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ISSN: 2663-9491 e-ISSN: 2789-6897

ORIGINAL ARTICLE

Clinicopathological Predictors of High-risk Endometrial Cancer: A series of 106 cases

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Received: 14 October 2026
Accepted: 04 November 2026
Published Online: 15 November 2026

Published by:
Gopalganj Medical College, Gopalganj, Bangladesh

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DOI: 10.5281/zenodo.24238335

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ABSTRACT

Introduction: *Endometrial cancer is a common gynecological malignancy with heterogeneous clinical and pathological characteristics. Identification of high-risk disease is essential for appropriate treatment planning and prognostic assessment, particularly in settings where molecular classification is not routinely available. This study aimed to evaluate the clinicopathological characteristics of patients with endometrial cancer and identify factors independently associated with high-risk disease.* ***Methods & Materials:*** *This retrospective observational study included 106 patients with histopathologically confirmed endometrial cancer treated or evaluated at the Department of Gynaecological Oncology, National Institute of Cancer Research and Hospital, from June 2023 to May 2024. Clinicodemographic and pathological data were collected from medical records, and patients were categorized into high-risk and non-high-risk groups. Associations were assessed using chi-square/Fisher's exact tests and multivariable binary logistic regression, with adjusted odds ratios (AORs), 95% confidence intervals (CIs), and p<0.05 considered statistically significant.* ***Results:*** *Among 106 patients, 30.2% had high-risk disease. Non-endometrioid histology, grade 3 tumors, deep myometrial invasion, LVSI, cervical stromal involvement, lymph-node metastasis, and advanced FIGO stage were significantly associated with high-risk disease. Multivariable analysis identified non-endometrioid histology (AOR 4.62), grade 3 tumor (AOR 2.71), deep myometrial invasion (AOR 3.84), and LVSI (AOR 3.21) as independent predictors, whereas age ≥60 years was not independently associated.* ***Conclusion:*** *Non-endometrioid histology, grade 3 tumor, deep myometrial invasion, and LVSI were independently associated with high-risk endometrial cancer. These routinely assessable pathological features may provide a practical basis for risk stratification and clinical decision-making, particularly where molecular profiling is unavailable.*

Keywords: *Endometrial cancer; high-risk endometrial cancer; histology; tumor grade; myometrial invasion; lymphovascular space invasion; risk stratification; FIGO stage.*

(The Insight 2026; 9(3): 915-920)

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INTRODUCTION

Endometrial cancer is one of the most common gynecological malignancies worldwide, and its incidence continues to increase in many countries. Global cancer estimates for 2022 reported a substantial burden of endometrial cancer, reflecting the growing impact of population ageing, obesity, and metabolic disorders on women's health [1]. Obesity is one of the strongest established risk factors for endometrial cancer, while diabetes mellitus and other metabolic abnormalities have also been associated with increased disease risk [2,3]. Although many patients present with early-stage disease and have a favorable prognosis, a clinically important proportion develop aggressive tumors characterized by a higher risk of extrauterine spread, recurrence, and cancer-related mortality. Early identification of patients with high-risk disease is therefore important for appropriate surgical staging, selection of adjuvant therapy, surveillance, and prognostic counseling. Endometrial carcinoma is a heterogeneous disease with considerable variation in histological appearance, biological behavior, and clinical outcome. Endometrioid adenocarcinoma represents the predominant histological subtype and is generally associated with a more favorable prognosis, whereas serous carcinoma, clear-cell carcinoma, carcinosarcoma, undifferentiated carcinoma, and high-grade tumors are more frequently associated with aggressive behavior. Conventional clinicopathological characteristics, including histological subtype, tumor grade, FIGO stage, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal involvement, and lymph-node metastasis, remain important determinants of prognosis and treatment planning [4,5]. The classification of endometrial cancer has evolved considerably with advances in molecular biology. The Cancer Genome Atlas demonstrated four major molecular subgroups—POLE ultramutated, microsatellite instability

hypermutated, copy-number low, and copy-number high/serous-like tumors—with distinct molecular characteristics and prognostic behavior [6]. Subsequent studies have demonstrated that integration of molecular classification with conventional histopathological parameters can improve prognostic stratification and may influence decisions regarding adjuvant treatment [7,8]. The 2023 FIGO staging system incorporated several advances in the understanding of histological and molecular characteristics of endometrial carcinoma, further emphasizing the importance of tumor biology in addition to the anatomical extent of disease [4]. Despite these advances, comprehensive molecular testing is not universally available, particularly in resource-limited settings. Consequently, routinely obtainable clinicodemographic and pathological characteristics continue to have substantial practical value in identifying patients at increased risk of aggressive disease. Age, menopausal status, obesity, diabetes, hypertension, histological subtype, tumor grade, depth of myometrial invasion, LVSI, cervical involvement, and lymph-node status can generally be obtained from routine clinical and pathological records and may provide useful information for risk assessment [5,7]. However, the relative importance of these factors may vary between populations because of differences in patient characteristics, disease presentation, referral patterns, and access to diagnostic and therapeutic services. In this context, retrospective evaluation of routinely available clinicopathological variables may help identify characteristics associated with high-risk endometrial cancer in a specific patient population. Such information may be particularly valuable in settings where molecular classification is not routinely available and where clinical decisions must rely predominantly on conventional pathological assessment. A simple and reproducible assessment of potential predictors could also assist clinicians in recognizing patients who require more intensive evaluation and treatment. Therefore, the present study was undertaken to evaluate the clinicopathological characteristics of endometrial cancer and identify factors associated with high-risk disease among patients with histologically confirmed endometrial carcinoma.

METHODS & MATERIALS

This retrospective observational study was conducted among patients with histopathologically confirmed endometrial cancer who underwent evaluation and/or definitive surgical treatment at the Department of Gynaecological Oncology, National Institute of Cancer Research and Hospital (NICRH), between June 2025 and May 2026. A total of 106 eligible patients were included in the study. Patients were identified through hospital records, histopathology reports, operative notes, and relevant clinical files. Patients with histopathologically confirmed endometrial carcinoma who had adequate clinical and pathological information available for analysis were included. Patients with a previous history of endometrial cancer, incomplete clinical or pathological records, or inadequate histopathological information were excluded. Data were extracted from the medical records using a structured case record form (CRF). The variables included sociodemographic and clinical characteristics such as age, body mass index (BMI), menopausal status, diabetes mellitus, hypertension, parity, abnormal uterine bleeding, pelvic pain, and family history of gynaecological cancer. Histopathological and tumour-related variables included histological type, tumour grade, FIGO stage, depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal involvement, and lymph-node metastasis. Patients were categorized into high-risk and non-high-risk endometrial cancer groups according to the predefined clinicopathological criteria adopted for this study [insert the exact institutional/guideline-based criteria used to define high-risk disease. The classification was determined from the available histopathological and staging information. The primary outcome of the study was the presence of high-risk endometrial cancer. The secondary objective was to assess the association of selected clinicodemographic and histopathological characteristics with high-risk disease. The collected data were analyzed using Statistica Package for Social Sciences (SPSS) version-27.0. Continuous variables were summarized using mean ± standard deviation (SD) for approximately normally distributed data and median with interquartile range (IQR) where appropriate. Categorical variables were presented as frequencies and percentages. Clinicodemographic and histopathological characteristics were compared between patients with high-risk and non-high-risk endometrial cancer. For continuous variables, the independent-samples t test was used for normally distributed data, while the Mann–Whitney U test was used when the distribution was non-normal. For categorical variables, the Pearson chi-square test or Fisher's exact test was used, as appropriate. Univariate binary logistic regression analysis was performed to estimate crude odds ratios (ORs) with 95% confidence intervals (CIs) for potential factors associated with high-risk endometrial cancer. Variables showing a statistically significant association in univariate analysis ($p<0.05$), together with clinically relevant variables, were considered for multivariable analysis. Considering the limited number of high-risk cases and potential overlap among pathological variables, selected variables were included in the final multivariable logistic regression model. Adjusted odds ratios (AORs) with 95% CIs were reported. A two-sided $p<0.05$ was considered statistically significant.A multivariate binary logistic regression model was subsequently fitted to identify factors independently associated with high-risk endometrial cancer. Adjusted odds ratios (AORs) with 95% CIs were reported. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Table I shows total of 106 patients with endometrial cancer were included in the analysis. The mean age of the study population was 58.4 ± 9.8 years, and 54 (50.9%) patients were aged ≥60 years. More than three-fifths of the patients had a BMI ≥25 kg/m^2 (67, 63.2%), while 82 (77.4%) were postmenopausal. Diabetes mellitus and hypertension were present in 32 (30.2%) and 48 (45.3%) patients, respectively. Fourteen patients (13.2%) were nulliparous. Abnormal uterine bleeding was the predominant presenting symptom, reported in 91 (85.8%) patients, whereas pelvic pain was reported in 21 (19.8%). A family history of gynecological cancer was present in 9 (8.5%) patients.

ISSN: 2663-9491 e-ISSN: 2789-6897

Table I: Distribution of baseline clinicodemographic characteristics of the study patients (*n*=106)

Variable	n (%), Mean ± SD
Age, years, mean ± SD	58.4 ± 9.8
Age ≥60 years	54 (50.9)
BMI ≥25 kg/m^2	67 (63.2)
Postmenopausal	82 (77.4)
Diabetes mellitus	32 (30.2)
Hypertension	48 (45.3)
Nulliparous	14 (13.2)
Abnormal uterine bleeding	91 (85.8)
Pelvic pain	21 (19.8)
Family history of gynecological cancer	9 (8.5)

Table II shows endometrioid adenocarcinoma was the most common histological type, accounting for 78 (73.6%) cases, followed by serous carcinoma (14, 13.2%), clear cell carcinoma (7, 6.6%), and carcinosarcoma (5, 4.7%). Two patients (1.9%) had other histological types. Regarding tumor grade, 36 (34.0%) tumors were grade 1, 39 (36.8%) were grade 2, and 31 (29.2%) were grade 3. Most patients presented with FIGO stage I disease (69, 65.1%), followed by stage III (19, 17.9%), stage II (13, 12.3%), and stage IV (5, 4.7%). Deep myometrial invasion (>50%) was observed in 38 (35.8%) patients, while lymphovascular space invasion (LVSI), cervical stromal involvement, and lymph-node metastasis were present in 31 (29.2%), 18 (17.0%), and 15 (14.2%) patients, respectively.

Table II: Distribution of histopathological characteristics of the study patients (*n*=106)

Characteristic	n (%)
Histological type	
Endometrioid adenocarcinoma	78 (73.6)
Serous carcinoma	14 (13.2)
Clear cell carcinoma	7 (6.6)
Carcinosarcoma	5 (4.7)
Other	2 (1.9)
Tumor grade	
Grade 1	36 (34.0)
Grade 2	39 (36.8)
Grade 3	31 (29.2)
FIGO stage	
I	69 (65.1)
II	13 (12.3)
III	19 (17.9)
IV	5 (4.7)
Deep myometrial invasion (>50%)	38 (35.8)
LVSI present	31 (29.2)
Cervical stromal involvement	18 (17.0)
Lymph-node metastasis	15 (14.2)

Table III shows of the 106 patients, 32 (30.2%) were classified as having high-risk endometrial cancer and 74 (69.8%) as non-high-risk diseases. Patients aged ≥60 years were significantly more frequent in the high-risk group than in the non-high-risk group (65.6% vs. 44.6%, respectively; p=0.049). In contrast, no statistically significant differences were observed between the two groups with respect to BMI ≥25 kg/m^2 (62.5% vs. 63.5%, p=0.921), postmenopausal status (87.5% vs. 73.0%, p=0.087), diabetes mellitus (40.6% vs. 25.7%, p=0.117), hypertension (53.1% vs. 41.9%, p=0.295), nulliparity (15.6% vs. 12.2%, p=0.635), or abnormal uterine bleeding (84.4% vs. 86.5%, p=0.771).

Table III: Comparison of clinicodemographic characteristics between high-risk and non-high-risk groups (*n*=106)

Variable	High-risk (n=32), n (%)	Non-high-risk (n=74), n (%)	p-value
Age ≥60 years	21 (65.6)	33 (44.6)	0.049
BMI ≥25 kg/m^2	20 (62.5)	47 (63.5)	0.921
Postmenopausal	28 (87.5)	54 (73.0)	0.087
Diabetes mellitus	13 (40.6)	19 (25.7)	0.117
Hypertension	17 (53.1)	31 (41.9)	0.295
Nulliparity	5 (15.6)	9 (12.2)	0.635
Abnormal uterine bleeding	27 (84.4)	64 (86.5)	0.771

ISSN: 2663-9491 e-ISSN: 2789-6897

Table IV shows significant differences were observed across all evaluated pathological characteristics. Non-endometrioid histology was substantially more common among high-risk patients than among non-high-risk patients (46.9% vs. 10.8%; p<0.001). Similarly, grade 3 tumors occurred in 53.1% of high-risk patients compared with 18.9% of non-high-risk patients (p<0.001). Advanced FIGO stage III–IV disease was present in 53.1% of the high-risk group versus 9.5% of the non-high-risk group (p<0.001). Deep myometrial invasion was observed in 65.6% and 23.0% of patients, respectively (p<0.001). LVSI was present in 56.3% of high-risk patients compared with 17.6% of non-high-risk patients (p<0.001). Cervical stromal involvement was also more frequent in the high-risk group (34.4% vs. 9.5%; p=0.002), as was lymph-node metastasis (37.5% vs. 4.1%; p<0.001).

Table IV: Comparison of pathological characteristics between high-risk and non-high-risk groups

Variable	High-risk (n=32), n (%)	Non-high-risk (n=74), n (%)	p-value
Non-endometrioid histology	15 (46.9)	8 (10.8)	<0.001
Grade 3 tumor	17 (53.1)	14 (18.9)	<0.001
FIGO stage III–IV	17 (53.1)	7 (9.5)	<0.001
Deep myometrial invasion	21 (65.6)	17 (23.0)	<0.001
LVSI present	18 (56.3)	13 (17.6)	<0.001
Cervical stromal involvement	11 (34.4)	7 (9.5)	0.002
Lymph-node metastasis	12 (37.5)	3 (4.1)	<0.001

Table V shows univariate analysis, age ≥60 years was associated with increased odds of high-risk disease (crude OR [OR] 2.37, 95% CI 1.00–5.61; p=0.049). Non-endometrioid histology demonstrated a strong association with high-risk disease (OR 7.28, 95% CI 2.61–20.31; p<0.001). Similarly, grade 3 tumors (OR 4.88, 95% CI 1.99–11.96; p<0.001), deep myometrial invasion (OR 6.38, 95% CI 2.60–15.67; p<0.001), and LVSI (OR 6.03, 95% CI 2.27–16.00; p<0.001) were significantly associated with high-risk disease. Cervical stromal involvement was also significantly associated with high-risk disease (OR 4.98, 95% CI 1.73–14.35; p=0.003). The strongest crude association was observed for FIGO stage III–IV, which was associated with more than ten-fold higher odds of high-risk disease (OR 10.81, 95% CI 3.84–30.44; p<0.001). In contrast, BMI ≥25 kg/m^2, diabetes mellitus, and hypertension were not significantly associated with high-risk disease.

Table V: Univariate logistic regression analysis of predictors of high-risk endometrial cancer (106)

Predictor	Crude OR(ORs)	95% CI	p-value
Age ≥60 years	2.37	1.00–5.61	0.049
BMI ≥25 kg/m^2	0.96	0.41–2.26	0.921
Diabetes mellitus	1.98	0.82–4.75	0.127
Hypertension	1.57	0.68–3.63	0.291
Non-endometrioid histology	7.28	2.61–20.31	<0.001
Grade 3	4.88	1.99–11.96	<0.001
Deep myometrial invasion	6.38	2.60–15.67	<0.001
LVSI present	6.03	2.27–16.00	<0.001
Cervical stromal involvement	4.98	1.73–14.35	0.003
FIGO stage III–IV	10.81	3.84–30.44	<0.001

Table VI shows multivariate logistic regression model, non-endometrioid histology, grade 3 tumor, deep myometrial invasion, and LVSI remained independently associated with high-risk endometrial cancer. Patients with non-endometrioid histology had significantly higher odds of high-risk disease (adjusted OR [AOR] 4.62, 95% CI 1.45–14.72; p=0.010). Grade 3 tumors were independently associated with approximately 2.7-fold higher odds of high-risk disease (AOR 2.71, 95% CI 1.01–7.28; p=0.048). Deep myometrial invasion (>50%) was associated with nearly four-fold higher odds (AOR 3.84, 95% CI 1.39–10.61; p=0.009), while the presence of LVSI was associated with more than three-fold higher odds (AOR 3.21, 95% CI 1.11–9.28; p=0.032). Although age ≥60 years was associated with high-risk disease in the univariate analysis, this association was no longer statistically significant after adjustment for other factors (AOR 1.91, 95% CI 0.72–5.07; p=0.192).

Table VI: Multivariate logistic regression analysis of selected factors associated with high-risk endometrial cancer (*n*=106)

Variable	AOR	95% CI	p-value
Age ≥60 years	1.91	0.72–5.07	0.192
Non-endometrioid histology	4.62	1.45–14.72	0.010
Grade 3 tumor	2.71	1.01–7.28	0.048
Deep myometrial invasion (>50%)	3.84	1.39–10.61	0.009
LVSI present	3.21	1.11–9.28	0.032

DISCUSSION

In this study of 106 patients with endometrial cancer, 30.2% had high-risk disease. The Major findings were non-endometrioid histology, grade 3 tumors, deep myometrial invasion, and LVSI were independently associated with high-risk disease, whereas age, BMI, diabetes mellitus, and hypertension were not independently associated. The mean age was 58.4 years, 77.4% of patients were postmenopausal, and abnormal uterine bleeding was the predominant presenting symptom (85.8%). The predominance of stage I disease (65.1%) is consistent with the relatively frequent detection of endometrial cancer at an early stage. However, the presence of adverse pathological characteristics among a proportion of apparently early-stage tumors emphasizes that anatomical stage alone may not adequately reflect tumor aggressiveness. Contemporary guidelines therefore recommend integrating histological subtype, grade, myometrial invasion, LVSI, and other pathological features into risk assessment [9-11]. Non-endometrioid histology was substantially more frequent in the high-risk group than in the non-high-risk group (46.9% vs. 10.8%) and remained independently associated with high-risk disease (AOR 4.62, 95% CI 1.45–14.72). Similarly, grade 3 tumors were significantly more common among high-risk patients and remained independently associated with high-risk status (AOR 2.71, 95% CI 1.01–7.28). These findings support established risk-classification systems in which aggressive histological subtypes and high tumor grade are considered major adverse prognostic features [12]. Deep myometrial invasion showed a strong association with high-risk disease, occurring in 65.6% of high-risk patients compared with 23.0% of non-high-risk patients. After adjustment, deep invasion remained associated with nearly four-fold higher odds of high-risk disease (AOR 3.84, 95% CI 1.39–10.61). This is consistent with a large meta-analysis of 79 studies involving 68,870 patients, which demonstrated that deep myometrial invasion was associated with LVSI, lymph-node metastasis, recurrence, and poorer overall survival [13].

LVSI was another independent predictor, being present in 56.3% of high-risk patients versus 17.6% of non-high-risk patients. Its presence was associated with more than three-fold higher adjusted odds of high-risk disease (AOR 3.21, 95% CI 1.11–9.28). This finding is clinically relevant because LVSI represents an important pathway for lymphatic and hematogenous dissemination. A recent systematic review and meta-analysis also demonstrated that LVSI is associated with increased recurrence and poorer overall and recurrence-free survival, even among patients with stage I disease [14]. Age ≥60 years was associated with high-risk disease in univariate analysis but not after adjustment, suggesting that its apparent effect may be partly explained by adverse tumor characteristics. Likewise, BMI ≥25 kg/m^2, diabetes, and hypertension were not associated with high-risk disease. These findings should be interpreted cautiously because obesity and metabolic disorders are established risk factors for the development of endometrial cancer. Diabetes has been associated with approximately 1.7-fold increased risk of endometrial cancer [15], while hypertension has also been associated with increased incidence [16]. Their lack of association with high-risk pathological status in our cohort may therefore reflect the distinction between carcinogenic risk and tumor aggressiveness. The strong association between advanced FIGO stage, lymph-node metastasis, and high-risk classification further supports the biological relationship between aggressive uterine pathology and extrauterine dissemination. The updated FIGO system increasingly incorporates histological and molecular characteristics because these factors provide additional prognostic information beyond conventional anatomical staging [17]. Molecular classification represents an important area for future investigation. The Cancer Genome Atlas demonstrated distinct molecular subgroups of endometrial carcinoma with substantially different biological and prognostic characteristics [18]. Subsequently, clinically applicable molecular classifiers such as ProMisE have shown that molecular subgroups can be identified using a practical diagnostic approach and may improve prognostic stratification [19]. Molecular data were not available in the present study; therefore, future studies should integrate molecular classification with conventional pathological parameters. The study has several limitations, particularly its relatively small sample size and the limited number of patients in the high-risk group, which may have reduced statistical power. In addition, the study assessed high-risk pathological status rather than recurrence or survival, and molecular markers were unavailable. Nevertheless, the consistent associations observed for histology, tumor grade, deep myometrial invasion, and LVSI support their importance in identifying patients with aggressive disease. Long-term studies integrating conventional pathology with molecular classification are warranted to improve individualized risk prediction and treatment selection [20].

CONCLUSION

This study identified non-endometrioid histology, grade 3 tumor, deep myometrial invasion (>50%), and LVSI as independent predictors of high-risk endometrial cancer. In contrast, age, BMI, diabetes mellitus, and hypertension were not independently associated with high-risk disease. These findings emphasize the importance of detailed histopathological assessment for risk stratification and clinical decision-making at the settings where molecular profiling is unavailable, these readily assessable pathological features may provide a practical basis for identifying patients with high-risk endometrial cancer.

LIMITATIONS

This study was limited by its relatively small, single-center sample, which may restrict statistical power and generalizability. The cross-sectional design precluded assessment of long-term outcomes such as recurrence and survival. Additionally, molecular markers were not evaluated, limiting comprehensive risk stratification. Larger multicenter prospective studies incorporating molecular classification and long-term outcomes are need to justify the results of this study.

RECOMMENDATIONS

Based on the findings of this study, comprehensive histopathological assessment of tumor histology, grade, depth of myometrial invasion, and LVSI should be emphasized for identifying patients with high-risk endometrial cancer. Where available, molecular classification should be incorporated to improve risk stratification and guide individualized management. Larger multicenter prospective studies with longer follow-up and survival outcomes are recommended to validate these predictors and improve risk-based treatment strategies.

CONFLICT OF INTEREST

None declared

FUNDING

Self

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