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Diagnostic Value of ADC in Distinguishing Endometrial Cancer from Atypical Endometrial Hyperplasia and Within Molecular Subtypes

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Purpose: The study aimed to evaluate the effectiveness of using specific indicators, particularly the apparent diffusion coefficient (ADC), alone or in combination to differentiate endometrial cancer (EC) from atypical endometrial hyperplasia (AEH) and to explore non-invasive biomarkers for the molecular classification of EC.

Methods: A retrospective analysis was conducted on 300 EC and 126 AEH cases who had undergone preoperative magnetic resonance imaging, complete blood count, coagulation profile testing, and tumor biomarkers assessment. Postoperative molecular classification was conducted on 76 EC samples. Diagnostic values were assessed using receiver operating characteristic (ROC) analysis and binary logistic regression with forward selection to determine the optimal indicator combinations. Furthermore, this study evaluated the variability of parameters across EC molecular subtypes.

Results: The ADC effectively balanced sensitivity and specificity in differentiating EC from AEH. An optimal diagnostic model including age, fibrinogen, and ADC achieved the area under the curve (AUC) of 0.9143, with 84.67% sensitivity and 88.89% specificity. ADC values were found to be lower in EC cases that exhibited a higher Ki-67 index or a higher histological grade. Notably, the NSMP subtype presented significantly higher ADC values compared to the other three molecular subtypes. The p53abn subtype exhibited the highest prevalence of abnormal HE4 levels and patients aged ≥65 (both 6/12, 50%) yet normal CA125 and CA19-9 levels.

Conclusion: This retrospective study demonstrated that ADC, especially when combined with age and fibrinogen, is a valuable biomarker for distinguishing EC from AEH. In addition to indicating the Ki-67 index and histological grade, ADC values also serve as a promising tool for identifying the NSMP subtype within EC. Future studies should focus on multi-center, prospective studies with larger sample sizes to validate and refine the diagnostic value of ADC in differentiating EC from AEH, as well as in the molecular classification of EC.

Keywords: endometrial cancer, atypical endometrial hyperplasia, apparent diffusion coefficient, histological grade, Ki-67 index, molecular subtype

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries,[1] with approximately 70% of EC-related deaths occurring in patients over the age of 65.[2] Clinical risk factors associated with EC include age, obesity, diabetes and so on.[3,4] Atypical endometrial hyperplasia (AEH) is a precancerous lesion with an annual risk of

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progressing to EC of approximately 8%.[5] The management and prognosis of the two conditions diverge markedly. EC typically requires more aggressive surgical intervention, such as total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection, followed by adjuvant therapy.[6] AEH is typically managed through less extensive surgery, which remains the preferred treatment option due to the associated risk of malignancy.[7] Hormonal treatment, which is not universally effective, could be an alternative when fertility preservation is desired or surgery is not feasible. When AEH is misdiagnosed as EC before surgery, it can lead to an unnecessary expansion of surgical procedures. Furthermore, the incidence of concurrent occult EC in individuals with AEH who undergo hysterectomy was approximately 43%.[8] Some patients could benefit from sentinel lymph node biopsy,[9] but others may still be at a high risk of undergoing secondary surgical interventions. Overall, it remains a challenging yet critical need to accurately differentiate between EC and AEH.

The molecular subtyping of EC has evolved significantly since The Cancer Genome Atlas (TCGA) project first proposed a classification system in 2013.[10] However, the integration of multi-platform and multi-omics data required for this classification limits its clinical applicability. To address this, simplified methodologies such as the TransPORTEC[11] and ProMisE[12] molecular subtyping strategies have been developed. These strategies classify EC into POLE mutation (POLE mut), mismatch repair-deficient (MMRd), no specific molecular profile (NSMP), and p53 abnormal (p53abn) subtypes. Among them, the POLE mut subtype has the best prognosis, while the p53abn subtype is associated with the worst prognosis.[13–16] In 2023, International Federation of Gynecology and Obstetrics (FIGO) updated the staging system for EC, recommending molecular typing tests for all patients with EC, and adjusting the staging for patients in stages I and II based on the results of molecular typing.[17] Understanding the distinct surgical requirements and the impact of molecular subtypes on treatment and prognosis is crucial for tailoring therapeutic strategies and improving patient outcomes.

Currently, there are no specific diagnostic biomarkers for EC. However, some inflammatory indicators[18] such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), as well as coagulation indicators[19,20] like D-dimer and fibrinogen, have shown certain diagnostic and prognostic values for EC in previous studies. Additionally, tumor biomarkers such as CA125, HE4, CA19-9, and CA153 also have significance in the diagnosis of EC. However, these indicators often have limited effectiveness when used alone, and they frequently need to be combined with other indicators to enhance sensitivity and specificity.[21,22] Regarding the imaging features, an endometrial thickness of ≤ 4mm measured by Ultrasound (US) has a considerably high negative predictive value for EC in postmenopausal women. However, relying solely on the thin echo of the endometrium cannot reliably exclude the possibility of type II EC.[23] Moreover, the US is not recommended for use alone in screening for EC in premenopausal women due to its low predictive value.[24] Magnetic resonance imaging (MRI) is considered the most accurate imaging technique for preoperative assessment of EC due to its excellent soft tissue contrast resolution.[4] At present, the apparent diffusion coefficient (ADC), derived from diffusion-weighted imaging (DWI) in MRI, has emerged as a valuable diagnostic biomarker for EC. In MRI examinations, malignant tumors are typically characterized by high cellular density and reduced extracellular space, leading to restricted diffusion of water molecules and consequently lower ADC values;[25,26] in contrast, benign tumors demonstrate the opposite characteristics. This characteristic renders ADC potentially powerful non-invasive biomarkers for tumor grading and differentiation.

In this retrospective study, we gathered data, including clinical risk factors, inflammatory indicators, coagulation profiles, tumor biomarkers, and MRI characteristics, which have been established as significantly valuable for the occurrence, diagnosis, and prognosis of EC. This study aimed to identify the most efficient combination of diagnostic indicators to accurately differentiate EC from AEH. Furthermore, we explored the molecular subtype-specific profiles of clinical, biochemical, and imaging parameters within EC. By doing so, we sought to enhance the precision of diagnostic determinations and contribute to the personalized medicine approach in EC.

Materials and Methods

Inclusion and Exclusion Criteria

This retrospective analysis included 310 EC and 143 AEH patients who underwent 1.5 or 3.0 T MRI scans at Nanjing Women and Children's Healthcare Hospital from January 2021 to May 2024. The scans were performed 4 weeks before surgery, either due to challenges in accurate assessment or when malignancy was suspected. The study then excluded

cases based on the following criteria: (1) patients with AEH who did not undergo hysterectomy due to the need for fertility preservation, (2) individuals with acute inflammatory or hematological disorders, (3) those with a history of other malignancies, and (4) patients with incomplete data on inflammatory markers, coagulation profiles, and tumor biomarkers. Finally, 300 EC and 126 AEH patients were included in this study. Additionally, a total of 76 EC patients enrolled in this study underwent molecular classification following surgical intervention.

Measurement of ADC Values

The ADC values were determined by selecting regions of interest (ROIs) on DWI sequences where the signal intensity is at its peak, indicative of areas with the most restricted diffusion. Briefly, 2–3 ROIs were meticulously placed by the radiologist in the local areas of the highest DWI signal within the lesion. The ADC maps were then generated through the MRI machine's automatic post-processing. The average ADC values across these 2–3 ROIs were calculated. To ensure reliability, the ADC values measured by two independent radiologists were averaged, and this average was recorded for further statistical analysis.

Data Collection

The clinical, biochemical, and imaging data comprised age, body mass index (BMI), tumor volumes, menopausal status, complete blood count, coagulation profile testing, tumor biomarkers, and ADC values. Complete blood count, serum tumor biomarker analysis, and coagulation profile testing within 2 weeks before surgery. The ADC values were retrospectively assigned by two experienced radiologists. The postoperative pathological outcomes were assessed by two experienced pathologists. Molecular subtypes of EC were analyzed using immunohistochemistry and next-generation sequencing and diagnosed by two pathologists and two molecular biology and medical geneticists. Data collection was sanctioned by the Ethics Committee at Nanjing Women and Children's Healthcare Hospital, adhering to the principles of the Declaration of Helsinki (2024KY-082). Given the retrospective study design, the informed consent has been waived by the institutional review board, and the authors have signed a statement to ensure the confidentiality of patients.

Statistical Analysis

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 19.0. Continuous variables were presented as mean ± standard deviation. The normality of data was assessed using the Kolmogorov–Smirnov test. Depending on the outcome of the normality test, differences between two groups were evaluated using either a *t*-test or Mann–Whitney test; differences between three or more groups were evaluated using either a one-way ANOVA or Kruskal–Wallis test. Differences in the proportions of two groups were analyzed using Fisher's exact test, while differences in the proportions of four groups were analyzed using the chi-square test. The cut-off values, sensitivity, and specificity for CA125, HE4, and CA19-9 were determined using well-established clinical reference levels, while the others were identified by the maximum Youden index derived from the receiver operating characteristic (ROC) curves. The most effective combination of indicators was identified through binary logistic regression with forward selection. P value <0.05 was considered statistically significant.

Results

Diagnostic Potential of Biomarkers in Distinguishing EC from AEH

According to the data in Table 1, all enrolled cases of EC and AEH were of East Asian ethnicity. The mean age of onset for patients with EC was 55.86 ± 9.228 years, which was significantly higher than the mean age of 48.45 ± 8.752 years observed in patients with AEH ($P < 0.0001$). The BMI of patients with EC and AEH was 25.62 ± 4.175 kg/m² and 25.14 ± 3.845 kg/m², respectively. However, there were no statistically significant differences in BMI between the two groups ($P = 0.4825$). Additionally, there were no significant differences in complete blood count, including neutrophil count (N), lymphocyte count (L), monocyte count (Mo), platelet count (PLT), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and hemoglobin levels (Hb), between the EC and AEH groups. The serum levels and abnormal rates of CA125, HE4, CA19-9, and CA153 were significantly lower in AEH

Table 1 Comparison of Clinical, Biochemical, and Imaging Parameters of EC and AEH

Variables		Endometrial Cancer	Atypical Endometrial Hyperplasia	Reference Level	*P*-Value
Number		300	126		
Ethnicity	East Asian	300	126	/	/
	Other	0	0		
Age (year)		55.86±9.228	48.45±8.752	/	<0.0001
BMI (kg/m^2)		25.62±4.175	25.14±3.845	18.5–23.9	0.4825
N (10^9/L)		3.861±1.404	3.669±1.252	1.8–6.3	0.252
L (10^9/L)		1.790±2.905	1.634±0.5499	1.1–3.2	0.9635
Mo (10^9/L)		0.2955±0.1191	0.3092±0.1081	0.1–0.6	0.2662
PLT (10^9/L)		245.7±81.05	251.2±76.96	125–350	0.475
NLR		2.571±1.224	2.423±0.9953	/	0.3222
PLR		162.5±66.14	165.8±62.52	/	0.4887
MLR		0.1896±0.0789	0.2007±0.0758	/	0.0969
Hb (g/L)		127.3±16.56	125.7±17.13	115–150	0.3695
CA125 (U/mL)		39.19±85.45	16.25±9.412	0–35	<0.0001
Abnormal CA125 (%)		59/300, 19.67%	7/126, 5.56%	/	0.0001
HE4 (pmol/L)		100.8±160.9 106.9±135.5	49.82±11.54 50.94±10.93	Premenopause <70 postmenopause<140	<0.0001 <0.0001
Abnormal HE4 (%)		44/105, 41.90% 37/195, 18.97%	3/87, 3.45% 0/39, 0%	/	<0.0001 0.0012
CA19-9 (U/mL)		35.99±108.3	9.46±6.912	0–27	<0.0001
Abnormal CA19-9 (%)		68/300, 22.67%	3/126, 2.38%	/	<0.0001
CA153 (U/mL)		13.38±11.15	10.34±4.902	0–25	0.0083
Abnormal CA153 (%)		22/300, 7.33%	1/126, 0.79%	/	0.0041
Fibrinogen (g/L)		2.915±0.7518	2.651±0.4940	1.8–3.5	0.002
D-dimer (mg/L)		0.6258±1.674	0.3071±0.2326	0–0.55	<0.0001
ADC (×10^{-3}mm^2/s)		0.7845±0.1888	1.144±0.2405	/	<0.0001

Abbreviations: BMI, body mass index; N, neutrophil count; L, lymphocyte count; Mo, monocyte count, PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; Hb, hemoglobin; /, not applicable.

cases compared to those with EC. Additionally, EC was associated with significantly higher serum levels of fibrinogen and D-dimer compared to AEH cases. The ADC value of EC ($0.7845 \pm 0.1888 \times 10^{-3}$mm^2/s) was significantly lower than those of AEH ($1.144 \pm 0.2405 \times 10^{-3}$mm^2/s). Preliminary results suggested that age, coagulation-related indicators such as fibrinogen and D-dimer, tumor biomarkers such as CA125, HE4, CA19-9, and CA153 as well as the ADC value hold significant clinical relevance for the differential diagnosis of EC and AEH.

Diagnostic Performance of Individual Biomarkers and the Combined Predictive Model for EC

The diagnostic value of these individual indicators in distinguishing EC from AEH is presented in Table 2. The performance of each indicator was assessed using area under the curve (AUC), sensitivity, and specificity. Age demonstrated an AUC of 0.7353 with a cut-off value of 52.5 years old, yielding a sensitivity of 70% and a specificity of 70.63%. When applied individually, CA125, HE4, CA19-9, and CA153 were evaluated using well-established clinical reference values as cut-off points, specifically 35 U/mL for CA125, 70/140 pmol/L for HE4 (premenopause/postmenopause), 27 U/mL for CA19-9, and 25 U/mL for CA153 demonstrating high specificity but exceedingly low sensitivity. When the Youden index reached the maximum, fibrinogen showed an AUC of 0.5949 with a cut-off value of 2.985g/L and a sensitivity and specificity of 35.67% and 79.37%, respectively. D-dimer had an AUC of 0.6403, a cut-off value of 0.225mg/L, and demonstrated a sensitivity of 65.67% and a specificity of 57.94%. ADC showed the highest AUC of 0.8867 among the individual indicators, a cut-off value of $0.9395\times10^{-3}mm^2/s$, a sensitivity of 84%, and a specificity of 84.13%. Ultimately, the variables of age, fibrinogen, and ADC were identified as integral components within the established predictive model. The model's AUC value was 0.9143, indicating a high discriminative capacity, and there was no need to consider the menopausal status. At a cut-off value of 0.2555, the model's sensitivity was 84.67%, and specificity was 88.89% (Table 2, Figure 1).

The Pathological Characteristics of 300 EC and the Correlation with ADC Values

The detailed investigation into the pathological characteristics of the enrolled EC cases and their correlation with ADC values is presented in Table 3. Among the 300 EC cases enrolled in this study, 265 were endometrioid carcinomas and 19 were serous carcinomas, composing the majority. No significant differences were found in ADC values between endometrioid carcinomas and serous carcinomas ($P = 0.7277$). Moreover, there were no significant differences in ADC values between the FIGO stage (2009) I–II and III–IV groups, between the negative and positive lymph node metastasis groups, or between the negative/focal and positive/extensive lymphatic-vascular space invasion groups. Regarding hormone receptors, it was demonstrated that cases with negative estrogen receptor (ER) show equal ADC values compared to those with positive ER ($P = 0.3952$), and the same finding was observed between the negative and positive progesterone receptor (PR) groups ($P = 0.2796$). However, cases with a Ki-67 index of less than 50% exhibited higher ADC values than those with a Ki-67 index of 50% or higher ($P < 0.0001$). Additionally, regarding histological grades of endometrioid carcinomas, the grade 1–2 group tended to have higher ADC values compared to the grade 3 group ($P < 0.0001$).

Table 2 Diagnostic Value of Individual and Combined Biomarkers for Distinguishing EC From AEH

Variables	Groups	AUC	Cut-off	Sensitivity (%)	Specificity (%)
Endometrial cancer vs atypical endometrial hyperplasia	Age (year)	0.7353	52.5	70	70.63
	CA125 (U/mL)	0.6773	35	19.67	94.44
	HE4 (pmol/L)	0.7302 0.7961	70 (premenopause) 140 (postmenopause)	41.9 18.97	96.55 100
	CA19-9 (U/mL)	0.6824	27	22.67	97.62
	CA153 (U/mL)	0.5810	25	7.33	99.21
	Fibrinogen (g/L)	0.5949	2.985	35.67	79.37
	D-dimer (mg/L)	0.6403	0.225	65.67	57.94
	ADC ($\times10^{-3}mm^2/s$)	0.8867	0.9395	84	84.13
	Age+Fibrinogen+ADC	0.9143	0.2555	84.67	88.89

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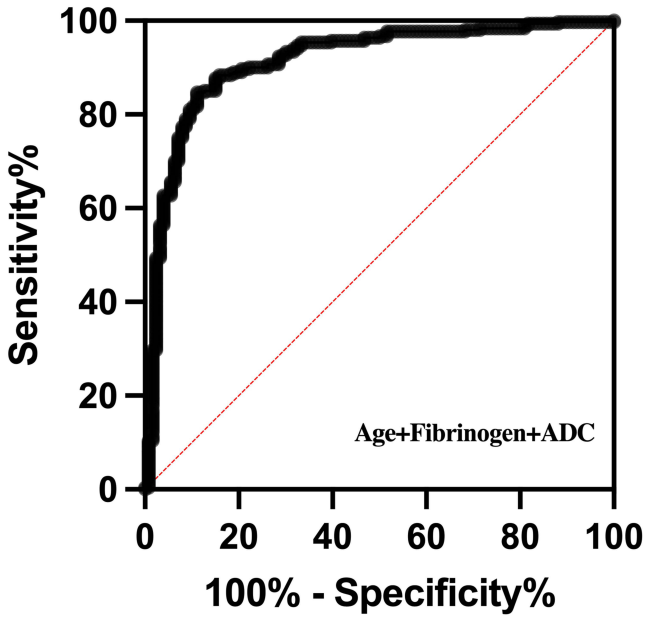

Figure 1 The ROC curve for diagnosing EC and AEH, combining age, fibrinogen, and ADC.

Molecular Subtype-Specific Profiles of Clinical, Biochemical, and Imaging Parameters in EC

A total of 76 EC cases were molecularly classified into four distinct subtypes: POLE mut (11 cases, 14.47%), MMRd (16 cases, 21.05%), NSMP (37 cases, 48.68%), and p53abn (12 cases, 15.80%), and the NSMP subtype accounted for an absolute majority. Table 4 presents a concise comparison of clinical, biochemical, and imaging parameters across molecular subtypes of EC. Parameters like tumor volume, BMI, complete blood count, and coagulation-related indicators did not show significant variations across subtypes. Additionally, the levels of CA153 were generally normal within each molecular subtype of EC.

Table 3 The Pathological Characteristics of 300 EC and the Correlation with ADC Values

Variables		**Endometrial Cancer (number)**	**ADC**	***P*-value**
Histological type	Endometrioid	265	0.7837±0.1888	0.7277
	Serous	19	0.7679±0.1714	
	Clear cell	3	/	
	Mixed	1	/	
	Undifferentiated and dedifferentiated	2	/	
	Carcinosarcoma	2	/	
	Mesonephric-like adenocarcinoma	7	/	
	Missing	1	/	
Histological grade (endometrioid carcinomas)	Grade 1–2	224	0.7963±0.1919	<0.0001
	Grade 3	31	0.6705±0.1170	
	Missing	11	/	

(*Continued*)

Table 3 (Continued).

Variables		Endometrial Cancer (number)	ADC	*P*-value
FIGO stage (2009)	I–II	230	7.835±1.854	0.6633
	III–IV	48	7.608±1.500	
	Missing	22	/	
Lymph node metastasis	Negative	251	0.7851±0.1817	0.1311
	Positive	25	0.7228±0.1565	
	Missing	24	/	
VISI	Negative/focal	244	0.7879±0.1914	0.4230
	Positive/extensive	42	0.7572±0.1476	
	Missing	14	/	
ER	Negative	29	0.7377±0.1421	0.3952
	Positive	253	0.7820±0.1859	
	Missing	18	/	
PR	Negative	41	0.7398±0.1410	0.2796
	Positive	241	0.7838±0.1878	
	Missing	18	/	
Ki-67 index	<50%	109	0.8310±0.1819	<0.0001
	≥50%	172	0.7470±0.1816	
	Missing	19		

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ER, estrogen receptor; PR, progesterone receptor; LVSI, lymphatic vascular space invasion; /, not included.

In terms of ADC values, the NSMP subtype demonstrated the highest mean ADC of $0.8414 \pm 0.1557 \times 10^{-3}mm^2/s$, statistical comparisons revealed that the ADC values for the NSMP subtype were significantly greater than those of the POLE mut ($P = 0.0467$), MMRd ($P = 0.0025$), and p53abn ($P = 0.0047$) subtypes.

Notably, the p53 abn subtype exhibited a significantly higher rate of patients aged 65 and over (6/12, 50%) compared to the other three subtypes. Additionally, the p53abn subtype of EC was characterized by the highest rate of abnormal HE4 levels (6/12, 50%), yet it exhibited the lowest rates of abnormal CA125 and CA19-9 levels (0/12, 0% each). The statistical analysis revealed that while there were notable differences in the rates of abnormal tumor biomarker levels between the p53abn subtype and other subtypes, these differences only reached statistical significance in comparisons with certain subtypes. For instance, the absence of abnormal CA125 and CA19-9 levels in the p53abn subtype was significantly different from the rates observed in the POLE mut subtype for CA125, and from the POLE mut and NSMP subtypes for CA19-9. Similarly, the high rate of abnormal HE4 levels in the p53abn subtype was significantly different from the NSMP subtype but not from the others. Significantly, it was also revealed that all patients aged 65 and above with elevated HE4 levels (4 cases in total) exclusively belong to the p53abn subtype (Supplementary data 1).

Discussion

This study was centered on the development of an optimal diagnostic panel that can accurately differentiate EC from AEH and inform treatment strategies and prognosis. Data, including clinical risk factors, inflammatory indicators,

Table 4 Clinical, Biochemical, and Imaging Parameters for Non-Invasive Prediction of Molecular Subtypes in EC

Variables	POLE mut [a] (11, 14.47%)	MMRd [b] (16, 21.05%)	NSMP [c] (37, 48.68%)	p53abn [d] (12, 15.80%)	Reference Level	*P*-Value
Tumor volume (cm^3)	37.77± 91.77	10.98±14.30	16.25±33.45	44.26±84.18	/	0.6481
Age ≥65 (%)	0/11, 0%	0/16, 0%	4/37, 10.81%	6/12, 50%	/	0.0137(a vs d) 0.0025(b vs d) 0.0082(c vs d)
BMI (kg/m^2)	24.22±3.398	23.05±3.262	26.42±3.783	25.83±4.403	18.5–23.9	0.0014(c vs b)
N (10^9/L)	3.395±1.213	3.654±1.593	3.796±1.220	4.254±1.413	1.8–6.3	0.4994
L (10^9/L)	1.617±0.5078	1.617±0.4485	1.659±0.4964	1.703±0.6456	1.1–3.2	0.08336
Mo (10^9/L)	0.2400±0.08343	0.3013±0.1466	0.2808±0.1079	0.2867±0.1406	0.1–0.6	0.5921
PLT (10^9/L)	264.5±73.95	258.0±161.0	234.1±66.32	245.8±110.7	125–350	0.4063
NLR	2.276±1.007	2.348±0.9359	2.372±0.6962	2.672±0.9975	/	0.7857
PLR	171.4±55.40	161.0±72.53	147.3±44.19	161.0±90.23	/	0.5777
MLR	0.1577±0.0616	0.1907±0.07146	0.1714±0.05018	0.1697±0.05733	/	0.7776
Hb (g/L)	123.5±23.65	127.9±17.13	130.1±16.29	123.4±18.65	115–150	0.6364
Abnormal CA125 (%)	4/11, 36.36%	4/16, 25%	5/37, 13.51%	0/12, 0%	0–35	0.0421(a vs d)
Abnormal HE4 (%)	3/11, 27.27%	6/16, 37.5%	6/37, 16.22%	6/12, 50%	Premenopause <70 postmenopause<140	0.0475(c vs d)
Abnormal CA19-9 (%)	4/11, 36.36%	3/16, 18.75%	11/37, 29.73%	0/12, 0%	0–27	0.0373(a vs d) 0.0451(c vs d)
Abnormal CA153 (%)	2/11, 18.18%	0/16, 0%	1/37, 2.70%	0/12, 0%	0–25	0.0664
Fibrinogen (g/L)	2.965±0.6717	2.867±0.5702	2.786±0.5296	2.951±0.5750	1.8–3.5	0.4384
D-Dimer (mg/L)	0.4900±0.5231	0.5313±0.4469	0.3354±0.2047	0.3967±0.1660	0–0.55	0.1887
ADC ($\times10^{-3}mm^2/s$)	0.7373±0.1176	0.6969±0.1410	0.8414±0.1557	0.6867±0.1602	/	0.0467(c vs a) 0.0025(c vs b) 0.0047(c vs d)

Abbreviations: BMI, body mass index; N, neutrophil count; L, lymphocyte count; Mo, monocyte count, PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; Hb, hemoglobin; /, not applicable.

coagulation indicators, tumor biomarkers, and MRI features that have been established to hold significant value in the diagnosis and prognosis of EC, were collected. However, due to the significant influence of the menstrual cycle on endometrial thickness in premenopausal women, this retrospective study cannot effectively eliminate the impact of differences in endometrial thickness across various stages of the menstrual cycle. Consequently, endometrial thickness is temporarily not considered for inclusion in the analysis. Moreover, preoperative computed tomography (CT) was utilized to evaluate cases with suspected distant metastases. However, due to the limited number of such cases available for statistical analysis, data on CT was not systematically collected and used as a criterion for inclusion or exclusion.

The significant differences in serum levels and abnormal rates of CA125, HE4, CA19-9, and CA153 between EC and AEH highlighted the potential utility of these conventional tumor biomarkers in differential diagnosis. The high specificity of these conventional tumor biomarkers indicated their potential effectiveness in confirming the absence of disease. However, the low sensitivity observed suggested that these tumor biomarkers alone may not be sufficient for disease detection,[27,28] emphasizing the need for a multi-biomarker approach to improve diagnostic accuracy. Notably, the

ADC values alone showed a relative balance between sensitivity and specificity. Moreover, the high AUC, sensitivity, and specificity of ADC combined with age and fibrinogen suggested its robustness in differentiating EC from AEH. It is worth mentioning that 11 cases of AEH in young patients, with an average age of 30 years, were diagnosed using curettage samples rather than hysterectomy samples in order to preserve fertility. Age is a risk factor of EC[2,3] and an important component for discriminating between EC and AEH in this combined diagnostic model. The exclusion of these young AEH cases, due to the possibility of concurrent EC,[8,9] may result in the current presentation of the combined diagnostic model appearing less effective than it would actually be. Therefore, more effective and reasonable approaches[7] are needed to handle such cases in future studies.

We further investigated the correlation between the pathological characteristics of EC and ADC values. ADC values tended to be higher in EC cases with a Ki-67 index of less than 50% compared to those with a Ki-67 index of 50% or higher. Due to the small sample size and the considerable histological variations in non-endometrioid carcinoma, the analysis of pathological grade was confined to endometrioid carcinoma. Notably, endometrioid carcinomas of grades 1–2 demonstrated higher ADC values in comparison to those of grade 3. These findings are consistent with previous studies,[29,30] indicating that higher proliferative activity, a larger nucleocytoplasmic ratio, and a higher proportion of solid components lead to increased cellular density and reduced extracellular space, and consequently, restricted diffusion of water molecules.

The non-invasive prediction of EC molecular subtypes is an important research field, as early molecular subtyping can help guide personalized treatment and predict prognosis. Our study provided a comprehensive molecular landscape of EC, revealing distinct clinical, biochemical, and imaging profiles across the POLE mut, MMRd, NSMP, and p53abn subtypes. The NSMP subtype was predominant among EC cases in our study, aligning with findings from other studies in the Chinese population.[31,32] Notably, in addition to distinguishing EC from AEH, ADC values played a significant role in differentiating between molecular subtypes. In our study, the ADC values of the NSMP subtype were found to be significantly higher compared to the other three subtypes. Consistently, a previous study in EC demonstrated that the ADC values of the POLE mut and MMRd groups were lower than those of the NSMP group. Although no statistically significant difference was observed, it is noteworthy that the ADC values in the p53abn group still tended to be lower compared to the NSMP group in the previous study.[32] Overall, our study suggested that the ADC value is a promising avenue for non-invasive diagnosis and subtype discrimination. However, a larger sample size and standardized imaging protocols are needed to confirm these findings.

Moreover, the p53abn subtype of EC was characterized by the lowest rates of abnormal CA125 and CA19-9 levels, but a notably highest rate of abnormal HE4 levels and the number of patients with age ≥65. Moreover, there were 4 cases with elevated HE4 levels and aged ≥65, and all exclusively belonged to the p53abn subtype. A recent study has demonstrated that the incidence of p53abn increased with age and advanced age has been identified as an independent prognostic factor associated with patient-specific mortality in EC.[33] Previous findings and our study suggested that the combination of HE4, age, and other tumor biomarkers could serve as a sensitive model for detecting the p53abn subtype. Future validation with a larger sample size will be essential, potentially providing valuable insights to guide treatment decisions and predict prognosis, particularly for elderly patients who may not tolerate surgery.

Some limitations need to be addressed in upcoming studies. First, this study is a single-center retrospective study with a relatively small sample size, which may limit the generalizability of the results. Future studies should focus on multi-center, prospective studies with larger sample sizes to validate and refine the diagnostic value of ADC in differentiating EC from AEH, as well as in the molecular classification of EC. Moreover, the information regarding demographic, clinical, imaging, and hysteroscopic characteristics in our study is not sufficiently comprehensive, particularly concerning the US features such as baseline endometrial thickness, blood flow patterns, and other specific MRI signal characteristics. These additional parameters could provide a more comprehensive understanding of the AEH and EC, and thereby improving diagnostic accuracy. Future studies should consider incorporating these factors to enhance the robustness and applicability of this predictive model.

Conclusion

These findings from this retrospective study underscore the diagnostic potential of ADC as a non-invasive biomarker. It effectively distinguishes EC from AEH, indicates the Ki-67 index and histological grade of EC cases, and differentiates

the NSMP subtype within molecular subtypes. Furthermore, a combined assessment of HE4, age, CA125, and CA19-9 may serve as a future strategy to identify the p53 abn subtype. Future research should focus on validating these biomarkers in multi-center, prospective studies involving larger cohorts, and on enhancing the diagnostic efficiency by combining with additional demographic, clinical, imaging, and hysteroscopic characteristics.

Data Sharing Statement

The data are not publicly accessible but are available upon reasonable request from the corresponding author.

Ethics Approval and Informed Consent/Consent for Publication

Data collection was sanctioned by the Ethics Committee at Nanjing Women and Children's Healthcare Hospital, adhering to the principles of the Declaration of Helsinki (2024KY-082). Given the retrospective study design, the informed consent has been waived by the institutional review board, and the authors have signed a statement to ensure the confidentiality of patients.

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 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.

Disclosure

The authors report no conflicts of interest in this work.

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