Section: Pathology

Original Research Article

ASSOCIATION OF P53 IN PREMALIGNANT AND MALIGNANT LESIONS OF ENDOMETRIUM

Y Soundarya[1], Ch Kishore Kumar[2], Srinivasa Rao Vavilapalli[3], G Parvathi[4]

[1]*Senior Resident, Department of Pathology, Guntur Medical College/GGH, Guntur, Andhra Pradesh, India.*
[2]*Associate Professor, Department of Pathology, Guntur Medical College/GGH, Guntur, Andhra Pradesh, India.*
[3]*Assistant Professor, Department of Pathology, Andhra Medical College/KGH, Visakhapatnam, Andhra Pradesh, India.*
[4]*Professor&HOD, Department of Pathology, Andhra Medical College/KGH, Visakhapatnam, Andhra Pradesh, India.*

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Corresponding Author:
Dr.Ch Kishore Kumar,
Associate Professor, Department of Pathology, Guntur Medical College / GGH, Guntur, Andhra Pradesh, India.
Email: kishore2703@gmail.com

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ABSTRACT

Background: Endometrial carcinoma is the most common gynecological malignancy, often preceded by premalignant endometrial hyperplasia. Early identification of lesions with malignant potential is essential for appropriate management and improved patient outcomes. The tumor suppressor gene p53 plays a pivotal role in cell cycle regulation and apoptosis, and its altered expression has been implicated in endometrial carcinogenesis. Immunohistochemical evaluation of p53 serves as a valuable adjunct in distinguishing benign, premalignant, and malignant endometrial lesions and provides important prognostic information.The aim and objective is to study the clinicopathological profile of premalignant and malignant lesions of endometrium. To observe the immunohistochemical expression of p53 in premalignant and malignant lesions of endometrium. To observe the imunohistochemical expression of Ki67 in premalignant and malignant lesions of endometrium.

Materials and Methods: This hospital-based observational study comprises cases of endometrial hyperplasias and endometrial carcinomas diagnosed using Hematoxylin and Eosin staining in the Department of Pathology at Andhra Medical College between April 2023 and March 2025.Female patients aged between third to seventh decades presenting with symptoms like bleeding per vagina and increased endometrial thickness on USG.Cases reported as endometrial hyperplasia, Endometrioid Intraepithelial Neoplasia(EIN) and Endometrial Carcinoma.

Results: In this hospital-based observational study conducted at Andhra Medical College, 50 cases comprising premalignant and malignant endometrial lesions were examined. Detailed clinicopathological profiling and immunohistochemical evaluation of p53 and Ki-67 expression were performed.The most common age group affected was 51–60 years.The most frequent clinical presentation was abnormal uterine bleeding, noted in over 80% of cases.Hyperplasia without atypia and hyperplasia with atypia accounted for 28% and 20% respectively. Endometrioid endometrial carcinoma was the most common malignancy (34%), followed by serous carcinoma (18%).A progressive increase in Ki-67 index was observed from hyperplasia without atypia (5.86%) to serous carcinoma (38.56%).The mean Ki-67 index correlated significantly with tumor grade, indicating its utility as a marker of proliferative activity and tumor aggressiveness.p53 mutant expression was predominantly observed in serous carcinoma (88.9%) and was less frequent in endometrioid carcinoma (11.8%).Wild-type p53 staining was noted in cases of hyperplasia without atypia and the majority of atypical hyperplasia.

Conclusion: The present study was including that, p53 immunohistochemical analysis into routine pathological evaluation can enhance diagnostic

confidence and aid in prognostication of both premalignant and malignant endometrial conditions.It also helps in guiding appropiate clinical management as now a days targeted therapy are being developed against p53.
Keywords: Endometrial Malignancy, p53, Immunohistochemical analysis, ki-67 Index, Hyperplasia.

INTRODUCTION

Endometrial carcinoma is one of the most prevalent gynecological cancers in developed countries.It makes up the vast majority of corpus uteri malignancies.It is sixth most commonly diagnosed cancer in women and second most commonly diagnosed female genital organ cancer.[1]

This malignancy predominantly affects postmenopausal women, with less than 25% of cases occurring in premenopausal individuals. A well-established link exists between prolonged estrogen exposure and the risk of developing endometrial carcinoma.

Common risk factors include obesity, diabetes, hypertension, infertility, and nulliparity.[2]

The progression of endometrial carcinoma is believed to follow a continuum of premalignant changes, starting from hyperplasia without atypia, advancing to atypical hyperplasia, and eventually culminating in well-differentiated adenocarcinoma.[3]

Endometrial carcinoma is classified into two types: Type 1, which is estrogen-dependent and usually presents with endometrioid morphology, and Type 2, which is estrogen-independent and typically exhibits serous or clear cell morphology.4However, this classification is not useful for tumour stratification due to significant features overlapping at clinical,pathological and molecular levels.[1]

The Cancer Genome Atlas integrated genomic characterization identified four groups of carcinomas based on POLE mutations,P53 mutations and Microsatellite instability.This has shown to be particularly useful in assessing prognosis.Combining microscopic features with molecular characteristics offers the most effective method for stratifying patients and predicting their prognosis.[1]

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p53 is a tumor suppressor protein essential for controlling cell cycle arrest, facilitating DNA repair, and inducing apoptosis. Mutations in the p53 gene are frequently observed

in several cancers, especially in high-grade endometrial carcinomas such as serous carcinoma. Overexpression or complete loss of p53 expression in endometrial tissue often indicates malignancy, as these alterations suggest dysregulated cell growth, resistance to apoptosis.[5]

Ki67, is a nuclear protein expressed in proliferating cells and serves as a marker of cellular proliferation. The Ki67 labeling index, which indicates the percentage of cells in the active phase of the cell cycle, is frequently used to differentiate between benign, hyperplastic, and malignant endometrial lesions. A higher Ki67 index is typically associated with increased cell proliferation, which can indicate a more aggressive lesion with a higher potential for progression to malignancy.[6]

The combined use of p53 and Ki67 as immunohistochemical markers has proven valuable in differentiating between benign, premalignant, and malignant endometrial lesions. Evaluating their expression patterns provides pathologists with additional diagnostic and prognostic information that complements traditional histopathological findings.[7]p53 also plays a critical role in treatment protocols of endometrial carcinoma.In p53 abnormal tumors,patient often receive adjuvant therapy in early stage disease with chemotherapeutic agents like carboplatin and paclitaxel.[8]

AIMS AND OBJECTIVES

1. To study the clinicopathological profile of premalignant and malignant lesions of endometrium.
2. To observe the immunohistochemical expression of p53 in premalignant and malignant lesions of endometrium.
3. To observe the imunohistochemical expression of Ki67 in premalignant and malignant lesions of endometrium.

MATERIALS AND METHODS

This hospital-based observational study comprises cases of endometrial hyperplasias and endometrial carcinomas diagnosed using Hematoxylin and Eosin staining in the Department of Pathology at Andhra Medical College between April 2023 and March 2025.

Inclusion Criteria

Female patients aged between third to seventh decades presenting with symptoms like bleeding per vagina and increased endometrial thickness on USG. Dilaton and curettage and hysterectomy specimens. Cases reported as endometrial hyperplasia, Endometrioid Intraepithelial Neoplasia(EIN) and Endometrial Carcinoma.

Exclusion Criteria

1) Patients not willing to give consent.
2) Specimens with inadequate history and material.
3) Patients diagnosed with other carcinomas.

Sample Size:50 cases

Materials Required:

1. Paraffin-embedded,formalin-fixed tissue blocks from cases ofendometrial hyperplasia and endometrial carcinoma.
2. Tissue sections stained with Hematoxylin and Eosin.
3. Sections mounted on positively charged slides for immunohistochemistry.
4. Reagents used for preparing wash buffers and antigen retrieval solutions.
5. A pressure cooker utilized for antigen retrieval.
6. Immunohistochemistry kits, including a universal detection kit and primary antibodies (p53, Ki-67).
7. A microscope used for evaluating IHC-stained slides.

Methodology

Collection of Blocks and Slides:

Preparation of Haematoxylin and Eosin (H&E) Slides

Slide Preparation for Immunohistochemistry (IHC):

Tissue sections were cut at 5 microns onto APES-coated slides and incubated at 60–70°C for one hour.

Antigen Retrieval Solutions:

Prepared as per the manufacturer‘s guidelines:

Tris-EDTA Buffer (pH 9): Tris (6.05 g), EDTA (0.744 g), 1N HCl (4 ml), and distilled water to 1 L.

Tris Wash Buffer (pH 7.6): Tris (6.05 g), NaCl (8 g), 1N HCl (4 ml), distilled water to 1 L.

Precautions:

A) Use clean, dry glassware.
B) Prepare fresh buffers and ensure accurate pH.
C) Maintain humidity during staining to avoid slide drying.
D) Handle DAB chromogen with care due to its carcinogenic potential.
E) Store reagents (antibodies, DAB, peroxidase block) at 4–6°C.
F) Include positive and negative controls with each slide batch for quality assurance.

Antigen Retrieval Method:

Microwave-based antigen retrieval was employed due to its uniform heating and minimal drawbacks.IHC Protocol Overview (as per kit instructions):

Antibodies	Clone	Dilution	Manufacturer	Antigen retrival buffer	TRIS Buffer pH	Visualisation kit manufacturer
P53	IgG2ABP-53-12	Prediluted	Pathin situ	Tris EDTA	9	Pathin situ

Interpretation of P53 Immunohistochemistry:

The evaluation of p53 staining was categorized into two main patterns: wild-type and mutant-type expression.

Mutant-type patterns are further divided into the following three distinct categories:

1. Overexpression
2. Cytoplasmic localization
3. Complete absence (null pattern)

KI67:

Immunohistochemical staining was conducted using the Leica Bond Max system, incorporating heat-induced epitope retrieval. The staining process followed a pre-validated, optimized protocol. Antigen retrieval was performed at a pH of 9 for 20 minutes. To minimize non-specific antibody interactions, a 30-minute casein-blocking step was applied. The tissue sections were then incubated at room temperature for one hour with the MIB-1 antibody (monoclonal mouse anti-human Ki-67; Leica Biosystems) at a 1:100 dilution. Detection of the primary antibody was achieved using the Leica Refine Detection Kit, which includes a rabbit anti-mouse IgG secondary antibody and an anti-rabbit poly-HRP IgG antibody, with 3,3′-diaminobenzidine (DAB) used as the chromogen. The slides were counterstained using hematoxylin. For quality control, appropriate negative controls (isotype control) and positive controls (lymph node tissue) were included.

Interpretation of Ki67 Staining:

Nuclear Localization – Ki-67 is predominantly nuclear in actively dividing cells. KI67 LABELLING INDEX(LI):

The Ki-67 labeling index (LI) is the percentage of tumor cells that show nuclear staining for Ki-67, indicating their proliferative activity.
Immunohistochemical (IHC) Staining:
Tumor sections are stained with Ki-67 antibody (e.g., MIB-1 clone).
Only nuclear staining is considered positive (cytoplasmic staining is ignored). Counting Positive Cells:
Select hot spots (regions with highest proliferation)
Count at least 500–1000 tumor cells in multiple high-power fields (HPF).
The Ki-67 index is calculated as:
Ki-67 LI (%) = Number of Ki-67 positive tumor cells x100 Total number of tumor cells counted.

RESULTS

Table 1: p53 HPE Report

P53	HPE Report			
	Atpical hyperplasia	Endometrial Hyperplasia without Atypia	Endometrioid Endometrial Carcinoma	High Grade Serous Carcinoma
Wild Type	8	14	15	1
Abnormal (Mutant)	2	0	2	6
Abnormal (null type)	0	0	0	2
Total	10	14	17	9

P value <0.001(Significant)

According to our study,out of 14 cases of endometrial hyperplasia without atypia all cases showed wild type staining of p53.Out of 10 cases of endometrial hyperplasia with atpyia 8 cases showed wild type staining of p53 and 2 cases were mutant (overexpression for p53).Among 17 cases of endometrioid endometrial carcinoma 15 showed wild type staining of p53 and 2 cases were mutant (overexpression of p53).
Among 9 cases of high grade serous carcinoma 1 case showed wild type staining of p53 and the remaining 8 cases were mutant.Out of 8 mutant cases 6 showed overexpression pattern and the remaining 2 cases were of null type.

Table 2: P53 in Malignant Lesions

P53 in Malignant Lesions	Lymphovascular Invasion in malignant lesions		Total
	Present	Not Identified	
Wild Type	0	16	16
Abnormal (Mutant)	3	5	8
Abnormal (Null Type)	0	2	2
Total	3	23	26

P value 0.066 (Not Significant)

Table 3: HPE Report of KI 67

HPE Report	KI67 (%)		P Value (ANOVA)
	Mean	Std. Deviation	
Endometrial Hyperplasia without Atypia	5.86	1.512	<0.001 (SIGNIFICANT)
Atpical hyperplasia	15.8	2.044	
Endometrioid Endometrial Carcinoma	21.12	4.859	
High Grade Serous Carcinoma	38.56	3.206	

Among 14 cases of endometrial hyperplasia without atypia mean KI67 index was 5.86%, in 10 cases of endometrial hyperplasia with atpyia mean KI67 index was 15.8%, among 17 cases of endometrioid endometrial carcinoma mean KI67 index was 21.12% and among 9 cases of serous carcinoma mean KI67 index was 38.56%.

Analysis:
Statistical analysis was done using SSPS 19 software. PEARSON Chi-square test with 2x2 contingency table was used to calculate p-value to ascertain statistical significance. Probability (p) values less than 0.05 were considered statistically significant.

Table 4: Analysis

AUC CURVE	0.954
P VALUE	<0.001
95% CI	0.905 TO 1.000

Estimated binormal ROC curves, with lower and upper bounds of the asymmetric 95% confidence interval for true-positive fraction at a variety of false-positive fraction were demonstrated. Area under Curve (AUC) is used as a quantitative measure of accuracy for each marker. AUC<0.75 was not clinically useful and AUC=1 is perfect.
In this study, Area under Curve for P53 marker was 0.954 with 95 % confidence interval (0.905 TO 1.000).

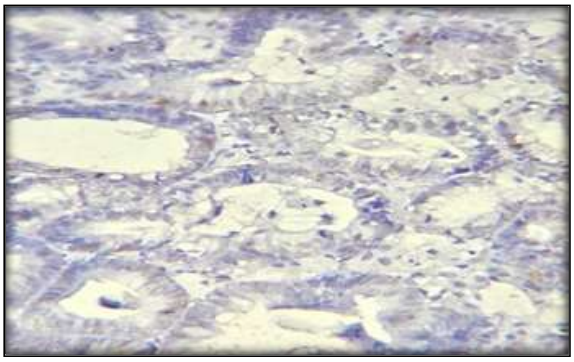

Figure 1: P53 Immunohistochemistry in a case of Endometrial Hyperplasia without atypia showing wild type expression (P53 IHC 400X)

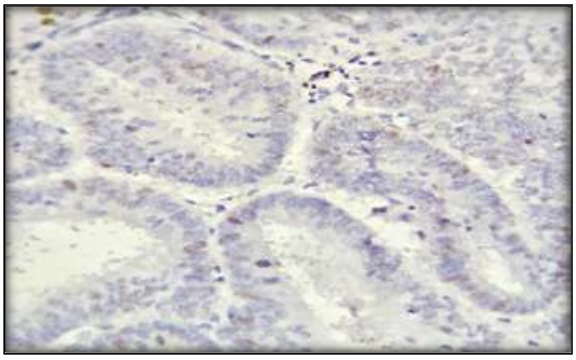

Figure 2: P53 Immunohistochemistry in a case of Atpical hyperplasia showing wildtype expression (P53 IHC 400X)

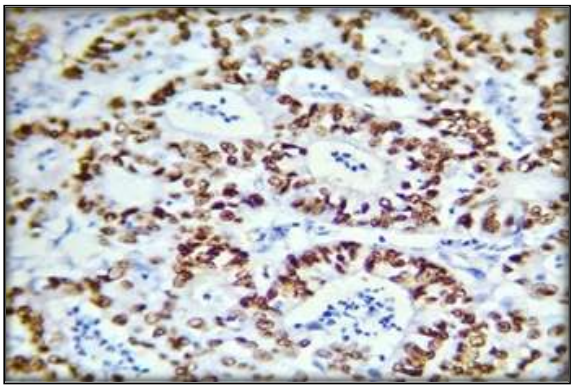

Figure 3: Aberrant (mutant) expression of P53 Immunohistochemistry in case of Atpical hyperplasia (P53 IHC 400X)

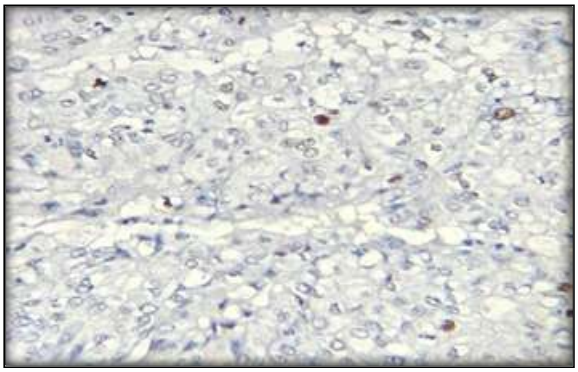

Figure 4: Wild type P53 expression in a case of Endometrioid Endometrial Carcinoma(P53 IHC 400X)

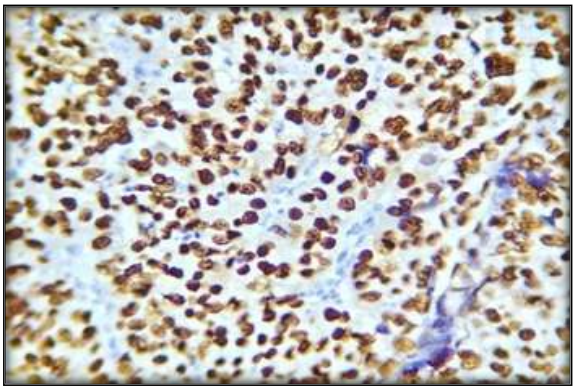

Figure 5:Aberrant (mutant) expression of P53 Immunohistochemistry in case of Endometrioid Endometrial Carcinoma (P53 IHC 400X)

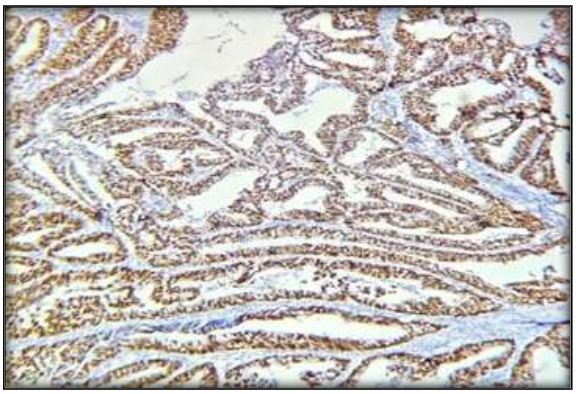

Figure 6: Aberrant (mutant) expression of P53 Immunohistochemistry in Uterine Serous Carcinoma (P53 IHC 100X)

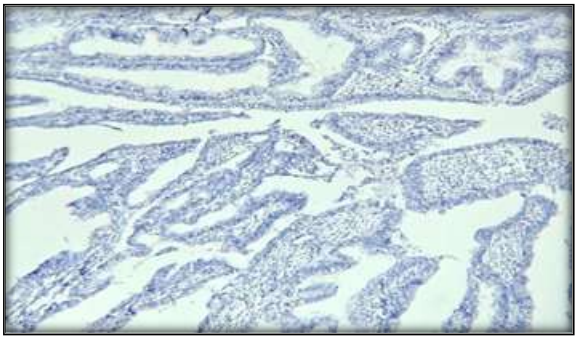

Figure 7:Aberrant (null type) expression of P53 Immunohistochemistry in Uterine Serous Carcinoma (P53 IHC 100X)

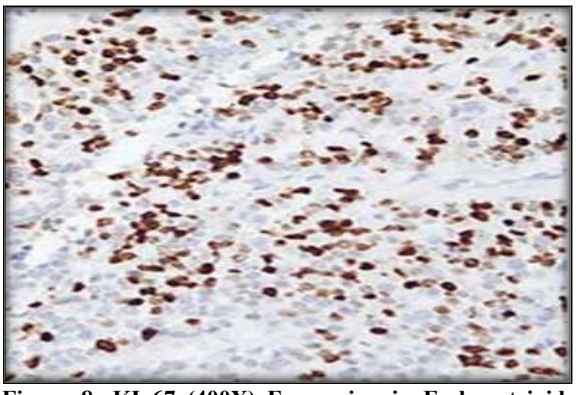

Figure 8: KI 67 (400X) Expression in Endometrioid endometrial Carcinoma

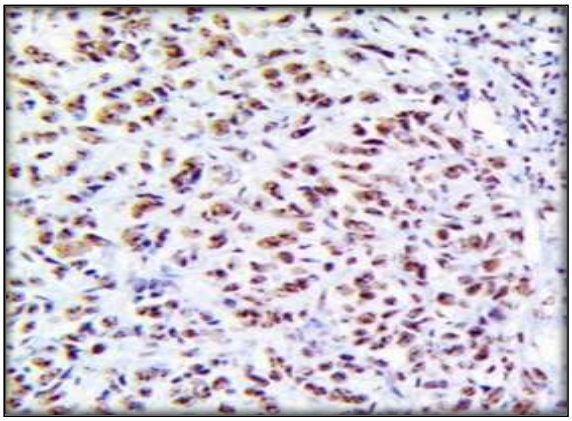

Figure 9: KI 67 (400X) Expression in Uterine Serous Carcinoma

DISCUSSION

Endometrial carcinoma ranks, as the fifth most prevalent malignancy among women globally.The annual incidence of endometrial carcinoma, according to Global statistics is 10-20% in 100,000 women. The incidence of endometrial carcinoma is on a steady increase, mainly attributable to better awareness and more effective screening programmes.[1]

Standard molecular classification of endometrial cancers (EC) is now endorsed by the WHO and identifies p53-abnormal (p53abn) EC as the subgroup with the poorest prognosis and the most likely to benefit from adjuvant chemo(radio)therapy. P53abn EC are POLE ultramutated, mismatch repair proficient and show abnormal immunohistochemical (IHC) staining for p53.Correct interpretation of routinely performed p53 IHC has therefore become of paramount importance.[1]

Age Distribution

In the present study, a total of 50 cases comprising premalignant and malignant lesions of the endometrium were analyzed. The specimens included both endometrial biopsies and hysterectomy samples. The age of the patients ranged from 30 to 70 years.

The most commonly affected age group was 51–60 years. This observation is consistent with the findings of Rekha et al, who also reported a peak incidence in the 51–60 year age group, indicating a common trend across similar studies. Suchandra et al,[9] likewise reported the most prevalent age group as 50–60 years, which closely aligns with our data. It was observed that the majority of patients diagnosed with endometrial carcinoma were above 45 years of age, highlighting the increased prevalence of malignancy in the perimenopausal and postmenopausal age groups.

Presenting Symptoms

In our study, abnormal uterine bleeding emerged as the most common presenting symptom in lesions of endometrium.This observation is consistent with the findings of Rekha et al. and Suchandra et al,[9]who also reported abnormal uterine bleeding as the predominant clinical manifestation in their respective studies. These similarities suggest a shared clinical pattern across diverse study populations. However, Karuna et al,[10] reported postmenopausal bleeding as the most frequently observed symptom in their cohort. The predominance of abnormal uterine bleeding in the majority of studies underscores its diagnostic relevance and the need for timely evaluation in patients presenting with this symptom to enable early detection and appropriate management of endometrial pathology.

Subtypes Distribution

In our study, histopathological evaluation of 50 cases of endometrial lesions, revealed 24 premalignant and 26 malignant lesions. Among the premalignant cases, 14 were diagnosed as endometrial hyperplasia without atypia, and 10 as Atpical hyperplasia. A This distribution pattern closely aligns with findings reported in earlier studies. The proportions of hyperplasia without atypia and with atypia in our study are comparable to those reported by Suchandra et al.[9] (20% each) and Sherman et al,[11] (24% and 19%, respectively).

Among the malignant cases, 17 were endometrioid adenocarcinomas and 9 were high-grade serous carcinomas. Endometrioid endometrial carcinoma emerged as the most common(34%) malignant subtype in our cohort, consistent with the observations of Suchandra et al, and Sherman et al,[11] both of whom reported a 47% incidence of this subtype. High-grade serous carcinoma, a more aggressive and less frequent subtype, was observed in 9 cases (18%) in our study—closely matching the frequencies reported by Suchandra et al,[9] (13%) and Sherman et al,[11] (10%).

Tumour Grading in Endometrioid Endometrial Carcinoma

In the present study, among 17 cases of endometrioid endometrial carcinoma, 9 cases (52.9%) were classified as grade I, 6 cases (35.3%) as grade II, and 2 cases (11.8%) as grade III. This distribution reflects a predominance of low- to intermediate-grade tumors, which is consistent with findings from multiple studies. Agarwal et al,[12] reported that out of 72 cases of endometrioid carcinoma, 44% were grade I, 39% were grade II, and 16% were grade III. Masjeed et al,[14] observed similar trends, with 11 of 22 cases being grade I, 9 grade II, and 2 grade III. Swami et al.73 reported 10 cases of grade I, 5 of grade II, and 2 of grade III among their endometrioid carcinoma cohort. In contrast, Lax et al.75noted a more even distribution with 15 grade I, 13 grade II, and 14 grade III tumors among 58 cases, suggesting a slightly higher proportion of high-grade lesions. Sherman et al,[11] reported 19 grade I, 18 grade II, and 8 grade III cases among 45 endometrioid carcinoma cases. Overall, the current study aligns with existing literature in showing that grade I tumors are the most common, followed by grade II and fewer grade

III lesions, reflecting the typically indolent nature of most endometrioid carcinomas.

Myometrial Invasion in Malignant Cases:

In our study, among the 50 cases of endometrial lesions evaluated, 29 specimens were obtained from hysterectomies. Out of these, 19 cases were malignant,16of the malignant cases were diagnosed as endometrioid endometrial carcinoma, while the remaining 3 were high-grade serous carcinomas. Among the endometrioid carcinoma cases, 11 (68.75%) showed <50% myometrial invasion, while 5 cases (31.25%)demonstrated >50% invasion. Notably, all 3 cases of serous carcinoma exhibited <50% myometrial invasion. These findings indicate that a majority of endometrioid carcinomas in our cohort presented with superficial myometrial invasion. This contrasts with the findings of Agarwal et al,[12] who reported that 46 cases (53.5%) of endometrial carcinoma had >50% myometrial invasion at the time of diagnosis, suggesting a higher rate of deep myometrial involvement in their study population. The relatively lower incidence of deep invasion in our cohort may reflect earlier detection or differences in tumor biology and patient demographics.

Lymphovascular Invasion in Malignant Cases

In our study, among the 26 malignant cases lymphovascular invasion (LVI) was identified in 3 cases (11.5%), while the remaining 23 cases (88.5%) exhibited no evidence of LVI. Specifically, within the 17 cases of endometrioid endometrial carcinoma, LVI was present in 2 cases (11.8%) and absent in 15 cases (88.2%). Among the 9 cases of serous carcinoma, LVI was observed in 1 case (11.1%) and absent in 8 cases (88.9%).

When correlating p53 expression patterns with lymphovascular invasion, it was found that out of 26 malignant cases, 14 cases with wild-type p53 showed no LVI. Among the 12 cases with mutant p53 expression, 3 cases exhibited LVI, and all of these demonstrated a p53 abnormal (mutant) pattern. The remaining abnormal p53 cases
(both mutant and null type) did not show LVI. This relationship yielded a p-value of 0.066, indicating no statistically significant association between p53 mutation status and LVI in our cohort. These findings are consistent with the results reported by AnilaTresa et al who, in their study on the clinical profile and survival outcomes of endometrial cancer with p53 mutation, found LVI in 12 out of 36 wild-type p53 cases and 14 out of 27 abnormal p53 cases, with a non-significant p-value of 0.140. This suggests that while LVI may occur in both wild-type and abnormal p53 cases, there is no statistically significant correlation between p53 status and the presence of lymphovascular invasion.

Figo Staging

In our study, out of 16 endometrioid endometrial carcinoma cases reported on hysterectomy specimens, 11 cases (68.8%) were classified as FIGO stage IA, 3 cases (18.8%) as stage IB, and 2 cases (12.5%) as stage IIC. All 3 cases of serous carcinoma were found to be at stage IIC. This indicates that a majority of endometrioid carcinomas in our study were detected at an early stage, particularly stage IA. In comparison, Agarwal et al,[12] reported that 59% of cases were diagnosed at stage I, 15% at stage II, 14% at stage III, and 12% at stage IV. Similarly, Karuna et al,[10] found 18 cases(51%) in stage I, 13 (37%)in stage II, 3(8%) in stage III, and 1 (4%)in stage IV. In contrast, Vermij et al,[13] documented a broader distribution, with only 13.2% of cases at stage IA and a larger proportion (43.1%) at stage III. These comparisons highlight a trend toward earlier-stage diagnosis in our cohort relative to larger or more diverse study populations,possibly due to differences in healthcare access, tumor biology, or patient demographics.

Expresssion of P53 in Premalignant and Malignant Cases

In our study, p53 immunohistochemical expression was evaluated across different histopathological subtypes of endometrial lesions. All cases of hyperplasia without atypia demonstrated wild-type p53 expression, which is consistent with the findings of Suchandra et al. Karuna et al,[10] and Sherman et al,[11] who also reported no mutant expression in this category. In hyperplasia with atypia, our study revealed wild-type expression in 80% of cases and abnormal p53 (mutant) expression in 20%. This closely parallels the results of Sherman et al. (84% wild-type, 16% p53 abnormal) and Karuna et al,[10] (88% wild-type, 12%p53 abnormal), while Suchandra et al,[9] observed wild-type expression in all such cases. These results suggest a progressive increase in p53 aberrations as lesions advance toward malignancy. Among 17 cases of endometrioid endometrial carcinomas (EEC), our findings showed that 15 cases (88.2%) were wild-type and 2 cases (11.8%) showed abnormal p53(mutant) expression. This aligns withSuchandra et al,[9] (91% wild-type, 9% p53 abnormal) and Karuna et al,[10] (84% wild-type, 16% p53 abnormal), and is comparable to Sherman et al,[11] (80% wild-type, 20% p53 abnormal), reinforcing that p53 mutations are less frequent in EEC but still present in a minority of cases. In contrast, serous carcinoma cases in our study exhibited a markedly higher frequency of abnormal p53 expression (88.9%), which is in close agreement with the data from Suchandra et al. (85%), Karuna et al,[10] (80%), and Sherman et al,[11] (86%). These observations are further supported by the work of Garg et al, who emphasized that p53 abnormal expression, is strongly associated with aggressive clinical behavior and poorer outcomes in high-grade serouscarcinomas. Collectively, the data from our study and prior literature substantiate the diagnostic and prognostic utility of p53 immunostaining, particularly in distinguishing high-grade malignancies and guiding clinical decision-making.

Ki67 in Premalignant and Malignant Cases:

In our study, the Ki-67 labelling index, an indicator of cellular proliferation, was evaluated across various endometrial lesions. The mean Ki-67 index in hyperplasia without atypia was 5.86%, which is comparable to the 4.97% reported by Masjeed et al,[14] and aligns with the <10% range observed in the study by Swami et al,[15] For hyperplasia with atypia, our study showed a mean Ki-67 index of 15.8%, which is significantly lower than the 27.5% reported by Masjeed et al,[14] but falls within the 10–20% range described by Swami et al,[15] Among malignant lesions, the mean Ki-67 index in endometrioid endometrial carcinoma was 21.12% in our study, which is notably lower than the 30.5% reported by Masjeed et al,[14] and fits within the 20–30% range found in Swami et al,[15] Serous carcinoma, being a more aggressive variant, showed the highest Ki-67 index across all studies. In our study, it was 38.56%, which, while lower than Masjeed et al.'s,[14] 47.5%, still supports the trend of high proliferative activity, in agreement with Swami et al,[15] who observed values >30%. These findings underscore a progressive increase in Ki-67 expression from benign to malignant endometrial lesions, consistent with its role as a proliferative marker and a potential adjunct in differentiating lesion severity.

The present study demonstrates that p53 immunohistochemistry provides significant diagnostic and prognostic value in evaluating premalignant and malignant endometriallesions. Abnormal p53 expression was highly associated with serous carcinoma, whereas wild-type p53 was predominant in endometrioid carcinoma and hyperplasias.

These findings are consistent with those reported in other studies, reaffirming the role of p53 in refining endometrial carcinoma classification and guiding patient management. Integrating histopathology with targeted immunohistochemistry enhances the accuracy of diagnosis, risk stratification, and therapeutic planning.

CONCLUSION

P53 mutation-type expression is significantly associated with high-grade malignancies, especially serous carcinoma of the endometrium, and is rare in endometrioid carcinomas and hyperplastic lesions with atypia.Ki-67 proliferation index increases parallel to the degree of malignancy, supporting its role as marker of tumor aggressiveness.p53 immunohistochemistry is a reliable surrogate for detecting TP53 mutations and can aid histopathological evaluation, especially in diagnostically challenging cases.Combining molecular markers with histological features improves diagnostic accuracy and provides better insight into the expected clinical behavior of endometrial lesions.Therefore, incorporating p53 immunohistochemical analysis into routine pathological evaluation can enhance diagnostic confidence and aid in prognostication of both premalignant and malignant endometrial conditions.It also helps in guiding appropiate clinical management as now a days targeted therapies are being developed against p53.

Strengths of the Study

1. Comprehensive Evaluation with Histology and Immunohistochemistry:

The study incorporated both routine histopathological examination and immunohistochemical markers (p53 and Ki-67), allowing for a detailed and more accurate diagnosis and stratification of premalignant and malignant endometrial lesions.

2. Inclusion of Premalignant and Malignant Lesions

By including cases ranging from hyperplasia without atypia to high-grade carcinomas,the study provided a broad spectrum analysis of the endometrial disease continuum.

3. Correlation of Clinicopathological Features with Molecular Markers

The study correlated clinical findings (like age, presenting symptoms) with p53 expression and Ki-67 proliferation index, adding depth to the interpretation and clinical relevance.

4. Use of Recent WHO 2020/FIGO 2023 Classifications

Diagnostic categories and staging were based on the most updated WHO (2020) and FIGO (2023) classifications, ensuring current relevance and standardization.

5. ROC Analysis for Diagnostic Accuracy

The use of Receiver Operating Characteristic (ROC) analysis to assess p53 diagnostic performance added statistical robustness to the results (AUC = 0.954).

6. Cross-Comparison with Other Studies

The findings were extensively compared with national and international literature, strengthening the validity and external comparability of the study results.

7. Emphasis on Early Detection and Prognostication

By focusing on molecular markers like p53 and Ki-67, the study emphasized the importance of early identification of aggressive tumors and individualized patient management.

Limitations

1. Sample Size: The study was limited to 50 cases, which may not fully represent the wide biological spectrum of endometrial lesions, particularly rare histological variants.
2. Short Follow-Up: This study did not include long-term follow-up of patients to correlate p53 and Ki-67 expression with clinical outcomes such as recurrence or survival.
3. Single Institution Study: Data was collected from a single center, potentially limiting the generalizability of the findings to wider or more diverse populations.

4. Lack of Full Molecular Profiling: Only immunohistochemical surrogates were used for p53 assessment; no genetic sequencing (e.g., TP53 mutation analysis) was performed to validate the immunohistochemical findings.
5. Limited Analysis of Correlates: Correlation of p53 expression with lymph node status, and adjuvant therapy response could not be comprehensively evaluated due to sample and data constraints.

Future Scope

The findings of this study open several avenues for future research and clinical application:

1. Larger, Multicentric Studies:Conducting studies with larger sample sizes across multiple institutions would help validate the observed trends and enhance the generalizability of results across different populations and ethnic groups.
2. Integration of Full Molecular Profiling:Incorporating molecular techniques such as Next-Generation Sequencing (NGS) for direct TP53 mutation analysis and other genomic markers (e.g., POLE mutations, microsatellite instability) would provide a more comprehensive understanding of tumor biology and better align with TCGA molecular subgroups.
3. Correlation with Clinical Outcomes: Prospective studies with long-term follow-up evaluating p53 and Ki-67 status against patient outcomes like recurrence, disease-free, and overall survival would further establish their prognostic value.
4. Expanded Immunohistochemical Panels: Future studies can include additional markers such as MMR proteins (MLH1, MSH2, MSH6, PMS2), L1CAM, and HER2/neu, which are gaining importance in modern endometrial carcinoma classification and therapy planning.
5. Therapeutic Implications:Exploring the role of targeted therapies directed against p53 pathway alterations, such as p53 reactivators (e.g., APR-246) or synthetic lethality approaches (e.g., Wee1 inhibitors), could offer newer treatment strategies for patients with p53-aberrant tumors.

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