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DIAGNOSTIC ACCURACY OF A HYSTEROSCOPIC SCORE FOR THE DETECTION OF ENDOMETRIAL CANCER IN PATIENTS WITH POSTMENOPAUSAL BLEEDING AND ENDOMETRIAL THICKENING

Exactitud diagnóstica de una escala histeroscópica para la detección de cáncer endometrial en pacientes con sangrado posmenopáusico y engrosamiento endometrial

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ABSTRACT

Objective: To assess the diagnostic accuracy of a hysteroscopic scale in endometrial cancer.

Materials and methods: Diagnostic accuracy study assembled within a cross-sectional study that included patients with postmenopausal bleeding and endometrial thickening greater than 5 mm in whom hysteroscopy was performed and then compared with endometrial biopsy as the diagnostic gold standard, in two high complexity hospitals. Clinical, sociodemographic variables, as well as hysteroscopic scores and the results of endometrial tissue histopathology were measured. Sensitivity and specificity, likelihood ratios and area under the curve with their respective confidence intervals were estimated in the analysis.

Results: With a 9% prevalence of endometrial cancer, the hysteroscopic assessment system was shown to have 75% sensitivity (95% CI; 30.1- 95.43), 95.1% specificity (95% CI; 83.9-98.7), a positive likelihood ratio of 15.38 (95%; CI 3.55- 66.56), a negative likelihood ratio of 0.26, and area under the curve of 85 %.

Conclusion: The standardized hysteroscopic assessment system was found to have an acceptable sensitivity for screening in patients with postmenopausal bleeding and endometrial thickening (≥ 5 mm). Further studies with larger sample sizes are required in order to arrive at a more precise estimation of the operational characteristics of the hysteroscopic assessment system for the detection of endometrial cancer.

Key words: Uterine hemorrhage; hysteroscopy; endometrial neoplasms; postmenopause.

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RESUMEN

Objetivo: evaluar la exactitud diagnóstica del sistema de puntaje histeroscópico de cáncer endometrial.

Materiales y métodos: estudio de exactitud diagnóstica ensamblado en estudio transversal, que incluyó pacientes con sangrado posmenopáusico y engrosamiento endometrial mayor o igual a 5 mm, a quienes se practicó histeroscopia, cuyo resultado se comparó con la biopsia endometrial como patrón de oro diagnóstico, en dos hospitales de alta complejidad. Se midieron variables sociodemográficas, clínicas, puntaje de evaluación histeroscópica y resultado histopatológico de tejido endometrial. En el análisis se estimó sensibilidad, especificidad, razones de probabilidades y área bajo la curva con sus respectivos intervalos de confianza.

Resultados: con una prevalencia del cáncer endometrial del 9 %, el sistema de evaluación por histeroscopia mostró una sensibilidad de 75 % (IC 95 %: 30,1-95,43), especificidad de 95,1 % (IC 95 %: 83,9-98,7), una razón de probabilidades positiva de 15,38 (IC 95 %: 3,55-66,56), una razón de probabilidades negativa de 0,26 y un área bajo la curva del 85 %.

Conclusión: el sistema de evaluación endometrial histeroscópico estandarizado mostró una sensibilidad aceptable para hacer la tamización en pacientes con sangrado posmenopáusico y engrosamiento endometrial (≥ 5 mm). Se requiere la realización de estudios con un mayor tamaño muestral que permitan hacer una estimación más precisa de las características operativas de este sistema de evaluación histeroscópico para la detección de cáncer endometrial.

Palaras clave: hemorragia uterina; histeroscopia; neoplasias endometriales; posmenopausia.

INTRODUCTION

Endometrial carcinoma is the primary cause of gynecological malignancy in the United States (1). According to the International Agency for Research on Cancer (IARC), 336,067 new cases of endometrial cancer were diagnosed in the world in 2018, in women over 45 years of age, representing an incidence rate of 29.8 for every 100,000 of these women. For that same year, close to 86,490 deaths attributed to this disease were recorded, for a mortality rate of 7.4 for every 100,000 women. Endometrial cancer is the fifth cause of death in this population after breast, colon, lung and cervical cancer. In Colombia, according to IARC, 1,448 new cases were reported in 2018, with an incidence of 18.5 for every 100,000 women over 45 years of age, with mortality of 4.4 for every 100,000 (2). According to these data, this disease condition is the ninth cause of cancer-related morbidity and the fourteenth cause of cancer-related deaths in our country (2).

Diagnosis is based on the presence of abnormal uterine bleeding, found in 90% of postmenopausal women (3-5), which further work-up in these patients (6). The American College of Obstetricians and Gynecologists (ACOG) recommends the use of transvaginal ultrasound as the initial diagnostic test (7); the cut-off point with the use of this technology in the diagnosis of endometrial cancer has been described as endometrial thickness of 5 mm or more, with 93.5% sensitivity and 74% specificity (8).

In terms of screening for early diagnosis, transvaginal ultrasound has been used in asymptomatic women (incidental finding); Da Cunha et al. report that endometrial thickness of 11 mm or more has been associated with a 6.7% risk of endometrial cancer (9). Therefore, it has been suggested that measurements of 10 mm or more in postmenopausal women with no bleeding, should prompt a detailed analysis of the clinical setting (10) and of the risk factors described above in order to determine the relevance of additional studies such as hysteroscopy or endometrial biopsy (7). Direct examination of the endometrial cavity using hysteroscopy has been described as more useful than biopsy alone for making the diagnosis of endometrial cancer (11,12). On the other hand, the use of the Hysteroscopic

Cancer Scoring System (HYCA) has been proposed as a hysteroscopic system for assessment and classification for women with postmenopausal bleeding for the diagnosis of endometrial cancer. This system is designed to assess three domains: a) the contour of the endometrial surface for the presence of irregularity or papillary projections; b) evidence of endometrial necrosis to determine the presence of superficial necrosis, cotton-candy pattern or white hyperintense spots; c) vascular pattern, to determine the presence of irregular branching and uneven distribution. One point is assigned for every characteristic identified, for a maximum score of 7. With a cut-off of 3 or more, the system has a sensitivity is 88.5%, specificity of 92.1%, positive likelihood ratio (LR) of 11.13, negative likelihood ratio of 0.12 and an area under the curve (AUC) of 0.97 (95% CI: 0.95-0.99), with a prevalence of 40% (13). The use of this score could contribute to the standardization of hysteroscopic findings, allowing for early diagnosis of the condition and more timely treatment (13).

Survival in patients diagnosed and taken to surgery in the early stages of the disease is close to 95%, as compared to late stages (stage IV), where 5-year survival ranges between 16 and 45% and these patients no longer being eligible for this type of management (14,15). Consequently, the use of tools that can help with early detection is important.

Considering that accuracy may vary depending on the prevalence of the condition in different populations (16) and on the cutoff point used (17), and considering also that the operational performance of this scale has not been evaluated at a local level, the objective of this study was to approach the evaluation of the operational characteristics of the HYCA system for endometrial cancer in women with postmenopausal thickening (≥ 5 mm), comparing the results against the targeted histopathology study of the endometrial specimen as a gold standard.

MATERIALS AND METHODS

Design and population. Diagnostic accuracy study assembled within a cross-sectional study. Women with postmenopausal bleeding and evidence of endometrial thickening (≥ 5 mm) who underwent hysteroscopy with targeted biopsy were included. Perimenopausal women with incomplete clinical record data (more than 10% of undocumented variables) or who did not attend scheduled postoperative follow-up were excluded. Patients were referred between January 01, 2018, and January 31, 2019, for gynecological endoscopy at San José University Hospital and Nuestra Señora de los Remedios Clinic, referral institutions located in the cities of Popayán and Cali, respectively, in southwestern Colombia. Both institutions serve populations covered by the contributive health system and the State-subsidized social security system. Consecutive convenience sampling was used. Sample size was not calculated.

Procedure. The list of patients who underwent hysteroscopy in the participating institutions during the study period was reviewed in order to identify the study population. Two researchers evaluated compliance with the inclusion and exclusion criteria of the candidates. Variables of interest for the women who met the inclusion criteria were extracted by one of the researchers, using a form designed specifically for that purpose. A second researcher verified the quality of the information.

Diagnostic hysteroscopy was performed using a Storz 5-mm rigid hysteroscope under office anesthesia with no cervical clamping, and a Karl Storz Full HD 4 K technology camera following distension of the endometrial cavity with normal saline. The exam was performed by two gynecologist with specialized training in endoscopic surgery and hysteroscopy. The exam began with the visualization of the cervix, the endocervical canal and the endometrial cavity, including anterior, posterior, lateral walls, uterine fundus, ostia and endometrial

characteristics. Hysteroscopic findings were documented and saved as high-quality photographic images for later analysis using the HYCA hysteroscopic scale: characteristics of the lesion in the endometrial surface (irregular surface, papillary projections); evidence of endometrial necrosis (superficial necrosis, cotton-candy pattern, hyperintense white spots); and vascular pattern (irregular branching and uneven distribution) (Figure 1a,b,c,d,e), according to the rating method described above, with scores ranging between 1 and 7. After the endometrial cavity was examined, fractionated sampling was used to obtain targeted endometrial specimens of suspect lesions in the different aspects of the uterus by means of a Novak curette. Microscopic assessment of the specimens was performed by two pathologists who had no knowledge of the hysteroscopic findings, working in the pathology units of the two participating institutions, standardized for reading the specimens. The classification proposed by the World Health Organization (WHO) and the International Society of Gynecological Pathologists was applied to the histopathology results (18).

Measured variables. Age, origin, health system affiliation, comorbidities (diabetes mellitus, hypothyroidism, obesity, breast cancer), use of tamoxifen or any other selective estrogen receptor modulator, hormonal replacement therapy, hysteroscopic findings with the HYCA score, and endometrial tissue histopathology.

Statistical analysis. Descriptive statistics were applied. Continuos variables were summarized according to normality distribution and proportions were calculated for categorical variables. The performance of the test was then analyzed, using a hysteroscopic score of ≥ 3 as the cut-off point; sensitivity, specificity, predictive values, positive and negative likelihood ratios and area under the curve, with their 95% confidence intervals, were evaluated. The STATA software package version 14 was used for the statistical analysis.

Ethical considerations. This study was approved by the Medical Ethics Committee of the San Jose University Hospital in Popayan as stated in Minutes 004 of 2019, and met the requirements for human medical research set forth in the Declaration of Helsinki (19) and in Resolution 8430 of 1993 that establishes the scientific, technical and administrative standards for health research (20). Confidentiality of the information was ensured.

RESULTS

A total of 400 operative hysteroscopies with targeted endometrial biopsies were performed during the study period. Clinical records were reviewed and, after applying the inclusion and exclusion criteria, 250 corresponding to non-postmenopausal women and 60 corresponding to women with no endometrial bleeding were excluded, leaving 90 candidates. Of these, 45 patients were excluded: 20 (22%) because no endometrial biopsy result was available, and 25 (28%) because of more than 10% incomplete data. In the end, 45 (50%) patients were included (Figure 2).

Mean age of the patients was 62 years (standard deviation [SD] $\pm$ 9.34 years). More than half of the population came from the rural area and was affiliated to the subsidized health system. The most frequent comorbidities in the study group were arterial hypertension and obesity (Table 1).

Benign lesions such as endometrial polyps, followed by endometrial atrophy and leiomyomas were the hysteroscopic findings in more than 80% of the patients. Polyps and endometrial atrophy were the main findings on histopathology. Hyperplasia without atypia was found in 6.7% of the population. The prevalence of endometrial cancer was 9.0% (Table 2).

In the final analysis, sensitivity was 75% (95% CI: 30.1-95.4), specificity 95.1% (95% CI: 83.9-98.7), positive likelihood ratio 15.38, negative likelihood ratio 0.26 (Table 3), and AUC 0.85. One of the patients classified as high risk did not

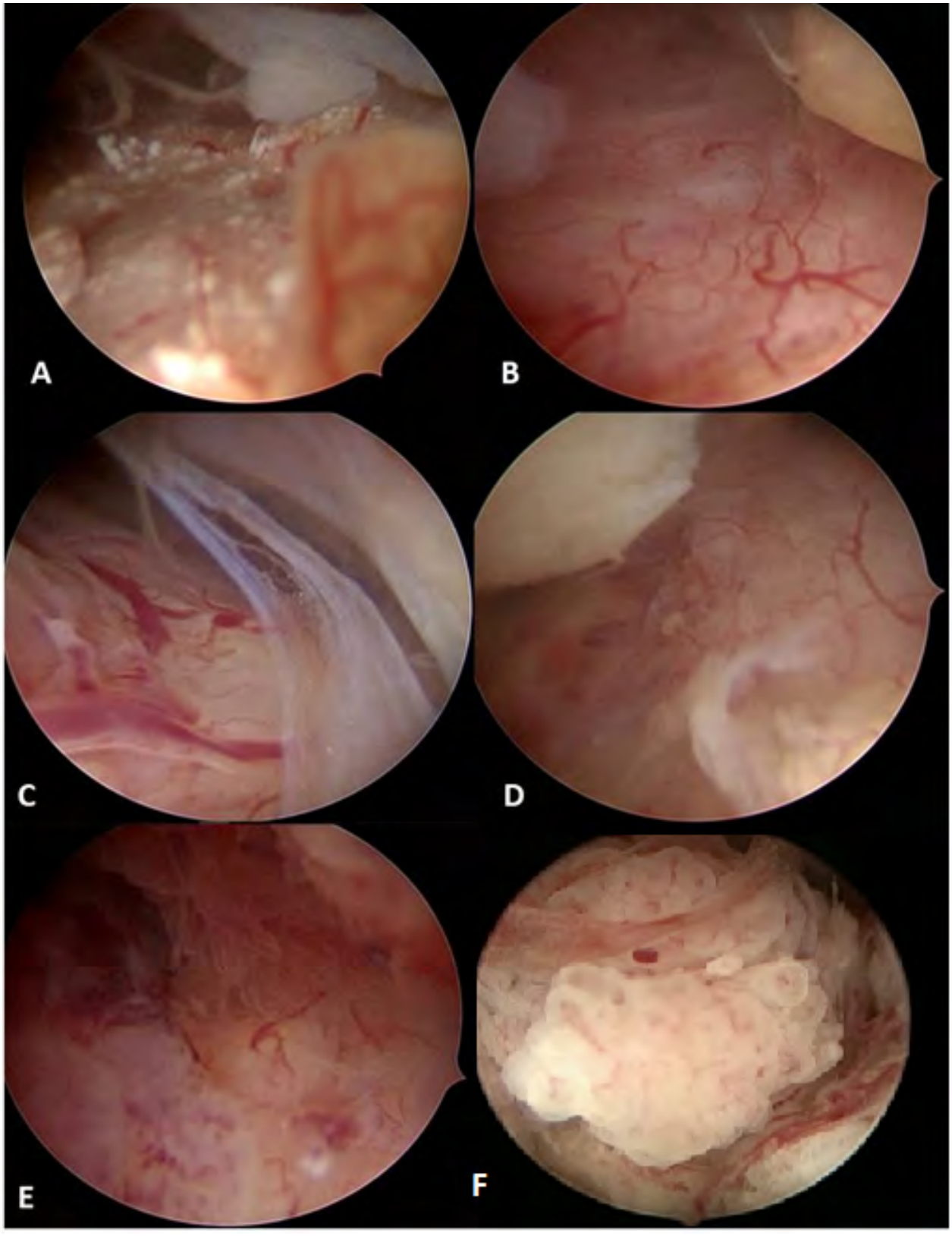

Figure 1. A. Hyperintense calcifications. B. Abnormal vascular pattern. C. Areas of necrosis, cotton-candy pattern. D. Irregular endometrial surface and areas of cotton-candy appearance. E. Irregular endometrial surface, areas of papillary projections, areas of necrosis and mixed vascular pattern. F. Endometrial papillary projections.

have endometrial cancer but was shown to have endometrial hyperplasia without atypia on biopsy.

DISCUSSION

A standardized hysteroscopic scale was applied for the diagnosis of endometrial cancer, showing the following operational performance: 75% sensitivity, 95% specificity, 60% positive predictive value, 97.5% negative predictive value, 15.38 positive likelihood ratio, 0.26 negative likelihood ratio, and AUC of 0.85.

Our results are similar to those described for the scale by Gkrozou et al. In a meta-analysis published in 2015 of 17 studies assessing sensitivity and specificity of hysteroscopy for the diagnosis of endometrial cancer involving 9,460 pre or postmenopausal women with abnormal uterine bleeding who underwent hysteroscopy, they found a sensitivity of 82.6% (95% CI: 66.9-91.8) and a specificity of 99.7% (95% CI: 98.1-99.9) (21). The results reported by Dueholm et al. are also similar, with a sensitivity of 88.5%, specificity of 92.1%, and a 40% prevalence of endometrial cancer (13).

For hysteroscopy in endometrial cancer, Lasmar et al., in a population of 4,054 patients, found a sensitivity of 80.0% (95% CI: 71.1-87.2), while specificity was 99.5% (95% CI: 99.2-99.7) (22), similar to our study. Clark et al., in a systematic quantitative review, showed that hysteroscopic findings suggestive of malignancy (LR 60.9) increased

Figure 2.
Patient selection flow diagram

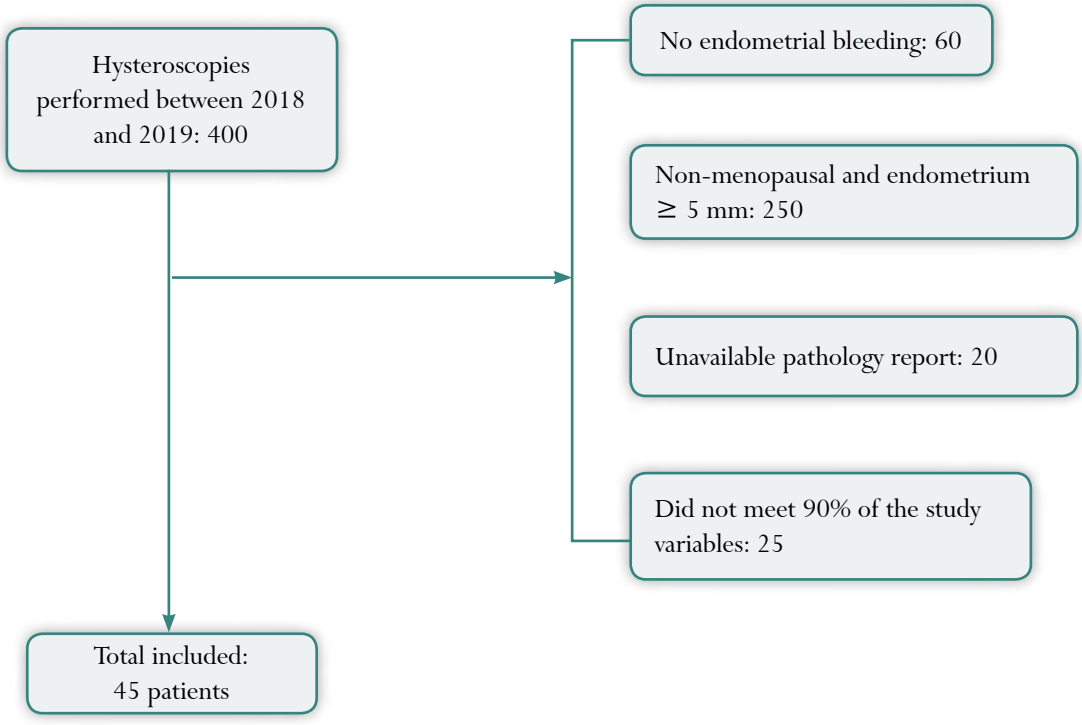

Table 1.
General characteristics of the patients with postmenopausal bleeding in two high complexity hospitals in Popayan and Cali, Colombia, 2018

Variable	N=45	Percentage
Age (Mean)	62.06 years (SD ± 9.34)	
Health system affiliation		
Contributive	10	22.2
Subsidized	35	77.8
Origin		
Rural	29	64.4
Urban	16	35.6
Comorbidities		
Arterial hypertension	17	37.8
Obesity (BMI ≥ 30)	14	31.1
Diabetes Mellitus	5	11.1
Hypothyroidism	3	6.7
Breast cancer managed with tamoxifen	2	4.4
Hormonal replacement therapy	0	0

BMI: Body Mass Index
Source: study data.

the probability of endometrial cancer to 71.8% from a pre-test probability of 3.9% (14), which suggests good usefulness of the test.

The strengths of this study are that the procedure was carried out by expert professionals who were familiar with the use of the standardized hysteroscopic scale. Moreover, the test was performed before the histopathological study, avoiding the probability of subjective findings that could alter the interpretation of the test or lead to overestimation of the results. Experience is one of the pillars on which to build competency with visual diagnosis. It is important to highlight that the expert pathologists were blinded to the hysteroscopic findings at the time of analyzing the histopathology specimens.

Small sample size is a limitation for the analysis of the test, as reflected in the wide confidence intervals obtained. Inter-observer agreement could not be analyzed and, moreover, data were lost in close to 50% of the candidates for inclusion, which could have affected disease prevalence estimation and the sensitivity of the system.

CONCLUSION

In this first approach to the accuracy of the standardized hysteroscopic system for endometrial assessment, sensitivity and specificity were respectively found to be acceptable and adequate for screening of patients with postmenopausal bleeding and endometrial thickening (≥ 5 mm). Further studies with a larger sample size are required to arrive at a more accurate estimation of the operational characteristics of this hysteroscopic assessment system in endometrial cancer detection.

Table 2.
Hysteroscopic and histopathological findings in patients with postmenopausal bleeding who underwent hysteroscopy in two hospitals in Popayan and Cali, Colombia, 2018

Lesion	N (%)
Hysteroscopic finding	
Endometrial polyp	21 (46.7)
Endometrial atrophy	12 (26.7)
Lesion suggestive of endometrial cancer(HYCA ≥ 3)	5 (11.1)
Submucosal myoma	3 (6.7)
Adenomyosis	3 (6.7)
Desquamative endometrium	1 (2.2)
Total	45 (100)
Endometrial biopsy report	
Endometrial polyp	19 (42.2)
Endometrial atrophy	17 (37.8)
Endometrial adenocarcinoma	4 (8.8)
Hyperplasia without atypia	3 (6.7)
Myoma	1 (2.2)
Unaltered endometrium	1 (2.2)
Total	**45 (100)**

Source: Study data.

Table 3.
Performance of the HYCA scale in postmenopausal women with uterine bleeding and endometrial thickening(≥ 5 mm) in two hospitals in Popayan and Cali, Colombia, 2018

	Endometrial cancer		
	Biopsy (+)	Biopsy (-)	Total
HYCA Scale (+)	3	2	5
HYCA Scale (-)	1	39	40
Total	4	41	45
		95% confidence interval	
Sensitivity	75 %	30.1 %	95.4 %
Specificity	95.1 %	83.9 %	98.7 %
PPV	60 %	23.1 %	88.2 %
NPV	97.5 %	87.1 %	99.6 %

PPV: Positive predictive value; NPV: negative predictive value; LR: Likelihood ratio
Source: Study data.

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AUTHOR'S CONTRIBUTIONS

Cesar Augusto Rendon-Becerra: original idea, theoretical basis and application of the tool.

Roberth Alirio Ortiz-Martinez: methodological basis and data analysis.

Alex Gómez-Bravo: theoretical basis, methodological basis and data analysis.

Andres Felipe Erazo-Narvaez: theoretical basis, methodological basis and data analysis.

Conflic of interest: none declared