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PREDICTION OF ENDOMETRIAL MALIGNANCY IN POSTMENOPAUSAL WOMEN WITH THICKED ENDOMETRIUM USING CLINICAL SIGN-BASED SCORING SYSTEM

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ABSTRACT

Introduction: In the Republic of North Macedonia, endometrial cancer is a significant health concern, being the second most common malignant neoplasm among women. The aim of this study is to enhance early diagnosis by developing a clinically based scoring system for predicting endometrial malignancy in postmenopausal women with a thickened endometrium.

Materials and Methods: In this cross-sectional study, for endometrial sampling were included 164 postmenopausal patients admitted to the surgery department at the University Clinic of Obstetrics and Gynaecology, Skopje. They were divided into two main groups based on their clinical presentation and further subdivided according to histopathological results. Comprehensive medical data were collected and histopathological analyses were performed. Univariate and multivariate logistic regression were utilized to determine the predictive values of clinical signs and the scoring system.

Results: Significant associations were found between endometrial malignancy and various factors including hypertension, diabetes, BMI, waist/hip ratio, and weak or profuse vaginal bleeding. Among these, the waist/hip circumference ratio showed the greatest influence on endometrial malignancy (Wald 37.76, $p < 0.001$), and BMI had the weakest influence (Wald = 0.97, $p > 0.05$). The clinical scoring system exhibited a sensitivity of 77.80%, specificity of 90.90%, and overall model accuracy of 86.60%.

Conclusion: The study demonstrated that almost all clinical parameters were found to be significant predictive factors. Thus, their combination could form a cost-effective, straightforward, and user-friendly clinical scoring system that could be used to identify a high risk of endometrial malignancy in women with a thickened endometrium at their first outpatient visit. This model does not require advanced diagnostic equipment or extensive clinical experience. The study found that the best individual predictive clinical sign was the waist/hip circumference ratio.

Key words: endometrial malignancy, scoring system, postmenopausal, clinical sign, Top of Form

INTRODUCTION

Endometrial cancer (EC) is the most common malignancy of the female genital tract in the developed world (1, 2). It is the 4th most common malignancy following breast, lung, and colorectal cancer with an incidence of 21.8/100,000 women (3). According to GLOBOCAN, in 2020, endometrial malignancy (EM) was diagnosed among 417 367 women, and 90 370 women have died because of EM (3). In the Republic of North Macedonia, endometrial cancer ranks as the second most common

malignant neoplasm in women (following breast cancer). In 2020, there were 360 diagnosed cases, and 80 died patient corresponding to an age-standardized incidence rate of 22.3 per 100,000 women (3).

In recent years, the incidence of endometrial cancer has been steadily increasing, along with an increased prevalence of risk factors obesity and lifestyle-related problems such as increasing incidences of nulliparity and infertility, prolonged life expectancy of women, and better diagnostic methods which allow the doctors

to diagnose the malignancy (4,5,6). Studies have clearly identified nulliparity, obesity, increasing age, diabetes, hypertension, late-onset menopause, unopposed estrogen (hormone replacement therapy, HRT), tamoxifen use and specific medical comorbidities such as polycystic ovary syndrome and hereditary non-polyposis colon cancer (Lynch syndrome) as risk factors for endometrial cancer (7-9).

Abnormal uterine bleeding is the presenting symptom in over 90-95% of women diagnosed with endometrial malignancy (10). However, only in 5-12% of the patients with postmenopausal uterine bleeding, endometrial malignancy will be diagnosed, depending on the presence of the risk factors for this malignancy in the examined population (11). Most patients with abnormal uterine bleeding and thickened endometrium will have some benign lesions of the endometrium like endometrial atrophy, polyps, or simple hyperplasia (Ref.). Therefore, to rule out malignancy, appropriate evaluation of the patients with these symptoms is obligatory.

According to ACOG Committee Opinion No 440 at 2009 year initial diagnostic procedure for clinical evaluation of women presenting with abnormal uterine bleeding is transvaginal ultrasonography or endometrial biopsy (12,13). In the Republic of N Macedonia, patients with abnormal uterine bleeding or thickened endometrium usually undergo dilatation and curettage (D&C) with or without hysteroscopy, with consecutive histopathological evaluation of the endometrial sample.

Many authors use a combination of noninvasive procedures to improve the diagnosis of endometrial cancer in patients with endometrial lesions. Different scoring systems are published in the literature, which are a combination of many clinical, sonographic, laboratory, and data from history and Doppler examination (13-23). Inspired by the work of these authors, we have developed a scoring system based on clinical signs.

OBJECTIVE

The aim of this study was to evaluate prediction of endometrial malignancy in postmenopausal women with thickened endometrium using clinical based scoring system.

MATERIAL AND METHODS

This cross sectional study involved 164 postmenopausal

patients admitted to the University Clinic of Obstetrics and Gynecology, Skopje, North Macedonia, from December 1, 2015, to July 31, 2017. Postmenopause was defined as: the absence of menstrual periods for at least 12 months prior to sampling. Patients were admitted to the surgical department of the clinic for endometrial sampling. The patients were divided into two groups: Group A - postmenopausal women with uterine bleeding and an endometrial thickness of more than 4mm, and Group B - postmenopausal women with sonographic signs of an endometrial lesion (those with an endometrial thickness exceeding 4mm). Based on the histopathological results, these groups were further divided into four subgroups: A1 and B1 - patients with endometrial malignancies, and A2 and B2 - patients with benign endometrial lesions.

The inclusion criterion was a postmenopausal patient with a thickened endometrium exceeding 4mm. Exclusion criteria included patients with postmenopausal bleeding who were on hormone replacement therapy and patients with vaginal bleeding due to vaginal atrophy or other systemic diseases.

All patients underwent a transvaginal examination to classify them into the appropriate group, performed in the lithotomy position with an empty bladder. Transvaginal ultrasonography was made by the same gynecologist. Sonographically, the endometrium is one of the most dynamic structures in the body, but in postmenopausal women, it should be thin, not more than 4mm. Endometrium was measured and if a thickened endometrium (more than 4mm) was detected, further endometrial evaluation for sampling was recommended to the patient. The procedure was thoroughly explained to the patient, including all the benefits and potential risk factors for complications.

After signing the consent, physicians collected general and clinical information about patient risk factors for endometrial cancer. The patients were asked about their comorbidities such as diabetes mellitus and hypertension. After that the physicians conducted a clinical examination to measure the Body Mass index (BMI) and waist-to-hip circumference ratio to examine whether the patient is obese. In the end, vaginal examination was performed to detect any vaginal bleeding. If the vaginal bleeding was detected, the patient was asked about the amount of the bleeding, whether is weak or profuse. The data for different clinical signs was detected at the specially designed scoring system based on clinical signs. Table 1

Scoring system based on clinical signs		
Hypertension	yes	0
	no	1
Diabetes mellitus	yes	0
	no	1
Body mass index (BMI)	<30kg/m ²	0
	> 30kg/m ²	1
waist-to-hip circumference	<0,85	0
	>0,85	1
Vaginal bleeding	no	0
	weak	1
	profuse	2

Table 1. Scoring system based on clinical signs

All 164 patients who met the inclusion criteria underwent dilatation and curettage or hysteroscopy for endometrial sampling. The procedure was done in the operating room under short-term intravenous anesthesia, by the same doctor. The material obtained from the endometrial biopsy was sent to the Institute of Pathology at the Faculty of Medicine for histopathological analysis where made by a different pathologist.

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Statistical analysis

The statistical analysis was conducted using STATISTICA 7.1 and SPSS 17.0 for Windows. We used univariate regression analysis to determine potential relationships between endometrial malignancy and clinical variables (diabetes, hypertension, BMI, waist/hip circumference ratio, and vaginal bleeding). A p-value of less than 0.05 in the likelihood ratio test was considered statistically significant. The predictive values of the scoring system were evaluated using multivariate logistic regression.

RESULTS

Mean age of the patients was 60, 05±9, 09; =95%CI: 58, 80-61, 30. The youngest patient was 40 years and the oldest was 85 years old.

Histopathological analysis at the examined groups (A and B) showed positive findings at 47 patients (28, 66%) with endometrial cancer and atypical endometrial hyperplasia at 7 (4, 27%). Other 110 patients had benign pathology as is shown in table No 2.

Table 2. Histopathological findings at examined groups A+B

Adenocarcinoma serosum endometrii	2	33	1,22	20,12
Endometrial endometrioid adenocarcinoma with squamous differentiation	4	37	2,44	22,56
Clear cell carcinoma endometrii	2	39	1,22	23,78
Malignant mixed Mullerian tumor (heterogenous type) of endometrii	2	41	1,22	25,00
Atypical endometrial hyperplasia or atypical endometrial polyp	7	48	4,27	29,27
Synchronized malignancy of endometrial and other female organs	2	50	1,22	30,49
Adenocarcinoma endometrioides endometrii + Adenocarcinoma mucinosum endometrii	4	54	2,44	32,93
Polypus endometrii	39	93	23,78	56,71
Endometrii atrophicans	33	126	20,12	76,83
Hyperplasio simplex (glandularis) endometrii	4	130	2,44	79,27
Hyperplasio complexa endometrii	2	132	1,22	80,49
Endometrii in under prolong estrogenic influence	23	155	14,02	94,51
Polypus glandularis cervicis uteri + Hyperplasio simplex Endometrii	4	159	2,44	96,95
Polypus endometrii + Endometrii atrophicans	5	164	3,05	100,00
Missing	0	164	0,00	100,00

Results about the predictive value of hypertension, diabetes, BMI, circumferences waist/hip ratio, and weak or profuse vaginal bleeding about endometrial malignancy in postmenopausal women are shown in table 3. The results of these clinical signs have shown that there is a significant association with endometrial malignancy Chi-square =114,32 and p<0,001 (p=0,000).

When determining the significance of each component, it was found that waist /hip circumference ratio has the greatest influence (Wald=37,76 / p<0,001) (p=0,000), profuse vaginal bleeding ex utero (Wald=12,10 / p<0,01) (p=0,001), weak vaginal bleeding (Wald=9,68 / p<0,01) (p=0,002), diabetes (Wald=4,95 / p<0,05) (p=0,03), hypertension (Wald=1,49 / p>0,05) (p=0,22) and the weakest influence has BMI (Wald=0,97 / p>0,05) (p=0,32).

The probability of endometrial malignancy was 78,60 times (Exp(B)=78,60) higher if the patients had waist /hip circumferences (H) > 0,85, compared to the patients who had waist /hip circumferences <0,85 and is statistically significant (95%CI:19,54-316,18) (p<0,001). This clinical sign

is the best predicting factor from all clinical signs. On the other hand probability of endometrial malignancy was 0,55 (Exp(B)=0,55) times lower if the patients had BMI (I) >30 kg/m², compared with the patients who had BMI (I) <30 kg/m², but this association was not statistically significant (95%CI:0,17-1,81)/p>0,05.

Table 3 Predictive value of clinical signs at prediction of endometrial malignancy in women

		b	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
Step 1 ^a	Hypertension(I)	,82	,67	1,40	1	,23	2,27	,61	8,58
	Diabetes mellitus(I)	1,44	,85	4,95	1	,03	4,24	1,39	15,35
	BMI(I)	-,60	,61	,90	1	,33	,55	,37	1,81
	Waist/hip circumferences ratio(I)	4,36	,71	37,76	1	,000	76,60	19,54	516,18
	Weak vaginal bleeding (I)	1,92	,62	9,68	1	,002	6,79	2,65	22,70
	Profuse vaginal bleeding (I)	3,45	,89	12,10	1	,001	31,58	4,51	221,03
	(Constant)	-4,99	,87	32,91	1	,000	,00		

a. Variables entered on step 1: hypertension, diabetes, BMI, circumferences waist/hip ratio and weak or profuse vaginal bleeding.

The sensitivity of the clinical sign scoring system is 77, 80%, the specificity is 90, 90%, and the global accuracy of the model is 86, 60%. The value of the ROC curves for this model is shown in Figure 1. The ROC zone (below the line) is 0.942.

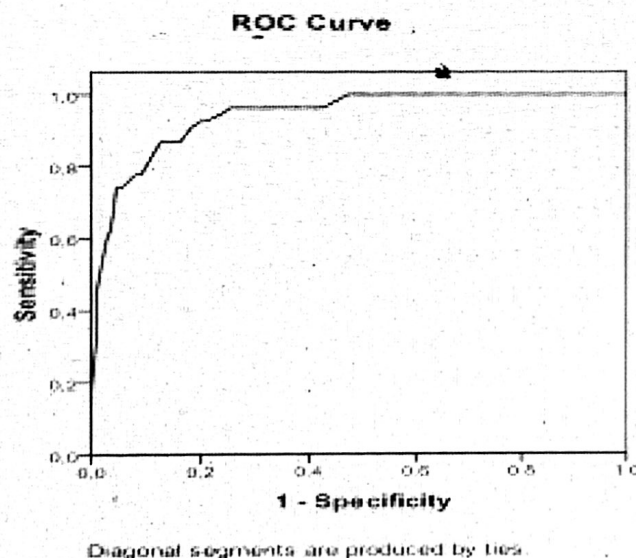


Figure 1 ROC curve of clinical signs based model

DISCUSSION

The main objective of the doctor, when having a patient with postmenopausal thickened endometrium is to exclude the genital malignancy. The goal of our study was to examine the predictive value of clinical signs based scoring system. This study describes a simple

and rapid method to identify a high risk of endometrial malignancy in women with thickened endometrium using different clinical signs at a first outpatient visit. For women with ET ≥ 4 mm, assessment of the presence of diabetes and hypertension, calculation of BMI and waist/hip circumferences ratio, and vaginal examination to evaluate the presence of weak or profuse vaginal bleeding could identify 94,2% of endometrial malignancy and correctly classify 86,6% of these women as benign or presence of malignant changes. Modern diagnostic equipment or extensive clinical experience is not required for this model. In the review paper of Van Hanegem, it was pointed out that the most ideal scoring system in the prediction of endometrial malignancy would be a scoring system composed of clinical parameters. (25)

Study results show that diabetes and hypertension proved to be significant individual risk factors in the prediction of endometrial malignancy. Patients with hypertension were 3, 14 times more likely to develop EM, and patients with diabetes were 2, 82 times more likely to have EM. Similar results have been published by Freiberg, with a relative risk of 3, 15 for the presence of EM in diabetic type I patients, and RR 2,22 for diabetic type II patients. (26) A recent review paper performed metanalysis of the available papers regarding hypertension as a risk factor for EM and noted that patients with hypertension were 1,61 times more likely to have EM than those without (27). Diabetes has been proved as a significant single parameter in the studies of Burbos, Opmeer, Madcour, and Dueholm, and hypertension in the studies of Burbos, Giannella and Opmeer (13,16,20,21,28). In the researches of Bachman and Opolskiene both parameters were shown to be insignificant. (29,30)

Recently many authors emphasize the importance of the type of obesity, announcing that the distribution of adipose tissue in the upper part of the body, which is determined by the waist/hip circumferences ratio, is a more significant risk factor than increased BMI. (31, 32). Kitson in his study include waist/hip circumferences ratio, and if greater than 0.80 classified the patients in a, even if they have a normal BMI. (31) The same has been confirmed after the meta analysis in Aune's review paper. (32) Results of our study proved waist/hip circumferences ratio as the best predicting factor in the diagnosis of EM. On the other hand, results have shown that BMI was not a statistically significant predicting factor. At the published scoring system, BMI is most often used as an indicator of obesity. Burbos included BMI in his scoring systems

DEFAM and DFAB and univariate analyses have shown BMI as a significant parameter. (13, 17) In the studies of Gianella and Opolskiene, univariate analysis showed that BMI had no significant influence in determining the risk for the presence of EM, similar to our results. (20,30)

Vaginal bleeding is a significant single clinical parameter in the prediction of EM according to our results. The amount of bleeding is also important in determining the risk of the patient. The probability of endometrial malignancy was 31, 58 times higher if the patient had profuse vaginal bleeding, compared to patients who do not have vaginal bleeding. Patients with weak vaginal bleeding had 6,79 times higher probability EM compared to patients who do not have bleeding. Bleeding was shown to be one of the best single parameters in Angioli's univariate analysis and was included in the REM scoring system. (22) Furthermore, there are some authors who include the frequency of bleeding in their scoring systems.(13)

Multivariate analysis of this scoring system based on clinical signs had shown a sensitivity of 77,80%, a specificity of 90,90%, and global accuracy of 86,60%. The ROC zone (below the line) for this model is 0,92. The use of this model could make an individual profile of the patient in a simple way and if belongs to a risk group, the patient should be immediately transferred to a better center with more sophisticated equipment.

CONCLUSION

Almost all clinical parameters have shown that are significant predictive factors. Their combination could obtain a cheap, simple, and easy-to-use clinical scoring system. It could be used to identify a high risk of endometrial malignancy in women with thickened endometrium at first outpatient visit. There is no need for modern diagnostic equipment, nor greater clinical experience of the doctor for this model. The results showed that the best predictive individual clinic sign is the waist /hip circumference ratio.

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