Validity of the Colposcopic Criteria Inner Border Sign, Ridge Sign, and Rag Sign for Detection of High-Grade Cervical Intraepithelial Neoplasia

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OBJECTIVE: To evaluate the association of three pathognomonic criteria, inner border, ridge sign, and rag sign with high-grade cervical intraepithelial neoplasia (CIN) using video exoscopy.

METHODS: Retrospective evaluation of video recordings of 335 patients, referred for diagnostic colposcopy, who underwent cervical biopsies, and, if indicated loop excisions, was performed. The most severe histologic diagnosis was recorded. Sensitivity, specificity, positive, negative predictive value, and likelihood ratios for high-grade CIN were calculated.

RESULTS: In 285 patients (85%), a single colposcopy directed biopsy was taken; 50 patients (15%) underwent two biopsies. One hundred sixty-two patients (48%) underwent subsequent magnification-guided loop excision. Sensitivity, specificity, positive predictive value, and negative predictive value of the inner border to detect high-grade CIN were 20%, 99%, 97.9%, and 34.8%, respectively. The positive likelihood ratio (LR+) was 20.3 and the negative likelihood ratio (LR−) was 0.81. Sensitivity, specificity, positive predictive value, and negative predictive value of the ridge sign to detect high-grade CIN were 52.5%, 96.4%, 96.8%, and 46.6%, respectively. The LR+ ratio was 13.2 and the LR– ratio was 0.49. Sensitivity, specificity, positive predictive value, and negative predictive value of the rag sign to detect high-grade CIN were 38.4%, 96%, 95.7%, and 40.2%, respectively. The LR+ ratio was 9.7 and the LR– ratio was 0.6. Only the ridge sign showed a correlation with young age. Presence of any two signs significantly increased the LR of the presence of high-grade CIN.

CONCLUSION: The inner border, ridge sign, and the newly defined rag sign are objective, effective colposcopic signs and are significantly associated with high-grade CIN.

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LEVEL OF EVIDENCE: II

Colposcopy is the basis for the correct identification of the atypical transformation zone, for the definition of the grade of the underlying lesion, for targeted biopsy in case of high-grade cervical intraepithelial neoplasia (CIN), and for excisional therapy. The literature on the accuracy of colposcopy is contradictory.[1–3] As a result of the transient character and duration of the changes of the abnormal cervical tissue, induced by acetic acid application and the subjective evaluation of colposcopic findings such as margins, vessel, and color, colposcopy is a subjective "art" and results in interobserver and intraobserver variability.[4–6]

Over the years, a number of grading indices, which are based on a variety of morphologic phenomena, have been created to help differentiate among normal, minor change, major change, and cancer.[7–12] One of these that has attempted to quantify grade by assigning points to each morphologic finding[7–10] has

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not been confirmed to be highly predictive of the ultimate histology.[3,11] Thus, International Federation for Cervical Pathology and Colposcopy[13] has revised the grading nomenclature by adding two recently described pathognomonic criteria, inner border sign and ridge sign, highly associated with the presence of high-grade CIN.[14,15] Pathognomonic signs differ from the other existing criteria in that they are simply present or absent: they should be dichotomously reported, and not graduated, their presence being significantly associated with high-grade CIN.

We identified another pathognomonic nongradeable criterion associated with high-grade CIN, the "rag sign," an iatrogenic small erosion of the epithelium generally caused by its partial ablation during mechanical trauma of the cervix at the time of the collection of the smear for cytology or human papillomavirus (HPV) testing, application of acetic acid or Lugol's solution, or both.[16]

We undertook the present study to evaluate the detection rate for high-grade CIN of three objective, pathognomonic, nongradeable features of the abnormal transformation zone: inner border sign, ridge sign, and rag sign. Additionally we evaluated a possible association with the age of the patient.

PATIENTS AND METHODS

Between November 2010 and July 2011, 389 patients were referred to the colposcopy and lower genital tract disease center of the Charité University, Berlin and the Colposcopy Clinic Wagner Stibbe, Bad Muender, Germany, with a history of an abnormal Pap smear, detection of high-risk HPV in a cervical smear, or both. Each patient underwent video exoscopy using the VITOM System and histologic evaluation by VITOM-guided biopsy or loop excision.

The VITOM System is a video exoscope based system consisting of the VITOM 25 scope, Xenon 300 light source, FULL HD camera system, AIDA HD documentation system, FULL HD monitor, a mechanical support arm, and a three-chip HD camera head providing a resolution of 1,920×1,080 pixels (FULL HD, progressive scan) with a frame rate of 50/60 frames per second. The camera has a 2× parfocal zoom and weighs 246 g. The VITOM System supporting a 25-cm to 60-cm working distance provides comfortable workspace. The VITOM System has shown to be accurate for the diagnosis of high-grade CIN[17] and hence has replaced traditional colposcopy in our center since July 2010. This system combines two decisive and equally important advantages over conventional colposcopy: it provides a FULL HD video documentation of colposcopic examination, and it allows its storage and reanalysis both for teaching and scientific purposes.

Patients with a history of hysterectomy or previous radiation were excluded. In addition, we decided to exclude from our analysis patients with transformation zone type 3 (n=44), as defined by International Federation for Cervical Pathology and Colposcopy 2003,[18] because colposcopic diagnosis is insufficient and unreliable in these instances.[19] Patients with invasive cancers (n=10) were also excluded, because the focus of this study is the evaluation of colposcopic criteria for the detection of high-grade CIN and not of invasive disease. Thus, 335 of 389 patients (86.1%) of the total cohort were eligible for evaluation.

All patients undergoing video recording procedures in our institution give written consent to the saving of both images and videos of their examination or operation. This study was approved by our internal review board.

All video exoscopies stored in the AIDA HD documentation system were evaluated independently, on a 26-inch HD monitor, with a luminance of 400 cd/m^2, by two senior colposcopists (S.A., B.G.) in a darkened, artificially lit room, with back-screen illumination, to provide optimal viewing conditions and to standardize the examination, thus enhancing reproducibility of the results. Both parties were blinded to all clinical data of the patients such as referring diagnosis, results of Pap smear, HPV test, medical history, and histology apart from age.[20]

The overall colposcopic impression was categorized as normal or benign abnormality (inflammation, atrophy), minor change, or major change. All video exoscopies were specifically checked for the presence of inner border, ridge sign, and rag sign at the level of the transformation zone. Video colposcopic findings and transformation zone (TZ) type were reported according to the criteria of the Committee on Nomenclature of the International Federation of Cervical Pathology and Colposcopy: "Type 1 TZ is completely ectocervical and fully visible; type 2 TZ has an endocervical component, is fully visible; type 3 TZ has an endocervical component that is not fully visible."[18]

The inner border is a dull, oyster white area, inside a less opaque acetic white area, in its turn demarcated from the normal squamous epithelium.[14] The peripheral area represents an earlier, minor grade change, the central area being the subsequent evolution of a high-grade CIN at the advancing edge of the new squamocolumnar junction with aging (Fig. 1).

The ridge sign is an opaque lesion, direct adjacent to the squamocolumnar junction, which resembles a mountain ridge[15] (Fig. 2).

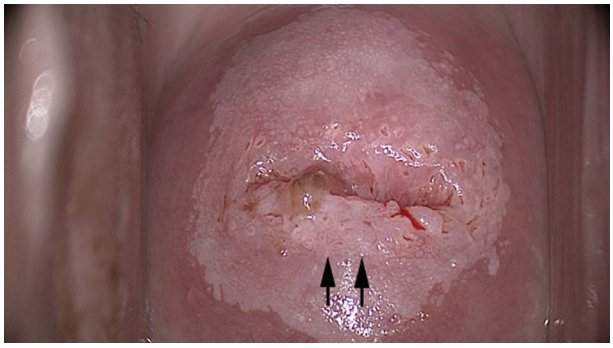

Fig. 1. Atypical transformation zone type 2 with inner border at 6 o'clock (*arrows*). Histology: cervical intraepithelial neoplasia 3.

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The rag sign is an opaque acetowhite area at the squamocolumnar junction, mechanically abraded during either collection of the smear for cytology or HPV testing, applying acetic acid or Lugol's solution, or both. In the rag sign, part of the epithelium is sloughed off, and either the underlying erosion or the detached epithelium, which resembles a rag, are visible (Figs. 3–5).

All punch biopsies or loop excisions were made under colposcopic or VITOM guidance[21] and the material was fixed in formalin, paraffin-embedded, sectioned in series, and stained with hematoxylin and eosin. CIN was classified according to the criteria described by Crum.[22] Statistical analysis was performed using PASW 20 and Medcal. Descriptive statistics including the mean age of patients and the frequency of each sign in different age groups was performed. Chi square analysis was used to compare categorical and ordinal data. We evaluated colposcopic performance for each colposcopic sign separately. For high-grade CIN, we estimated the sensitivity and specificity, positive predictive value

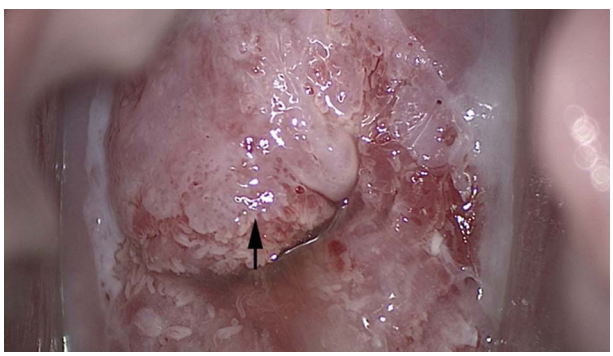

Fig. 2. Atypical transformation zone type 2 with ridge sign at 12 o'clock (*arrow*). Histology: cervical intraepithelial neoplasia 3.

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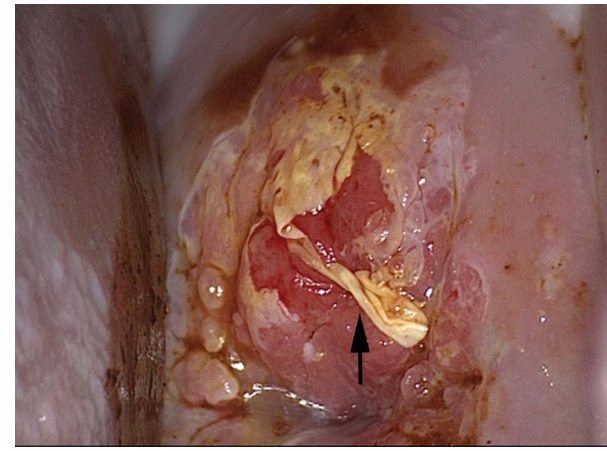

Fig. 3. Atypical transformation zone type 2 with the rag sign at the squamocolumnar junction. Part of the epithelium is sloughed off in a rag as a result of mechanical trauma (*arrow*). Histology: cervical intraepithelial neoplasia 3.

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(PPV), and negative predictive value (NPV), negative likelihood ratio (LR−), and positive likelihood ratio (LR+), and the 95% confidence intervals for those statistics in different age groups.

Likelihood ratios determine whether presence of a colposcopic sign usefully changes the probability that CIN exists by using sensitivity and specificity. The LRs have advantages over predictive values because they are less likely to change with the prevalence of the disorder, and they can be calculated for several levels of the symptom or sign or test.[23] An

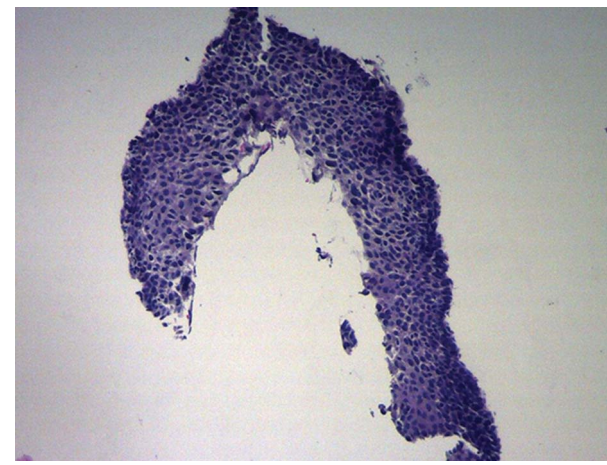

Fig. 4. Histologic specimen of the rag sign of the above exoscopy; exclusively, the epithelial rag has been harvested (hematoxylin and eosin stain magnification ×200, with permission of Prof. W. Kühn).

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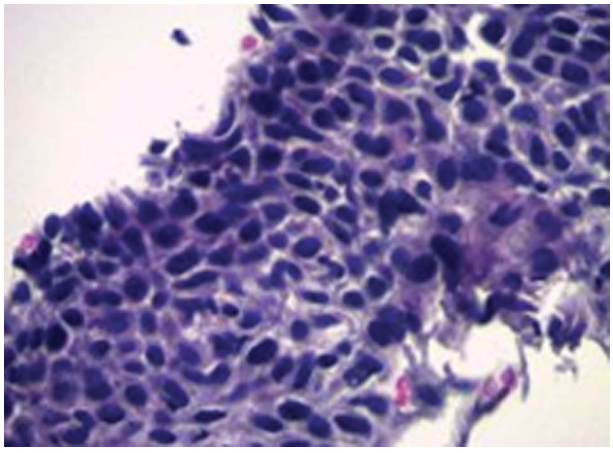

Fig. 5. Zoom of a particular aspect of Fig. 4. Hematoxylin and eosin stain, magnification ×400, with permission of Prof. W. Kühn.

Vercellino. Colposcopic Signs for Detecting CIN. Obstet Gynecol 2013.

LR between 1 and 5 indicates a small increase in the likelihood of disease; however, an LR between 5 and 10 and more than 10 indicates a moderate and strong conclusive likelihood of disease, respectively. A negative LR between 0.5 and 1 indicates a minimal decrease in the likelihood of disease, and an LR between 0.2 and 0.5 indicates a small decrease in the likelihood of disease. However, a negative LR between 0.1 and 0.2 and less than 0.1 indicates a moderate and large decrease in the likelihood of disease, respectively. A P value $<.05$ was considered statistically significant.

RESULTS

A total of 335 patients were included in the study. The mean age of patients was 33.02±7.7 years. 14.3% of patients were younger than 25 years, 53.1% of patients were between 25 and 35 years, 25.1% of patients were between 35 years and 45 years, and 7.5% of patients were older than 45 years of age. Median age for patients with inner border was 31.5 years, 30 years for patients with the ridge sign and 31 years in patients with the rag sign. The Pap smear result was normal, atypical squamous cells of uncertain significance, low-grade squamous intraepithelial lesion, and high-grade squamous intraepithelial lesion in 12.4%, 5.9%, 32.3%, and 49.4% of patients, respectively. Of 335 patients, 287 patients were tested for the presence of HPV DNA: 64.5% were high-risk HPV-positive and 1.8% were low-risk HPV-positive. In 19.4% of patients, no HPV was detected. In 285 patients (85%), a single VITOM-directed biopsy was taken; 50 patients (15%) underwent two biopsies. One hundred sixty-two patients (48%) underwent subsequent magnification-guided loop excision and had thus two histologic results (Table 1). In these patients, the most severe histologic diagnosis was recorded. Cervical intraepithelial neoplasia 1 or high-grade CIN were diagnosed in 10.1% and 69.8% of patients, respectively; in the rest of the patients, the histologic diagnosis was normal. In women younger than 25 years old, 23%, 10%, and 67% had normal histology, CIN 1, or high-grade CIN, respectively. In women between 25 and 35 years old, 16%, 10%, and 74% had normal histology, CIN 1, or high-grade CIN, respectively. In women older than 35 years old, 25%, 11%, and 64% had normal histology, CIN 1, or high-grade CIN, respectively.

One hundred thirty-eight patients (41.2%) had transformation zone type 1 and a median age of 30 years; 197 patients (58.8%) had transformation zone type 2 zones. Inner border, the ridge sign, and the rag sign were seen in 14.3% (n=48), 37.9% (n=127), and 28.1% (n=94) of women, respectively.

The frequency of inner border sign and rag sign was not different between younger than 25 years old, 25–35 years old, and older than 35 years old. Ridge

Table 1. Demographic Characteristics of Patients Included in the Study

Demographic Characteristics (n=335)	
Age (y)	33.02±7.7
Younger than 25	14.3
25–35	53.1
35–45	25.1
Older than 45	7.5
Biopsy	
Single colposcopic biopsy	285 (85)
Two colposcopic biopsies	50 (15)
Loop electrosurgical excision procedure	162 (48)
Transformation zone	
T1	138 (41.2)
T2	197 (58.8)

Data are mean±standard deviation, %, or n (%).

Table 2. Prevalence of Three Colposcopic Criteria in 335 Women With Atypical Transformation Zone Correlated With Histologic Diagnosis in Punch or Cone Magnification-Guided Biopsy

	Ridge Sign	Inner Border	Rag Sign
No CIN	2 (1.6%)	1 (2.1%)	4 (4.3%)
CIN 1	2 (1.6%)	0	0
High-grade CIN	123 (96.8%)	47 (97.9%)	90 (95.7%)
Total	127	48	94

CIN, cervical intraepithelial neoplasia.
Data are n (%) or n.

Table 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratios in Different Age Groups

High-Grade CIN	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)
Inner border			
0–25 y	15.6 (5.33–32.80)	93.7 (69.69–98.96)	83.3 (36.10–97.24)
25–35 y	19.7 (13.29–27.51)	97.7 (92.22–99.6)	97.3 (80.97–99.38)
Older than 35 y	22.8 (13.67–34.45)	99.5 (86.79–99.58)	94.1 (71.24–99.02)
All ages	20 (15.15–25.80)	99 (94.59–99.83)	97.9 (88.89–99.65)
Ridge sign			
0–25 y	53.1 (34.75–70.89)	87.5 (61.62–98.08)	89.4 (66.82–98.39)
25–35 y	57.5 (48.68–66.13)	95.6 (85.13–99.34)	97.4 (91.02–99.61)
Older than 35 y	42 (30.24–54.52)	97.5 (86.79–99.58)	96.6 (82.72–99.44)
All ages	52.5 (45.96–59.11)	96.4 (90.16–98.89)	96.8 (92.12–99.12)
Rag sign			
0–25 y	34.3 (18.59–53.19)	87.5 (61.62–98.08)	84.6 (54.54–97.63)
25–35 y	34.8 (26.77–43.63)	97.8 (88.43–99.64)	97.8 (88.66–99.64)
Older than 35 y	47.1 (35.09–59.45)	97.4 (86.47–99.57)	97 (84.62–99.51)
All ages	38.4 (32.20–45.02)	96 (90.16–98.89)	95.7 (89.45–98.80)

CIN, cervical intraepithelial neoplasia; CI, confidence interval.
Inner border, ridge sign, and rag sign are found to be relevant tests to diagnose high-grade CIN.

sign was the only pathognomonic criterion, which showed a correlation with age ($P<.05$). Ridge sign was significantly less common in women older than 35 years old. Inner border was present in 12.5% 14.6%, and 14.7% of women younger than 25 years old, 25–35 years old, or older than 35 years old ($P=.92$). Ridge sign was found in 39.6%, 43.8%, and 27.5% of women younger than 25 years old, 25–35 years old, or older than 35 years old ($P<.05$). The rag sign was found in 27.1%, 26.4%, and 31.2% of women younger than 25 years old, 25–35 years old, or older than 35 years old ($P=.67$).

A total of 2.1%, 0%, and 97.9% of inner border positivity was found in women with normal, CIN 1, and high-grade CIN histology, respectively ($P<.001$). A total of 1.6%, 1.6%, and 96.8% of ridge sign positivity was found in women with normal, CIN 1, and high-grade CIN histology, respectively ($P<.001$). A total of 4.3%, 0%, and 95.7% of rag sign positivity was found in women with normal, CIN 1, 2, and 3 histology, respectively ($P<.001$) (Table 2).

Of 234 patients with high-grade CIN, 47 showed inner border in colposcopic examination. Sensitivity, specificity, PPV, and NPV of inner border to detect high-grade CIN were 20%, 99%, 97.9%, and 34.8%, respectively. The LR+ was 20.3 and the LR− was 0.81 (Table 3).

Of 234 patients with high-grade CIN, 123 showed the ridge sign. Sensitivity, specificity, PPV, and NPV of the ridge sign to detect high-grade CIN were 52.5%, 96.4%, 96.8%, and 46.6%, respectively. The LR+ was 13.2 and the LR− was 0.49 (Table 3).

Of 234 patients with high-grade CIN, 90 showed the rag sign. Sensitivity, specificity, PPV, and NPV of the rag sign to detect high-grade CIN was 38.4%, 96%, 95.7%, and 40.2%, respectively. The LR+ was 9.7 and the LR− was 0.6 (Table 3).

Inner border, the ridge sign, and the rag sign are good diagnostic tests to determine high-grade CIN (Tables 3 and 4). Diagnostic test performance of all three colposcopic signs was significantly improved in women 25–35 years old and older than 35 years old compared with women younger than 25 years old (Table 3) ($P<.05$). Of 234 patients with high-grade CIN, 182 (77.8%) patients had a combination of at least one of three pathognomic signs; 114 (49.5%) patients had one single sign and 58 (24.7%) patients had two of three signs and 10 (4.2%) patients had all three signs.

Inner border sign alone was seen in 20 patients, ridge sign alone was seen in 61 patients, and rag sign alone was present in 38 patients. Inner border and ridge sign were combined in 24 patients, inner border and rag sign were combined in 14 patients, and ridge sign and rag sign were combined in 52 patients. A combination of all three criteria was seen in 10 patients.

All 24 patients with a combination of the ridge sign and inner border were diagnosed with high-grade CIN. Of 52 patients with a combination of the ridge sign and rag sign, 51 patients were diagnosed with high-grade CIN. In 14 patients, a combination of the rag sign and inner border was seen and 13 of these patients were diagnosed with high-grade CIN. All 10 patients with a combination of ridge sign, inner border, and rag sign were diagnosed with high-grade CIN.

Negative Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
35.7 (21.56–51.97)	2.5 (0.32–19.64)	0.9 (0.74–1.09)
30.2 (23.08–38.23)	9.2 (1.29–66.34)	0.8 (0.75–0.90)
41.9 (31.78–52.62)	9.1 (1.26–66.39)	0.7 (0.69–0.91)
34.8 (29.34–40.66)	20.3 (2.84–145.02)	0.81 (0.75–0.86)
48.2 (29.46–67.46)	4.2 (1.12–16.18)	0.5 (0.35–0.81)
44 (34.08–54.28)	13.2 (3.39–51.77)	0.44 (0.36–0.55)
49.3 (37.92–60.86)	16.8 (2.38–118.77)	0.5 (0.48–0.73)
46.6 (39.71–53.66)	13.2 (5.04–34.94)	0.49 (0.43–0.57)
40 (23.88–57.88)	2.7 (0.69–10.95)	0.7 (0.55–1.02)
34.3 (26.28–43.15)	16 (2.27–112.96)	0.6 (0.58–0.76)
50.6 (38.87–62.41)	18.3 (2.61–129.30)	0.5 (0.43–0.68)
40.2 (34.00–46.74)	9.7 (3.67–25.72)	0.6 (0.57–0.71)

A combination of inner border sign and ridge sign has a specificity of 100%, a sensitivity of 10.3%, PPV of 100%, and NPV of 32.5% for detection of high-grade CIN. A combination of the ridge sign and rag sign has a specificity of 99% a sensitivity of 21.8%, PPV of 98.1%, and NPV of 35.3% for detection of high-grade CIN. A combination of the rag sign and inner border sign has a specificity of 99.0%, a sensitivity of 5.6%, PPV of 92.9%, and NPV of 31.2% for detection of high-grade CIN.

When at least one of the pathognomonic criteria was present, specificity was 93%, sensitivity was 77.8%, PPV was 96.2%, and NPV was 63%. Positive likelihood ratio was 11.2 and LR− was 0.2. Presence of at least two of three criteria has a specificity of 98.0%, a sensitivity of 29.1%, PPV of 97.1%, and NPV of 37.4%. Positive likelihood ratio was 14.6 and LR− was 0.7. A patient with a combination of two of the three pathonogmonic signs had a significant likelihood for the presence of high-grade CIN (Table 4). Therefore, the diagnosis of high-grade CIN should be considered in the presence of any two signs such as inner border, ridge sign, or rag sign.

DISCUSSION

Twenty-seven years ago Reid introduced the sharpness of the peripheral margins in his improved colposcopic graduating index and, although not separately analyzing the diagnostic power of each colposcopic sign, Reid described the importance of rolled edges, peeling edges, and internal border between lesions of different severity to differentiate minor and major change lesions.[7]

We highlight the rag sign, a sloughing off of atypical squamous epithelium in a rag mechanically abraded during either collection of the smear for cytology or HPV testing, applying acetic acid or Lugol's solution, or both. Its biological basis is unclear. The rag sign is a new pathognomonic, objective, colposcopic criterion, whose presence, alone or combined with one or both of the two other objective signs, "inner

Table 4. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratios for at Least One Colposcopic Sign or at Least Two Signs

High-Grade CIN	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
At least one sign	77.8 (70.53–81.77)	93 (86.23–97.16)	96.2 (92.40–98.47)	63 (54.80–70.84)	11.2 (5.38–22.63)	0.2 (0.20–0.32)
At least two signs	29.1 (23.73–35.78)	98 (94.59–99.83)	97.1 (92.27–99.76)	37.4 (31.88–43.87)	14.6 (3.7–58.7)	0.7 (0.65–0.78)

CIN, cervical intraepithelial neoplasia.

border" sign and "ridge" sign,[14,15] is strongly associated with high-grade CIN. Because the most prominent areas of colposcopic change does not always coincide with the areas of greatest histologic abnormality, if present, pathognomonic signs can help colposcopists to focus their attention on the most prominent areas of morphologic change and to correctly diagnose high-grade CIN in up to 70% of the patients.

A multitude of different grading systems have been proposed and implemented in the daily praxis over the last 40 years[24,25] but have failed to provide reproducible results. Therefore, some colposcopists recommend random biopsies.[23,26,27]

Diagnostic comparability between colposcopy and the VITOM System has been previously described.[17] The efficacy of pathognomonic signs to suggest the presence of high-grade CIN can be better objectified through real time videos than by means of static photograms.[6]

To prove the simplicity and reproducibility of detection of pathognomonic signs, we opted for the evaluation of unselected, consecutive, previously recorded video exoscopies of patients referred for diagnostic colposcopy to our outpatient center for cervical and lower genital tract pathology. Videos were recorded by eight different colposcopists, in a diagnostic setting, and are thus fully representative of everyday colposcopic practice, which allows generalization of our results. In addition, because the video exoscopies are original and full length, not edited videos, it minimizes the retrospective nature of our study.

Colposcopy is mainly useful in a diagnostic setting with high prevalence of high-grade CIN as opposed to screening setting.[23] The prevalence of high-grade CIN in our cohort is 69%, which will influence positively the predictive values of colposcopic criteria for high-grade CIN. Therefore, we calculated the LRs for each colposcopic sign, which, unlike PPV and NPV, are independent of prevalence of disease. It is remarkable that 77.8% of patients (182/234) with high-grade CIN showed at least one of the three criteria: inner border, ridge sign, or rag sign. This means that despite being very specific for high-grade CIN, a combination of pathognomonic signs is present in more than 75% of patients with high-grade CIN.

Simultaneous presence of pathognomonic criteria was highly indicative of high-grade CIN.

Because of the known high regression rate of CIN 2 in women younger than 25 years[28] and of the significant difference of the acetic white reaction in women younger than 35 years,[20] we set different age cutoffs and analyzed the association of pathognomonic signs with age. The ridge sign was the only pathognomonic criterion that showed a correlation with age ($P<.05$).

This study has a number of limitations. We exclusively focused our attention on three pathognomonic signs, disregarding standard grading signs, which are still the most widely used colposcopic diagnostic tools for diagnosis of high-grade CIN.[13] Specifically we did not analyze the grade of the acetic white reaction[20,29,30] the location,[11,31] the size of the lesion,[32,33] and the presence of cuffed glandular openings.[13,34] Such comparisons are the focus of other ongoing prospective studies. In addition, the reviewer had no influence on the actual punch guided biopsy site, which in some occasions differed from the best possible target. The statistical limitation of the study is a high prevalence of high-grade CIN. However, the prevalence of high-grade CIN is always higher in a reference colposcopy clinic (20–60%) compared with a screening population. The prevalence of diseases effects PPV and NPV, but not the LR. At the same time, our study has some decisive strengths. First, the dynamic process of colposcopy is recorded by video exoscopy in real time, which allows subsequent evaluation of the cervix and of underlying pathology as opposed to static photograms.[6] Second, to fully evaluate the three pathognomonic signs objectively, reviewers were blinded to smoking habits, cytologic index,[35] and HPV status.[36] Previous studies have shown that the knowledge of these results may increase the sensitivity for detection of high-grade CIN.[2,36,37] Third, the search for pathognomonic signs resulting from their intrinsic dichotomy, present compared with absent, can increase the specificity of colposcopic grading.

Inner border sign, the ridge sign, and the newly defined rag sign yield a sensitivity of 77.8%, specificity of 93%, PPV of 96.2%, and NPV of 63% for detection of high-grade CIN if at least one of these signs is present. Positive likelihood ratio was 11 and LR− was 0.2. Pathognomonic signs, introduced in the latest International Federation for Cervical Pathology and Colposcopy terminology (2011), are objective, present or absent, easy to see and learn, with smaller risk for subjectivity.[13] Their presence is highly suggestive for high-grade CIN, and their validity is independent of the age of the patient.

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