Assessment of Risk Scoring Model for Prediction of Endometrial Cancer Among Symptomatic Postmenopausal Women (A Prospective Cohort Study)

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By

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List of Abbreviations

Abbrev.	Full term
AGC	**:** Abnormal glandular cells
AGC-NOS	**:** Abnormal glandular cells not otherwise specified
BMI	**:** Body mass index
CIN	**:** Cervical intraepithelial neoplasia
DNA	**:** poly-merase epsilon (POLE),
EEC	: Endometrioid endometrial carcinoma
EPT	**:** Estrogen and progesterone therapy
ESGO	**:** European society of gynecological oncology
ESMO	**:** European society of medical oncology
ESTRO	**:** European society for Radiotherapy & Oncology
HE4	**:** Human epididymis protein 4
HGSOCs	**:** High-grade serous ovarian carcinomas
HIR-EC	**:** High intermediate risk endometrial carcinoma
HNPCC	**:** Hereditary nonpolyposis colorectal cancer
HRT	**:** Hormone replacement therapy
MELF	**:** Microcystic elongated and fragmented
MMRd	**:** Dysfunctional mismatch repair proteins
MSI	**:** Microsatellite instability
OS	**:** Overall survival
PI3K	**:** Phosphatidylinositol 3-kinase
PORTEC	**:** Post-Operative Radiation Therapy in Endometrial Cancer trial
RFS	**:** Recurrence-free survival

SCNAs **:** Somatic copy number alterations

SEER **:** Surveillance, Epidemiology, and End Results database

TAH : Total abdominal hysterectomy

TCGA **:** Cancer Genome Atlas

TP53 **:** Tumor protein P53

WHI : Women's Health Initiatives trial

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Abstract

Background: Endometrial carcinoma is the most common gynecological malignancy in the developed countries and the third common gynecological malignancy in Egypt after breast and ovarian cancers. **Aim of the Work:** to evaluate this risk scoring model on Egyptian patients and to study the effect of adding other patient characteristics (DM, BMI and relevant family history) on the sensitivity and specificity of RHEA scoring model. **Patients and Methods:** The current study was conducted in Ain Shams University Maternity Hospital in the period between September 2017 and December 2018. A total of 100 women with postmenopausal bleeding and endometrial thickness > 4mm were included in the study. **Results:** Histological examination revealed that benign pathology (n=65) (73%) was found to be: most common cause was endometrial hyperplasia without atypia (20.3%) followed by chronic endometritis (13.5%), then endometrial polyp (11.3%), cystic atrophy of endometrium (8.9%), proliferative endometrium (8.9%), endometrial hyperplasia with atypia (6.7%) and lastly mucous polyp (3.4%) while malignant histopathology(n=24)(27%) which is significantly higher than the international rates showed: Endometriod adenocarcinoma (n=19)(21.3%), papillary serous carcinoma (n=4)(4.5%) and undifferentiated carcinoma (n=1)(1.1%).

The current study showed that RHEA score performs in our study population with a comparable validity to that reported by its inventors with sensitivity 79.2% (57.8% - 92.9%) vs. 87.5% and specificity 84.6% (73.5% - 92.4%) vs. 80.1% respectively. In results of the current study it was found that the time since onset of menopause rather than age was associated with endometrial cancer with the optimum cut-off for post-menopausal duration was estimated to be 9 years achieving a sensitivity of 87.5% and a specificity of 60.0%, but it needs multivariate analysis on larger and more representative sample size to confirm this association, A statistically significant regression model was including only postmenopausal duration, recurrent bleeding and endometrial thickness. None of age, BMI, family history or hypertension proved a statistically significant predictive effect after adjustment for other predictive variables.

Conclusion: Taking in consideration the higher prevalence of endometrial carcinoma in the sample of the current study, the wide 95% confidence intervals for the different validity indices for the RHEA scores derived from this study, it seems that RHEA score performs in this study population with a comparable validity to that reported by its inventors.

Key words: Risk Scoring Model, endometrial cancer, postmenopausal women

Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract in developed countries while the incidence rates in developing countries and Jaban are four to five times lower than Western industrialized nations, with the lowest rates being in India and South Asia, and the fourth most common cancer in women after breast, lung, and colorectal cancer ***(Prazzini et al., 1991).***

According to the American Cancer Society (ACS) it's the most common gynecological malignancy in the United States, with 61,880 new cases expected to occur in 2019 and an estimated 12,160 women expected to die of the disease ***(American Cancer Society, 2019).***

In Egypt it's the third most common gynecological malignancy after breast and ovarian cancers ***(Ibrahim et al., 2014).***

There is no ideal method for outpatient sampling of the endometrium till now, and no blood test of sufficient sensitivity and specificity has been developed. So, mass screening of the population is not practical ***(Hacker and Friedlander, 2015).***

So all efforts are directed to early detection of endometrial carcinoma rather than screening, fortunately about 90%-95% of postmenopausal women with endometrial cancer

report vaginal bleeding experience ***(Goldstien et al., 2002)***, whereas about 10% of symptomatic postmenopausal women reveal intrauterine malignancy ***(Bignardi et al., 2009).***

So postmenopausal vaginal bleeding is a sign that shouldn't be underestimated. In this regard, a good clinical practice provides - as a first diagnostic step - a transvaginal ultrasound in order to discriminate a woman at high risk or low risk of malignancy ***(Giannella et al., 2014).***

Transvaginal ultrasound examination is an acceptable initial test as an alternative to endometrial sampling in postmenopausal women who cannot tolerate office biopsy and in women in whom evaluation for uterine pathology (eg, polyp, leiomyoma) or of the adnexa is indicated ***(Sladkevicius et al., 2017).***

Usually, an endometrial thickness of 4mm or less is a cutoff value for which a conservative management should be adopted. In the latter case, the probability of having endometrial cancer drops from 10% to 0.8% ***(Van Hanegem et al., 2011).***

Conversely, among symptomatic postmenopausal women with endometrial thickness more than 4 mm, there is an increased risk of cancer ***(Goldstien et al., 2009).***

In these cases further examinations are needed and usually an endometrial sampling or outpatient hysteroscopy should be performed, however approximately 80%-90% of these examinations will not reveal cancer in a population considered at risk of malignancy ***(Salman et al., 2013).***

This apparent "inappropriateness" is justified by the fact the main goal is not to miss any of women with malignancy as much as possible ***(Giannella et al., 2014).***

Since a malignancy is found in only one in ten women with postmenopausal bleeding, the aim of the first assessment was to rule out disease without over investigation ***(Gupta et al., 2002).***

Several studies including patient characteristics or sonographic features were performed in order to test their clinical usefulness, yet they have only reached the phase of internal validation ***(Van Hangem et al., 2012).***

For those studies endometrial thickness remains the most important feature to be evaluated, adding some patient characteristics to endometrial thickness has built a risk-scoring model involving recurrent vaginal bleeding, hypertension, endometrial thickness and age (RHEA risk model) ***(Giannella et al., 2014).***

Giannella et al. (2014) studied prospectively 624 postmenopausal women with vaginal bleeding and endometrial thickness more than 4 mm undergoing diagnostic hysteroscopy whereas patient characteristics and endometrial assessment of women with and without endometrial carcinoma were compared in half of the included patients then a risk scoring model including the best predictors of endometrial carcinoma was created and tested on the other half of the patients, and the best predictors for endometrial carcinoma were found to be: recurrent vaginal bleeding (defined as any bleeding that lasted seven or more days, or two or more separate episodes of vaginal bleeding over the last year) (odds ratio = 2.96), the presence of hypertension (odds ratio = 2.01), endometrial thickness more than 8 mm (odds ratio = 1.31) and age above 65 years (odds ratio = 1.11). These variables were used to create a risk scoring model (RHEA risk-model) for prediction of intrauterine malignancy with area under the curve of 0.878 (95% CI 0.842 to 0.908; p less than 0.0001), at the best cut-off value (score equal or more than 4), sensitivity and specificity were 87.5% and 80.5% respectively.

However at present these results are not generalizable and further studies of external validation are mandatory ***(Giannella et al., 2014)***.

This study is designed to evaluate this risk scoring model on Egyptian patients and to study the effect of adding other patient characteristics on the sensitivity and specificity of RHEA scoring model.