Razi Med J. 2026;2(2):363-368
https://doi.org/10.69667/rmj.26229
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

Original article

The Nuclear β-Catenin Expression as a Prognostic Indicator and Its Clinicopathologic Correlates in Endometrial Adenocarcinoma: A Retrospective Study from Albayda Medical Center, Libya

Jameelah Sulayman[1]*, Ahmed Elsayed[2], Bushra Abogharsa[1], Ahmad Mohammed[3]

[1] *Pathology Department, Faculty of Medicine, Omar Al-Mukhtar University, Al-Bayda, Libya*
[2] *Pathology Department, Director of Medical Program, Apollonia University, Benghazi, Libya*
[3]*Pathology Department, Tanta Center, Egypt*
Corresponding email. *jameelah.sulayman@omu.edu.ly*

Abstract
Endometrial carcinoma is the most frequent gynecological malignancy in developed countries; however, despite its rising incidence, there remains a critical deficiency in validated biomarkers for early-stage detection. The Wnt/β-catenin signaling axis is frequently dysregulated, typically as a consequence of oncogenic CTNNB1 mutations, and plays a key role in tumor development by facilitating nuclear β-catenin accumulation, an indicator of more aggressive disease. This study aimed to explore the potential of nuclear β-catenin expression as a prognostic biomarker by retrospectively analyzing 30 cases of endometrioid adenocarcinoma diagnosed between 2014 and 2022 at Albayda Medical Center in Libya. Immunohistochemistry was used to score nuclear β-catenin expression on a 0–3 scale, with a score of ≥2 considered high. Associations with clinicopathological variables, including age, marital status, menopausal status, tumor grade, stage, metastasis, and family history, were evaluated. The results revealed that high nuclear β-catenin expression occurred in 30% (9/30) of tumors and significantly correlated with younger age (<56 years; 54.5% vs 15.8%; p = 0.026), premenopausal status (75% vs 9.1% perimenopausal and 33.3% postmenopausal; p = 0.044), single marital status (53.8% vs 11.8% married; p = 0.013), positive family history (50% vs 7.1%; p = 0.011), high tumor grade (80% Grade III vs 14.3% Grade I; p = 0.026), advanced stage (80% Stage II and IV vs 10.5% Stage I; p = 0.015), and metastasis (83.3% vs 16.7% non-metastatic; p = 0.001). These findings suggest that nuclear β-catenin accumulation serves as a strong marker of aggressive disease, linking hormonal exposure, reproductive history, and potential hereditary cancer risk into a unified molecular framework. Despite limitations of a small sample size and retrospective design, this study underscores the clinical utility of β-catenin immunohistochemistry as a cost-effective tool for improved risk assessment, early identification of high-risk patients, and personalized treatment planning.
Keywords: *Endometrial Carcinoma, B-Catenin, Immunohistochemistry, Prognostic Biomarker.*

Received: *27/03/26*
Accepted: *25/05/26*
Published: *01/06/26*

Introduction

Endometrial carcinoma is among the most prevalent gynecological cancers, with approximately 319,500 new cases and a 23% mortality rate annually [1]. Key risk factors include genetic predispositions such as Lynch and Cowden syndromes [2], prolonged estrogen exposure, and metabolic syndrome, with rising incidence linked to lifestyle changes [3]. Diagnosis relies on curettage or hysteroscopic biopsy followed by clinical staging [4], while treatment involves surgery and chemoradiotherapy [5], with targeted therapy and immunotherapy also being prevalent options [6]. Prognosis depends on age, disease stage, tumor differentiation, and pathological type [7]. Bokhman (1983) classified endometrial cancer into Type I (hormone-dependent, favorable prognosis) and Type II (hormone-independent, poor prognosis), while the Cancer Genome Atlas (TCGA) further stratifies tumors into four molecular subgroups: POLE-mutated, microsatellite instability-high (MSI-H), copy-number high (CNH), and copy-number low/no specific molecular profile (NSMP), with the NSMP subgroup frequently harboring CTNNB1 mutations [8,9].

The CTNNB1 gene encodes β-catenin, a key regulator of the canonical Wnt/β-catenin pathway facilitating cellular differentiation and proliferation [10]; mutations within exon 3 lead to β-catenin accumulation and pathway hyperactivation, contributing to tumorigenesis [11]. CTNNB1 mutations occur in 20–25% of endometrioid carcinomas and are associated with adverse outcomes even in low-risk patients [12,13]. Given the prognostic implications of altered β-catenin expression in endometrial cancer, this study investigates the immunohistochemical expression pattern of β-catenin and its prognostic significance in endometrial adenocarcinoma, along with its association with

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clinicopathological parameters.

Methods

This retrospective study analyzed 30 cases of endometrial adenocarcinoma (endometrioid type) diagnosed between 2014 and 2022 at Albayda Medical Center, Libya, with cases graded using WHO 2020 [14] and FIGO classifications [15], into 7 Grade I, 18 Grade II, and 5 Grade III, and specimens obtained via D&C biopsies and hysterectomies with clinical data extracted from medical records. The study protocol was reviewed and approved by the bioethics committee at Libyan Academy Jabal Al-Akhdar for postgraduate studies (Ref: NBC: 004. H. 25. 5).

Formalin-fixed paraffin-embedded sections of 4 μm thickness were prepared for routine H&E staining and immunohistochemical analysis using a monoclonal mouse anti-β-catenin antibody (Dako) with a universal streptavidin-biotin peroxidase complex kit (Lot M3539), where sections were deparaffinized in xylene, rehydrated through graded ethanol, washed in PBS (pH 7.4), treated with 3% hydrogen peroxide to block endogenous peroxidase, and incubated with normal serum to minimize non-specific binding. Antigen retrieval was performed in citrate buffer (pH 6.0) via microwave heating at 100°C for three 5-minute cycles, followed by sequential incubation with primary antibody for 1 hour, biotinylated secondary antibody for 30 minutes, and streptavidin-HRP for 30 minutes at room temperature, with PBS washes between each step, then detection using DAB chromogen for 5–15 minutes, counterstaining with Mayer's hematoxylin, dehydration through graded ethanol, clearing in xylene, and mounting with DPX. Nuclear β-catenin expression was evaluated using the Allred scoring system graded as 0 (negative), 1 (weak), 2 (intermediate), and 3 (strong), then dichotomized into low (0–1) and high (2–3) expression [16], for statistical analysis and associations between β-catenin expression and clinicopathological parameters were analyzed using the Chi-square test with $P < 0.05$ considered statistically significant using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Routine H&E staining revealed characteristic histopathological features of endometrial adenocarcinoma, including High-grade endometrial adenocarcinoma, which microscopically shows sheets of markedly atypical epithelial cells, enlarged pleomorphic hyperchromatic nuclei (Figure 1, A–B), and low-grade endometrial adenocarcinoma, which microscopically shows crowded but recognizable endometrial-type glands, these malignant glands lined by mildly enlarged columnar cells (Figure, C–D).

Immunohistochemistry was performed with mouse monoclonal anti-β-catenin (Dako). The IHC examination demonstrates negative nuclear β-catenin immunohistochemistry in endometrial adenocarcinoma, showing tumor-cell nuclei that are completely unstained (no nuclear brown pigment) (Figure E–F).

The Positive nuclear β-catenin immunohistochemistry in endometrial adenocarcinoma appears as sharply defined, brown chromogen filling the nuclei of scattered tumor cells (Figure G–H)

Histopathological features using hematoxylin and eosin (H&E) staining. **(A)**: High-grade endometrial endometroid adenocarcinoma, high grade with groups of malignant cells with high N/C ratio, pleomorphism, and hyperchromatism (H&E x100). **(B)**: High-grade endometrial endometroid adenocarcinoma, high grade with groups of malignant cells with high N/C ratio, pleomorphism, and hyperchromatism (H&E x400).

(C): Low-grade endometrial endometroid adenocarcinoma with malignant glands that are lined by malignant cells (H&E x100). **(D)**: Low-grade endometrial endometroid adenocarcinoma with malignant glands that are lined by malignant cells (H&E x400). **(E)**: Picture shows Endometrial adenocarcinoma with negative nuclear expression of B-catenin immunohistochemistry (B-catenin x100).**(F)**: Picture shows Endometrial adenocarcinoma with negative nuclear expression of B-catenin immunohistochemistry (B-catenin x400).**(G)**: Picture shows Endometrial adenocarcinoma with positive nuclear expression of B-catenin immunohistochemistry (B-catenin x100).**(H)**: Picture shows Endometrial adenocarcinoma with positive nuclear expression of B-catenin immunohistochemistry (B-catenin x400)

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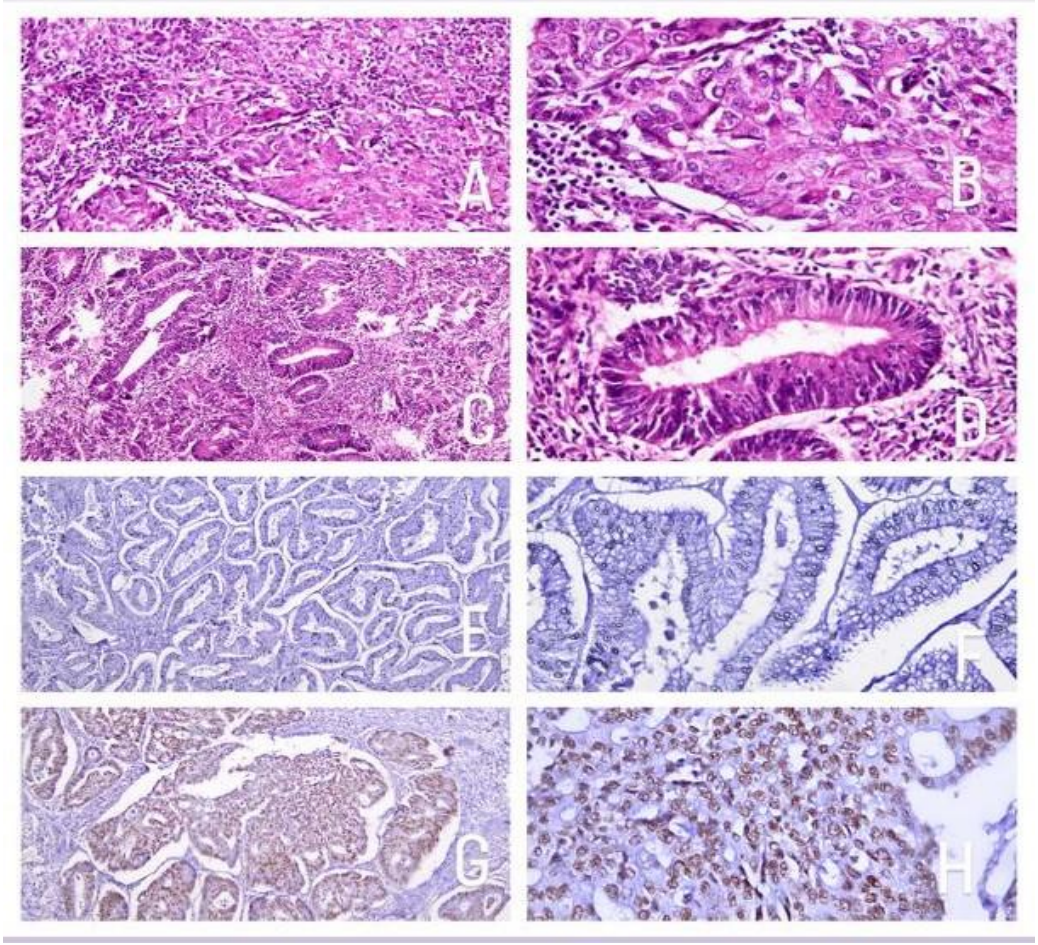

Figure 1: Histopathological and immunohistochemical features of endometrial adenocarcinoma:

Patient and Tumor Characteristics and Association of Social and Clinical Characteristics with Beta-catenin Immunohistochemical Findings in Endometrial Adenocarcinoma

This retrospective study of 30 endometrial adenocarcinomas treated at Albayda Medical Center (Libya, 2014–2022) evaluated nuclear β-catenin expression by immunohistochemistry and its links to patient and tumor characteristics. High nuclear β-catenin (≥30% of nuclei positive) was observed in 30% of cases (9/30), with the remainder showing low or absent expression. High β-catenin was strongly associated with a distinct clinical profile: younger age (54.5% vs. 15.8% in older patients; p = 0.026), single status (53.8% vs. married 11.8%; p = 0.013), premenopausal state (75% vs. menopausal9.1% and postmenopausal 33%; p = 0.044), and family history of cancer (50% vs. no family history7.1%; p = 0.011). It was markedly enriched in aggressive disease,83.3% of metastatic tumors were β-catenin–high versus 16.7% of non-metastatic (p = 0.001) and correlated with higher grade (80% of grade III vs. 22.2% grade II and 14% of grade I; p = 0.026) and advanced stage (80% of stage II and 50%stage III,50%stageIV vs**.** 10.5% of stage I; p = 0.015). "(see **Table 1**)."

Table 1: Association of Social and Clinical Characteristics with Beta-catenin Immunohistochemical Findings in Endometrial Adenocarcinoma

Characteristics	N.	β-catenin		Chi-square test
		High Expression	Low Expression	
		9 cases (30 %)	21 cases (70 %)	
Age group				
<56	11	6 (54.5%)	5 (45.5%)	P=0.02559*
≥ 56	19	3 (15.8%)	16 (84.2%)	
Marital status				

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Married	17	2 (11.8%)	15 (88.2%)	P=0.01268*
Single	13	7 (53.8%)	6 (46.2%)	
Menopausal status				
Pre-Menopausal	4	3 (75%)	1 (25%)	P=0.04445*
Menopausal	11	1 (9.1%)	10 (90.9%)	
Post-Menopausal	15	5 (33.3%)	10 (66.7%)	
Family history of cancer				
Yes	16	8 (50%)	8 (50%)	P=0.01061*
No	14	1 (7.1%)	13 (92.9%)	
Tumor metastases to other body parts				
Yes	6	5 (83.3%)	1 (16.7%)	P=0.00143*
No	24	4 (16.7%)	20 (83.3%)	
Tumor grade				
Grade I	7	1 (14.3%)	6 (85.7%)	P=0.02607*
Grade II	18	4 (22.2%)	14 (77.8%)	
Grade III	5	4 (80%)	1 (20%)	
Tumor stage				
Stage I	19	2 (10.5%)	17 (89.5%)	P=0.01458*
Stage II	5	4 (80%)	1 (20%)	
Stage III	2	1 (50%)	1 (50%)	
Stage IV	4	2 (50%)	2 (50%)	

Discussion

This study investigated nuclear β-catenin expression in 30 Libyan patients with endometrial adenocarcinoma, revealing that high β-catenin expression occurred in 30% of tumors and significantly correlated with younger age, premenopausal status, single marital status as a parity-related variable reflecting nulliparity and prolonged unopposed estrogen exposure, positive family history, high tumor grade, advanced FIGO stage, and metastatic disease, suggesting that β-catenin accumulation serves as a marker of aggressive disease biology driven by hormonal, hereditary, and molecular factors.[16] The association between marital status and β-catenin expression, where 53.8% of single women versus 11.8% of married women showed high expression, indirectly reflects parity-related hormonal influences, as nulliparity extends the duration of estrogen dominance without progesterone counteraction, a mechanism supported by previous studies showing that estradiol promotes nuclear β-catenin accumulation through PI3K/AKT-mediated GSK-3β inhibition. In contrast, progesterone suppresses Wnt signaling via DKK1 induction, thereby resetting β-catenin localization from nucleus to membrane [17,18].

The inverse correlation between age and β-catenin expression in our cohort contrasts with recent reports that found no age-related differences in β-catenin status [19,20], possibly reflecting local genetic or environmental factors or our single-institution design; however, the strong association with premenopausal status supports the estrogen-dominant hormonal model described in the literature [21]. The family history association parallels pooled epidemiologic evidence showing doubled endometrial cancer risk with affected first-degree relatives [22], suggesting potential Lynch syndrome-related hereditary susceptibility, though other studies noted lower CTNNB1 mutation rates in Lynch syndrome, indicating alternative molecular pathways in hereditary cases [23].

Regarding tumor grade and stage, high β-catenin expression was observed in 80% of Grade III tumors and 80% of Stage II–IV cases, aligning with previous research identifying β-catenin activation as a driver of epithelial-mesenchymal transition and invasive potential [24,25], while reflecting the "prognostic paradox" described in recent literature: β-catenin identifies aggressive biology even in histologically low-risk tumors while simultaneously marking high-grade advanced disease, as 83.3% of metastatic cases exhibited high expression compared to only 16.7% of non-metastatic tumors [26,27]. These findings support integrating β-catenin immunohistochemistry into routine pathology for enhanced risk stratification, with genetic counseling and MMR/CTNNB1 testing warranted for patients with elevated β-catenin particularly those with positive family history, and combined Wnt-pathway inhibitors with immunotherapy

representing a promising therapeutic direction for mismatch repair-deficient, β-catenin-high tumors [28]. Limitations include the retrospective design, small sample size, absence of MMR/germline mutation data, and unverified self-reported family histories, necessitating validation in larger multi-center cohorts with comprehensive molecular profiling.

Conclusion

This study identifies nuclear β-catenin expression as a clinically relevant biomarker in endometrial adenocarcinoma, linking hormonal, reproductive, and genetic risk factors into a unified molecular framework. In 30 patients from Albayda Medical Center, high β-catenin expression significantly correlated with younger age, premenopausal status, single marital status, positive family history of cancer, higher tumor grade, advanced stage, and distant metastases. These findings highlight its utility in detecting aggressive disease, including early-stage or low-grade tumors. Mechanistically, β-catenin accumulation—driven by Wnt pathway activation or CTNNB1 mutations—promotes proliferation, epithelial-to-mesenchymal transition, and reduced cell adhesion, consistent with prolonged estrogen exposure and GSK-3β inhibition. A potential association with Lynch syndrome is also suggested. Despite limitations of retrospective design and small sample size, routine immunohistochemical assessment of β-catenin offers a cost-effective tool for improved risk stratification, treatment planning, and hereditary cancer evaluation, supporting its integration into standard pathology practice.

Conflict of interest. Nil

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