

ORIGINAL ARTICLE

Risk of Endometrial Cancer after Insufficient Endometrial Biopsy – A Retrospective Cohort Study at NICRH

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This article is licensed under a [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/).**ABSTRACT**

Background: Endometrial biopsy is the first-line diagnostic tool for abnormal uterine bleeding (AUB) and suspected endometrial pathology. However, insufficient biopsy is a common challenge and may delay diagnosis or mask underlying malignancy. Data from Bangladesh on the clinical significance of inadequate biopsy are limited. **Objective:** To evaluate the association between insufficient endometrial biopsy and the risk of endometrial cancer, and to assess diagnostic delays among the screened women of different ages who underwent endometrial biopsy. **Methods & Materials:** This retrospective cohort study included 320 women who underwent outpatient or inpatient endometrial biopsy at the Department of Gynecology and Obstetrics in National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, between December 2023 to November 2024. Participants were categorized into adequate biopsy (n=240) and insufficient biopsy (n=80) groups. Baseline characteristics, histopathological outcomes, and time to final diagnosis were collected from hospital and pathology records. Descriptive statistics were calculated, and differences between groups were assessed using t-tests and chi-square tests. Logistic regression was performed to estimate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for endometrial cancer, adjusting for age, menopausal status, BMI, and diabetes. Statistical significance was set at $p < 0.05$. **Results:** The mean age of women was 53.7 ± 8.9 years; 214(66.9%) women were ≥ 50 years, and 198 (61.9%) were postmenopausal. Insufficient biopsy samples were significantly more common in older and postmenopausal women had higher BMI ($p < 0.05$). Endometrial cancer was diagnosed in 54 (16.9%) women, with a higher incidence in the insufficient biopsy group (26/80; 32.5%) versus the adequate biopsy group (28/240; 11.7%) ($p < 0.001$). Insufficient biopsy was independently associated with endometrial cancer (adjusted OR 3.12; 95% CI: 1.62–5.99 ($p < 0.001$). Median time to diagnosis was longer in the insufficient biopsy group (45 vs. 18 days; ($p < 0.001$), and 70% experienced delays > 30 days. Age ≥ 50 years and postmenopausal status were additional independent predictors. **Conclusion:** Insufficient endometrial biopsy is a strong predictor of endometrial cancer diagnosis and is associated with significant diagnostic delays. Prompt repeat evaluation and standardized follow-up protocols are essential to ensure early detection and timely management in high-risk patients.

Keywords: Endometrial cancer, Insufficient biopsy, Diagnostic delay, Postmenopausal bleeding, Retrospective cohort, Bangladesh

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in high-income countries and its incidence has been steadily rising in low and middle-income nations, including South Asia, due to increasing life expectancy, obesity, and diabetes prevalence [1]. Early diagnosis remains essential because most patients present with abnormal uterine bleeding (AUB), and timely evaluation of the endometrium greatly improves outcomes [2]. Endometrial biopsy is considered the first-line, minimally invasive diagnostic tool for evaluating AUB, especially in postmenopausal or high-risk women [3]. It offers high sensitivity for detecting endometrial carcinoma and atypical hyperplasia when adequate tissue is obtained [4]. However,

insufficient or inadequate endometrial tissue sampling is a common clinical challenge, reported in 6–33% of outpatient biopsies [5]. Several factors contribute to insufficient sampling, including cervical stenosis, endometrial atrophy, obesity, and operator technique [6]. Insufficient biopsy often necessitates repeat procedures or alternative diagnostic modalities such as hysteroscopy or dilation and curettage (D&C), potentially delaying definitive diagnosis and increasing healthcare burden [7]. Clinical concerns arise from evidence that women with insufficient biopsy samples may have an underlying risk of missed endometrial pathology, including endometrial cancer, particularly among postmenopausal women with persistent symptoms [8]. A recent study has suggested that insufficient tissue may not always be a benign finding; instead,

it can be associated with significant disease in a notable proportion of cases [9]. Furthermore, delays caused by repeated attempts at diagnosis can lead to advanced-stage presentation, poorer prognosis, and increased mortality [10]. Bangladesh lacks comprehensive data evaluating the clinical significance of insufficient endometrial biopsy, especially regarding its association with endometrial cancer risk. The National Institute of Cancer Research and Hospital (NICRH), being the apex cancer center in the country, provides an important opportunity to assess real-world diagnostic outcomes in this high-risk population. Therefore, this retrospective cohort study aims to determine whether insufficient endometrial biopsy is associated with a higher likelihood of endometrial cancer and to examine diagnostic delays among patients treated at NICRH. Understanding this relationship will support clinicians in making timely decisions regarding repeat sampling and appropriate surveillance strategies.

METHODS & MATERIALS

This retrospective cohort study was conducted at the Department of Gynecology and Obstetrics in National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh from December 2023 to November 2024. A total of 320 screened women of different ages who underwent outpatient or inpatient endometrial biopsy for evaluation of abnormal uterine bleeding, postmenopausal bleeding, or suspected endometrial pathology during the study period were retrospectively included in this study. The enrolled cases were categorized into two cohorts based on the adequacy of the initial biopsy sample: Adequate biopsy (n=240) and Insufficient biopsy (n=80). Consecutive sampling technique was used and the data were collected using a pre-structured case record form (CRF) from hospital records and pathology database. Time interval from initial biopsy to final diagnosis was calculated using documented clinical timelines. The primary outcome was assessed on the occurrence of endometrial cancer, and the secondary outcome was diagnostic delay. The collected data were analyzed using statistical Package for Social Sciences (SPSS), version-23.0. Descriptive statistical analysis were performed to summarize baseline variables, with comparisons between adequate and insufficient biopsy groups. Chi-square test and independent t-tests were performed to compare the difference between the adequate and insufficient biopsy groups. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated performing logistic regression analysis, to assess the association between insufficient biopsy and endometrial cancer, adjusting for age, menopausal status, BMI, and diabetes. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 320 women who underwent endometrial biopsy during the study period were included in the analysis. The mean age of the participants was 53.7 ± 8.9 years, and 214

(66.9%) were aged ≥ 50 years. When stratified by biopsy adequacy, women in the insufficient biopsy group were significantly older than those with adequate biopsy samples (58.4 ± 9.1 vs. 52.1 ± 8.4 years ($p=0.001$)). The proportion of women aged ≥ 50 years was markedly higher in the insufficient biopsy cohort (71 (88.8%) vs. 143 (59.6%) ($p<0.001$)). The overall mean BMI was 27.3 ± 3.9 kg/m², and women in the insufficient biopsy group had significantly higher BMI (28.7 ± 4.1 vs. 26.8 ± 3.5 kg/m², ($p=0.02$)). More than half of the women 182 (56.9%) had parity ≥ 3 , with no significant difference between groups ($p=0.32$). Postmenopausal women constituted 198 (61.9%) of the study population, and this proportion was substantially higher in the insufficient biopsy group (66 (82.5%) vs. 132 (55.0%) ($p<0.001$)). Diabetes mellitus was more prevalent in women with insufficient biopsy (33 (41.3%) vs. 59 (24.6%) ($p=0.004$)), while hypertension and abnormal uterine bleeding showed no significant differences (Table I). Histopathological follow-up revealed that 54 (16.9%) women were diagnosed with endometrial cancer. The incidence of cancer was significantly higher in the insufficient biopsy group 26 (32.5%) compared to the adequate biopsy group 28 (11.7%) ($p<0.001$). Atypical hyperplasia was detected in 26 (8.1%) women, with no significant difference between groups ($p=0.42$). Benign hyperplasia and atrophic endometrium were common non-malignant outcomes, found in 89 (27.8%) and 104 (32.5%) women, respectively, with similar distribution across groups. Normal proliferative/secretory endometrium was more frequently seen in the adequate biopsy group 41 (17.0%) vs. 6 (7.5%) ($p=0.03$) (Table II). Among women diagnosed with cancer, 26 (48.1%) initially had an insufficient biopsy, compared with 64 (20.3%) of those without cancer. The crude odds ratio showed a 3.64-fold increased cancer risk (95% CI: 2.01–6.57). After adjusting for age, menopausal status, BMI, and diabetes, insufficient biopsy remained a strong independent predictor of endometrial cancer (adjusted OR: 3.12; 95% CI: 1.62–5.99; $p<0.001$). Age ≥ 50 years 40 (74.1%) and postmenopausal status 42 (77.8%) were also significant predictors, while diabetes showed borderline significance (Table III). Analysis of diagnostic timelines showed a substantial delay among women with insufficient biopsy samples. The median time from initial biopsy to final diagnosis was significantly longer in the insufficient biopsy group (45 days; IQR 28–70) than in the adequate biopsy group (18 days; IQR 12–31) ($p<0.001$). Diagnostic delay >30 days occurred in 56 (70.0%) women with insufficient biopsy compared to 74 (30.8%) in the adequate biopsy group ($p<0.001$) (Table IV). The final multivariate logistic regression model confirmed insufficient biopsy as the strongest independent predictor of endometrial cancer (AOR 3.12; 95% CI: 1.62–5.99; $p<0.001$). Age ≥ 50 years (40 (74.1%)) and postmenopausal status (42 (77.8%)) also significantly increased cancer risk. High BMI ≥ 28 kg/m² and diabetes mellitus did not show statistically significant associations in the adjusted model ($p=0.12$ and ($p=0.08$, respectively) (Table V).

Table – I: Baseline Characteristics of Study Participants (n = 320)

Variables	Total (N=320)	Adequate Biopsy (n=240)	Insufficient Biopsy (n=80)	p-value
Age (years), mean $\pm$ SD	53.7 $\pm$ 8.9	52.1 $\pm$ 8.4	58.4 $\pm$ 9.1	0.001
Age ≥ 50 years, n (%)	214 (66.9%)	143 (59.6%)	71 (88.8%)	<0.001
BMI (kg/m ²), mean $\pm$ SD	27.3 $\pm$ 3.9	26.8 $\pm$ 3.5	28.7 $\pm$ 4.1	0.02
Parity ≥ 3 , n (%)	182 (56.9%)	140 (58.3%)	42 (52.5%)	0.32
Post-menopausal, n (%)	198 (61.9%)	132 (55.0%)	66 (82.5%)	<0.001
Diabetes Mellitus, n (%)	92 (28.7%)	59 (24.6%)	33 (41.3%)	0.004
Hypertension, n (%)	111 (34.7%)	78 (32.5%)	33 (41.3%)	0.12
Abnormal Uterine Bleeding (%)	268 (83.7%)	202 (84.2%)	66 (82.5%)	0.72

Table II. Histopathological Final Diagnosis after Follow-up (n=320)

Final Diagnosis	Total (N=320)	Adequate Biopsy (n=240)	Insufficient Biopsy (n=80)	p-value
Endometrial Cancer	54 (16.9%)	28 (11.7%)	26 (32.5%)	<0.001
Atypical Hyperplasia	26 (8.1%)	18 (7.5%)	8 (10.0%)	0.42
Benign Hyperplasia	89 (27.8%)	70 (29.2%)	19 (23.8%)	0.32
Atrophic Endometrium	104 (32.5%)	83 (34.6%)	21 (26.3%)	0.14
Normal/Proliferative/Secretory	47 (14.7%)	41 (17.0%)	6 (7.5%)	0.03

Table - III: Association between Insufficient Biopsy and Endometrial Cancer (n=230)

Variable	Endometrial Cancer Present (n=54)	No Cancer (n=266)	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Insufficient biopsy	26 (48.1%)	54 (20.3%)	3.64 (2.01–6.57)	3.12 (1.62–5.99)	<0.001
Age ≥ 50 years	45 (83.3%)	169 (63.5%)	2.88 (1.37–6.05)	2.41 (1.05–5.54)	0.04
Postmenopausal	43 (79.6%)	155 (58.3%)	2.87 (1.43–5.75)	2.62 (1.23–5.57)	0.01
Diabetes Mellitus	23 (42.6%)	69 (25.9%)	2.11 (1.16–3.82)	1.79 (0.92–3.47)	0.08

Table - IV: Time from Initial Biopsy to Final Diagnosis (n=320)

Time Interval	Adequate Biopsy (n=240)	Insufficient Biopsy (n=80)	p-value
Median time to diagnosis (days)	18 days (IQR 12–31)	45 days (IQR 28–70)	<0.001
Delay > 30 days, n (%)	74 (30.8%)	56 (70.0%)	<0.001

Table - V: Logistic Regression Model Predicting Endometrial Cancer Risk

Predictor	OR	(95% CI)	p-value
Insufficient biopsy	1.14	3.12 (1.62–5.99)	<0.001
Age ≥ 50 years	0.88	2.41 (1.05–5.54)	0.04
Postmenopausal	0.96	2.62 (1.23–5.57)	0.01
High BMI ≥ 28	0.53	1.70 (0.88–3.28)	0.12
Diabetes Mellitus	0.58	1.79 (0.92–3.47)	0.08

DISCUSSION

This retrospective cohort study demonstrated that insufficient endometrial biopsy is strongly associated with a higher likelihood of underlying endometrial cancer and significant diagnostic delays, emphasizing the clinical importance of prompt further evaluation. Women with insufficient samples in our study were significantly older, had higher BMI, and were predominantly postmenopausal characteristics known to increase the risk of both insufficient sampling and endometrial malignancy. These demographic trends are consistent with previous research. Clark et al. reported that inadequate biopsy samples were more common in postmenopausal women due to cervical stenosis and atrophic endometrium, limiting tissue acquisition [11]. Similarly, Yela et al. found age and high BMI to be major contributors to insufficient endometrial sampling [12]. The cancer prevalence of 16.9% in this cohort aligns with findings from Western and Asian studies evaluating high-risk groups undergoing biopsy. More importantly, the significantly higher cancer detection rate among women with insufficient biopsy (32.5%) underscores the potential danger of falsely reassuring inadequate tissue reports. Visser et al. observed that up to 30% of women with insufficient biopsy were later diagnosed with cancer or atypical hyperplasia on further testing, comparable to our findings [13]. Likewise, Bakour et al. reported that insufficient biopsy results often underestimate serious pathology, particularly in symptomatic women [14]. After adjusting for confounders, insufficient biopsy remained an independent predictor of endometrial cancer in this study (AOR 3.12). This aligns with the systematic review by Van Hanegem et al., who demonstrated that inadequate biopsies could miss up to 20–25% of endometrial cancers [15]. Dueholm et al. also reported that insufficient sampling often necessitates repeat procedures and contributes to delayed diagnosis, particularly in high-risk postmenopausal women

[16]. Our results reaffirm these concerns, supporting active follow-up rather than conservative management. Age ≥50 years and postmenopausal status were also strong predictors of malignancy in our model. Numerous studies support this, including the epidemiological review by Renehan et al., which highlighted advancing age and menopausal transition as major determinants of endometrial cancer risk [17]. A large cohort study by Saed et al. reported seven-fold increased cancer risk in women over 55 years, independent of other clinical factors [18]. Similarly, Setiawan et al. demonstrated that postmenopausal estrogen imbalance plays a crucial role in carcinogenesis, enhancing susceptibility in older women [19]. Although BMI and diabetes mellitus are recognized risk factors for endometrial cancer, they were not statistically significant in the adjusted model. This may reflect confounding by age and menopausal status, which exert stronger influence. Nevertheless, obesity remains a global driver of endometrial cancer. A pooled analysis by Bhaskaran et al. showed that each 5 kg/m² increase in BMI substantially elevates risk [20]. Diabetes has also been linked to endometrial malignancy through hyperinsulinemia and chronic inflammation, as reported by Friberg et al. [21]. Even if not independently significant in this dataset, these factors remain clinically relevant and may contribute to biopsy inadequacy, as observed in studies by Kucukmetin et al. [22]. This study also highlighted significant diagnostic delays among women with insufficient biopsy samples, with a median delay of 45 days more than double that of women with adequate samples. Diagnostic delay >30 days occurred in 70% of the insufficient biopsy group. Such delays may allow disease progression, as emphasized in a multicenter study by Clark et al., which associated prolonged diagnostic pathways with worse clinical outcomes [23]. Our findings reinforce the urgent need for accelerated workup in women with insufficient biopsy results, particularly those in high-risk categories. Collectively, the

evidence suggests that insufficient endometrial biopsy is not a benign finding. Instead, it should serve as a warning sign requiring early repeat biopsy, hysteroscopy, or dilation and curettage. Establishing standardized follow-up protocols may reduce diagnostic delays, prevent missed malignancies, and improve patient outcomes.

Limitations of the Study

This study has some limitations. It was a single center study with limited samples over a short study period, which may restrict the generalizability of the findings to broader populations of the whole country. These limitations highlight the need for future prospective, multicenter studies using uniform biopsy criteria and comprehensive risk-factor data.

CONCLUSION

In this retrospective cohort study, insufficient endometrial biopsy was strongly associated with a higher risk of underlying endometrial cancer and significant diagnostic delays. Age ≥ 50 years and postmenopausal status were additional independent predictors of malignancy. These findings highlight that an insufficient biopsy should not be considered benign and warrants prompt repeat evaluation to ensure timely diagnosis. Implementing standardized follow-up protocols for inadequate biopsy results may improve early cancer detection and reduce delays in management.

RECOMMENDATIONS OF THE STUDY

Based on the study findings, it is recommended that all women with insufficient endometrial biopsy, particularly those who are older or postmenopausal, undergo prompt repeat evaluation using hysteroscopy-guided biopsy or dilation and curettage. Standardized protocols should be established to ensure timely follow-up and reduce diagnostic delays. Clinicians should also consider patient risk factors, including age, menopausal status, and comorbidities, when deciding on the urgency of re-biopsy, to improve early detection of endometrial malignancy and optimize patient outcomes.

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