



Research Article

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Assessment of P53 and E-cadherin Immunohistochemical Expression in Endometrial Hyperplasia and Endometrial Carcinoma: A Comparative Clinicopathological Study

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Abstract

Background: Diverse molecular mutations have been implicated in the pathogenesis of endometrial carcinoma. P53 and E-cadherin are among them and may have a role in the conversion of endometrial hyperplasia to endometrial carcinoma. **Objective:** To compare the frequency of P53 and E-cadherin expression in endometrial hyperplasia with that in carcinoma and study their association with clinicopathological parameters in endometrial carcinoma. **Methods:** In a cross-sectional study, 20 cases of endometrial hyperplasia without atypia and 52 cases of primary endometrial cancer were included. Formalin-fixed, paraffin-embedded blocks of these cases were collected from Kirkuk General Hospital, Azady Teaching Hospital, and private laboratories in Kirkuk and Mosul cities. **Results:** In endometrial carcinoma, P53 mutant-type and E-cadherin downregulation were detected (40.4% and 53.8%, respectively), while in endometrial hyperplasia, they were 20% and 15%, respectively. A significant association was reported when comparing the frequency of E-cadherin expression in endometrial hyperplasia with that of endometrial carcinoma. Mutant P53 expression pattern was significantly related to tumor grade, metastasis, and stage; E-cadherin downregulation was significantly associated with lymphovascular invasion, metastasis, and stage. **Conclusions:** There was a significant difference in the expression of E-cadherin between endometrial hyperplasia and endometrial carcinoma; downregulation of this marker in endometrial hyperplasia cases may predict a higher risk of these cases changing into cancer. In endometrial carcinoma, P53 mutation and E-cadherin downregulation can be used as supportive biomarkers to identify a subgroup of patients with aggressive behavior and poor prognosis, and P53 appeared as a better predictor than E-cadherin for metastasis and stage.

Keywords: Endometrial neoplasm; Endometrial hyperplasia; E-cadherin; Immunohistochemistry; P53.

تقييم التعبير النسيجي المناعي P53 و E-cadherin في فرط تنسج بطانة الرحم وسرطان بطانة الرحم: دراسة سريرية مقارنة

الخلاصة

الخلفية: تم ربط طفرات جزيئية متنوعة بمسببات سرطان بطانة الرحم. من بينها P53 و E-cadherin وقد يكون لهما دور في تحويل فرط تنسج بطانة الرحم إلى سرطان بطانة الرحم. **الهدف:** مقارنة تكرار تعبير P53 و E-cadherin في فرط تنسج بطانة الرحم مع ذلك في سرطان بطانة الرحم ودراسة ارتباطهما بالمعلمات السريرية المرضية في سرطان بطانة الرحم. **الطرائق:** في دراسة مقطعية، تم تضمين 20 حالة من تضخم بطانة الرحم بدون انضمام و 52 حالة من سرطان بطانة الرحم الأولي. تم جمع كتل مثنية بالفورمالين ومدمجة بالبارافين من هذه الحالات من مستشفى كركوك العام، ومستشفى آزادي التعليمي، ومختبرات خاصة في مدينتي كركوك والموصل. **النتائج:** في سرطان بطانة الرحم، تم اكتشاف انخفاض في اضطراب P53 و E-cadherin (40.4% و 53.8% على التوالي)، بينما في فرط تنسج بطانة الرحم، كان 20% و 15% على التوالي. تم الإبلاغ عن ارتباط مهم عند مقارنة تكرار تعبير E-cadherin في فرط تنسج بطانة الرحم مع سرطان بطانة الرحم. كان نمط تعبير P53 المتحولين مرتبطاً بشكل كبير بدرجة الورم، والنقائل، والمرحلة؛ كان انخفاض تنظيم E-cadherin مرتبطاً بشكل كبير بالغزو المفاوي الوعائي، والنقائل، والمرحلة. **الاستنتاجات:** هناك فرق كبير في تعبير E-cadherin بين فرط تنسج بطانة الرحم وسرطان بطانة الرحم؛ قد يتنبأ انخفاض تنظيم هذه المؤشر في حالات فرط تنسج بطانة الرحم بزيادة خطر تحول هذه الحالات إلى سرطان. في سرطان بطانة الرحم، يمكن استخدام طفرة P53 وخفض تنظيم E-cadherin كمؤشرات حيوية داعمة لتحديد مجموعة فرعية من المرضى ذو السلوك العدواني وتوقعات ضعيفة، وظهر P53 كمؤشر أفضل من E-cadherin للنقائل والمرحلة.

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INTRODUCTION

Endometrial hyperplasia (EH) is demarcated by the overgrowth of the glands relative to the surrounding stroma in a ratio of 3:1 [1]. There are two types of EH: EH without atypia and EH with atypia [1]. EH is regarded as a precancerous lesion for endometrial carcinoma (ECa), which is the sixth most commonly diagnosed malignancy among females worldwide, with the highest occurrence detected in developed countries [1]. Its incidence has continued to increase over recent decades, mainly due to rising obesity rates and changing reproductive patterns [1]. There are two kinds of ECa pathogenesis: type 1: endometrioid ECa (arises from hyperplastic endometrium, is estrogen-associated, and is less aggressive) and type 2: non-endometrioid ECa

(NEC) (arises from atrophic endometrium, is not linked to estrogen, and has an aggressive phenotype) [2]. TP53 codes the P53 protein, which is a tumor suppressor protein that performs a critical function in regulating a number of tumor pathways (cell cycle arrest, DNA repair, autophagy, and apoptosis) [3]. When assessing the prognosis of four types of endometrial cancer categorized by the World Health Organization (WHO), the P53 mutation group had the poorest prognosis and outcome but gained an advantage from the addition of chemotherapy to adjunct radiotherapy [4]. E-cadherin is a critical cell adhesion protein that works in preserving cellular integrity and tissue architecture [5]. In many human cancers, decreased E-cadherin expression is linked to invasion, poor differentiation, metastases, and

eventually an unfavorable prognosis [6]. It was reported that the disturbance of E-cadherin expression in ECa begins very early, and it was similarly noticed in EH [7]. Though several studies have studied the immunohistochemical expression of P53 and E-cadherin in EH and ECa, most of the available data have been developed from research outside Iraq. Based on the available data, no published Iraqi study has thoroughly evaluated the combined immunohistochemical expression of P53 and E-cadherin in EH and ECa; therefore, this research aimed to assess the immunohistochemical expression of P53 and E-cadherin in EH and ECa, as well as their associations with various clinicopathological parameters in ECa, including patient age, tumor size, tumor grade, myometrial invasion, lymphovascular invasion, metastasis, and tumor stage.

METHODS

Study design, setting, and Patients

In this comparative cross-sectional study, 20 cases of EH without atypia (tissue specimens were obtained from 16 cases via hysterectomy and 4 cases via dilation and curettage (D&C)) and 52 cases of primary ECa (obtained via hysterectomy) were included. After obtaining ethical approval, formalin-fixed, paraffin-embedded (FFPE) tissue blocks of these cases, which were diagnosed during a period extending from the 1st of January 2023 to the 10th of April 2026, were collected from Kirkuk General Hospital, Azady Teaching Hospital, and private laboratories in Kirkuk and Mosul city. The collection period of tissue blocks extended from the 25th of December 2025 to the 10th of April 2026.

Inclusion criteria

All cases that were diagnosed as EH based on D&C &/or hysterectomy specimens and the cases that were diagnosed according to the WHO (2020) histological classification as primary ECa (endometrioid and non-endometrioid type) [8], based on hysterectomy specimens, were enrolled in this study.

Exclusion criteria

Cases with insufficient or poor-quality tissue samples, patients diagnosed with ECa depending on the D&C procedure, patients diagnosed with cancer types other than pure carcinoma (e.g., endometrial sarcoma or carcinosarcoma), patients with recurrent ECa, patients with incomplete clinical or pathological information, and cases that had received radiation, chemotherapy, or hormonal therapy before the operation were excluded.

Outcome measurements

For all the cases included in the study, hematoxylin and eosin (H&E) stained slides were prepared and reviewed. For EHs, subtypes were classified according to the 2014 WHO classification, and for ECa, FIGO grading, myometrial invasion, and lymphovascular invasion were reassessed. Other data

(age of the patient, tumor size, tumor metastasis, and stage) were obtained from the medical records. For immunohistochemical analysis, the FFPE tissue block of each case of EH and ECa with little or no necrosis was chosen, and sections were cut at a thickness of 4 μ m; then the sections were mounted on the slides. Deparaffinization, rehydration, and heat-induced epitope (HIER) were performed. The mounted tissue sections were immersed in the preheated EnVision FLEX Target Retrieval solution in PT Link tanks and incubated for 20-40 minutes at 97°C, then the sections were left to cool in the PT Link to 65°C. Each Autostainer slide rack with the slides was removed from the PT Link tank and immediately dipped into a jar (PT Link Rinse Station, code PT109) with diluted, room-temperature EnVision FLEX Wash Buffer (20X) with high pH (Tris-EDTA PH 9) for P53 and low pH (citrate buffer PH 6) for E-cadherin. The slides were kept in the diluted, room-temperature EnVision FLEX Wash Buffer (20X) for 1-5 minutes. The slides were placed on an Autostainer Link instrument to perform an immunohistochemical staining procedure with primary antibodies (anti-P53 antibody, Dako, mouse monoclonal DO-7, code M7001, with incubation time 20-30 min diluted as 1:100; anti-E-cadherin antibody, thermos Fisher Scientific, rabbit monoclonal antibody, clone EP700Y, with incubation time 60 min, diluted as 1:50). The detection system was done by the EnVision FLEX visualization system (FLEX + mouse and FLEX + mouse 2x5 DAB were used for P53, while the FLEX + Rabbit and FLEX + Rabbit 2x5 DAB protocol was used with E-cadherin). After staining, dehydration, clearing, and permanent mounting were performed on the stained slides. For P53, a section from normal tonsillar tissue was used as a positive control, while for E-cadherin, the positive control used with each run was normal endometrial tissue.

P53 scoring system

P53 expression is detected as brown nuclear staining and is divided into wild-type and mutant-type patterns. Wild-type P53 is characterized by an uneven proportion of tumor cell nuclei staining (from 1% to 80%) with different intensities. Mutant-type P53 is categorized as overexpression (> 80% of tumor cell nuclei staining), cytoplasmic staining, and complete absence of staining. The mutant-type P53 was called a subclonal P53 staining pattern when 10% of the entire region showed mutant-type staining patterns, while other regions showed wild-type P53 IHC staining [9].

E-cadherin scoring system

E-cadherin expression was separated into two groups: the normal expression group, which is characterized by homogeneous, strong brown membranous staining of $\geq 70\%$ of tumor cells, and the downregulation group, which is characterized by abnormal staining patterns, such as membrane and cytoplasmic staining, cytoplasmic only, and complete loss or showing staining of <70% of tumor cells

[10,7,5]. To minimize assessment bias, all slides were independently evaluated by two histopathologists who were blinded to the clinical and pathological data of the cases. using predefined and standardized scoring criteria.

Ethical considerations

Ethical approval was obtained from the Kirkuk Health Department (Certificate ID: 836, date: 24-12-2025). Written informed consent was obtained for the prospective component, while informed consent was waived for the retrospective component involving archival tissue and previously recorded data.

AI Use declaration

Grammarly AI was used solely for language and grammar editing of the manuscript. It was not used for data analysis, generation of scientific content, interpretation of results, or formulation of conclusions. The authors are fully responsible for the accuracy and integrity of the manuscript.

Statistical analysis

The obtained data were processed using the Statistical Package for the Social Sciences (SPSS) version 24. Patients' ages were presented as a range with a mean $\pm$ SD. Qualitative variables were demonstrated as frequencies and percentages. For categorical variables, the chi-square test was used, while Fisher's exact test was used when the assumptions for the Pearson chi-square test were not satisfied, particularly when expected cell frequencies were small. For the multivariable logistic regression models, stage and metastasis were entered as covariates because both showed statistically significant associations with P53 and E-cadherin expression on chi-square analysis. A p -value <0.05 was considered statistically significant.

RESULTS

In this study, 20 cases of EH without atypia and 52 cases of primary ECa (type 1, endometrioid ECa) were included. 68 of the cases were of hysterectomy specimens, and only 4 cases of EH were of D&C specimens. In this study, the majority of cases (40.3%) were within the age group ranging from 50 to 60 years (Figure 1). For patients with EH, the age ranged from 41 to 54 years, with a mean of 47.7 ± 5.3 years. For the patients with ECa, the age ranged from 40 to 81 years (59.38 ± 9.05). In the 52 cases of ECa, the tumor size in 24 cases (46.1%) was <3 cm;

most of the cases, 47 (90.4%) out of 52 cases, were of lower grade (grade I and II); only 5.0 cases (9.6%) were of grade III; 19 cases (36.5%) showed $<50\%$ myometrial invasion, and 19 cases (36.5%) showed lymphovascular invasion. Regarding metastasis, 9 cases (17.3%) of ECa were presented with metastasis at the time of diagnosis (3 of them metastasized to the cervix, and 6 of the cases showed ovarian metastasis). In this study, tumor stage was divided into 3 categories, stage IA, IB, and stage II-IV. The majority of the cases, 43 (82.7%) out of 52 cases were of stage I, and 9 cases (17.3%) were of a higher stage (4 cases were stage II, 4 cases were stage III, and only one case was stage IV) (Table 1).

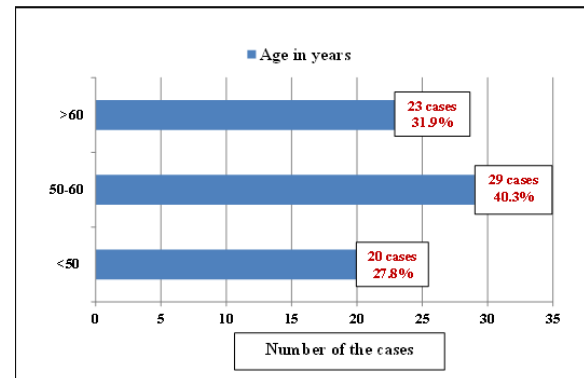


Figure 1: Age distribution of all cases included in the study.

Table 1: Clinicopathological characteristics of the endometrial carcinoma cases included in the study

Variable parameters	n(%)
Tumor size (cm)	
< 3	24(46.1)
3-5	20(38.5)
> 5	8(15.4)
Grade	
I	22(42.3)
II	25(48.1)
III	5(9.6)
Myometrial invasion (%)	
<50%	19(36.5)
>50%	33(63.5)
Lymphovascular invasion	
Positive	19(36.5)
Negative	33(63.5)
Metastasis	
Positive	9(17.3)
Negative	43(82.7)
Tumor stage	
IA	19(36.5)
IB	24(46.2)
II-IV	9(17.3)

In the current study, 4 cases (20%) with EH showed expression of the P53 mutant-type pattern, while 21 out of 52 cases (40.4%) of ECa showed the P53 mutation pattern; this association was not significant ($p= 0.1$). E-cadherin expression was downregulated in 28 cases (53.8%) of ECa, while in EH, it was downregulated in only 3 cases (15%). This association was statistically significant ($p= 0.002$) (Table 2).

Table 2: Comparison between the frequency of P53, and E-cadherin expression in endometrial hyperplasia without atypia and endometrial carcinoma

Markers	Endometrial hyperplasia	Endometrial carcinoma	p-value
P53 expression			
Wild-type	16(80)	31(59.6)	0.1
Mutant-type	4(20)	21(40.4)	
Total	20(100)	52(100)	
E-cadherin expression			
Normal	17(85)	24(46.2)	0.002
Downregulated	3(15)	28(53.8)	
Total	20(100)	52(100)	

Values are presented as frequency and percentage. Statistical analysis was performed using the Chi-square (χ^2) test at $p<0.05$.

In this study, the relation of P53 expression with the tumor grade and stage was statistically significant ($p=0.01$ and 0.03 , respectively), in which most of the cases with high grade and stage showed a mutant P53 expression pattern, and the P53 mutant pattern was more detected (77.8%) in the cases that showed metastasis, and this relationship was also significant ($p=0.01$). Although 11 (79.5%) out of 19 cases with lymphovascular invasion showed a mutant pattern of P53 expression, and 23 (69.7%) out of 33 with no invasion showed a wild pattern, the association with lymphovascular invasion was not significant, but it was close to significant ($p=0.05$). No significant association was detected between P53 expression and patients' age, tumor size, and myometrial invasion ($p=0.3$ and 0.5 , 0.3 , respectively). In the current study, 16 (84.2%) out of 19 cases with lymphovascular invasion showed downregulation of E-cadherin, and 21 (63.6%) out of 33 cases with no invasion showed normal E-cadherin expression. This

relation was highly significant ($p<0.001$); the expression of E-cadherin was significantly downregulated in the cases with metastasis and with a high stage ($p=0.02$ and 0.03 , respectively), meaning that most of the cases with metastasis and with a higher stage showed E-cadherin downregulation. No significant relationship was observed between E-cadherin and patients' age, tumor size, and tumor grade ($p=0.5$, 0.5 , and 0.1 , respectively). Twenty-one of the cases (63.6%), out of 33 cases with $>50\%$ myometrial invasion, showed E-cadherin downregulation, and 12 cases (63.2%) out of 19 cases with $<50\%$ myometrial invasion showed normal E-cadherin expression; the association was not significant ($p=0.06$) (Table 3). By using multivariable logistic regression analyses, P53 appeared as an important independent predictor for both tumor metastasis and stage ($p=0.03$ and 0.04 , respectively) (Table 4).

Table 3: Correlation between P53 and E-cadherin expression with variable clinicopathological parameters of the cases with endometrial carcinoma (total $n=52$)

Variable parameters	n	P53 expression		p-value	E-cadherin expression		p-value
		Mutant type	Wilde type		Down-regulated	Normal	
Age (year)	<50	7	4(57.1)	3(42.9)	5(71.4)	2(28.6)	0.5
	50-60	22	10(45.5)	12(54.5)	11(50)	11(50)	
	>60	23	7(30.4)	16(69.6)	12(52.2)	11(47.8)	
Tumor size (cm)	<3	24	10(41.7)	14(58.3)	11(45.8)	13(54.2)	0.5
	3-5	20	7(35)	13(65)	12(60)	8(40)	
	>5	8	4(50)	4(50)	5(62.5)	3(37.5)	
Grade	I	22	6(27.3)	16(72.7)	9(40.9)	13(59.1)	0.1
	II	25	10(40)	15(60)	15(60)	10(40)	
	III	5	5(100)	0(0)	4(80)	1(20)	
Myometrial Invasion (%)	>50	33	15(45.5)	18(54.5)	21(63.6)	12(36.4)	0.06
	<50	19	6(31.6)	13(68.4)	7(36.8)	12(63.2)	
Lympho-vascular Invasion	Present	19	11(57.9)	8(42.1)	16(84.2)	3(15.8)	<0.001
	Absent	33	10(30.3)	23(69.7)	12(36.4)	21(63.6)	
Metastasis	Present	9	7(77.8)	2(22.2)	8(88.9)	1(11.1)	0.02
	Absent	43	14(32.6)	29(67.4)	20(46.5%)	23(53.5)	
Tumor stage	IA	19	7(36.8)	12(63.2)	7(36.8)	12(63.2)	0.03
	IB	24	7(29.2)	17(70.8)	13(54.2)	11(45.8)	
	II-IV	9	7(77.8)	2(22.2)	8(88.9)	1(11.1)	

Values are presented as frequency and percentage. Statistical analysis was performed by using Chi-square (χ^2) and Fisher exact tests when indicated at $p<0.05$.

Table 4: Multivariable regression analyses of P53 and E-cadherin expression as predictors of metastasis and stage in endometrial carcinoma

Outcome	Type of regression	Predictor	OR	95% CI	p-value
Metastasis	Binary logistic regression	P53 (mutant-type expression)	6.93	1.18–40.7	0.03
		E-cadherin (downregulated)	8.78	0.9–81.6	0.056
FIGO stage	Ordinal logistic regression	P53 (mutant-type expression)	0.31	0.101–0.9	0.04
		E-cadherin (downregulated)	0.75	0.25–2.15	0.58

OR: odds ratio; CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics.

Representative photographs of cases included in this study are shown in Figures 2 and 3.

DISCUSSION

Diagnosing EH cases with a high risk of progression to ECa at an initial stage is a critical issue, and the detection of the biomarkers that play a role in this change is significantly required [11]. Growth of EC, which is the predominant infiltrating cancer of the female reproductive system, includes the gradual gaining of numerous genetic changes in proto-oncogenes and tumor suppressor genes [3]. Endometrial carcinoma is currently classified into four main groups based on a combination of histological and molecular findings according to

WHO (2020) classification: POLE-mutant, mismatch repair-deficient (MMRd), P53-abnormal, and no specific molecular profile (NSMP). Immunohistochemical evaluation of P53 offers a useful method for molecular classification in routine pathology. It is frequently employed as a surrogate marker for detecting the P53-abnormal molecular subgroup [4], and it considerably influences an individualized risk assessment and consequent treatment [4]. In this study, the frequency of the P53 mutant-type pattern in EH without atypia was detected in 20% of the cases. This result does not match with that of Ahmed *et al.* [12] and Swami *et al.* [13].

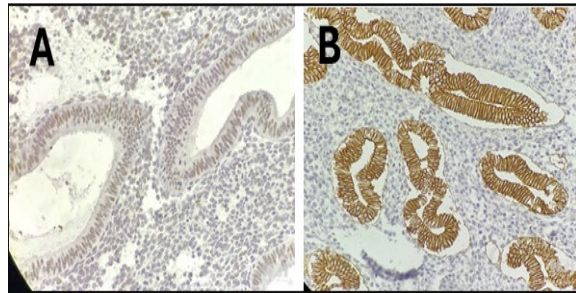


Figure 2: Endometrial hyperplasia without atypia. A: Immunohistochemical staining for P53, wild-type pattern (Magnification x400). B: Immunohistochemical staining for E-cadherin, normal membranous expression (Magnification x 400).

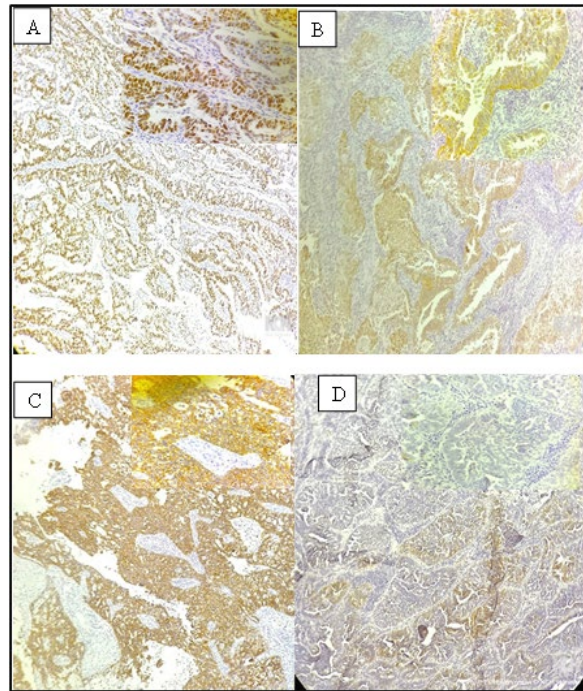


Figure 3: Endometrial carcinoma. A) Immunohistochemical staining for P53, mutant-type pattern (nuclear overexpression); B) Immunohistochemical staining for P53, mutant-type pattern (cytoplasmic expression); C) Immunohistochemical staining for E-cadherin, downregulation (cytoplasmic expression); D) Immunohistochemical staining for E-cadherin, downregulation (<70% of cells stained). Magnification x100; the inset displays a higher-magnification view (x400).

In their studies, there was no immune positivity in cases of EH without atypia; this discrepancy may be because of variation in the primary antibody used, scoring system, and heterogeneity of cases included. The frequency of the P53 mutant-type pattern in ECa was noticed in 40.4% of the cases included in this study, and this rate was close to the results of studies done by Tresa *et al.* [14], Acat *et al.* [15], and Ahmed *et al.* [12] (42.8%, 37.5%, and 32.5%, respectively). Although the rate of the P53 mutant pattern in ECa was twice the rate in EH, no significant difference was detected in P53 expression between EH and ECa. According to the available data, no other previous study compared the expression of P53 in EH with that of ECa. No significant association was detected between P53 expression and patients' age; this result was correlated with other studies [3,9,14,16]. When comparing P53 expressions to the tumor size, it was found that the frequency of mutation is higher in the

cases with larger tumor sizes, but the relation was not statistically significant. This discrepancy may be attributed to the relatively small sample size of this study; however, this finding agreed with Tresa *et al.* [14]. Regarding P53 expression and tumor grade, it was found that the frequency of the mutant P53 expression pattern is increased with the increasing of the tumor grade, that the rate of P53 mutant-type in grade III was greater than that in grades I and II, and this finding was similar to that of Ahmed *et al.* [12], Stavropoulos *et al.* [16], and Opric *et al.* [17]. This result suggests that the P53 mutation contributes to an increased tumor grade by causing a loss of genomic stability and antitumor transcriptional action, frequently acquiring oncogenic functions that promote tumor proliferation and invasion, which in turn leads to a more aggressive phenotype [14]. In comparing P53 expression with myometrial invasion, no significant association was detected; this finding correlated with studies done by Acat *et al.* [15], Tresa *et al.* [14], and Stavropoulos *et al.* [16]. In this study, although most of the cases with lymphovascular invasion showed mutant P53 expression, and most of the cases with no lymphovascular invasion showed a wild-type pattern, the association was not statistically significant. Previous studies conducted by Chang *et al.* [9], Tresa *et al.* [14], and Stavropoulos *et al.* [16] also found no significant association. About the relation of P53 with tumor metastasis, the higher frequency of the P53 mutant pattern seen in the cases that showed tumor metastasis, and the relation were statistically significant; this finding correlated with that of Ahmed *et al.* [12], Tresa *et al.* [14], and Stavropoulos *et al.* [16]. In the present study, a significant relationship was noticed between the expression of the P53 mutant pattern and the pathological stage; the frequency of P53 mutation was lower in the cases with stage I. Acat *et al.* [15], Tresa *et al.* [14], and Sunita *et al.* [18] reported comparable results in their respective studies; however, this finding does not agree with a study done by Chang *et al.* [9], because in their study, all cases were in stage I (IA, IB). The downregulation of E-cadherin is established as part of the molecular event that leads to cancer metastasis [10]. In this research, the E-cadherin downregulation in EH was detected in 15% of the cases; this result was near to that of Carico *et al.* [19] (25%), while it disagreed with that of Yadav *et al.* [6], and in Jayaraman *et al.* [7], in their studies, E-cadherin downregulation was detected in 63% and 70.6%, respectively. This difference may be due to variations in the number of cases, the heterogeneity of the cases, different primary antibodies, and different scoring systems used. The frequency of E-cadherin downregulation in ECa was 53.8%, and this rate was close to Koyuncuoglu *et al.* [20] and Yadav *et al.* [6] (50.5% and 69%, respectively). Significant association was noticed when comparing the frequency of E-cadherin expression in EH with that of ECa. The current study stands out, as no other studies focus on this association for comparison. The frequency of E-cadherin downregulation in ECa was higher than that in EH; this finding may indicate that

EH cases with E-cadherin downregulation are more likely to change into ECa. The finding may suggest that screening for E-cadherin downregulation in EH is crucial to identify EH cases with a high risk of progressing to ECa. No correlation was noticed between the age of the patients and E-cadherin downregulation, and this result agreed with others [3,21]. When comparing the frequency of E-cadherin downregulation to tumor size, a higher frequency was observed in larger tumors, although this relationship was not statistically significant; this finding is consistent with the results of Ahmed *et al.* [22]. Concerning E-cadherin expression and tumor grade, it was found that the frequency of E-cadherin downregulation was higher in cases with a high grade; however, no significant relation was detected. This result was compatible with others [3,21], but it does not agree with Ahmed *et al.* [22]. This discrepancy may be due to the fact that most of their cases were high-grade tumors, and their study also included cases of the serous type, which is classified as a high-grade tumor. In this study, a higher frequency of E-cadherin downregulation was observed in cases with more than 50% myometrial invasion; this result was close to being statistically significant and agrees with Lizawati *et al.* [10] but does not align with Kunchy *et al.* [3]. These discrepancies may be attributed to the fact that, in their study, non-endometrioid types of endometrial carcinoma were also included, a different scoring system, and a different primary antibody were used. About E-cadherin expression and lymphovascular invasion, it was found that E-cadherin was significantly downregulated in cases with lymphovascular invasion. This result agreed with Ahmed *et al.* [22], but it is not compatible with that of Lizawati *et al.* [10]. This discrepancy may be because their study showed few cases of lymphovascular invasion (11 out of 70 cases). The present study indicated that tumors with metastasis were more likely to exhibit downregulation of E-cadherin expression, a finding that was statistically significant and consistent with the study by Lizawati *et al.* The frequency of E-cadherin downregulation in cases with high stage was about 88.9%, while it was greatly lower in cases with low stage; this association was statistically significant and was compatible with that of others [3,5]. In this study, both P53 and E-cadherin were significantly associated with tumor metastasis and stage; statistically, P53 appeared as an important independent predictor for both tumor metastasis and stage rather than E-cadherin. According to the available data, no other research has concentrated on this association to compare with the results of this study.

Study Limitations

Power calculation was not done, as the study was based on the available eligible cases. The relatively small sample size, particularly in the EH group (n=20), and the small numbers in some clinicopathological subgroups limited the statistical power of subgroup analyses. Therefore, some associations may not have achieved statistical

significance. The small number of metastatic cases may lead to overfitting, as demonstrated by the wide confidence intervals. Therefore, the regression results should be analyzed carefully. The difference in tissue sampling (four EH cases assessed on D&C specimens rather than hysterectomy specimens) may have resulted in under-sampling and missed focal P53 or E-cadherin alterations. Further studies with larger cohorts would be valuable to validate and extend the results of this study. POLE mutation and mismatch repair protein status were not evaluated in the current study. Therefore, the P53 findings should be interpreted within the context of immunohistochemical evaluation and do not represent a complete molecular classification.

Conclusion

Abnormal expressions of P53 and E-cadherin biomarkers were observed in EH, and there was a significant difference in the expression of E-cadherin between EH and ECa. These findings may suggest that alterations in the expression of this biomarker may be implicated in the pathogenesis of ECa and have an important role in the conversion of EH to ECa; therefore, E-cadherin immunoexpression may serve as a promising supportive biomarker, offering additional information concerning the biological features of EH. P53 and E-cadherin may act as supportive prognostic markers in ECa and can predict ECa cases with aggressive behavior, with P53 appearing as a better predictor of tumor metastasis and stage than E-cadherin.

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Conflict of interests

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Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

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