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ORIGINAL RESEARCH

Model Predicting the Risk of Endometrial Hyperplasia Developing into Endometrial Cancer

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Background: This study retrospectively analyzed the medical records of 200 patients with endometrial hyperplasia to predict the risk of concurrent endometrial cancer.

Methods: Patients were categorized into either the endometrial cancer group or the endometrial hyperplasia group based on post-hysterectomy pathology. The investigation compared general information, tumor indices, fertility history, preoperative endometrial sampling methods, comorbidities, and clinical symptoms between the groups to identify risk factors for endometrial hyperplasia complicating endometrial cancer.

Results: (1) Of the 200 patients, 68 (34.0%) were diagnosed with concurrent endometrial cancer post-hysterectomy. Among these, 60 (88.24%) had endometrioid adenocarcinoma, while 8 (11.76%) had other types. Stage I was identified in 58 patients (85.29%) and Stage II in 10 patients (14.71%). High differentiation was observed in 57 cases (83.82%), moderate differentiation in 7 cases (10.29%), and poor differentiation in 4 cases (5.89%), indicating that most endometrial cancers complicated by hyperplasia were early-stage, well-differentiated endometrioid carcinomas; (2) Univariate analysis revealed statistically significant differences in age, menopausal status, length of menopause, and preoperative endometrial pathology of severe atypical hyperplasia between the groups; (3) Multivariate analysis indicated significant differences for age ≥ 53.5 years (OR: 4.307, 95% CI: 2.018–9.192, $p < 0.05$), menopausal status (OR: 5.250, 95% CI: 2.449–11.252, $p < 0.05$), and severe atypical endometrial hyperplasia (OR: 4.817, 95% CI: 1.260–18.419, $p < 0.05$); (4) Significant differences were observed among patients with endometrial hyperplasia when stratified by the presence of zero, one, two, or three high-risk factors.

Conclusion: In conclusion, patients aged ≥ 53.5 years, those who are menopausal, and those with severe atypical endometrial hyperplasia preoperatively are at higher risk for endometrial cancer. The risk increases with the number of high-risk factors present in patients with atypical endometrial hyperplasia.

Keywords: retrospective, endometrial hyperplasia, endometrial cancer, clinical features, high-risk factors, regression

Introduction

Endometrial cancer (EC) is a significant malignancy affecting women's health, with its incidence rising in many countries over recent decades. This increase is hypothesized to be linked to the growing prevalence of obesity and changes in female reproductive patterns.[1,2] EC can be categorized into estrogen-dependent and non-estrogen-dependent types. In the early stages, patients may exhibit clinical symptoms or lack typical signs, but as the disease progresses, symptoms such as bleeding, vaginal discharge, and pain become apparent. These symptoms are believed to result from unopposed estrogen action, leading to endometrial hyperplasia and subsequent carcinogenesis.[3,4] Although approximately 70% of early-stage EC cases are diagnosed effectively due to abnormal vaginal bleeding, about 30% are detected at an advanced stage due to a lack of obvious symptoms, resulting in a poor prognosis and significant negative impacts on individuals, society, and families.[5,6] Hence, improving early diagnosis is

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essential for enhancing the prognosis and overall survival of patients with EC. While there are no established screening programs for EC, early detection and management of precancerous endometrial lesions can prevent the progression to cancer.

Endometrial hyperplasia (EH) is a common gynecological endocrine disorder caused by excessive estrogen stimulation, leading to abnormalities in endometrial tissue. All forms of hyperplasia exhibit common morphological changes, including an increased gland-to-stroma ratio and irregularities in gland shape and size.[7] In 2014, the World Health Organization classified EH into two categories: endometrial hyperplasia without atypia EH and atypical hyperplasia (AH) or endometrial intraepithelial neoplasia (EIN). Common symptoms include irregular vaginal bleeding, infertility, and, in severe cases, malignancy.[8] Untreated endometrial dysplasia has a notable tendency to progress to cancer.[9]

In cases of EH, transvaginal ultrasound is the primary diagnostic tool for symptomatic patients.[10] However, a definitive diagnosis of EH requires histological evaluation of specimens obtained via diagnostic hysteroscopy. Needle scraping, a blind procedure, has several limitations, including sampling less than 50% of the uterine cavity and obtaining few specimens, leading to inadequate diagnoses.[11] Hysteroscopy, offering direct visualization of the uterine cavity,[12] is now considered the gold standard for diagnosing EH due to its high sensitivity and specificity (95%).[13] Research indicates that EH and EC frequently coexist in patients. The risk of endometrial atypical hyperplasia combined with EC ranges from 25.76% to 59.22%,[14] and many reports suggest that women with a preoperative diagnosis of AH are often found to have EC post-hysterectomy.[15] Clinically, there is also a significant incidence of underdiagnosis in EC detection.[16] Early detection and intervention in AH are crucial for improving patient prognosis.[17] Identifying patients at a higher risk of developing EC among patients with EH is essential to guide clinical diagnostic strategies and enhance patient outcomes. Therefore, in this study, patients were categorized based on pathological findings after total hysterectomy. The clinical data of these groups were compared and analyzed to predict the risk of EC complicating EH.

Materials and Methods

Participants

The clinical data of patients treated for endometrial hyperplasia and who underwent total hysterectomy at the Obstetrics Department of People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University from January 2019 to December 2022 were collected for analysis. All patients received total hysterectomies and were categorized into the endometrial cancer group (68 patients) and the endometrial hyperplasia group (132 patients) based on postoperative pathological findings. The study was approved by the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region (2022-NZR-007), and informed consent was obtained from all participants.

The inclusion criteria were as follows: (1) Preoperative pathological reports issued by the People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University or its Department of Pathology; (2) Pathological diagnosis of endometrial hyperplasia; (3) Receiving hysterectomy at the People's Hospital of Ningxia Hui Autonomous Region, with the resected specimen sent to the Department of Pathology; (4) Complete postoperative pathology.

The Exclusion criteria were as follows: (1) Absence of a pathology report issued by the People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University or not examined by the Department of Pathology; (2) Preoperative endometrial biopsy pathology not indicating endometrial hyperplasia; (3) Not receiving hysterectomy at the People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University; (4) Incomplete postoperative pathology.

Clinical Data Collection

The clinical data of patients in the EC and EH groups were compared and analyzed, encompassing morbidity factors and disease duration (age, menopausal status, length of menopause, body mass index, preoperative endometrial thickness, and the interval between diagnosis of endometrial hyperplasia and total hysterectomy), tumor indicators (CA125 and CA199 levels), fertility history (number of pregnancies and deliveries, history of maternity), preoperative endometrial sampling methods (hysteroscopy, curettage), type of endometrial hyperplasia pathology diagnosed prior to hysterectomy, comorbidities (hypertension, diabetes mellitus, fibroids, ovarian cysts, endometriosis), and clinical symptoms (irregular vaginal bleeding, abnormal vaginal discharge, lower abdominal pain). Types of EH diagnosed by preoperative endometrial

biopsy were categorized into three groups: simple and complicated endometrial hyperplasia, mild-to-moderate endometrial atypia, and severe endometrial atypia.[8,18]

Diagnosis of Endometrial Hyperplasia

All patients underwent hysteroscopy (XD-1000C, Xinda Medical Electronic Equipment Co., Ltd., Xuzhou, China) 3–7 days post-menstruation. In cases of severe bleeding, symptomatic treatment was administered to reduce bleeding prior to the procedure. Before the examination, patients were instructed to empty their bladder and assisted into the cystotomy position. Standard disinfection and toweling procedures were followed, and the size and position of the uterus were assessed via bimanual examination. The vulva, vagina, and cervix were disinfected again, the cervix was dilated using a dilator, and the hysteroscope was slowly inserted into the uterine cavity under direct vision, advancing toward the uterine fundus. The cervical canal, uterine shape, posterior wall, uterine fundus, right and left uterine horns, and fallopian tube openings were thoroughly observed. Tissue biopsy and diagnostic scraping of the abnormal endometrium were conducted, followed by pathological diagnosis.

Statistical Methods

Statistical analyses were performed using SPSS 25.0. Measurements following a normal distribution were presented as mean ± standard deviation and compared between groups using the *t*-test or F-test; non-normally distributed data were presented as medians and compared using the rank-sum test. Count data were expressed as the number of cases and analyzed using the chi-square test or Fisher's exact probability test. Risk factors were analyzed via logistic regression. Receiver operating characteristic (ROC) curves were plotted to determine the endometrial thickness cut-off value. Differences were considered statistically significant at $P < 0.05$.

Results

Factors Associated with the Onset and Course of the Disease

In this study, 200 patients with a preoperative diagnosis of EH were analyzed. Postoperative diagnoses revealed 68 cases of EC and 132 cases of EH. A univariate analysis, as shown in Table 1, compared various factors between the two groups. The age range for the EC group was 33–70 years, with a mean age of 51.58 ± 7.72 years, while the EH group ranged from 36–62 years, with a mean age of 48.27 ± 4.85 years, indicating a statistically significant difference ($p < 0.05$). Regarding menopausal status, 47 patients (69.12%) in the EC group were menopausal compared to 35 patients (26.52%) in the EH group. Conversely, 21 patients (30.88%) in the EC group and 97 patients (73.48%) in the EH group were non-menopausal, with statistically significant differences ($p < 0.05$). The mean duration of menopause was 6.21 ± 5.82 years in the EC group and 4.14 ± 2.97 years in the EH group, also showing a statistically significant difference ($p < 0.05$).

Tumour Markers and Fertility

Univariate analysis of CA125 and CA199 levels, as shown in Table S1, indicated no significant differences between the two groups ($p > 0.05$).

Table 1 Factors Associated with Morbidity and Univariate Analysis of Disease Course

Factors		Endometrial Cancer (n=68)	Endometrial Hyperplasia (n=132)	X^2/t value	*p* value
Age (years)		51.58 ± 7.72	48.27 ± 4.85	3.484	0.001
Menopausal status	Yes	47 (69.12%)	35 (26.52%)	29.412	<0.001
	No	21 (30.88%)	97 (73.48%)		
Length of menopause (years)		6.21 ± 5.82	4.14 ± 2.97	2.221	0.029
BMI (Kg/m^2)		25.62 ± 4.24	24.96 ± 3.88	0.889	0.375
Pre-operative endometrial thickness Degree (mm)		12.60 ± 5.72	11.21 ± 4.60	1.731	0.086
Time interval between diagnosis and surgery (days)		20.22 ± 13.32	23.99 ± 18.42	−1.530	0.128

The mean number of births was 1.38 ± 0.85 in the EC group and 1.17 ± 0.65 in the EH group, with no statistically significant difference ($p > 0.05$). Additionally, 64 patients (94.12%) in the EC group had a history of pregnancy compared to 125 patients (94.70%) in the EH group, while 4 patients (5.88%) in the EC group and 7 patients (5.30%) in the EH group had no history of pregnancy, showing no statistically significant difference ($p > 0.05$), as detailed in Table S1.

Pre-Operative Sampling Methods and Pathological Typing

In the EC group, preoperative endometrial sampling by diagnostic scraping was performed on 64 patients (94.12%), while hysteroscopy was utilized for 4 patients (5.88%). In the EH group, 123 patients (93.18%) underwent diagnostic scraping, and 9 patients (6.82%) had hysteroscopy for endometrial sampling, with no statistically significant difference between the groups ($p > 0.05$). Comparing the types of pathological findings from preoperative endometrial biopsies, 4 patients (5.88%) in the EC group had simple or complex EH (Figure 1A), 20 patients (29.41%) had mild to moderate AEH (Figure 1B), and 44 patients (64.71%) had severe AEH (Figure 1C). In the EH group, 21 patients (15.91%) had simple or complex EH, 53 patients (40.15%) had mild to moderate AEH, and 58 patients (43.94%) had severe AEH. No statistically significant difference was found between simple and complex EH and mild to moderate AEH ($p > 0.05$), while a significant difference existed between simple and complex EH and severe AEH ($p < 0.05$), as well as between mild to moderate AEH and severe AEH ($p < 0.05$), as shown in Table 2.

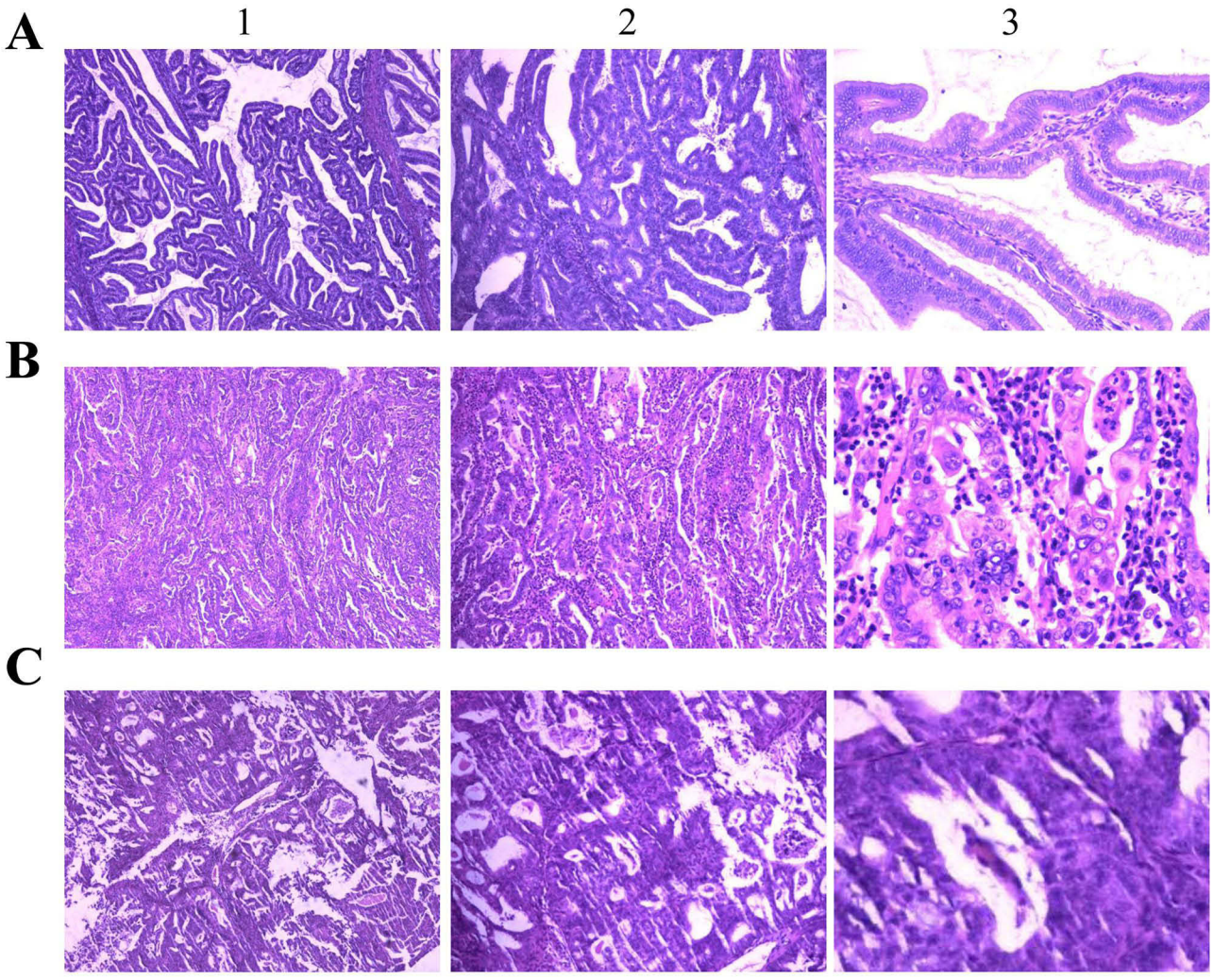

Figure 1 HE-stained endometrial cancer stage I, II, III.
Notes: (A) stage I; **(B)** stage II; **(C)** stage III. 1. 40 ×; 2. 100 ×; 3. 400 ×.

Table 2 Pre-Operative Sampling Methods and Pathological Typing

Factors		Endometrial Cancer (n=68)	Endometrial Hyperplasia (n=132)	X^2/ t value	*P* value
Pre-operative endometrial sampling method	Diagnostic scraping	64 (94.12%)	123 (93.18%)	0.611	0.435
	Hysteroscopy	4 (5.88%)	9 (6.82%)		
Pre-operative endometrial pathology	Simple, complicated endometrial hyperplasia	4 (5.88%)	21 (15.91%)	1.308	0.253^{1-2}
	Mild to moderate endometrial atypia	20 (29.41%)	53 (40.15%)	6.120	0.013^{2-3}
	Severe endometrial atypical hyperplasia	44 (64.71%)	58 (43.94%)	7.429	0.006^{1-3}

Comorbidities and Clinical Symptoms

Regarding medical comorbidities, hypertension and diabetes mellitus were included in the study. As shown in Table S2, no statistically significant differences were found between the two groups for these conditions ($p > 0.05$). Additionally, other benign gynecological comorbidities such as uterine fibroids, ovarian cysts, and endometriosis were included. In the EC group, 18 patients (26.47%) had uterine fibroids, while 50 patients (73.53%) did not. For ovarian cysts, 8 patients (11.76%) in the EC group had them, compared to 60 patients (88.24%) without. In the EH group, 16 patients (12.12%) had ovarian cysts, and 116 patients (87.88%) did not. Endometriosis was present in 15 patients (22.06%) in the EC group and absent in 53 patients (77.94%), whereas in the EH group, 24 patients (18.18%) had endometriosis, and 108 patients (81.82%) did not. None of these differences were statistically significant ($p > 0.05$).

Clinical symptoms of EH and EC were diverse. This study included three common symptoms: irregular bleeding, abnormal vaginal discharge, and lower abdominal pain. In the EC group, 20 patients (29.41%) had abnormal vaginal discharge, while 48 patients (70.59%) did not. In the EH group, 33 patients (25.0%) had abnormal vaginal discharge, compared to 99 patients (75.0%) without. Lower abdominal pain was reported by 7 patients (10.29%) in the EC group, with 61 patients (89.71%) not experiencing it. In the EH group, 15 patients (11.36%) had lower abdominal pain, while 117 patients (88.64%) did not. The differences in the presence of lower abdominal pain between the groups were not statistically significant ($p > 0.05$), as detailed in Table S2.

Diagnostic Evaluation of Age and Duration of Menopause

The difference in age was statistically significant ($p < 0.05$), as demonstrated by the ROC curve shown in Figure 2A. The area under the curve (AUC) was 0.630, with a 95% confidence interval (CI) of 0.546–0.714. The critical age value was 53.5 years, where the Youden index was at its maximum (Table 3). For the duration of menopause, the difference between the two groups was also statistically significant ($p < 0.05$), with the ROC curve presented in Figure 2B. The AUC was 0.606, with a 95% CI of 0.485–0.728, and the critical value for the duration of menopause was 2.25 years at the maximum Youden index (Table 3).

Multivariate Analysis

Univariate analysis revealed statistically significant differences in age, menopausal status, length of menopause, and simple versus complex endometrial hyperplasia. Logistic regression analysis showed that the differences between age ≥ 53.5 years, menopausal status, length of menopause, and simple versus complex endometrial hyperplasia, as well as severe AEH (1–3), and between mild-moderate endometrial AEH and severe AEH (2–3), were statistically significant ($p < 0.05$), as detailed in Table 4. However, the difference in the duration of menopause between the two groups was not statistically significant ($p > 0.05$).

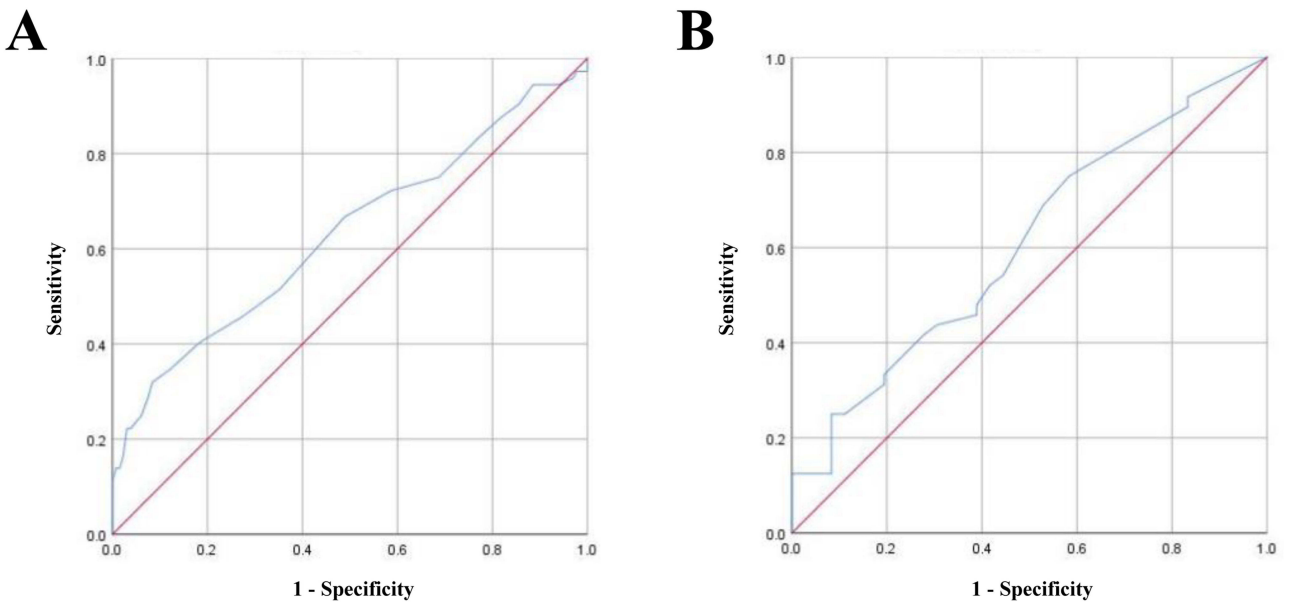

Figure 2 ROC curves for endometrial cancer detection based on age and duration of menopause.
Notes: (A) Area under the ROC curve for the age comparison of the two groups; **(B)** Area under the ROC curve for the time to menopause comparison of the two groups.

Analysis of the Number of High-Risk Factors

In the EC group, 7 patients (10.29%) had no high-risk factors, 25 patients (36.76%) had one high-risk factor, 26 patients (38.24%) had two high-risk factors, and 10 patients (14.71%) had three high-risk factors. In the EH group, 47 patients (35.60%) had no high-risk factors, 51 patients (38.64%) had one high-risk factor, 24 patients (18.18%) had two high-risk factors, and 10 patients (7.58%) had three high-risk factors. Analysis in Table 5 indicates statistically significant differences when comparing no high-risk factors to one (0–1), two (0–2), and three (0–3) high-risk factors, as well as

Table 3 Sensitivity, Specificity and Cut-off Values for Age, Length of Menopause

	AUC	95% CI	Threshold Values	Sensitivity (%)	Specificity (%)	Jorden Index
Age	0.630	0.546–0.714	53.5 years	31.9	91.6	0.235
Length of menopause	0.606	0.485–0.728	2.25 years	75.0	41.7	0.167

Table 4 Multi-Factor Analysis of High-Risk Factors in Both Groups

High Risk Factors		Cancer Rate	Regression Coefficient	Standard Deviation	Wald	*p* value	OR	95% CI
Age	<53.5	28.99%	1.633	0.404	16.353	<0.001	5.121	2.320–11.301
	≥53.5	67.65%						
Menopausal status	Yes	57.14%	1.664	0.317	27.452	<0.001	5.278	2.833–9.833
	No	20.17%						
Length of menopause	<2.25	44.44%	0.762	0.475	2.577	0.108	2.143	0.845–5.434
	≥2.25	63.16%						
Preoperative endothelial pathology staging	Simple, complicated endometrial hyperplasia[1]	16.00%	1.486	0.580	6.575	0.010^{1-3}	4.421	1.419–13.770
	Mild to moderate endometrial atypia[2]	27.40%	0.803	0.327	6.008	0.014^{2-3}	2.232	1.175–4.240
	Severe endometrial atypical hyperplasia[3]	45.71%						

Table 5 Analysis of the Number of High-Risk Factors

High Risk Factors (pcs)	Endometrial Cancer (n=68)	Endometrial Hyperplasia (n=68)	X^2/p value		
0	7 (10.29%)	47 (35.60%)	6.488/0.0110^{-1}	17.781/<0.001^{-2}	16.960/<0.001^{-3}
1	25 (36.76%)	51 (38.64%)	4.569/0.033$^{1-2}$	4.962/0.026$^{1-3}$	
2	26 (38.24%)	24 (18.18%)	0.262/0.609$^{2-3}$		
3	10 (14.71%)	10 (7.58%)			

between one and two (1–2) and one and three (1–3) high-risk factors (all $p < 0.05$). However, the difference between two and three high-risk factors (2–3) was not statistically significant ($p > 0.05$).

Multivariate analysis of high-risk factors, as shown in Table 6, reveals statistically significant odds ratios (OR) for endometrial cancer: OR 4.307 (95% CI: 2.018–9.192, $p < 0.001$), OR 7.119 (95% CI: 2.700–18.772, $p < 0.001$), and OR 9.200 (95% CI: 2.954–28.656, $p < 0.001$). The risk of endometrial cancer increases with two high-risk factors (OR 2.210, 95% CI: 1.062–4.598, $p = 0.034$) and three high-risk factors (OR 2.856, 95% CI: 1.113–7.327, $p = 0.029$). As the number of combined risk factors increases, so does the risk of endometrial cancer complications.

Histological Features of Endometrial Cancer

This study included 200 patients with EH, of whom 68 (34.0%) had postoperative pathology indicating complications of EC following total hysterectomy, as shown in Table 7. Among these 68 EC cases, 60 (88.24%) were diagnosed with endometrioid adenocarcinoma (Figure 3A), while 8 (11.76%) had other types of special endometrial cancer (Figure 3B). All 68 cases were either stage I or stage II, with no patients at stage III or IV. The differentiation status revealed 57 cases (83.82%) as highly differentiated (Figure 4A), 7 cases (10.29%) as moderately differentiated (Figure 4B), and 4 cases (5.89%) as poorly differentiated (Figure 4C). These findings indicate that, despite the high incidence of EC among patients with EH, the majority are early-stage, well-differentiated endometrioid adenocarcinomas.

Table 6 Multi-Factor Analysis of High-Risk Factors

High Risk Factors (pcs)	Regression Coefficient B	Standard Error	Wald Chi Square	p Value	OR	95% CI
0–1	1.170	0.474	6.103	0.013	3.221	1.273–8.148
0–2	1.963	0.495	15.742	<0.001	7.119	2.700–18.772
0–3	2.219	0.580	14.656	<0.001	9.200	2.954–28.656
1–2	0.793	0.374	4.500	0.034	2.210	1.062–4.598
1–3	1.049	0.481	4.767	0.029	2.856	1.113–7.327

Table 7 Pathological Features of Endometrial Cancer

Pathological Findings After Total Uterine Surgery		Number	Percentage (%)
Histological types	Endometrioid adenocarcinoma	60	88.24%
	Other types of endometrial cancer	8	11.76%
Pathological staging	I Period	58	85.29%
	II Period	10	14.71%
	III–IV Period	0	0
Degree of differentiation	Highly differentiated	57	83.82%
	Middle Divergence	7	10.29%
	Undifferentiated	4	5.89%

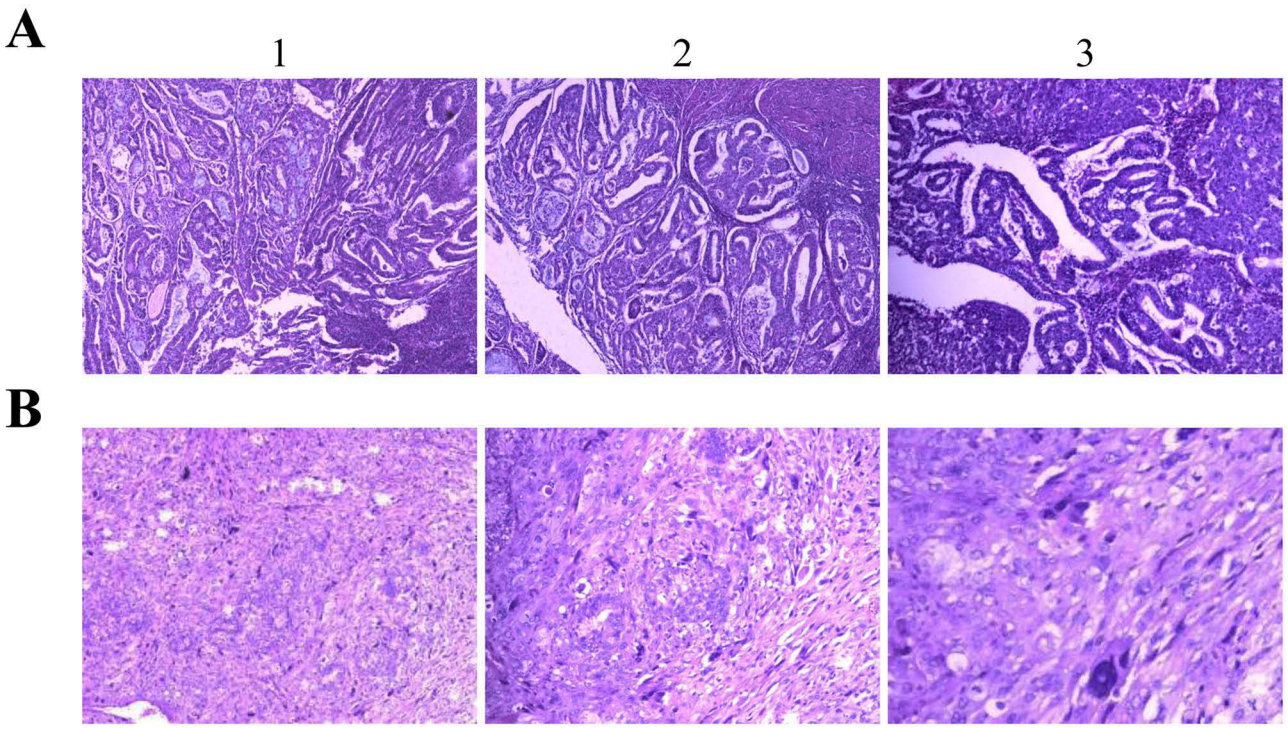

Figure 3 HE-stained adenocarcinoma of the endometrium and other types of endometrial cancer.
Notes: (A) HE-stained adenocarcinoma of the endometrium; **(B)** HE-stained other types of endometrial cancer. 1, 40 ×; 2. 100 ×; 3. 400 ×.

Discussion

EH is a prevalent benign gynecological endocrine disorder affecting women of childbearing age, characterized by the overgrowth of the endometrium due to various factors. This condition often arises from ovulatory disturbances and the presence of endometrial lesions, which directly impact egg fertilization.[19] Consequently, many patients experience infertility. Terakawa's study found that 22–66% of patients with AEH are infertile, and 90% of patients with AEH under 40 years old have no history of fertility.[19] Most AEH patients without fertility needs undergo surgical treatment with total hysterectomy, while younger patients desiring fertility receive conservative treatment.

EC is a common gynecological malignancy originating from the endometrial epithelium, with a 5-year survival rate ranging from 65% to 92%.[20] EC is typically classified into type I and type II. Type I, comprising 80% of cases, includes endometrial adenocarcinoma and mucinous carcinoma, while type II, accounting for 20% of cases, includes plasmacytoma and clear cell carcinoma, with a later average age of onset compared to type I.[21] In this study, postoperative pathology indicated that 68 patients had EC, with 60 cases (88.24%) being endometrioid adenocarcinoma. Clinical staging, using the FIGO (International Federation of Gynecology and Obstetrics) method, showed 58 cases (85.29%) were stage I and 10 cases (14.71%) were stage II, with no cases in stage III or IV. Additionally, 57 cases (83.82%) were highly differentiated, 7 cases (10.29%) were moderately differentiated, and 4 cases (5.89%) were poorly differentiated. These findings indicate that EC combined with EH often presents at earlier stages and with better differentiation. Many well-differentiated early-stage EC cases are pathologically challenging to distinguish from AEH, leading to postoperative pathology revealing combined EC in patients initially diagnosed with AEH. This can result in inadequate surgical coverage and necessitate further treatment. Literature indicates that postoperative pathology suggestive of EC in patients with a preoperative diagnosis of EH occurs in approximately 10–59% of cases.[22] Identifying risk factors and improving diagnostic accuracy are crucial to guiding effective treatment.

EH primarily affects women of childbearing age, whereas EC is more common in perimenopausal women, with the progression from EH to EC spanning 1–15 years.[23] The prevalence of EC increased to 13.74% among women aged under 50,[24] suggesting that older age correlates with a higher risk of developing EC and declining survival rates. Matsuo et al identified

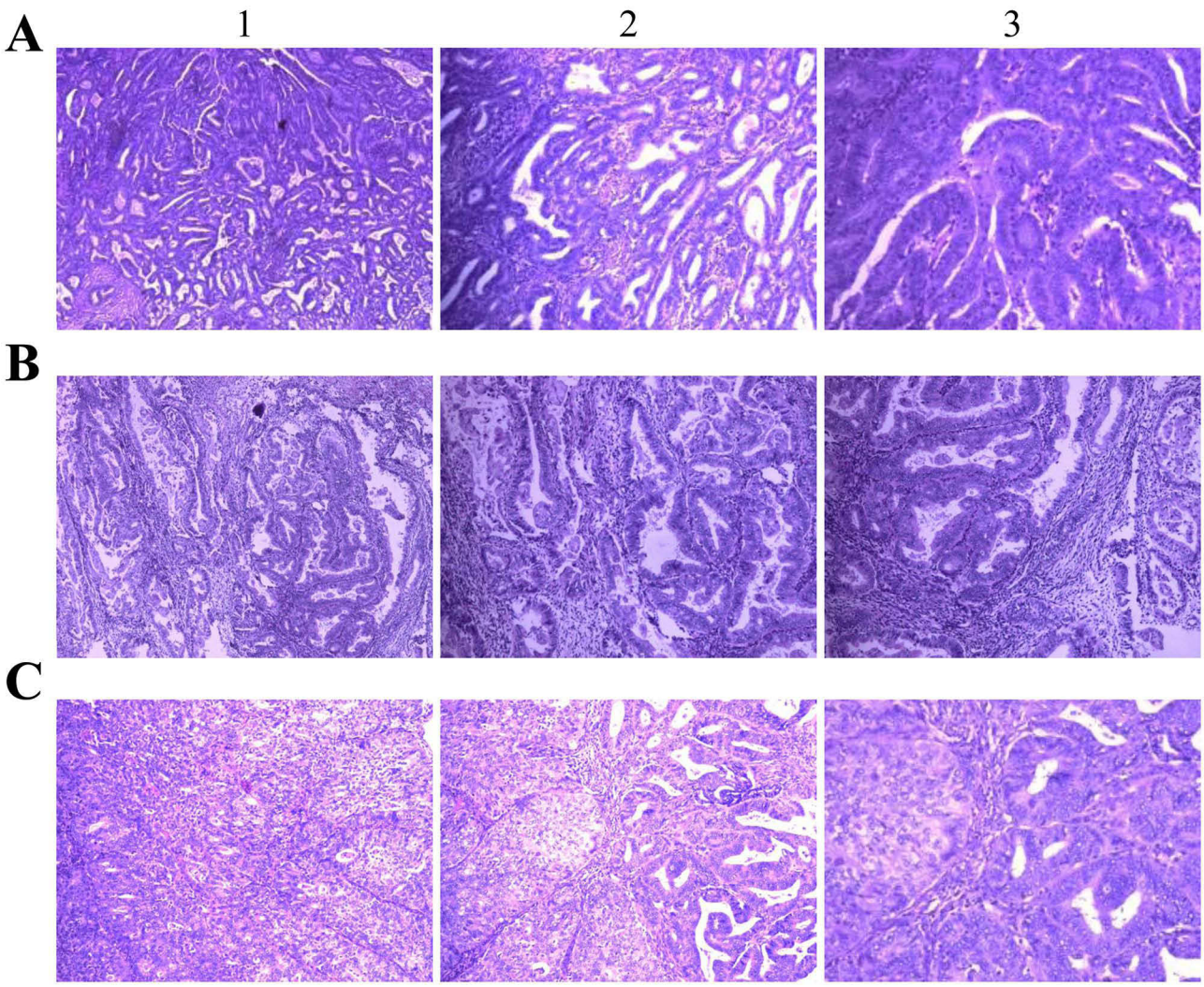

Figure 4 HE-stained highly, middle and low differentiated.
Notes: (A) highly differentiated; **(B)** middle differentiated; **(C)** low differentiated.1. 40 ×; 2. 100 ×; 3. 400 ×.

age as the sole high-risk factor in patients with complex AEH.[25] However, Valenzuela et al contested this, finding no statistically significant age difference predictive of EC.[26] In the present study, patients in the EC group ranged from 33–70 years old, with a mean age of 51.58 ± 7.72 years. Postoperative patients with EH ranged from 36–62 years old, with a mean age of 48.27 ± 4.85 years. Univariate analysis revealed a statistically significant age difference between the groups (OR: 5.121, 95% CI: 2.320–11.311). The ROC curve indicated an area of 0.630 and a cut-off age of 53.5 years. Thus, age ≥ 53.5 years is considered a high-risk factor for EC complications in EH, potentially due to increased apoptosis and inflammatory factors in older patients, leading to decreased immune function and a higher risk of EC.[27]

Additionally, studies have shown that 70–75% of patients with EC are menopausal women.[28] In this study, 47 patients (69.12%) in the EC group were menopausal, compared to 35 patients (26.52%) in the EH group, with a statistically significant difference (OR: 5.278, 95% CI: 2.833–9.833, $p < 0.001$). During the perimenopausal period, the ovaries may still produce small amounts of estrogen affecting the endometrium. Some studies have shown that within 5 years of menopause, women may exhibit a proliferative and secretory phase of the endometrium, whereas after 5 years, most exhibit an atrophic endometrium.[29] The prevalence of EC is related to the duration of menopause; longer menopause durations increase EC risk, prevalence, and the proportion of poorly differentiated specific EC types.[30,31] Univariate analysis in this study showed a statistically significant difference in the length of menopause ($p < 0.05$), with a cut-off

value of 2.25 years. However, multiple logistic regression analysis found no statistically significant difference in menopause duration ($p > 0.05$).

Numerous studies and clinical data confirm that EH can co-exist with EC.[32,33] Various international classifications of EH exist, with the WHO classification being the primary reference for clinicians. A prospective study by Trimble et al, involving a large sample, demonstrated a 42.6% chance of EC occurring in conjunction with atypical endometrial hyperplasia.[34] In the present study, 200 patients were categorized into three groups based on the pathological staging of EH: simple and complex endometrial hyperplasia, mild to moderate AEH, and severe AEH. Univariate and multifactorial analyses showed no statistically significant differences between the simple and complex hyperplasia group and the mild to moderate AEH group ($p > 0.05$). However, significant differences were observed when comparing the simple and complex hyperplasia group to the severe AEH group (OR: 4.421, 95% CI: 1.419–13.770, $p = 0.010$), and the mild to moderate AEH group to the severe AEH group (OR: 2.232, 95% CI: 1.175–4.240, $p = 0.014$). These results indicate that severe AEH is a high-risk factor for concurrent EC. Consequently, patients with severe AEH should receive thorough preoperative counseling, and, if necessary, undergo rapid intraoperative pathological examination. Surgeons should be prepared to expand the scope of surgery based on intraoperative findings.

BMI is a reliable measure of obesity, combining height and weight. According to Asian standards, a BMI ≥ 23 is considered overweight, and ≥ 30 indicates severe obesity requiring intervention. High estrogen levels increase the risk of EH lesions. Studies suggest that a BMI > 27 is a significant risk factor for EC,[35] with a 1.6-fold increase in cancer risk for every 5 kg/m^2 increase in BMI.[36] Furthermore, higher BMI is linked to poorer treatment outcomes and increased mortality.[37] However, in this study, the difference in BMI between the EC and EH groups was not statistically significant ($p > 0.05$). Diabetes, often associated with high insulin and estrogen levels, increases insulin-like growth factor-1 activity and activates the pro-value-added kinase pathway, leading to EH pathology. It has been identified as an independent risk factor for EC,[38] with type II diabetes significantly increasing the risk (RR: 2.1).[39] The combination of diabetes and obesity further elevates the likelihood of developing EC.[40] Although older age correlates with higher diabetes prevalence, recent trends show younger patients increasingly developing diabetes, potentially reducing the age-related difference between the EC and EH groups. In this study, the presence of diabetes did not show a statistically significant difference between the two groups ($p > 0.05$). Hypertension is widely recognized as a risk factor for EC. Hypertensive patients often lack progesterone secretion due to abnormal pituitary gonadotropic axis function, leading to endometrial disease or cancer without progesterone antagonism. However, some studies argue that hypertension does not impact EC risk.[40] Although obesity, hypertension, and diabetes mellitus were not identified as high-risk factors in this study, all three conditions significantly influence treatment outcomes, survival rates, and quality of life. Therefore, addressing these factors remains essential in the management of patients with EC.

A history of pregnancy serves as a protective factor against the development of EC, irrespective of whether the pregnancy resulted in birth. The protective effect increases with the number of pregnancies, with the risk of developing EC reduced by 0.6 following a full-term birth. In this study, the mean number of births was 1.38 ± 0.85 in the EC group and 1.17 ± 0.65 in the EH group, showing no statistically significant difference ($p > 0.05$). Among patients with EC, 63 (92.65%) had completed labor and 5 (7.35%) had not, compared to the EH group, where the difference was also not statistically significant ($p > 0.05$). In the EC group, 64 patients (94.12%) had a history of pregnancy, while 4 (5.88%) did not. Similarly, in the EH group, 125 patients (94.70%) had a history of pregnancy, and 7 (5.30%) did not, with no statistically significant difference ($p > 0.05$). In clinical practice, CA125 is often considered a valuable indicator for assessing lymphatic metastases, treatment outcomes, and prognosis in EC. Some studies have reported CA125 as an independent risk factor for predicting EC (OR: 13.97, 95% CI: 2.49–78.37),[41,42] although this view is contested by others. In this study, the mean CA125 level in the EC group was 37.81 ± 28.02 U/mL, compared to 32.60 ± 15.75 U/mL in the EH group, with no statistically significant difference ($p > 0.05$). This lack of significance may be due to the early-stage nature of most cases in this study, with small lesions confined to the uterine cavity and no extrauterine spread or lymphatic involvement. CA199, a common antigen associated with gastrointestinal tumors, is frequently used as an adjunct test for gastric, colorectal, and pancreatic cancers, as well as an indicator of recurrence. However, in this study, the difference in CA199 levels between the EC and EH groups was not statistically significant ($p > 0.05$), suggesting that CA199 is not a high-risk factor for predicting the coexistence of EH with EC.

Normal endometrial thickness varies with the menstrual cycle: 1–4 mm in the ovulatory phase, 4–8 mm in the proliferative phase, 6–12 mm in the secretory phase, and up to 12–16 mm in the late secretory phase. Studies have shown that an endometrial thickness of < 8 mm on ultrasound has a sensitivity of 83.8% and a specificity of 58.8% for detecting malignant endometrial disease. The risk of EC increases with greater endometrial thickness,[43] and guidelines recommend ultrasound measurement of endometrial thickness as a primary screening test for EC.[44] In this study, no statistically significant difference in endometrial thickness was found between the two groups ($p > 0.05$), potentially due to the sample size. Additionally, the variability in ultrasound presentations of endometrial lesions, which can range from focal hyperplasia to diffuse thickening with irregular morphology and uneven echogenicity, complicates accurate measurement and can introduce significant errors. Recent studies suggest using endometrial blood flow to predict EC.[45] Increased vascular proliferation and abnormal vessel patterns near EC foci lead to higher blood perfusion compared to normal endometrial tissue. Morotti et al reported an incidence of EC in EH ranging from 17% to 52%.[46] In this study, of the 200 patients with EH, 68 had postoperative pathology suggestive of EC, indicating an incidence of 34.0% and a high rate of preoperative omission. This high omission rate is likely due to the small, scattered nature of early-stage EC lesions, which are often located at the uterine base and corners, making them easy to miss during diagnostic and hysteroscopic scraping. Moreover, the experience of the surgeon plays a pivotal role, as even senior surgeons only scrape 75–80% of the uterine cavity.[47] Endometrial thickness also varies significantly due to hormonal influences and individual differences. In this study, 60 of the 68 patients with EC were diagnosed with endometrial adenocarcinomas; among them, 57 were highly differentiated, 7 were moderately differentiated, and 4 were poorly differentiated. The diagnosis of AEH is highly dependent on clinical experience and subjective interpretation, leading to variability among pathologists. One survey found that pathologists' diagnostic consistency for AEH was 39.5%, with a repeat rate of 61%-76%,[48] also influenced by specimen collection and preparation. In conclusion, accurate diagnosis of EH and EC remains challenging due to variability in clinical presentations, diagnostic techniques, and individual pathology interpretations. This underscores the importance of improving diagnostic methods and training to enhance detection rates and treatment outcomes.

This study has several limitations. While many studies have identified obesity, pregnancy, and childbirth as risk factors for the development of endometrial cancer, this study did not find them to be significant. This discrepancy may be due to population-specific physical differences, a small sample size, and the use of a single statistical method. Future research should involve multi-center, large-sample size, and prospective studies to more accurately confirm the predictive role and value of high-risk factors affecting endometrial atypical hyperplasia and its progression to endometrial cancer.

Conclusion

In conclusion, this study identified age ≥ 53.5 years, menopausal status, and preoperative endometrial pathology of severe atypical endometrial hyperplasia as high-risk factors for endometrial hyperplasia combined with endometrial cancer. The risk of developing endometrial cancer increases with the number of high-risk factors present in patients with AEH. These findings, which have been seldom reported in previous studies, provide a theoretical basis for clinical identification and risk assessment.

Data Sharing Statement

Data supporting the results are available upon request.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University. Relevant information, including the study's purpose, procedures, potential risks and benefits, confidentiality measures, and the rights of the participants, was provided to all participants before including them in the study. All participants in this study provided written informed consent before intervention.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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