

Correlation of p53 Expression with Histopathological Grading and Myometrial Invasion in Endometrioid Endometrial Carcinoma

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Abstract

Endometrioid endometrial carcinoma (EEC) is commonly assessed using histopathological grade and myometrial invasion, while p53 expression may provide complementary molecular information. This study aimed to assess the correlation of p53 expression with histopathological grade and myometrial invasion in EEC. This retrospective analytic observational study included 60 hysterectomy specimens diagnosed as EEC at Dr. Saiful Anwar General Hospital, Malang, during 2022–2025. p53 expression was evaluated by immunohistochemistry and classified as wild-type or abnormal. Associations were analyzed using Fisher's exact test and correlations using Spearman's test. p53-abnormal expression was identified in 13.3% of cases and was more frequent in high-grade than low-grade EEC (21.4% vs. 6.3%; OR=4.09; $p=0.130$) and in tumors with myometrial invasion $\geq 50\%$ than $<50\%$ (20.0% vs. 4.0%; OR=6.00; $p=0.123$). Correlations with histopathological grade ($p=0.223$; $p=0.131$) and myometrial invasion ($p=0.232$; $p=0.124$) were weak and not statistically significant. Although no significant associations or correlations were found, p53 immunohistochemistry may provide additional biological information after histopathological diagnosis, particularly where access to comprehensive molecular testing is limited. Integrating p53 status with histopathological, clinicopathological, and other molecular parameters may support more comprehensive EEC risk stratification and potentially help optimize patient management within resource-limited clinical settings and tertiary referral hospitals.

Keywords: Endometrioid endometrial carcinoma; p53; histopathological grading; myometrial invasion; immunohistochemistry.

INTRODUCTION

Endometrial cancer has increasing incidence and mortality worldwide. According to GLOBOCAN 2022, endometrial cancer ranks as the sixth most common cancer among women worldwide, with 420,368 new cases and 97,723 deaths annually, and is the third leading cause of death among gynecologic cancers (Bray et al., 2024; Zhu et al., 2024). In Indonesia, incidence increased from 2.1 to 4.2 per 100,000 women over the past two decades (Kementerian Kesehatan Indonesia, 2021). Endometrioid endometrial carcinoma (EEC) is the most common histopathological subtype of endometrial cancer, accounting for approximately 80–90% of cases. EEC is a malignant epithelial neoplasm of the endometrium that exhibits differentiation resembling endometrial epithelium and is frequently associated with estrogen exposure and molecular alterations, including mutations in *PTEN*, *PIK3CA*, and *ARID1A*, as well as mismatch repair deficiency (WHO, 2020).

Histopathological grading and the depth of myometrial invasion are important parameters for

determining prognosis and risk stratification in patients with EEC. Histopathological grading remains useful for estimating the clinical behavior of EEC, whereas the depth of myometrial invasion is an important parameter for staging and is associated with patient prognosis. However, advances in molecular classification have shown that the assessment of EEC should not rely solely on histopathological characteristics. The molecular approach recommended in the 2025 ESGO-ESTRO-ESP guidelines integrates the evaluation of *POLE* status, mismatch repair (MMR), and p53 into the molecular classification of endometrial carcinoma, complementing conventional histopathological assessment by providing more comprehensive prognostic information and supporting more accurate risk stratification and targeted therapeutic decision-making. In this context, p53 abnormalities may reflect more aggressive tumor biology and complement histopathological assessment in EEC (Arciuolo et al., 2022; Concin et al., 2025).

Previous studies have shown that p53-abnormal expression is associated with clinicopathological characteristics of EEC, including histopathological grade

and depth of myometrial invasion. Chang et al. (2024) reported that 22.6% of patients with stage I, grade 1–2 EEC exhibited p53-abnormal expression, despite all cases being morphologically classified as low-grade EEC. In general, p53-abnormal expression is more frequently observed in tumors with higher histopathological grades and deeper myometrial invasion (Jamieson et al., 2023; Meijs-Hermanns et al., 2025). However, the association between p53 abnormalities and morphological parameters is not always consistent. Yano et al. (2019) reported that, among p53-abnormal EEC cases, 61% still exhibited low-grade morphology, while approximately 40% showed <50% myometrial invasion. These findings suggest that histopathological characteristics alone may not fully reflect the overall biological characteristics of the tumor.

Data on the correlation between p53 expression and histopathological parameters in EEC remain very limited in Indonesia. Therefore, it is still unclear whether the associations between p53 expression, histopathological grade, and depth of myometrial invasion reported in other populations are also applicable to the Indonesian population. In Indonesia, conventional assessment still relies largely on morphological parameters, including histological type, grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI) (HOGI, 2018), whereas advances in molecular classification have established p53 as an important component of risk stratification in EEC (Concin et al., 2025). Therefore, data from the Indonesian population are needed to strengthen the scientific basis for the association of p53 expression with histopathological grade and depth of myometrial invasion in the context of developing EEC risk stratification that integrates histopathological and molecular characteristics.

Based on this background, this study aimed to determine the correlation between p53 expression, histopathological grade, and depth of myometrial invasion in EEC at Dr. Saiful Anwar General Hospital, Malang. Specifically, this study evaluated differences in p53 expression across histopathological grades and depths of myometrial invasion and analyzed the correlation between p53 expression and these two histopathological parameters.

MATERIALS AND METHODS

Study Design and Setting

This was an analytical observational study with a retrospective approach designed to determine the correlation between p53 expression, histopathological grade, and depth of myometrial invasion in EEC. The study was conducted from January to June 2026 at the Anatomical Pathology Department of Dr. Saiful Anwar General Hospital, Malang. The study data were obtained from EEC cases diagnosed in hysterectomy specimens examined at the Anatomical Pathology Department of

Dr. Saiful Anwar General Hospital, Malang, between January 2022 and December 2025. This study received ethical approval from the Health Research Ethics Committee of Dr. Saiful Anwar General Hospital, Malang (No. 400/097/K.3/102.7/2026).

Study Population and Sample

The study population comprised all EEC specimens obtained from hysterectomy procedures and examined histopathologically at the Anatomical Pathology Department of Dr. Saiful Anwar General Hospital, Malang, from January 2022 to December 2025, totaling 114 cases. The study samples consisted of paraffin-embedded tissue blocks from EEC cases that met the study criteria. Cases were selected using convenience sampling based on case availability, completeness of data, and the quality of the available specimens. The minimum sample size was calculated using the sample size formula for a correlation test based on Fisher's transformation, with a significance level of 5% and a statistical power of 80%, resulting in a minimum required sample size of 58. A total of 60 samples were included in the analysis.

The inclusion criteria were paraffin-embedded tissue blocks from hysterectomy specimens with a histopathological diagnosis of EEC during the study period, containing adequate endometrial tumor tissue, demonstrating myometrial invasion, and sufficient for p53 immunohistochemical examination. Samples were excluded if the tumor tissue was predominantly composed of >50% necrotic areas or if the remaining tumor tissue measured <2 mm.

Histopathological Evaluation

Histopathological slides from cases that met the study criteria were reviewed using hematoxylin and eosin staining to confirm the diagnosis of EEC, determine the histopathological grade, and assess the depth of myometrial invasion. Histopathological grading of EEC was assessed using the binary grading system according to the *WHO Classification of Female Genital Tumours*, 5th edition (2020), and categorized as low-grade or high-grade. The low-grade group included FIGO grades 1 and 2, whereas the high-grade group included FIGO grade 3. Grade 1 was characterized by a solid component of <5%, grade 2 by a solid component of 6–50%, and grade 3 by a solid component of >50%. The presence of marked nuclear atypia in grade 1 or 2 tumors increased the grade by one level. The depth of myometrial invasion was assessed from the endomyometrial junction toward the myometrium. The depth of invasion was measured in millimeters and expressed as a percentage of the total myometrial thickness, and was subsequently categorized as <50% or ≥50% invasion.

p53 Immunohistochemical Examination and Interpretation

p53 immunohistochemical staining was performed manually using a mouse monoclonal primary antibody against p53 (clone DO-7) at a 1:100 dilution (Biocare Medical, USA). Following deparaffinization, antigen retrieval was performed using DIVA solution in a decloaking chamber at 90°C for 45 minutes. The slides were subsequently incubated with the primary antibody for 60 minutes, followed by application of a polymer-based secondary antibody. Immunoreactivity was visualized using 3,3'-diaminobenzidine (DAB) chromogen, followed by counterstaining with hematoxylin.

p53 expression was manually evaluated using a light microscope in at least 500 tumor cells across five high-power fields at 400× magnification using a semi-quantitative approach. p53 expression was interpreted as either a p53 wild-type or p53-abnormal pattern. The p53 wild-type pattern was characterized by heterogeneous nuclear staining in 1–80% of tumor cells. The p53-abnormal pattern included: (1) an overexpression pattern, defined as strong and diffuse nuclear staining in >80% of tumor cells; (2) a null pattern, defined as complete absence of nuclear staining in tumor cells (0%) in the presence of positive internal controls in fibroblasts, endothelial cells, and lymphocytes; and (3) a cytoplasmic pattern, defined as predominant strong cytoplasmic staining in >80% of tumor cells accompanied by nuclear staining. Ovarian high-grade serous carcinoma was used as an external positive control for the overexpression pattern.

Statistical Analysis

Data were analyzed descriptively to characterize the clinicopathological features of the study sample, including age, histopathological grade, depth of myometrial invasion, stage, and p53 expression pattern. Categorical data were presented as frequencies and percentages, whereas age was summarized using appropriate numerical measures according to its distribution. The associations between p53 expression and histopathological grade and between p53 expression and depth of myometrial invasion were analyzed using Fisher's exact test. The magnitude of the associations was expressed as odds ratios (ORs) with 95% confidence intervals. Spearman's correlation test was used to assess the direction and strength of the correlations between p53 expression and histopathological grade and between p53 expression and depth of myometrial invasion. Correlation results were expressed as Spearman's correlation coefficient (ρ) and p -value. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Results

Clinicopathological Characteristics of the Study Sample

This study included 60 EEC cases from hysterectomy specimens obtained from the paraffin block archives of the Anatomical Pathology Laboratory at Dr. Saiful Anwar General Hospital, Malang, as well as from medical records and the Hospital Management Information System (SIMRS), in accordance with the study criteria. The demographic and clinicopathological characteristics of the study sample are presented in **Table 1**.

Table 1. Demographic and clinicopathological characteristics of the study samples

Characteristics	n	%
Age group (years)		
21–30	3	5.0
31–40	5	8.3
41–50	9	15.0
51–60	27	45.0
61–70	12	20.0
71–80	3	5.0
81–90	1	1.7
Histopathological grade		
Low-grade (FIGO grade 1–2)	32	53.3
High-grade (FIGO grade 3)	28	46.7
Myometrial invasion		
<50%	25	41.7
≥50%	35	58.3
FIGO stage		
IA	24	40.0
IB	10	16.7
II	10	16.7
IIIA	15	25.0
IIIB	1	1.7
IV	0	0.0

The mean age of the patients was 54.65 ± 11.79 years, with an age range of 29–84 years. The largest age group was 51–60 years, comprising 27 patients (45.0%), followed by the 61–70-year age group with 12 patients (20.0%) and the 41–50-year age group with 9 patients (15.0%). Based on histopathological grading, 32 cases (53.3%) were classified as low-grade (FIGO grades 1–2), whereas 28 cases (46.7%) were classified as high-grade (FIGO grade 3). Regarding the depth of myometrial invasion, 35 cases (58.3%) showed invasion of ≥50% of the myometrial thickness, whereas 25 cases (41.7%) showed invasion of <50%. Representative histopathological features of EEC according to grade are shown in **Figure 1**. Regarding stage, most cases were stage IA, comprising 24 cases (40.0%), followed by stage IIIA with 15 cases (25.0%). Stages IB and II were each identified in 10 cases (16.7%), whereas stage IIIB was identified in 1 case (1.7%). No stage IV cases were identified in the study sample.

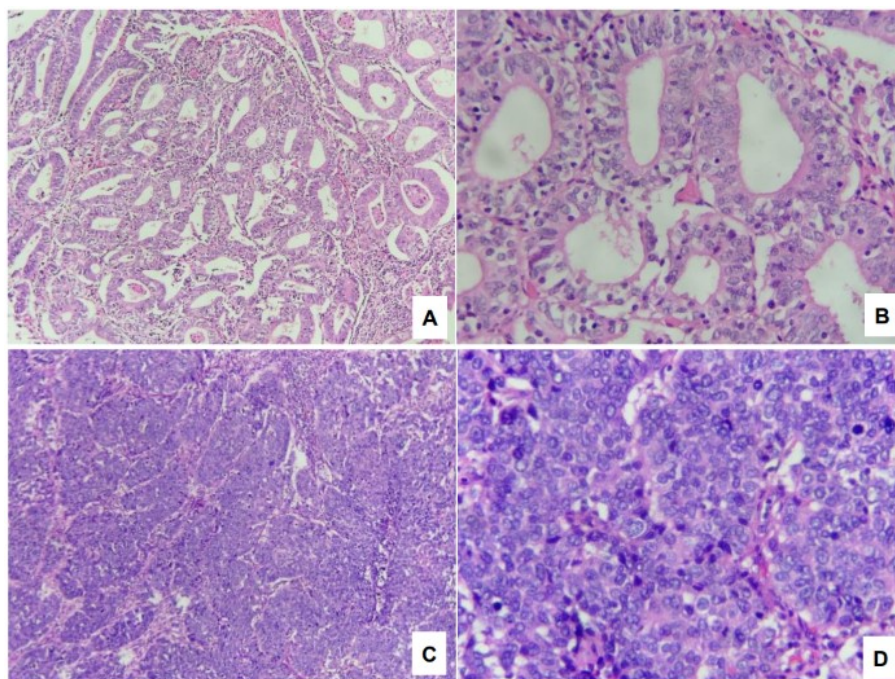


Figure 1. Representative hematoxylin and eosin (H&E)-stained endometrioid endometrial carcinoma according to histopathological grade. (A) Low-grade EEC, H&E $\times 100$; (B) low-grade EEC, H&E $\times 400$; (C) high-grade EEC, H&E $\times 100$; and (D) high-grade EEC, H&E $\times 400$.

p53 Expression in Endometrioid Endometrial Carcinoma

Most EEC cases showed a p53 wild-type expression pattern, observed in 52 cases (86.7%), whereas a p53-abnormal pattern was identified in 8 cases (13.3%). p53-abnormal expression was identified in patients with EEC aged 56–84 years, with most cases (87.5%) occurring in

patients aged ≥ 60 years. All p53-abnormal cases demonstrated an overexpression pattern, characterized by strong and diffuse nuclear staining in $>80\%$ of tumor cells. Neither a null pattern nor a cytoplasmic pattern was identified among the p53-abnormal cases in this study. Representative p53 expression patterns are shown in **Figure 2**.

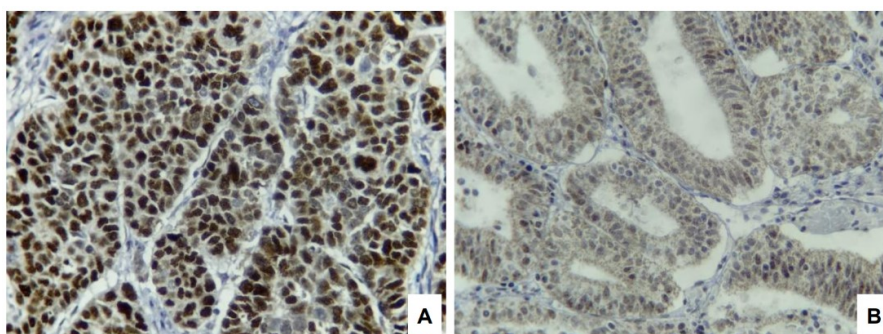


Figure 2. Representative immunohistochemical expression patterns of p53 in endometrioid endometrial carcinoma. (A) p53-abnormal with an overexpression pattern; (B) p53 *wild-type* pattern.

Comparison of p53 Expression Between Histopathological Grade Groups in Endometrioid Endometrial Carcinoma

In both histopathological grade groups, most cases showed a p53 wild-type pattern. In the low-grade group, the p53 wild-type pattern was observed in 30 cases

(93.8%), whereas it was observed in 22 cases (78.6%) in the high-grade group. Conversely, the p53-abnormal pattern was identified in 2 cases (6.3%) in the low-grade group and 6 cases (21.4%) in the high-grade group (**Table 2**). Representative p53 expression patterns in the low-grade and high-grade groups are shown in **Figure 3**.

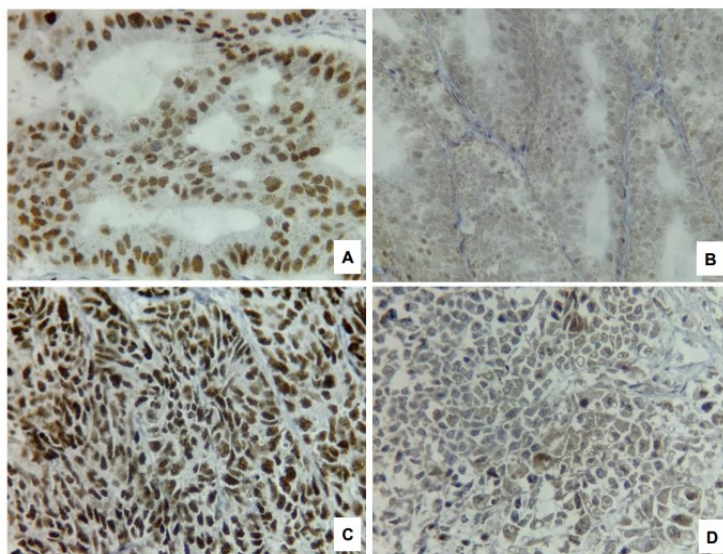


Figure 3. Representative immunohistochemical expression patterns of p53 in endometrioid endometrial carcinoma according to histopathological grade. (A) p53-abnormal expression in low-grade EEC; (B) p53 wild-type expression in low-grade EEC; (C) p53-abnormal expression in high-grade EEC; and (D) p53 wild-type expression in high-grade EEC.

Fisher's exact test showed no statistically significant association between p53 expression and histopathological grade ($p=0.130$). An OR of 4.09 (95% CI, 0.75–22.22) indicated that cases with a p53-abnormal pattern had 4.09 times the odds of being classified as high-grade compared with cases with a p53 wild-type pattern, although the association was not statistically significant.

Comparison of p53 Expression Between Myometrial Invasion Depth Groups in Endometrioid Endometrial Carcinoma

In both myometrial invasion depth groups, most cases showed a p53 wild-type pattern. In the <50% myometrial invasion group, the p53 wild-type pattern was observed in 24 cases (96.0%), whereas it was observed in 28 cases (80.0%) in the $\geq 50\%$ invasion group. Conversely, the p53-abnormal pattern was identified in 1 case (4.0%) in the <50% invasion group and 7 cases (20.0%) in the $\geq 50\%$ invasion group (Table 2). Representative p53 expression patterns according to the depth of myometrial invasion are shown in Figure 4.

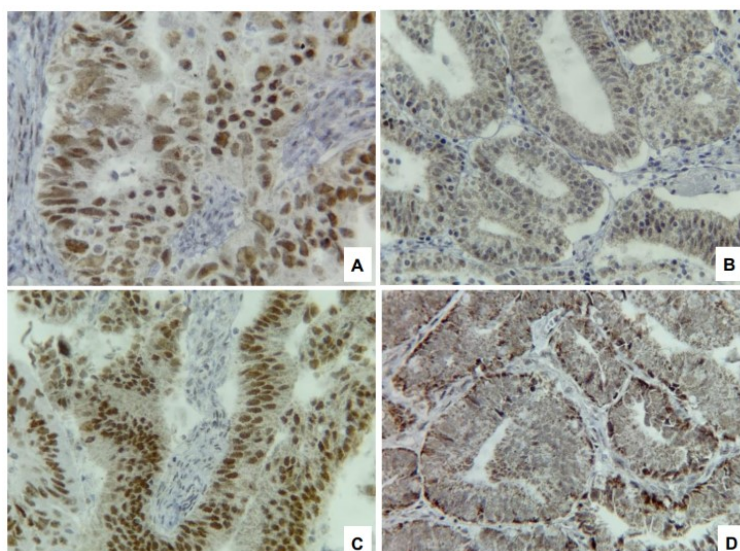


Figure 4. Representative immunohistochemical expression patterns of p53 in endometrioid endometrial carcinoma according to myometrial invasion depth. (A) p53-abnormal expression in EEC with myometrial invasion <50%; (B) p53 wild-type expression in EEC with myometrial invasion <50%; (C) p53-abnormal expression in EEC with myometrial invasion $\geq 50\%$; and (D) p53 wild-type expression in EEC with myometrial invasion $\geq 50\%$.

Fisher’s exact test showed no statistically significant association between p53 expression and the depth of myometrial invasion ($p=0.123$). An OR of 6.00 (95% CI, 0.69–52.29) indicated that cases with a p53-abnormal

pattern had 6.00 times the odds of having myometrial invasion $\geq 50\%$ compared with cases with a p53 wild-type pattern, although the association was not statistically significant.

Table 2. Association of p53 expression with histopathological grade and myometrial invasion in endometrioid endometrial carcinoma.

Variable	p53 wild-type, n (%)	p53-abnormal, n (%)	OR	95% CI	p-value
Histopathological grade					
Low-grade (FIGO grade 1–2)	30 (93.8)	2 (6.3)	Ref.		
High-grade (FIGO grade 3)	22 (78.6)	6 (21.4)	4.09	0.75–22.22	0.130
Myometrial invasion					
<50%	24 (96.0)	1 (4.0)	Ref.		
$\geq 50\%$	28 (80.0)	7 (20.0)	6.00	0.69–52.29	0.123

Note: OR, odds ratio; CI, confidence interval. p-values were obtained using Fisher’s Exact Test.

Correlation of p53 Expression with Histopathological Grade and Depth of Myometrial Invasion in Endometrioid Endometrial Carcinoma

Spearman’s correlation analysis between p53 expression and histopathological grade showed a weak positive

correlation ($\rho=0.223$; $p=0.131$). Similarly, the correlation between p53 expression and the depth of myometrial invasion was also weak and positive ($\rho=0.232$; $p=0.124$). Neither correlation was statistically significant (**Table 3**).

Table 3. Correlation of p53 expression with histopathological grade and myometrial invasion in endometrioid endometrial carcinoma

Variables	Spearman’s ρ	p-value
p53 expression and histopathological grade	0.223	0.131
p53 expression and myometrial invasion	0.232	0.124

Note: Spearman’s rank correlation test.

Discussion
Clinicopathological Characteristics of the Study Sample

This study included 60 patients with EEC, with a mean age of 54.65 ± 11.79 years and a median age of 56 years. The largest age group was 51–60 years, accounting for 45.0% of cases. This finding is consistent with the epidemiological profile of endometrial cancer, which is most commonly diagnosed in peri- and postmenopausal women (WHO, 2020; Memon et al., 2022; Clarke et al., 2025). A similar pattern was reported in a retrospective study conducted at Dr. Hasan Sadikin General Hospital, Bandung, where the largest proportion of patients was in the sixth decade of life, accounting for 34.8% of cases (Erfiandi et al., 2023). In addition, EEC in patients aged <40 years was identified in 13.3% of cases, comparable to the 10.53% reported at Dr. Soetomo Regional General Hospital, Surabaya (Sofyan et al., 2020).

Based on histopathological grade, the proportion of low-grade EEC (53.3%) was slightly higher than that of high-grade EEC (46.7%). This finding is consistent with Casanova et al. (2024), who reported a predominance of low-grade EEC at 80%, as well as a study from Japan that reported a low-grade proportion of 87%. Myometrial invasion $\geq 50\%$ was observed in 58.3% of cases. This proportion differed from that reported by Yano et al. (2019), who found that most cases had myometrial

invasion <50%, but was consistent with the findings of Chandra et al. (2019) in West Sumatra, where myometrial invasion $\geq 50\%$ was identified in 85.7% of cases. The high proportion of myometrial invasion $\geq 50\%$ reported in Indonesian studies suggests that a subset of EEC cases in the Indonesian population may exhibit histopathological characteristics associated with more aggressive biological behavior. This finding is clinically relevant because deep myometrial invasion is an important prognostic parameter in endometrial carcinoma and is associated with an increased risk of lymph node involvement, recurrence, and poorer outcomes. Stage IA was the most common stage (40.0%), followed by stage IIIA (25.0%).

Descriptively, low-grade tumors and myometrial invasion <50% were more frequently observed in stage IA, whereas high-grade tumors and myometrial invasion $\geq 50\%$ were more common in stage IIIA. However, the presence of low-grade tumors with deep myometrial invasion and high-grade tumors with superficial invasion indicates that this pattern is not absolute. Therefore, histopathological grade and depth of myometrial invasion should be considered together with other prognostic factors, including the molecular characteristics of the tumor (Yano et al., 2019; Concin et al., 2025; Meijs-Hermanns et al., 2025).

p53 Expression in Endometrioid Endometrial Carcinoma

The results showed that most EEC cases exhibited a p53 wild-type expression pattern (86.7%), whereas a p53-abnormal pattern was identified in 13.3% of cases. This finding falls within the range reported in the international literature, in which *TP53* mutations have been identified in approximately 10–40% of EEC cases (Köbel et al., 2019; Nakamura et al., 2019). p53 immunohistochemistry has practical value as a surrogate marker for assessing abnormalities in the *TP53* pathway. Singh et al. (2020) reported strong concordance between p53 immunohistochemical patterns and genetic mutation analysis, whereas Vermij et al. (2022) demonstrated approximately 90% concordance between p53 immunohistochemical interpretation and *TP53* next-generation sequencing (NGS).

All p53-abnormal cases in this study showed an overexpression pattern, whereas null and cytoplasmic patterns were not identified. The limited variation in abnormal p53 patterns may be related to the relatively small number of p53-abnormal cases in this study. For comparison, Vermij et al. (2022) reported that overexpression was the most frequently observed p53-abnormal pattern (68%), followed by the null pattern (9%) and cytoplasmic pattern (3.2%). Thus, the predominance of the overexpression pattern in this study is consistent with the pattern most commonly reported in previous studies, although the spectrum of p53 abnormalities observed in the present sample was more limited.

p53 Expression According to Histopathological Grade

Descriptively, the p53-abnormal pattern was more frequently observed in the high-grade group (21.4%) than in the low-grade group (6.3%). This pattern is consistent with the literature showing that p53 abnormalities are more commonly found in higher-grade tumors (Köbel et al., 2019). Meijs-Hermanns et al. (2025) reported a p53-abnormal pattern in 9.4% of low-grade EEC cases and 37.2% of high-grade cases. In another study, Jamieson et al. (2023) identified p53-abnormal expression in 2.5% of low-grade EEC cases, whereas Chang et al. (2024) reported that most low-grade EEC cases showed a p53 wild-type pattern (77.4%), while 22.6% showed a p53-abnormal pattern.

In this study, Fisher's exact test showed no statistically significant association between p53 expression and histopathological grade ($p=0.130$). Nevertheless, an OR of 4.09 suggested that cases with a p53-abnormal pattern had approximately fourfold higher odds of being classified as high-grade than cases with a p53 wild-type pattern. The lack of statistical significance may partly reflect the molecular heterogeneity of EEC, as high-grade cases are not exclusively associated with p53 abnormalities but may also belong to *POLE*-ultramutated or MMR-deficient subtypes, which were not evaluated in this study (Arciuolo et al., 2022; Casanova et al., 2024).

Spearman's correlation analysis also showed a weak positive correlation between p53 expression and histopathological grade ($\rho=0.223$; $p=0.131$), which was not statistically significant. This finding suggests that morphological grade does not always reflect p53 status. Yano et al. (2019), for example, reported that 61% of p53-abnormal EEC cases still exhibited low-grade morphology. These findings support the importance of considering molecular characteristics as a complement to morphological evaluation rather than as a replacement for histopathological grading (Yano et al., 2019; Meijs-Hermanns et al., 2025). The lack of statistical significance in this study may also be influenced by the limited number of p53-abnormal cases. In addition, dysregulation of the MDM2/MDMx pathway may impair p53 function without producing a p53-abnormal immunohistochemical pattern, while molecular heterogeneity, including *POLE*-mutated and MMR-deficient subtypes, may also be present in high-grade EEC (Nakamura et al., 2019; Arciuolo et al., 2022).

p53 Expression According to the Depth of Myometrial Invasion

Descriptively, the p53-abnormal pattern was more frequently observed in cases with myometrial invasion $\geq 50\%$ (20.0%) than in those with invasion $< 50\%$ (4.0%). This finding is consistent with Stavropoulos et al. (2019), who reported that p53 overexpression was more frequently observed in tumors with myometrial invasion $\geq 50\%$. Fisher's exact test showed no statistically significant association between p53 expression and the depth of myometrial invasion ($p=0.123$). Nevertheless, an OR of 6.00 indicated a tendency for cases with a p53-abnormal pattern to have higher odds of myometrial invasion $\geq 50\%$, although the association was not statistically significant. This finding is consistent with Chang et al. (2024), who reported no significant differences in p53 expression patterns according to the depth of myometrial invasion.

Biologically, loss of p53 function may disrupt cell-cycle control and increase genomic instability, potentially affecting the ability of tumor cells to infiltrate the myometrial stroma (Nakamura et al., 2019). However, this biological mechanism cannot be used to infer an association in the present study because the statistical analysis did not demonstrate significance. Data from PORTEC-3 also showed that p53-abnormal status was associated with a more aggressive disease course (Jamieson et al., 2023).

Spearman's correlation analysis showed a weak positive correlation between p53 expression and the depth of myometrial invasion ($\rho=0.232$; $p=0.124$), which did not reach statistical significance. This finding is consistent with Yano et al. (2019), who reported relatively similar proportions of p53-abnormal cases in the $< 50\%$ and $\geq 50\%$ myometrial invasion groups (40% vs. 39%). These findings suggest that the relationship between p53 status and the depth of myometrial invasion

may vary across populations. Therefore, according to the 2025 ESGO-ESTRO-ESP algorithm, molecular evaluation is performed comprehensively by integrating *POLE* mutation analysis, MMR immunohistochemistry, and p53 assessment.

Clinical Implications and Study Limitations

The clinical implications of these findings are particularly relevant in the context of advances in the molecular classification of endometrial carcinoma. The 2025 ESGO-ESTRO-ESP guidelines incorporate molecular classification as an integral component of prognostic assessment, risk stratification, and clinical decision-making. In contrast to the 2018 HOGI guidelines, which rely predominantly on histopathological parameters such as histological type, histopathological grade, depth of myometrial invasion, and LVSI, the 2025 ESGO-ESTRO-ESP guidelines integrate molecular characteristics into four groups: *POLE*-mutated (POLEmut), mismatch repair-deficient (MMRd), no specific molecular profile (NSMP), and p53-abnormal (p53abn). In multiple-classifier tumors, the final molecular classification is determined according to the dominant genomic driver (HOGI, 2018; Concin et al., 2025).

Within this classification, p53 is an important component for identifying the p53-abnormal group, which is generally associated with more aggressive biological characteristics and the poorest prognosis. Molecular evaluation integrates *POLE* mutation analysis, MMR immunohistochemistry, and p53 expression assessment, while *TP53* sequencing may be considered in cases with equivocal or heterogeneous p53 staining patterns (Concin et al., 2025). Although this study evaluated only p53 expression without *POLE* mutation analysis or MMR assessment, p53 evaluation still provides information on the molecular characteristics of the tumor and their association with histopathological grade and the depth of myometrial invasion.

The correlations of p53 expression with histopathological grade and depth of myometrial invasion did not reach statistical significance in this study. Nevertheless, identification of p53 status in patients with EEC at Dr. Saiful Anwar General Hospital, Malang, remains relevant in the context of current developments in the molecular classification and risk stratification of EEC. The findings of this study indicate that abnormalities in the *TP53* pathway are not limited to EEC with more aggressive morphological characteristics but may also be identified in low-grade EEC and in tumors with superficial myometrial invasion. Clinically, p53 immunohistochemistry may therefore provide additional biological information following histopathological diagnosis, particularly in settings with limited access to molecular testing. Integration of p53 status with histopathological and clinicopathological parameters, as well as with other molecular classification

components in accordance with the 2025 ESGO-ESTRO-ESP guidelines, may support more comprehensive risk stratification and potentially contribute to the optimization of EEC management (Concin et al., 2025).

This study has several limitations. Although the total sample size met the minimum required sample size, p53-abnormal expression was identified in only 8 of 60 cases (13.3%). All of these cases showed an overexpression pattern, whereas null and cytoplasmic patterns were not identified, indicating that the full spectrum of p53 abnormalities in the study population may not have been captured (Köbel et al., 2019; Singh et al., 2020). In addition, this study evaluated p53 only as a surrogate marker without assessing *POLE* mutations or MMR status; therefore, comprehensive molecular classification of EEC could not be performed, and cases with a p53 wild-type pattern could not be definitively classified into other molecular subtypes (Arciulo et al., 2022; Concin et al., 2025). The generalizability of the findings is also limited by the retrospective, single-center design conducted at a referral hospital. Furthermore, recurrence and survival outcomes were not evaluated, precluding direct assessment of the prognostic value of p53 expression.

CONCLUSION

Most EEC cases showed a p53 wild-type expression pattern, whereas all p53-abnormal cases demonstrated an overexpression pattern. Descriptively, p53-abnormal expression was more common in high-grade tumors, in cases with myometrial invasion $\geq 50\%$, and among patients aged >55 years. Although not statistically significant, p53-abnormal cases showed numerically higher odds of being classified as high-grade (OR=4.09) and of having myometrial invasion $\geq 50\%$ (OR=6.00) compared with p53 wild-type cases. Overall, no statistically significant associations or correlations were found between p53 expression and either histopathological grade or depth of myometrial invasion in EEC. Nevertheless, p53 immunohistochemistry remains an important component of molecular classification and risk stratification in EEC and may provide additional prognostic information to support more precise patient management.

Authors' Contributions: Amelinda Natania Nurasih, Eviana Norahmawati, and Muhammad Luqman Fadli conceived and designed the study. Amelinda Natania Nurasih collected the data, performed the histopathological and immunohistochemical evaluations, analyzed the data, and drafted the manuscript. Eviana Norahmawati and Muhammad Luqman Fadli supervised the study and critically revised the manuscript. Diah Prabawati Retnani and Rachmad Sarwo Bakti reviewed the study and provided critical intellectual input.

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