN2+ and CIN3+ population, the AUC were 0.736 and 0.821, respectively.

Significantly higher rate of pathology results [?]CIN1 with negative TS than positive TS results

In ASCUS patients with negative TS results, 190/213 (89.2%) patients were [?]CIN1 pathologically, while 83/117 (70.9%) ASCUS patients with positive TS results were [?]CIN1. And in LSIL patients with negative TS results, 49/61 (80.3%) patients were [?]CIN1, 34/57 (59.6%) LSIL patients with positive TS results were [?]CIN1. In ASCUS and LSIL group, both rates of pathology results [?]CIN1 with negative TS were

significantly higher than which with positive TS results (P<0.001 for ASCUS, P=0.014 for LSIL) (Table S6).

Correlation between TS and IHC staining p16, Ki-67

In analysis of correlation between TS and p16, correlation was found in overall population (ρ=0.223, P<0.001) and ASCUS patients (ρ=0.226, P<0.001) (Table S7). We divided quantitative Ki-67 results into three groups for correlation analysis (<5%, 5%-30% and >30%) [22, 23]. Correlation between TS and Ki-67 were found in overall population (ρ=0.276, P<0.001), ASCUS patients (ρ=0.266, P<0.001) and LSIL patients (ρ=0.213, P=0.037).

Discussion

Main Findings

In this study, we evaluated the efficacy of a real-time and non-invasive optoelectronic cervical screening device (TruScreen) in patients with abnormal TCT results, aiming to broaden the current screening strategies. This is meaningful in nowadays context of COVID-19 post-pandemic. Firstly, we found that TS had significantly higher specificity and PPV either alone or combined with hrHPV than hrHPV alone. Secondly, TS was found to have a higher sensitivity in incomplete cervical TZ type than TZ type I. Particularly, significantly higher specificity and NPV were found in incomplete cervical TZ type. Thirdly, TS demonstrated significantly higher sensitivity in non-menopausal women with TZ type III in detecting CIN1+ and CIN3+. Finally, in ASCUS and LSIL patients with negative TS result, rate of pathology [?]CIN1 were significantly higher than whom with positive TS result.

These findings indicate that TS can play an important role in making up the over-diagnosis and over-referral to colposcopy by hrHPV test. Moreover, TS may overcome the limitations for colposcopists in examining patients with incomplete cervical TZ type and provide a new screening choice for non-menopausal women. For patients with TCT results of ASCUS and LSIL, they can be recommended to do follow-up within 6 months when the TS results are negative.

Strengths and Limitations

This study has several strengths. The first one is the relatively large sample size. To our knowledge, this study had the biggest sample size regarding the abnormal TCT results in TS studies. The second one is the quality-assured colposcopy examination supporting in our hospital. Moreover, we took cervical TZ types into analysis, which had not been done before.

There are a few limitations of this study. Firstly, TS could not detect the cervical canal and endocervix directly, as the tip of the device could not reach into the cervical canal. Secondly, the TCT reports of enrolled participants were from different hospitals, which might cause subtle bias. Thirdly, we enrolled patients and executed TS detection at colposcopy examination room and outpatient department. Patients who were enrolled and TS-examined at outpatient department were not to have colposcopy examination immediately, usually within one week. The interim might cause patients' vaginal condition changed (for example, vaginitis, menses and intercourse).

Interpretation

Current recommended primary cervical screening methods are hrHPV tests, cervical cytology or co-testing. However, high sensitivity of hrHPV tests may cause patients' psychological burden, over-referral to colposcopy examination and over-treatment for HPV infection. Cervical cytology assessment has a lower sensitivity and requires qualified cytopathologists. In many rural areas in China, cytopathologists are lacked [24]. Besides, women usually need to wait for several days or longer to be informed of their results. Since COVID-19 broke out in 2020, routine cervical screening has become a challenge for all women and gynecologists, as both HPV test and cervical cytology examination could not avoid specimen contact and increase the risk of COVID-19 exposure. Until today, in COVID-19 post-pandemic, the same concern still exists. Therefore, a simple, non-invasive and immediate screening method is warrant.

TS detection requires no cytopathologists because of the easiness of operation and objective results. In previous studies, TS has demonstrated a promising diagnostic efficacy. A mate-analysis reported the pooled sensitivity, specificity and AUC of TS was 76%, 69% and 0.7859, respectively [20]. Compared with it, TS in our study had a relatively lower sensitivity (53.1% for CIN1+, 65.7% for CIN2+ and 67.3% for CIN3+) but a higher specificity detecting CIN1+ (77.1%) and similar specificity detecting CIN2+ (66.7%) and CIN3+ (62.7%). A recent study demonstrated similar diagnostic value of TS applied in patients with abnormal Pap smear results (the sensitivity and specificity were 65% and 55%, respectively) [19].

Among 17 ASC-H patients enrolled, 2 were TS negative. One was pathologically confirmed CIN1, the other one was CIN3. The misdiagnose of CIN3 by TS was TZ type I and TS-examined at outpatient department. Colposcopically-directed three biopsies (1, 6, 11 o'clock) were obtained. Only 1 o'clock was pathologically confirmed CIN3 while the other two reported no lesion. We inferred that the tip of the device did not cover the lesion since the cervix was not located in the middle and leaning to the right, leading to the 1 o'clock area not exposed satisfactorily.

For the missed cases of CIN2+ by TS in our study, 24 of 36 cases were with cervical TZ type II and III (Figure 2 A3-D3). No cancer was missed by TS. We deduced the relatively low sensitivity of TS was because of the undetectable cervical canal and endocervix. Therefore, we defined TZ type II and III as incomplete cervical TZ type because of the unseen SCJ to compare with TZ type I. We unexpectedly found that TS had a better diagnostic performance in incomplete cervical TZ type. Higher sensitivities and significantly higher specificities and NPVs were observed in this group. This might be attributed to the systematic bias, as the TS operator would put the tip of device as inwardly into the cervical canal as possible when the SCJ unexposed naturally, aiming not to miss any lesion. Currently, women with incomplete cervical TZ type are recommended to undergo ECC which may cause discomfort for patients as well as operating difficulty for colposcopists. Our result indicated that TS could reduce misdiagnosis of CIN and predict no CIN occurred effectively, thus might decrease the frequency of ECC.

A recent study about TS applied in hrHPV infected women reported TS combined with HPV 16/18 had the highest specificity (83.6%) comparing with TS alone or HPV 16/18 alone [18]. Our study reported similar specificities of TS combined with hrHPV of significancy (82.8% for CIN1+, 73.3% for CIN2+) and significantly higher PPV of CIN1+ comparing with hrHPV alone. This demonstrated that combination of TS and hrHPV test could reduce misdiagnosis of CIN1+ and predict CIN1+ effectively comparing with hrHPV alone.

Post-menopausal women usually present with cervical TZ type III. To analyze the influence of menopause on TS detection, we compare it between non-menopausal and post-menopausal women with cervical TZ type III. As a result, sensitivities of non-menopausal women detecting CIN1+ and CIN3+ were significantly higher comparing with post-menopausal women. This suggested that TS was more effective in non-menopausal women.

In current COVID-19 post-pandemic context in China, we are eager to find an effective screening triage method to lower the rate of colposcopy. In our study, 89.2% and 80.3% women with negative TS result in ASCUS group and LSIL group, respectively, were pathologically confirmed [?]CIN1. To decrease COVID-19 exposure, gynecologists could suggest these patients to follow up with 6 months instead of further colposcopy or biopsy.

At last, we analyze the correlation of TS between IHC staining p16 and Ki-67, which are important auxiliary indicators in diagnosing CIN2+ [25, 26]. We found the correlation between TS and p16, TS and Ki-67 in overall participants and ASCUS group, but all the correlation strength were not strong. Even so, the correlations proved TS was of high quality in diagnosing CIN.

Conclusion

TS is an effective triage screening method for women with cervical cytology ASC and LSIL, especially whom with incomplete cervical TZ type. It probably provides an optional method for national cervical cancer

screening in China. Further research should be generalized with whole population to validate the efficacy of TS as a screening method.

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Disclosure of interest

The authors have no competing interests to declare.

Contribution to authorship

All authors contributed to the conception and design of the study. YX carried out the research, analyzed the data, interpreted the data and drafted the article. HL operate colposcopy examination and biopsy. XX, YL, SL, RZ, CH coordinated the cervical screening activities. FC interpreted the data and drafted the article. All authors reviewed the article and critically revised it for important intellectual content. All authors reviewed and approved the final article for publication.

Details of ethic approval

This study was reviewed and prospectively approved by the Ethics Committee of the Second Xiangya hospital in September 2020 (Reference number: LYG2020061).

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Table 1. Overall performance of different screening tests for detecting CIN2+

				Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	AUC (95%CI)	P-
[?]CIN2		Yes	No						
ASCUS	TS positive	34	83	59.6 (45.8-72.2)	69.6 (63.7-74.9)	29.1 (21.2-38.3)	89.2 (84.1-92.9)	0.646 (0.566-0.727)[b]	<0
	TS negative	23	190						
	hrHPV+	56	172	98.2 (89.4-99.9)	36.8 (31.1-42.8))	24.6 (19.2-30.8)	99.9 (93.8-99.9)	0.675 (0.611-0.739)[b]	<0
	hrHPV-	1	100						
	TS+hrHPV positive[a]	33	68	57.9 (44.1-70.6)	75.0 (69.3-79.9)	32.7 (23.9-42.8)	89.5 (84.6-93.0)	0.665 (0.584-0.756)[b]	1.0
	TS+hrHPV negative[a]	24	204						
LSIL	TS positive	23	34	65.7 (47.7-80.3)	59.0 (47.7-69.5)	40.4 (27.8-54.2)	80.3 (67.8-89.0)	0.624 (0.514-0.734)[b]	0.0
	TS negative	12	49						
	hrHPV+	32	58	91.4 (75.8-97.8)	30.1 (20.8-41.3)	35.6 (25.9-46.4)	89.3 (70.6-97.2)	0.608 (0.502-0.713)	0.0
	hrHPV-	3	25						
	TS+hrHPV positive	23	25	65.7 (47.7-80.3)	69.9 (58.7-79.2)	47.9 (33.5-62.6)	82.9 (71.6-90.5)	0.678 (0.570-0.786)[b]	1.0
	TS+hrHPV negative	12	58						
ASC-H	TS positive	12	3	92.3 (62.1-99.6)	25.0 (1.3-78.1)	80.0 (51.4-94.7)	50.0 (2.7-97.3)	0.587 (0.240-0.934)	1.0
	TS negative	1	1						
	hrHPV+	13	3	100.0 (71.7-100.0)	25.0 (1.3-78.1)	81.3 (53.7-95.0)	100.0 (5.5-100.0)	0.625 (0.272-0.978)	1.0
	hrHPV-	0	1						
	TS+hrHPV positive	12	3	92.3 (62.1-99.6)	25.0 (1.3-78.1)	80.0 (51.4-94.7)	50.0 (2.7-97.3)	0.587 (0.240-0.934)	1.0
	TS+hrHPV negative	1	1						

				Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	AUC (95%CI)	P-
Overall	TS positive	69	120	65.7 (55.7-74.5)	66.7 (61.5-71.5)	36.5 (29.7-43.8)	87.0 (82.3-90.6)	0.662 (0.602-0.721)[b]	<0
	TS negative	36	240						
	hrHPV+	101	233	96.2 (90.0-98.8)	35.1 (30.2-40.3)	30.2 (25.4-35.5)	96.9 (91.8-99.0)	0.656 (0.604-0.709)[b]	<0
	hrHPV-	4	126						
	TS+hrHPV positive	68	96	64.8 (54.8-73.7)	73.3 (68.3-77.7)	41.5 (33.9-49.4)	87.7 (83.3-91.7)	0.690 (0.631-0.750)[b]	1.0
	TS+hrHPV negative	37	263						

[a]TS+hrHPV is positive only if both TS and hrHPV are positive, either one of them being negative is considered TS+hrHPV negative.

[b]$p<0.05$ compared with each AUC with 0.5.

[c, d, e]compared between TS and hrHPV, hrHPV and TS+hrHPV, TS and TS+hrHPV, respectively.

ASCUS: atypical squamous cells of undetermined significance. LSIL: low-grade squamous intraepithelial lesion. ASC-H: atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion. hrHPV: high-risk human papillomavirus. CIN: cervical intraepithelial neoplasia. PPV: positive predictive value. NPV: negative predictive value. AUC: area under the curve.

Table 2. Performance of TS for detecting CIN1+, CIN2+ and CIN3+ classified by TZ type

	Incomplete TZ (type II and III, n=367)	Incomplete TZ (type II and III, n=367)	Incomplete TZ (type II and
	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)
[?]CIN1			
ASCUS	45.5 (37.0-54.3)	83.1 (75.0-89.0)[a]	74.4 (63.4-83.1)
LSIL	54.1 (40.9-66.7)	74.3 (56.4-86.9)[a]	78.6 (62.8-89.2)
ASC-H	92.3 (62.1-99.6)	-	100.0 (69.9-100.0)
Overall	51.0 (44.0-57.9)	81.1 (74.0-86.7)[a]	77.9 (69.9-84.4)
[?]CIN2			
ASCUS	59.0 (42.2-74.0)	73.1 (66.6-78.7)[a]	28.4 (19.0-39.2)
LSIL	70.4 (49.7-85.5)	66.7 (54.2-77.3)	45.2 (30.2-61.2)
ASC-H	100.0 (62.9-100.0)	25.0 (1.3-78.1)	75.0 (42.8-93.3)
Overall	68.0 (56.1-78.0)	70.0 (65.3-76.0)[a]	37.5 (29.5-46.2)
[?]CIN3			
ASCUS	50.0 (25.5-74.5)	69.4 (63.1-75.1)[a]	9.8 (4.6-18.8)
LSIL	80.0 (51.4-94.7)	63.0 (51.5-73.2)[a]	28.6 (16.2-44.8)
ASC-H	100.0 (56.1-100.0)	16.7 (0.9-63.5)	58.3 (28.6-83.5)
Overall	71.1 (53.9-84.0)	66.9 (61.5-71.9)[a]	19.9 (13.7-27.7)[a]

[a]p<0.05 compared between incomplete TZ and TZ type I.

[b]p<0.05 compared with each AUC with 0.5.

PPV: positive predictive value. NPV: negative predictive value. AUC: area under the curve. ASCUS: atypical squamous cells of undetermined significance. LSIL: low-grade squamous intraepithelial lesion. ASC-H: atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion. TS: TruScreen. TZ: transformation zone. CIN: cervical intraepithelial neoplasia.

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