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E-Cadherin and Beta-Catenin Immunoexpression In Endometrioid Endometrial Carcinoma

Anu T R[1], Rahul Rajeev[2], Lovely Jose[3], Krishna Raj J S[4], Seeja Sumedhan[5]

ABSTRACT

Background

Endometrial carcinoma is the most common invasive cancer of female genital tract. It is classified into type 1 and type 2, of which endometrioid carcinoma belongs to type 1 endometrial carcinoma and accounts for 85% of cases reported. It is an estrogen–sensitive carcinoma. Better understanding of molecular mechanisms leading to high grade endometrioid carcinoma can aid in early detection and management.

Objectives

To assess the association between the immunoexpression of Beta-Catenin/E-Cadherin and histopathological prognostic factors in endometrioid endometrial carcinoma.

Methodology

Sample size was 61. Endometrioid carcinoma grading was determined for each case from routine Hematoxylin (H) and Eosin (E) sections. Then immunohistochemical staining of E-Cadherin and Beta -Catenin was done. E-Cadherin and Beta-Catenin expression was correlated with tumour grade, TNM, depth of myometrial invasion and lymph node status.

Results

A low Beta-Catenin expression was obtained in 100% of grade 3 tumours when compared to 37.8% and 22.8% of grade 1 and 2 tumours respectively. Beta-Catenin expression was low, being 78.6%, 40% and 31% of Stage T3, T2 and T1 respectively. But expression of E- Cadherin and Beta -Catenin were not significantly correlated with lymph node invasion and depth of myometrial invasion.

Conclusion

E-Cadherin expression was significantly reduced in high grade endometrioid carcinoma, however this study could not document a significant correlation of E- Cadherin expression with TNM staging, lymph node metastasis, and depth of myometrial invasion. Beta-Catenin expression was significantly low in grade 3 endometrioid carcinoma, but no significant correlation of Beta -Catenin expression with depth of myometrial invasion and lymph node status was obtained.

Keywords: E-Cadherin, Beta-Catenin , Endometrioid,Carcinoma, Immunoexpression

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INTRODUCTION

Endometrial cancer is responsible for approximately 4 % of all cancers worldwide especially after menopause. It is categorised into type 1 which is more common in woman with obesity, hyperstrogenism and as type 2 which arises in background of endometrial atrophy. It is an estrogen–sensitive carcinoma that arises in presence of endometrial hyperplasia and are considered biologically indolent with the exception of grade 3 endometrioid carcinoma, which behaves aggressively(1).Histological grading, stage of disease, depth of myometrial invasion and lymph node status are being documented as the various parameters that affect the prognosis in endometrial carcinoma(2). Aggressiveness of tumour is explained by intervention of epithelial mesenchymal transition process – loss of intercellular adhesion that is associated with lower E-Cadherin expression. Decreased E-Cadherin expression is associated with invasive and malignant potential in endometrial and other carcinoma. Reduced expression of E-Cadherin is found in 5-40% of endometrioid carcinomas. Tumours without E-Cadherin expression are more likely to be poorly differentiated or non-endometrioid and are often associated with poor prognosis (3).Beta-Catenin is a cytoplasmic molecule that bind to intracytoplasmic domain of cadherins and supports adhesion capacity of cadherins. The expression of Beta-Catenin is induced by stimuli like extracellular wnt/wingless signal and is metabolized by GSK 3-beta and APC. Activation of wnt/Beta-Catenin can promote cancer development. Mutation in catenin gene or APC gene induce intracellular accumulation of Beta–Catenin (4). The accumulated Beta-Catenin is reported to bind TCL and be translocated to the nucleus and nuclear Beta-Catenin act as a transcriptional activator of c-myc and cyclin-D1 for growth acceleration(5) .Beta-Catenin gene(CTNNB1) mutation leads to decreased cell-cell adhesion and have been reported in 15% of endometrioid carcinomas(6). Altered E-Cadherin expression has been associated with decreased cell–cell adhesion, metastatic potential, tumor dedifferentiation, and deep myometrial invasion in endometrial carcinoma. As part of the adherens junction complex, Beta-Catenin links E-Cadherin through alpha-catenin to the cytoskeleton. Thus, malfunction of Beta-Catenin may lead to decreased cell–cell adhesion and facilitate metastatic spread of carcinoma cells. Methods that allow more accurate prediction of the clinical behaviour are needed. In this respect, the identification of molecular prognostic markers has now gained importance, E-Cadherin and Beta-Catenin is among them. Therefore an attempt is made in this study to compare the immunohistochemical expression of Beta-Catenin and E-Cadherin in a set of uterine endometrioid carcinoma. This may aid in diagnostic and management purposes.

Methods

A Cross-sectional study was conducted at Department of Pathology, Government Medical College,Thrissur.Hysterectomy specimens of endometrioid endometrial carcinoma received in Histopathology were taken as the study population during 1-01-2019 to 1-02-2021. **Inclusion criteria**: Hysterectomy specimens received in Histopathology laboratory diagnosed to have endometrioid adenocarcinoma in Government Medical College, Thrissur. **Exclusion criteria**: Not properly fixed specimen. Sample size was calculated using the formula 4pq/d2 Where p 87% was the prevalence taken from the study "E-Cadherin and Betacatenin immunoexpression in endometrioid endometrial carcinoma" by Florescu" (3) and the relative precision of 10% ,giving 61 cases of endometrioid endometrial carcinoma was studied in this study.The diagnosed endometrial carcinoma samples were collected from the total hysterectomy specimens received in Histopathology Laboratory of Government Medical College, Thrissur. The specimens were fixed in 10% formalin, processed by paraffin embedding, cut with microtome and haematoxylin and eosin stained. Clinical and morphological parameters investigated were age, differentiation degree, lymph node status, depth of invasion and pTNM stage. For immunohistochemical analysis a panel of antibodies Beta-Catenin and E-Cadherin were used. The amplification system was represented by LSAB2 System-HRP (Horseradish peroxidise). After chromagen treatment the tissue which stains

brown(membranous) was taken as positive. Membranous E-Cadherin and Beta-Catenin expression was assessed as using Immunohistochemical Analysis:

- A panel of antibodies for **E-Cadherin** and **Beta-Catenin** was used.
- The **LSAB2 System-HRP (Horseradish Peroxidase)** was employed as the amplification system.
- After chromagen treatment, tissue staining **brown (membranous)** was considered positive.

E-Cadherin and Beta-Catenin staining was evaluated using regular light microscope at the magnification of 40x. Membranous staining was evaluated.The antibody quantification was performed using a score found by multiplying number of marked cells (P) with immunostaining intensity (I). According to number of tumour cells with membranous staining, the study cases were divided into following categories:

1 Absence of cells
2 10% cells with membranous staining
3 10-25% cells with membranous staining
4 25-50% cells with membranous staining
5 More than 50% cells with membranous staining

The intensity of tumour cells with membranous staining was divided in four categories

0 absent
1 poor
2 moderate
3 strong

For statistical analysis the resulting scores obtained by multiplication of intensity and percentage was further categorized into 5 categories

E-CADHERIN /BETA-CATENIN SCORE OBTAINED BY MULTIPLYING INTENSITY AND PERCENTAGE OF MARKED CELLS (I x P)	FINAL E-CADHERIN SCORE
0-3	SCORE 0
4-6	SCORE 1
7-9	SCORE 2
10-12	SCORE 3
13-15	SCORE 4

Those obtained a final score of 0,1 and 2 was considered to have a low E-Cadherin and Beta-Catenin expression and those with a score of 3 and 4 were considered to have high immunohistochemical expression of both markers. Data obtained was entered in Microsoft office excel sheet 2016. This was then analysed using SPSS software version 20.0. The statistical test used is Fischer's exact test. P value < 0.05 was considered statistically significant. The findings are presented in appropriate charts and tables.

Results

This study, conducted in the Department of Pathology at Government Medical College, Thrissur, between January 2019 and February 2021, analyzed 61 cases of endometrioid endometrial adenocarcinoma. Histopathological evaluation was performed using Hematoxylin and Eosin staining for tumour grading, glandular differentiation and nuclear features. The age distribution of the patients ranged from 41 to 80 years, with a mean age of 59 years. The majority of patients were within 51-60 age group (Figure 1).

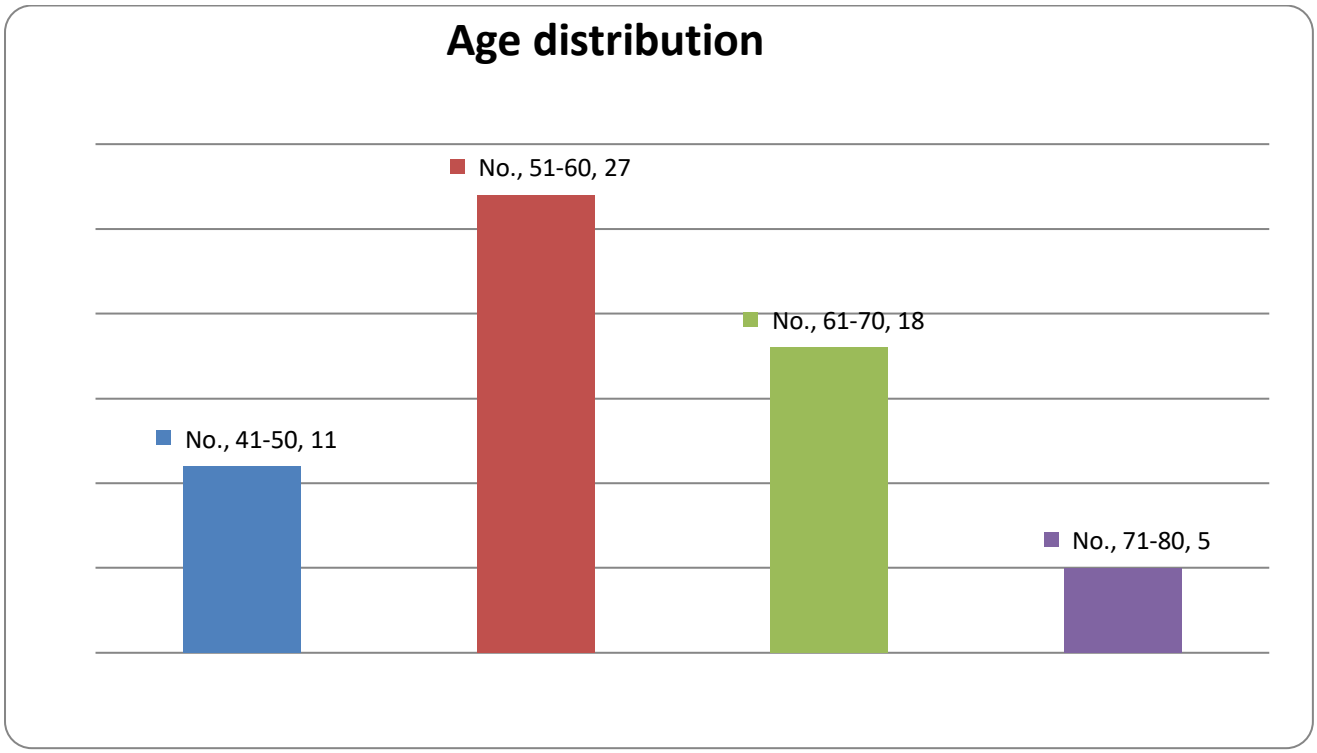
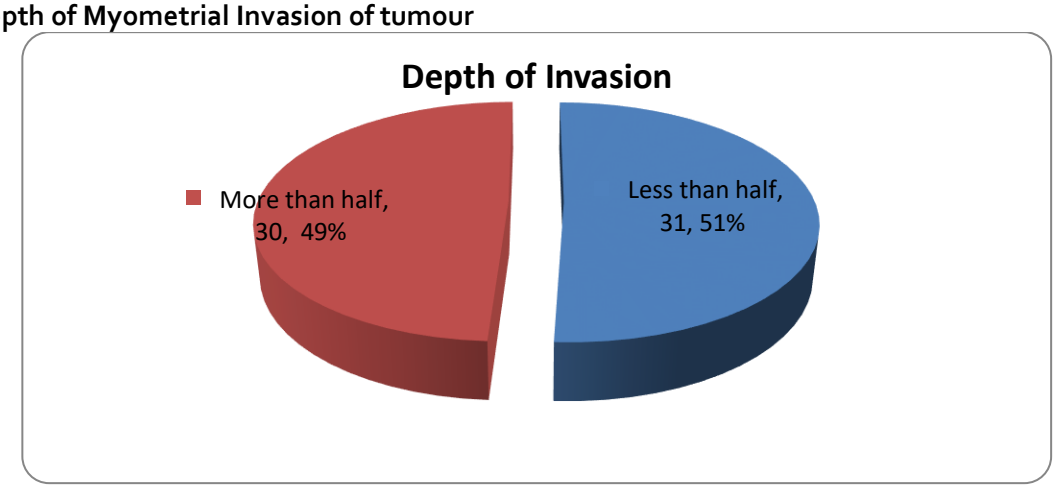


Figure1: Age Distribution of the participants

The age of the patients ranged from 41-80 years. The maximum number of patients were in the age group of 51-60 years. The mean age was 59 years. Of the 61 cases examined, 31 cases (50.8%) demonstrated less than half myometrial invasion, while 30 cases (49.2%) exhibited more than half myometrial invasion (Figure 2).

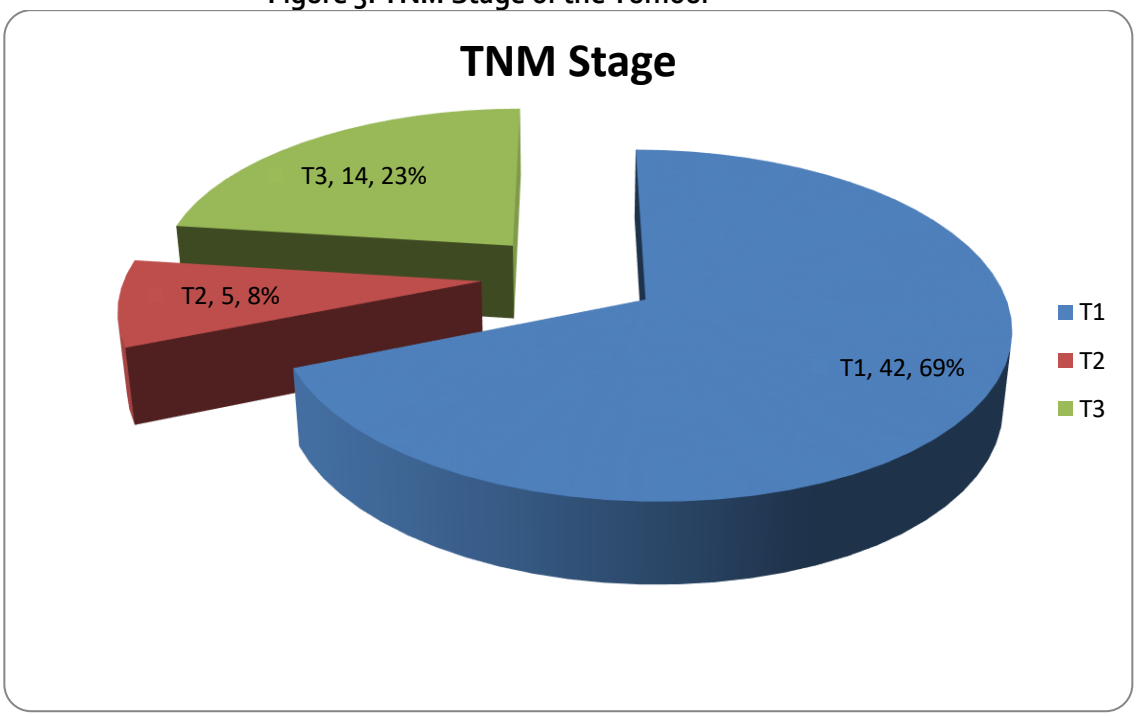
Figure :2 Depth of Myometrial Invasion of tumour



Out of the 61 hysterectomy cases; 30 cases showed more than half of myometrial invasion; 31 cases showed less than half of myometrial invasion.Tumor grading revealed that 45 cases (73.8%) were classified as grade 1, 9 cases (14.8%) as grade 2, and 7 cases (11.5%) as grade 3. Among the 44 cases undergoing lymphadenectomy, 4 cases (9%) showed lymph node metastasis, while 40 cases (91%) exhibited no metastasis. TNM staging indicated that 42 cases (69%) were categorized as

stage T1, 14 cases (8%) as stage T2, and 5 cases (23%) as stage T3 (Figure 3).

Figure 3: TNM Stage of the Tumour



Out of the 61 cases anlaysed,42 cases (69%) were of T1 stage,14 cases (8%) were T2 stage and 5 cases (23%) were of T3 stage. Correlation analyses revealed no statistically significant association between the depth of myometrial invasion and E-Cadherin scores or expression (P = 0.777) Table 1.

Table 1: Association between E-Cadherin Score And Depth Of Invasion using Fisher's exact test

DEPTH OF INVASION	ECADHERIN.SCORE				Total	P value
	1	2	3	4		
Less than half	1 (3.2%)	2 (6.5%)	20 (64.5%)	8 (25.8%)	31 (100%)	0.777
More than half	1 (3.3%)	3 (10%)	15 (50%)	11 (36.7%)	30 (100%)	
Total	2 (3.3%)	5 (8.2%)	35 (57.4%)	19 (31.1%)	61 (100%)	

There was no significant correlation of E-Cadherin scores with depth of myometrial invasion (P value 0.777).

Similarly, no significant relationship was found between the depth of invasion and Beta-Catenin scores or expression (P = 0.353 and P = 0.252, respectively) Table 2.

Table 2: Association between Depth Of Invasion And Beta-Catenin Score using Fisher's exact test

DEPTH OF INVASION	BETA-CATENIN SCORE					Total	p value
	0	1	2	3	4		
Less than half	0 (0%)	7 (22.6%)	4 (12.9%)	19 (61.3%)	1 (3.2%)	**31 (100%)**	0.353
More than half	3 (10%)	9 (30%)	3 (10%)	15 (50%)	0 (0%)	**30 (100%)**	
Total	**3 (4.9%)**	**16 (26.2%)**	**7 (11.5%)**	**34 (55.7%)**	**1 (1.6%)**	**61 (100%)**	

There was no significant association between Beta –Catenin score and depth of myometrial invasion (P value 0.353).

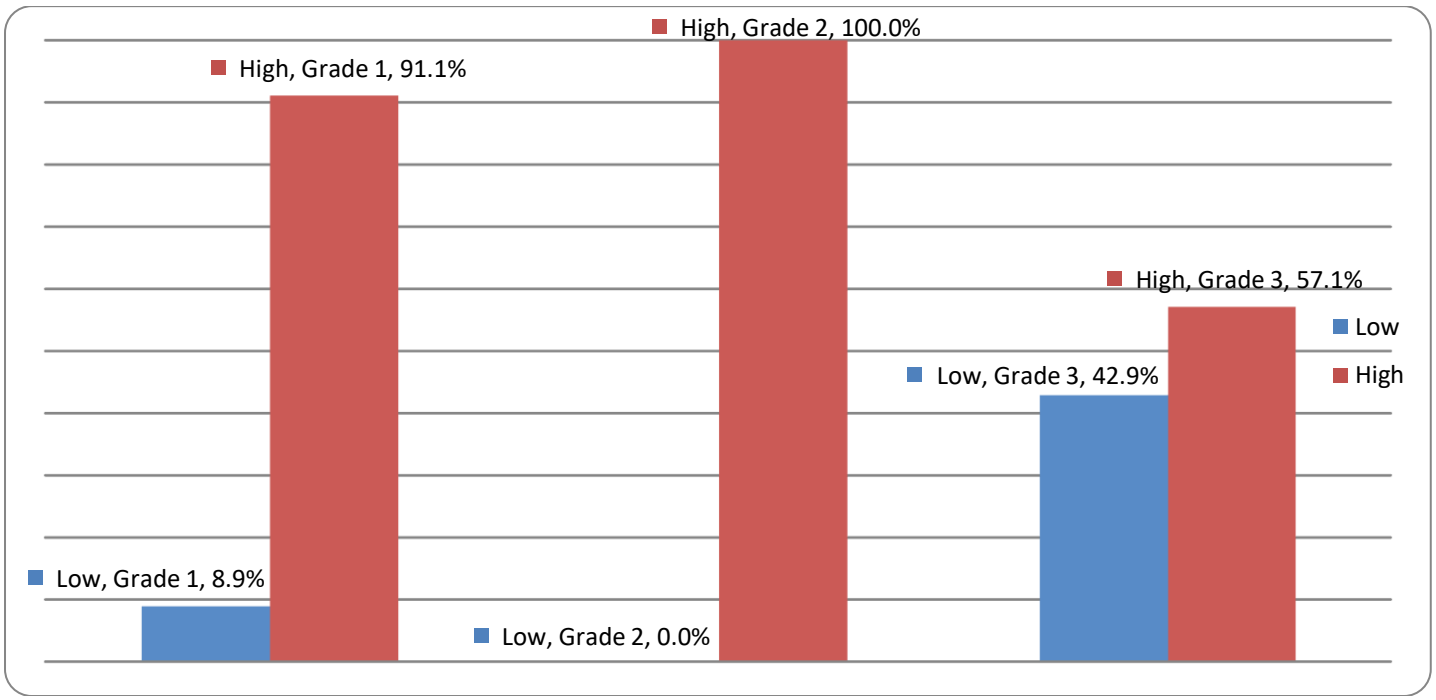
All four cases with lymph node metastasis displayed high E-Cadherin expression, though this finding was not statistically significant (P = 1.000). Furthermore, no significant correlation was noted between lymph node status and Beta-Catenin scores or expression (P = 0.806 and P = 1.000, respectively).E-Cadherin expression did not demonstrate a statistically significant correlation with TNM stage (P = 0.401) Table 3.

Table 3: Association between TNM and E-Cadherin Score using Fisher's exact test

TNM	ECADHERIN SCORE				Total	P value
	1	2	3	4		
T1	1 (2.4%)	3 (7.1%)	25 (59.5%)	13 (31%)	42 (100%)	0.585
T2	0 (0%)	0 (0%)	2 (40%)	3 (60%)	5 (100%)	
T3	1 (7.1%)	2 (14.3%)	8 (57.1%)	3 (21.4%)	14 (100%)	
Total	**2 (3.3%)**	**5 (8.2%)**	**35 (57.4%)**	**19 (31.1%)**	**61 (100%)**	

7.1% and 14.3% of stage T3 endometrioid carcinoma obtained a low score of 1 and 2 respectively, whereas only 2.4% and 7.1% of stage T1 obtained a score of 1 and 2 respectively. None of the stage 2 tumours obtained a low score. Association between TNM and E-Cadherin was statistically insignificant (P value 0.585).However, Beta-Catenin expression was found to decrease significantly with advancing TNM stage (P = 0.005) Figure 4.

Figure 4: Grade of Tumour and E-Cadherin Expression



57.1% of grade 3 cases showed high E-Cadherin expression whereas 91.1% of grade 1 cases showed high E-Cadherin expression and grade 2 cases showed highest E-Cadherin expression with 100%.

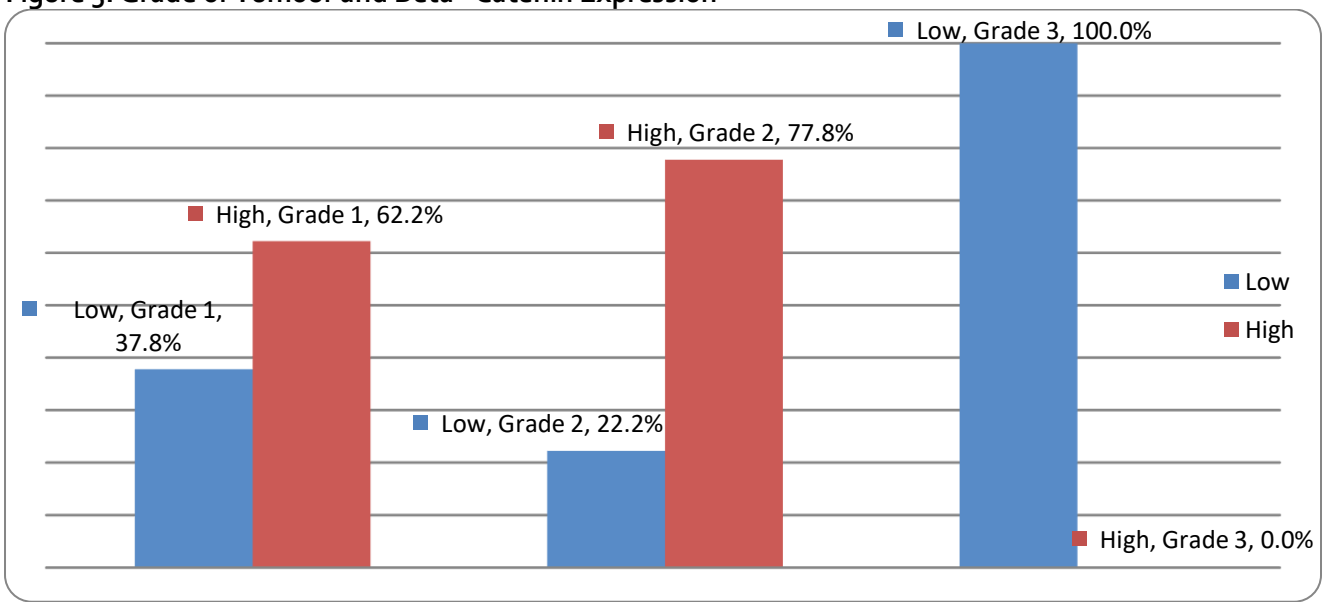
Analysis of tumor grade revealed a significant association between low E-Cadherin expression and grade 3 tumors (P = 0.038) Table 4.

Table 4: Association between TNM and and Beta-Catenin Score using Fisher's exact test

TNM	BETA-CATENIN SCORE					Total	p value
	0	1	2	3	4		
T1	0 (0%)	7 (16.7%)	6 (14.3%)	28 (66.7%)	1 (2.4%)	**42 (100%)**	*0.001
T2	0 (0%)	1 (20%)	1 (20%)	3 (60%)	0 (0%)	**5 (100%)**	
T3	3 (21.4%)	8 (57.1%)	0 (0%)	3 (21.4%)	0 (0%)	**14 (100%)**	
Total	**3 (4.9%)**	**16 (26.2%)**	**7 (11.5%)**	**34 (55.7%)**	**1 (1.6%)**	**61 (100%)**	

Beta-Catenin score was significantly lower as TNM scores increases with 57.1% of T 3 stages obtaining a score of 1 and 21.4% obtaining score of 0..This was also statistically significant (P value 0.001).Additionally, all grade 3 tumors exhibited low Beta-Catenin expression, with a significant correlation observed (P = 0.002) Figure 5.

Figure 5: Grade of Tumour and Beta –Catenin Expression



Beta-Catenin expression was low with 100% in grade 3 tumours, whereas 37.8% and 22.2% of grade 1 and 2 tumours respectively showing inverse relationship of Beta-Catenin expression with grade of tumours.The correlation between tumor grade and E-Cadherin score indicated no statistically significant association (P = 0.230) Table 5.

Table 5: Association between Grade of tumour and E-Cadherin Score using Fisher's exact test

Grade	ECADHERIN SCORE				Total	P value
	1	2	3	4		
Grade 1	1 (2.2%)	3 (6.7%)	27 (60%)	14 (31.1%)	45 (100%)	0.230
Grade 2	0 (0%)	0 (0%)	5 (55.6%)	4 (44.4%)	9 (100%)	
Grade 3	1 (14.3%)	2 (28.6%)	3 (42.9%)	1 (14.3%)	7 (100%)	
Total	**2 (3.3%)**	**5 (8.2%)**	**35 (57.4%)**	**19 (31.1%)**	**61 (100%)**	

E-Cadherin score of 1 and 2 was obtained in 14.3% and 28.6% of grade 3 tumours respectively. However only 2.25 % and 6.7% of grade 1 tumours obtained a score of 1 and 2 respectively. But none of the grade 2 tumours obtain a low score (score 1 or 2). **Association between Grade of tumour and E-Cadherin Score** showed no statistical significance (P value 0.230).

DISCUSSION

Carcinoma endometrium is a significant gynecological malignancy globally, with endometrioid adenocarcinoma being the most common subtype, constituting approximately 75–80% of cases. This study investigates the immunohistochemical expression of E-Cadherin and Beta-Catenin in endometrioid carcinoma and correlates these findings with prognostic factors like tumor grade, TNM status, myometrial invasion, and lymph node involvement.

Endometrioid carcinoma predominantly affects postmenopausal women, with the mean age of diagnosis being 60 years. However, younger women under 40 account for 5% of cases, often presenting with high-grade tumors and poor prognosis (7). In this study, 61 hysterectomy specimens were analyzed, with the majority (73.8%) being well-differentiated (Grade 1), followed by moderately differentiated (14.8%) and poorly differentiated (11.5%) cases..**Tumor Grading**: FIGO grading categorized tumors based on solid area percentages—Grade 1 (≤5%), Grade 2 (6–50%), and Grade 3 (>50%). Tumor grades are critical in predicting outcomes, as high-grade tumors demonstrate greater invasiveness and poorer prognosis (8). **E-Cadherin Expression** is a transmembrane glycoprotein critical for epithelial cell adhesion and polarity. Dysfunction in E-Cadherin/Beta-Catenin complexes compromises cell adhesion, enabling metastasis. A statistically significant reduction in E-Cadherin expression was observed in Grade 3 tumors compared to Grade 1 and 2 tumors ($p = 0.038$).Low E-Cadherin expression was noted in 42.9% of Grade 3 cases, consistent with findings by Florescu et al. and Ahmed R.H., where high-grade tumors showed diminished E-Cadherin levels (3, 9). However, our study denoted a significant decrease in E-Cadherin expression in grade 3 tumours, with respect to grade 2 and grade 1 tumours. This was statistically significant, p value was 0.038.This was similar to the findings in Florescu et al(3), Ahmed R.H et.al(9) studies, wherein they were able to establish a low E-Cadherin expression in grade 3 tumours as compared to grade 2 and grade 1. **TNM Stage**: Tumors in advanced stages (T3) exhibited lower E-Cadherin scores, though not statistically significant ($p > 0.05$). Similar trends were reported in Florescu et al. (3). **Myometrial Invasion**: While E-Cadherin expression was reduced in cases with deeper myometrial invasion, the correlation was not significant. Florescu et al. also reported insignificant p-values for this parameter (3). **Lymph Node Involvement**: Interestingly, lymph node-positive cases retained higher E-Cadherin expression, suggesting a nuanced role in metastatic mechanisms. Mell et al. demonstrated low E-Cadherin expression in 88.2% of Grade 3 tumors, albeit with insignificant p-values (10). Schlosshauer et al. identified weak E-Cadherin expression in high-grade endometrioid and non-endometrioid carcinomas, highlighting its diagnostic relevance (4). **Beta-Catenin** essential for E-Cadherin signaling, also regulates intracellular pathways. Aberrant Beta-Catenin expression contributes to tumor progression. **Grading**: A significant reduction in Beta-Catenin expression was observed in Grade 3 tumors compared to Grades 1 and 2 ($p = 0.002$). Weak membranous staining and reduced scores were prevalent in 100% of Grade 3 cases, mirroring findings by Sarkar et al., where high-grade tumors showed decreased membranous and increased nuclear Beta-Catenin expression (11). **TNM Stage**: Stage T3 tumors exhibited significantly lower Beta-Catenin expression compared to earlier stages ($p = 0.001$). This aligns with Florescu et al., who reported similar stage-dependent variations (3). **Myometrial Invasion and Lymph Nodes**: No significant relationship was found between Beta-Catenin expression and myometrial depth or lymph node status, potentially due to the limited sample size. Schlosshauer et al. noted a tendency for strong nuclear Beta-Catenin expression coupled with weak E-Cadherin levels in high-grade endometrioid carcinomas (4). Saegusa et al. documented a progressive decline in membranous Beta-Catenin immunoreactivity from normal endometrium to high-grade carcinoma (12). Low E-Cadherin and Beta-Catenin membranous expression are hallmarks of high-grade and advanced-stage endometrioid carcinomas, emphasizing their potential as prognostic markers. While correlations with lymph node status and myometrial invasion were not statistically significant, larger studies could validate these trends. **Standardized Guidelines**: The absence of established scoring systems for E-

Cadherin and Beta-Catenin necessitates standardization for consistent interpretation. **Personalized Medicine**: Molecular profiling integrating these markers could guide targeted therapies, particularly for high-grade cases with poor outcomes. **Expanded Studies**: Larger, multi-institutional cohorts are vital for refining these findings and exploring therapeutic implications.

Conclusion

A significant association between Beta-Catenin expression and tumor grade and stage was observed. High-grade tumors (grade 3) and advanced-stage tumors (T3) demonstrated significantly lower Beta-Catenin expression compared to lower-grade and earlier-stage tumors. However, no significant correlation was found between Beta-Catenin expression and myometrial invasion or lymph node metastasis. The findings suggest Beta-Catenin expression and its potential role in predicting aggressive behavior of endemetroid tumors and its value in tumor grade and stage differentiation for diagnostic and prognostic purposes.E-Cadherin expression was significantly related to tumor grade, especially grade 3 tumors exhibiting low expression, while grade 2 and most grade 1 tumors retained high expression. No significant differences were noted concerning myometrial invasion or tumor stage, despite higher E-Cadherin expression in stages I and II and less extensive myometrial invasion. E-Cadherin and its membranous expression could serve as a marker of prognosis in endometrioid carcinoma.

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