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Serum HE4 as a Preoperative Predictor of Myometrial Invasion and Risk Stratification in Endometrial Carcinoma: Comparison with histopathology

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Abstract

Background: Endometrial cancer is one of the common female genital tract cancers in developed countries. Human epididymis protein 4 (HE4) is known as whey acidic protein. Elevated levels of HE4 in the blood or tissue can be associated with several malignancies, making it a potential biomarker for cancer detection and monitoring.

Objective: This study was conducted to determine the predictive value of serum HE4 as a pre-operative biomarker for myometrial invasion and risk categorization in endometrial carcinoma, comparing its performance with histopathological assessment.

Methods: This was a cross-sectional analytical study conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from July 2022 to June 2023. In this study, we included 40 women with a diagnosed case of endometrial cancer who were admitted to the Department of Gynecological Oncology at our institution.

Results: The study revealed, the majority of patients were in the 55-64 years age group, with post-menopausal bleeding being the most common symptom (82.5%). The mean duration of symptoms was 6.0±3.79 months. A significant proportion of patients were obese (42.5%). In terms of contraceptive use, most respondents (85.5%) were not using any contraceptive method, while 12.5% used oral contraceptive pills. Family history of first-degree relatives with cancer was found in 5% of the study subjects. A predominant histopathological type of endometrial cancer was endometrioid adenocarcinoma, accounting for 85.0% of the cases, and approximately one-third of the study subjects (32.5%) were classified as stage IA. In terms of risk categorization, 60.0% were classified into the high-risk group, 22.5% into the intermediate-risk group, and 17.5% as low-risk individuals. Serum HE4 levels exhibited a significant association with histopathological grade ($p = 0.031$) and more extensive myometrial invasion (>50%) ($p < 0.001$). The mean HE4 level was significantly lower in the low-intermediate risk group than the high-risk groups (94.88±29.28 vs. 136.06±62.98 pmol/L, respectively; $p=0.02$), and a significant correlation between preoperative serum HE4 levels and clinical risk categories was observed ($rs= 0.385$, $p=0.014$). The diagnostic performance of HE4 for risk categorization yielded a sensitivity of 70.83%, specificity of 81.25%, PPV of 77.27%, and NPV of 61.11%. For myometrial invasion prediction, HE4 demonstrated a sensitivity of 69.23%, specificity of 64.29%, PPV of 78.26%, NPV of 52.94%, and an accuracy of 67.50%.

Conclusion: Serum HE4 levels display noteworthy sensitivity and specificity for both myometrial invasion and risk categorization in patients with endometrial cancer. This suggests that HE4 can be a valuable adjunct in predicting preoperative myometrial invasion and risk stratification in these patients.

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Keywords: Serum HE4 level, Myometrial invasion, Endometrial carcinoma

Introduction

Endometrial carcinoma (EC) arises from the inner lining of the uterus and represents the most common malignancy affecting this organ. [1] Globally, it ranks as the sixth most common cancer in women, with approximately 61,880 new cases and 12,160 deaths reported in the United States in 2019. [2] In the United Kingdom, an estimated 9,500 women are diagnosed each year. Fortunately, about 75% of cases are identified at an early, treatable stage, contributing to a relatively favorable 5-year survival rate of 84%.[3] In contrast, incidence rates in India are significantly lower, around 4.3 per 100,000 women. [4] Notably, a study in Bangladesh found that 26% of women with diabetes mellitus had endometrial cancer, highlighting a critical need for early detection and comprehensive preoperative assessment of myometrial invasion to guide surgical planning and improve patient outcomes [5,6]. Clinical examination alone is insufficient to accurately determine the extent of myometrial invasion or cervical canal involvement.[7] However, EC often presents with abnormal vaginal bleeding or discharge, facilitating early detection. Studies show that endometrial cancer is found in 4–8% of postmenopausal women presenting with bleeding. [8,9] Obesity is also a significant risk factor, with the risk increasing proportionally with body mass index (BMI). [10]

Endometrial tumors are classified across three dimensions: pathogenetic, histopathological, and molecular. Bokhman's 1983 classification introduced two pathogenetic subtypes—type I and type II. Type I is estrogen-dependent, associated with obesity and metabolic disturbances, and generally has a favorable prognosis due to its lower grade and responsiveness to progestins. In contrast, type II is typically estrogen-independent, high-grade, deeply invasive, and associated with a poorer prognosis. Histopathologically, endometrial carcinomas include subtypes such as endometrioid (most common), serous, clear cell, mucinous, neuroendocrine, undifferentiated/dedifferentiated, and carcinosarcoma. Of the newly diagnosed cases, approximately 85% or more are classified as endometrioid carcinoma, 10% as serous carcinoma, 23% as clear cell carcinoma, and less than 2% as carcinosarcoma, with the remaining cases classified as other histologic types [11,12]. Preoperative staging is essential for tailoring treatment strategies, particularly in distinguishing patients with deep myometrial invasion (FIGO stage IB) from those with less than 50% invasion (stage IA). This distinction can determine the need for pelvic lymphadenectomy, which requires a specialized surgical approach. Evidence of cervical stromal invasion (stage II) may necessitate a radical hysterectomy. Comprehensive surgical staging often involves total hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and lymph node assessment.[13] Risk stratification is largely based on histologic subtype, tumor grade, and depth of myometrial invasion.[14] Histology and grade are usually determined from preoperative endometrial biopsy, allowing for early risk categorization. This enables better surgical planning and may reduce unnecessary lymphadenectomy in low-risk patients.[15] Common diagnostic tools include transvaginal ultrasound (TVUS), endometrial biopsy, and occasionally outpatient hysteroscopy. While these methods effectively detect EC, they may lack specificity or be invasive and uncomfortable. [16]

Serum Cancer Antigen 125 (CA125) has traditionally been used in preoperative assessments; elevated levels are linked to advanced disease. However, its low sensitivity and specificity, especially in early-stage disease, where only 10–20% of stage I patients show elevated levels, limit its clinical utility. Human epididymis protein 4 (HE4), encoded by the WFDC2 gene on chromosome 20q12-13.1, is an acidic whey protein originally identified in the distal epididymis. [17] It is expressed in the epithelial tissues of the reproductive tract and is overexpressed in several cancers. Although its precise biological role remains unclear, HE4 has been implicated in promoting endometrial carcinoma's proliferation, invasion, and progression. [18,19] Currently approved for diagnosing and monitoring ovarian cancer, HE4 is found to be overexpressed in more than 90% of endometrial cancers, suggesting its potential as a promising biomarker for this disease [17]. Recent studies have shown that HE4 is elevated not only in ovarian cancer but also in endometrial cancer, particularly in the serous and endometrioid subtypes. [20] Furthermore, HE4 has demonstrated greater sensitivity than CA125 in detecting EC. [3, 21,22] Serum HE4 levels have been correlated with tumor size and depth of myometrial invasion, indicating its potential role in preoperatively identifying high-risk cases and guiding the need for complete surgical staging. [23]. Therefore, the present study was conducted to determine the predictive value of serum HE4 as a pre-operative biomarker for myometrial invasion and risk categorization in endometrial carcinoma, comparing its performance with histopathological assessment.

Methodology & Materials

This was a cross-sectional analytical study conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from July 2022 to June 2023. In this study, we included 40 women with a diagnosed case of endometrial cancer who were admitted to the Department of Gynecological Oncology at our institution.

These are the following criteria to be eligible for enrollment as our study participants:

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Inclusion Criteria

a) Women aged ≥ 45 years;
b) Women with histopathologically diagnosed endometrial carcinoma;
c) Women who were willing to participate.

Exclusion Criteria

a) Women with a history of smoking;
b) Women with known renal failure, ischemic heart disease, and chronic liver disease;
c) Women who will not go for surgical treatment;
d) Women with any other malignancies, like breast, HNPCC, dual malignancy;
e) Women receiving preoperative chemotherapy or radiotherapy for any other malignancy.

Study Procedure: All patients were informed about the study's nature, and written informed consent was obtained from all participants for the collection and analysis of their data for scientific purposes. Data regarding patients' age, parity, menstruation status, personal and familial history of breast and endometrial cancer, and the number of relatives (up to second-degree family members) with a history of cervical or uterine cancer were collected. All patients underwent a complete clinical examination. Five ml of blood for serum HE4 was obtained through peripheral venous puncture before surgery and either processed immediately or stored at -20°C until needed. Clotted blood tubes were centrifuged at 800g for 10 minutes, after which the serum was separated. The serum samples for estimating HE4 levels were then sent to Lalpath Laboratory in Dhaka using HE4 reagent kits. The extent of surgery was determined based on staging ultrasound examinations and knowledge of histotype and grading. All patients underwent Type A radical hysterectomy with bilateral salpingo-oophorectomy. Systematic pelvic and paraaortic lymphadenectomy was performed when indicated. Preoperative HE4 levels, TVUS results regarding the depth of myometrial invasion, and pathological data from biopsies (tumor type and grade) were recorded. Final pathological data, including stage, histotype, and grade, were assessed postoperatively according to the International Federation of Gynecology and Obstetrics 2009 staging system (FIGO) and the World Health Organization 2003 pathologic classification of female reproductive organs.

Grading system [24]:

- G1: 5% or less of a non-squamous or non-morular solid growth pattern.
- G2: 6% to 50% of a non-squamous or non-morular solid growth pattern.
- G3: More than 50% of a non-squamous or non-morular solid growth pattern.

Stage	Anatomic involvement
Stage I	Tumor confined to the uterine corpus
IA	No or <50% myometrial invasion
IB	≥50% myometrial invasion
Stage II	Cervical stromal involvement
Stage III	Local and/or regional tumor spread
IIIA	Tumor invasion into uterine serosa and/or adnexal involvement
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to lymph nodes
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive para-aortic lymph nodes
Stage IV	
IVA	Bladder and/or bowel involvement
IVB	Distant metastases, including abdominal disease and/or inguinal lymph node involvement

Figure 1: FIGO Stage-2009 Staging system for endometrial cancer

Risk group	ESMO guidelines
Low-risk	Stage IA (G1 and G2) with EC
Intermediate-risk	Stage IA G3 with EC
	Stage IB (G1 and G2) with EC
High-risk	Stage IB G3 with EC
	All stages with non-EC
	Stage II*

Figure 2: Risk Categorization

Data Collection and Analysis: Data was collected from the patients on variables of interest using the semi-structured questionnaire designed for interviews, observations, hematological investigations, and from the history sheet of patients. All data were recorded systematically in a pre-formatted data collection form. Quantitative data was expressed as mean and standard deviation, and qualitative data was expressed as frequency distribution and percentage. Serum HE4 level was categorized based on the cut-off value as normal and high (>140 pmol/L). An ANOVA was done to determine the difference in mean serum HE4 levels between the risk-category groups. Chi-square tests were done to observe the association between serum HE4 levels and histologic characteristics of endometrial cancer. A p-value <0.05 was considered significant. Statistical analysis was performed using SPSS 27 (Statistical Package for Social Sciences) for Windows version 10. This study was ethically approved by the Institutional Review Board (IRB) of the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Results

Table 1 shows that the majority of patients fell in the 55-64 years category (62.5%), followed by those aged 45-54 (25.0%), and those aged 65 and above (12.5%). The mean age of the patients was 57.33±7.57 years, with a range from 45 to 70 years. The vast majority of patients were married (92.5%),

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Table 1: Distribution of sociodemographic characteristics of the study population (n = 40)

Characteristics	Frequency (n)	Percentage (%)
Patient's Age (years)		
45–54	10	25
55–64	25	62.5
≥ 65	5	12.5
Mean ± SD (min–max)	**57.33 ± 7.57 (45–70)**	
Marital Status		
Married	37	92.5
Unmarried	1	2.5
Widow/Widower	2	5
Level of Education		
Illiterate	16	40
Primary	9	22.5
Secondary	9	22.5
Higher Secondary	5	12.5
Graduate	1	2.5
Monthly Income Status (in Taka)		
Lower Class (<7,378 Tk)	1	2.5
Lower Middle Class (7,379–28,819 Tk)	9	22.5
Upper Middle Class (28,811–89,280 Tk)	22	55
Upper Class (>89,281 Tk)	8	20

with a small percentage being unmarried (2.5%) or widowed/widower (5.0%). Regarding education level, the highest percentage of patients were illiterate (40.0%). The majority of patients belonged to the upper middle class (55.0%).

Table 2 illustrates that 35.0% of patients experienced menorrhagia, only 5.0% had dysmenorrhea, and 20.0% of patients had intermenstrual bleeding. The majority of patients (82.5%) experienced postmenopausal bleeding. In terms of parity, 15.0% were nulliparous, 65.5% had 1-2 children, and 17.5% were multiparous. The mean duration of the symptoms among the study subjects was 6.0±3.79 months.

Table 3 presents the distribution of patients based on their BMI (Body Mass Index) and risk factors. A significant portion of patients were categorized as obese (42.5%), followed by those with a normal BMI (35.0%), and overweight individuals (22.5%). The mean BMI among the patients was 26.21±4.96 kg/m^2. The majority of respondents were not using any contraceptive method (85.5%), while a small percentage used oral contraceptive pills (OCP) (12.5%). None of the patients had a history of hormone replacement therapy (HRT), and 5% of the respondents had a family history of cancer.

Table 4 presents the distribution of patients according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The majority of patients were

Table 2: Distribution of risk factors and obstetric characteristics of the study population (n = 40)

Parameters	Frequency (n)	Percentage (%)
Menorrhagia		
Yes	14	35
No	26	65
Dysmenorrhea		
Yes	2	5
No	38	95
Intermenstrual Bleeding		
Yes	8	20
No	32	80
Postmenopausal Bleeding		
Yes	33	82.5
No	7	17.5
Parity		
Nullipara	6	15
Para (1–2)	27	67.5
Multipara	7	17.5
Duration of symptoms (months)	6.0±3.79	

Table 3: Distribution of body mass index and risk factors of the study population (n = 40)

BMI (kg/m2)	Frequency *(n)*	Percentage *(%)*
Normal (18.5-24.9)	14	35
Overweight (25-29.9)	9	22.5
Obesity (>30)	17	42.5
Mean ± SD	26.21 ± 4.96	
Risk Factors		
Contraceptive use		
OCP	5	12.5
Implanon/Norplant	1	2.5
None	34	85.5
History of HRT		
Yes	0	0
No	40	100
Family history of cancer		
Yes	2	5
No	38	95

categorized as stage IA (32.5%), followed by stage IB (25.0%), stage II (22.5%), stage IIIA (5.0%), and stage IIIC1 (15.0%).

Table 5 shows that the majority of cases were classified as type 1: endometrioid adenocarcinoma (85.0%), while a smaller proportion were type 2: high-grade serous (15.0%). In terms of histopathological grade, grade 3 was the most

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common (42.5%), followed by grade 2 (30.0%) and grade 1 (27.5%). Regarding myometrial invasion, more than half of the cases had >50% invasion (65.0%). The majority of tumors were larger than 2 cm (72.5%), and the remaining were smaller (27.5%). Lymphovascular space invasion (LVSI) was present in 47.5%, and pelvic lymph nodes were involved in 20.0% of cases. Cervical stromal involvement was observed in 27.5% of the respondents.

Table 4: Distribution of FIGO staging of the study population (n = 40)

Parameters	Frequency *(n)*	Percentage *(%)*
IA	13	32.5
IB	10	25
Stage II	9	22.5
IIIA	2	5
IIIC1	6	15
Total	40	100

Table 5: Distribution of histopathological type, grade, invasion, size, LVSI, lymph node involvement, and cervical stromal involvement of the study population (n = 40)

Parameters	Frequency (n)	Percentage (%)
Histopathological Type		
Type 1: Endometrioid Adenocarcinoma	34	85
Type 2: High Grade Serous	6	15
Histopathological Grade		
Grade 1	11	27.5
Grade 2	12	30
Grade 3	17	42.5
Myometrial Invasion		
>50% (more than 1/2)	26	65
<50%	14	35
Tumor Size		
>2 cm	29	72.5
<2 cm	11	27.5
Lymphovascular Space Invasion (LVSI)		
Present	19	47.5
Absent	21	52.5
Pelvic Lymph Node Involvement		
Present	8	20
Absent	32	80
Cervical Stromal Involvement		
Involved	11	27.5
Not Involved	29	72.5

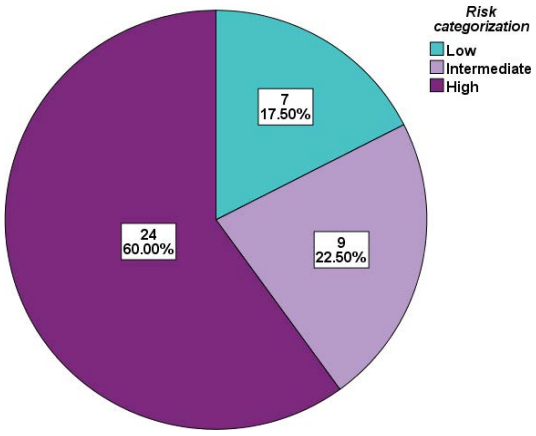

Figure 3: Distribution of the study population according to low, intermediate, and high risk (n = 40)

Figure 3 illustrates that 24(60.0%) respondents belonged to high-risk group, 9(22.5%) to intermediate group and 7(17.50%) in low-risk group.

Table 6 reveals the relationship between serum HE4 levels and key histopathological parameters in endometrial cancer. There was no significant difference in HE4 levels between Type 1 and Type 2 endometrial cancer types ($p = 0.603$). However, HE4 levels differed significantly based on histopathological grade ($p = 0.031$), with Grade 3 cancers having the highest HE4 levels (144.15±62.88 pmol/L). Myometrial invasion >50% was associated with elevated HE4 levels ($p < 0.001$), while tumor size (>2 cm vs. <2 cm) did not show a significant difference ($p = 0.335$). HE4 levels were not significantly affected by LVSI, pelvic lymph node involvement, or cervical stromal involvement ($p > 0.05$ for all).

Table 7 presents the distribution of serum HE4 levels in the risk groups based on clinical criteria. The mean HE4 level was significantly lower in the low-intermediate risk group (94.88±29.28 pmol/L) compared to the high-risk groups (136.06±62.98 pmol/L), with a significant p-value of 0.020.

The correlation between preoperative serum HE4 levels and clinical risk categories are shown in Figure 4, where a significant correlation was observed ($rs= 0.385$, $p=0.014$).

Table 8 presents data from the ROC curve constructed using serum HE4 levels. A cut-off value of 109.45 pmol/L gives 70.8% sensitivity and 81.3% specificity for predicting high risk of endometrial cancer.

Table 9 shows that a significant difference was observed in preoperative HE4 levels between high-risk and intermediate-low-risk groups for endometrial carcinoma. Patients with HE4 >109.45 pmol/L had 5.3 times higher odds of being in the high-risk group for endometrial carcinoma compared to those with HE4 ≤109.45 pmol/L (OR = 5.34; 95% CI = 1.35–21.14).

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Table 6: Association of HE4 with histopathological type, grade, invasion, size, LVSI, lymph node involvement, and cervical stromal involvement of the study population

Parameters	HE4 (Mean ± SD)	P value
Histopathological type		
Type 1: Endometrioid adenocarcinoma (n=34)	128.63 ± 54.00	0.603[b]
Type 2: High-grade serous (n=6)	116.55 ± 35.98	
Histopathological grade		
Grade 1 (n=11)	119.35 ± 32.99	0.031[b]
Grade 2 (n=12)	133.37 ± 45.77	
Grade 3 (n=17)	144.15 ± 62.88	
Myometrial invasion		
>50% (n=26)	144.81 ± 8.54	<0.001[b]
<50% (n=14)	97.94 ± 31.05	
Tumor size		
>2 cm (n=29)	119.03 ± 56.51	0.335[b]
<2 cm (n=11)	101.13 ± 35.04	
LVSI (Lymphovascular space invasion)		
Present (n=19)	115.15 ± 67.98	0.906[b]
Absent (n=21)	113.16 ± 32.42	
Pelvic lymph node involvement		
Present (n=8)	102.68 ± 37.26	0.492[b]
Absent (n=32)	116.98 ± 54.84	
Cervical stromal involvement		
Involved (n=11)	142.41 ± 79.50	0.243[b]
Not involved (n=29)	103.37 ± 32.12	

Table 10 shows that patients with HE4 >109.45 pmol/L had 4.05 times higher odds of having myometrial invasion ≥50% compared to those with HE4 ≤109.45 pmol/L (OR = 4.05; 95% CI = 1.03–16.01).

Table 11 shows that HE4's diagnostic performance for risk categorization, including a sensitivity of 70.83%, specificity of 81.25%, PPV of 77.27%, NPV of 61.11%, and an accuracy of 70%. For myometrial invasion prediction, HE4 exhibited a sensitivity of 69.23%, specificity of 64.29%, PPV of 78.26%, NPV of 52.94%, and an accuracy of 67.50%.

Table 7: Comparison of HE4 level and histopathological risk categorization of samples (n = 40)

Serum HE4 level	High	Low-Intermediate	P value
(pmol/l)	(n = 24)	(n = 16)	
Mean ± SD	**136.06 ± 62.98**	**94.88 ± 29.28**	**0.020[b]**

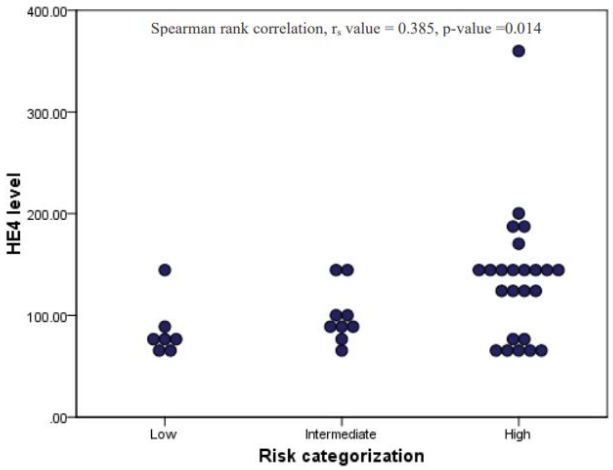

Figure 4: Correlation of HE4 level with low, intermediate and high risk (n = 40)

Table 8: Different sensitivity and specificity at different scores according to the serum HE4 levels (coordinates of the ROC)

S. HE4 levels (pmol/L)	Sensitivity	Specificity	Youden Index (Sensitivity + Specificity -1)
82.80	0.708	0.438	0.15
88.10	0.708	0.500	0.21
89.40	0.708	0.563	0.27
90.25	0.708	0.625	0.33
94.75	0.708	0.688	0.40
109.45	**0.708**	**0.813**	**0.52**
124.00	0.667	0.813	0.48
128.10	0.625	0.813	0.44
134.25	0.542	0.813	0.35
140.35	0.500	0.813	0.31
140.85	0.500	0.875	0.38

Table 9: OR with 95% CI of HE4 >109.45 pmol/L and high risk of endometrial carcinoma (n = 40)

HE4 level (pmol/L)	Risk Categorization		p-value	OR (95% CI)
	High (n = 24)	Intermediate-Low (n = 16)		
> 109.45	17 (70.8%)	5 (31.3%)	0.014[a]	5.34 (1.35-21.14)
≤ 109.45	7 (29.2%)	11 (68.8%)		

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Table 10: OR with 95% CI of HE4 >109.45 pmol/L and myometrial invasion (n = 40)

HE4 level (pmol/L)	Myometrial Invasion		p-value	OR (95% CI)
	≥50% (n = 26)	<50% (n = 14)		
> 109.45	18 (69.2%)	5 (35.7%)	0.041[a]	4.05 (1.03-16.01)
≤ 109.45	8 (30.8%)	9 (64.3%)		

Table 11: Diagnostic accuracy of the HE4 for Risk categorization and myometrial invasion (n = 40)

Diagnostic performance	Risk categorization (Value with 95% CI)	Myometrial invasion (Value with 95% CI)
Sensitivity (%)	70.83 (48.91-87.38)	69.23 (48.21-85.67)
Specificity (%)	81.25 (54.35-95.95)	64.29 (35.14-87.24)
Positive predictive value (%)	77.27 (61.13-88.02)	78.26 (63.02-88.38)
Negative predictive value (%)	61.11 (43.69-76.09)	52.94 (35.93-69.30)
Accuracy (%)	70.0 (53.47-83.44)	67.50 (50.87-81.43)

Discussion

This cross-sectional study investigated the potential of serum HE4 as a pre-operative biomarker for myometrial invasion and risk categorization in endometrial carcinoma, comparing its performance to histopathological assessment. The present study included 40 women with histologically confirmed endometrial cancer. The majority of the women belonged to the 55-64 years age group, with a mean age of 57.33±7.57 years. Svanvik et al. (2019) enumerated that older age was associated with lower educational level and more advanced stages [25]. A case-control study by Angioli et al. (2013) also showed the average age of 64.9 years among the case group of women [26]. Post-menopausal bleeding was the most prevalent symptom (82.5%) among women with endometrial carcinoma. The mean duration of the symptoms among the study subjects was 6.0±3.79 months. In terms of parity, 15.0% were nulliparous, 65.5% had 1-2 children, and 17.5% were multiparous. Epstein et al. (2001) in their study found that 80% of the women with postmenopausal bleeding and endometrium ≥5 mm had pathological endometrium. [27] This finding was similar to the present study. A substantial proportion of patients fell into the obese category (42.5%), followed by those with a normal BMI (35.0%), and individuals classified as overweight (22.5%), and the mean BMI was 26.21±4.96 kg/m². Geels et al. (2013) in their study showed that the median BMI was 28.1 for the endometrial cancer patients. [28] Angioli et al. (2013) also showed that the average BMI was 23.7 among the endometrioma cancer cases compared to 24.2 in controls, which was not statistically significant.[26]

In the present study, the majority of respondents were not using any contraceptive method (85.5%), while a small percentage used oral contraceptive pills (12.5%). A cohort study by Burchardt et al. (2021) showed that oral contraceptive use was associated with a significantly lower risk of endometrial cancer relative to never OCP use. [29] A family history of first-degree relatives with cancer was found in 5% of the present study subjects. In a systematic review and meta-analysis conducted by Win et al. (2015), the presence of a first-degree relative with endometrial cancer was associated with a population-attributable risk of 3.5% (95% CI 2.8-4.2). [30] This suggests that having a close family member with endometrial cancer may contribute to a modest increase in the risk of developing the disease.

In the current study, the predominant histopathological type of endometrial cancer was endometrioid adenocarcinoma, accounting for 85.0% of the study subjects. Regarding the staging of the disease, approximately one-third of the study subjects (32.5%) were classified as stage IA. In terms of risk categorization, the majority of the respondents (60.0%) were classified into the high-risk group, while 22.5% fell into the intermediate-risk- risk group, and 17.50% were categorized as low-risk individuals. The study results show a significant association between serum HE4 levels and histopathological grade in endometrial cancer patients (p = 0.031). Specifically, Grade 3 cancers exhibited the highest HE4 levels, with a mean of 144.15±62.88 pmol/L.

Patients with HE4 levels >109.45 pmol/L had a 5.3 times higher chance of being in the high-risk group compared to those with HE4 levels ≤109.45 pmol/L (OR = 5.34; 95% CI = 1.35-21.14). Additionally, there was a substantial difference in HE4 levels between patients with more extensive myometrial invasion (>50%) and those with less extensive invasion (<50%). Among the former group, the mean serum HE4 level was 144.81 ± 8.54 pmol/L, whereas in the latter group, the mean serum HE4 level was significantly lower at 97.94 ± 31.05 pmol/L (p < 0.001). Patients with HE4 levels >109.45 pmol/L had a 4.05 times higher chance of having

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myometrial invasion ≥50% compared to those with HE4 levels ≤109.45 pmol/L (OR = 4.05; 95% CI = 1.03-16.01). These findings suggest that elevated HE4 levels may be associated with higher histopathological grade and more extensive myometrial invasion. Moore et al. (2011) found that serum HE4 levels >70 pM had a sensitivity of 94% and a negative predictive value of 97% for distinguishing between stage IA (≥50% myometrial invasion) and stage IB (<50% myometrial invasion) tumors. For advanced tumors, the sensitivity and negative predictive value were both 82% [31]. Brennan et al. (2014) demonstrated through ROC analysis Area under the curve (AUC)=0·76) was a better predictor of outer-half myometrial invasion than CA125 (AUC=0·65), particularly in patients with low-grade endometrioid tumours (AUC 0·77 vs 0·64 for CA125) [22]. A systematic review also showed HE4 was strongly associated with prognostic factors such as myometrial invasion, tumor grade, FIGO stage, and lymph node involvement. It also predicts recurrence and can serve as a monitoring tool, as reported by a 2018 meta-analysis with a hazard ratio of 1.94 (P < 0.001) [32].

In the present study, the low-intermediate risk group exhibited a significantly lower mean HE4 level (94.88±29.28 pmol/L) in contrast to the high-risk groups (136.06±62.98 pmol/L). Importantly, this difference reached statistical significance with a p-value of 0.020. The HE4 level demonstrated a statistically significant positive correlation with the risk categories, as indicated by a Spearman's rank correlation coefficient (rs) of 0.385 and a p-value of 0.014. The diagnostic performance of HE4 for risk categorization yielded a sensitivity of 70.83%, specificity of 81.25%, PPV of 77.27%, and NPV of 61.11%. Regarding myometrial invasion prediction, HE4 demonstrated a sensitivity of 69.23%, specificity of 64.29%, PPV of 78.26%, NPV of 52.94%, and an overall accuracy of 67.50%. Moore et al. (2011) found that serum HE4 levels >70 pmol/L had a sensitivity of 94% and a negative predictive value of 97% for distinguishing between stage IA (≥50% myometrial invasion) and stage IB (<50% myometrial invasion) tumors. For advanced tumors, the sensitivity and negative predictive value were both 82%. [31] Angioli et al. (2013) reported in their study that HE4 levels >150 pmol/L exhibited a sensitivity of 35.6%, specificity of 100.0%, positive predictive value (PPV) of 100.0%, and negative predictive value (NPV) of 61.3% for detecting malignant endometrial disease. [26]

Kalogera et al. (2012) reported a significant association between elevated serum HE4 levels and several tumor characteristics in patients with type I endometrial carcinoma (EC). Specifically, higher HE4 levels were linked with deep myometrial invasion (>50%, P<0.001) and larger primary tumor diameter (>2 cm, P=0.002). Notably, patients classified as low-risk, defined by type I histology, myometrial invasion ≤50%, and tumor diameter ≤2 cm, had significantly lower median HE4 levels compared to other type I EC cases (P<0.01).[33] Similarly, Stiekema et al. (2017) found that serum HE4 concentrations were significantly associated with advanced disease features, including disease stage (P=0.001), deep myometrial invasion (P<0.001), precise depth of invasion (≥4 mm, P=0.01), minimal distance to the serosa (≤7 mm, P<0.001), extensive lymphovascular space invasion (LVSI) (P=0.04), and cervical involvement (P=0.001). Although HE4 levels also appeared to correlate with lymph node involvement, this finding did not reach statistical significance (P=0.17).[34] Wang et al. (2017) also demonstrated that HE4 levels increased significantly with patient age and tumor histologic grade (P<0.01 for both). In the context of lymph node metastasis, HE4 exhibited higher sensitivity and a better negative predictive value than CA125 [35]. Additionally, Moore et al. (2008) highlighted that HE4 levels were elevated across all stages of endometrial cancer and showed greater sensitivity than CA125 in detecting early-stage disease [36]. Therefore, the results indicated that HE4 is important for predicting disease characteristics and risk stratification in endometrial cancer. This highlights the potential of HE4 as a critical tool in the preoperative assessment of patients with this cancer.

Limitations of the study

Our study was a single-center study, so the study may limit the generalizability of the findings. We took a small sample size due to the short study period. The unavailability of the HE4 testing kit in the country could affect the accuracy and accessibility of the test. The cross-sectional design used in the study prevents the establishment of causal relationships between variables.

Conclusion and Recommendations

This study shows that serum HE4 has a sensitivity of 69.23% and a specificity of 64.29% for predicting myometrial invasion. In addition, HE4 has a sensitivity of 70.83% and a specificity of 81.25% for risk categorization. These suggest that HE4 has the potential to predict myometrial invasion and assess the risk categorization of patients with endometrial cancer. Further multicentric prospective studies can be conducted to validate the findings and expand the knowledge on HE4's utility in endometrial cancer management.

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