



A Correlation Study For Prediction Of Carcinoma Endometrium And Premalignant Lesion Of Endometrium With Risk Factors In Women With Postmenopausal Bleeding

Dr. Sneha M. H.¹, Dr. Jyothi Mallappa Myageri², Dr. Kiran Kumar M.^{3*}

¹Senior Resident, Department of Obstetrics and Gynaecology, KLE JGMM Medical College, Hubballi, Karnataka, India

²Senior Resident, Department of Pediatrics, KLE JGMM Medical College, Hubballi, Karnataka, India

³Assistant Professor, Department of Radiodiagnosis, Karnataka Medical College and Research Institute (KMCR), Hubballi, Karnataka, India



Correspondence:

Dr. Kiran Kumar M.

Assistant Professor,
Department of Radiodiagnosis
Karnataka Medical College and
Research Institute (KMCR)
Hubballi, Karnataka, India

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Abstract

Background: Postmenopausal bleeding (PMB) is an important clinical symptom that may indicate premalignant or malignant endometrial pathology. Identification of associated risk factors may help in early diagnosis and appropriate management. **Objective:** To evaluate the association of demographic, reproductive and clinical risk factors with premalignant and malignant endometrial pathology among women presenting with PMB. **Materials and Methods:** A descriptive observational study was conducted among women presenting with PMB at hospitals attached to Bangalore Medical College and Research Institute, Bengaluru, from February 2022 to May/June 2023. A total of 59 women were included. Demographic and clinical variables, including age, parity, hypertension, diabetes mellitus, recurrent vaginal bleeding, age at menarche and age at menopause, were assessed. Endometrial pathology was evaluated by histopathological examination. Data were analysed using appropriate statistical tests, with $p < 0.05$ considered statistically significant. **Results:** Among 59 women, 10 (16.9%) had premalignant/malignant endometrial pathology and 49 (83.1%) were controls. Significant associations were observed with age ($\chi^2=15.428$, $p=0.002$), diabetes mellitus ($\chi^2=4.584$, $p=0.042$), recurrent vaginal bleeding ($\chi^2=13.577$, $p=0.002$), and age at menopause ($t=2.361$, $p=0.022$). The mean age at menopause was higher in the premalignant/malignant group than in controls (51.60 ± 5.68 vs. 47.41 ± 5.00 years). Parity ($p=0.350$), hypertension ($p=0.494$), and age at menarche ($p=0.880$) were not significantly associated with histopathological outcome. **Conclusion:** Older age, diabetes mellitus, recurrent vaginal bleeding and later age at menopause were significantly associated with premalignant or malignant endometrial pathology in women with PMB. Recognition of these risk factors may facilitate early evaluation and timely endometrial assessment.

Keywords: Postmenopausal bleeding; endometrial carcinoma; endometrial hyperplasia; diabetes mellitus; risk factors; histopathology; menopause.



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INTRODUCTION

Endometrial carcinoma is one of the most common malignancies of the female genital tract and predominantly affects women in the postmenopausal period. The disease is strongly associated with increasing age, obesity, metabolic disorders and prolonged exposure to endogenous estrogen. Several reproductive, hormonal and metabolic factors contribute to the development of endometrial neoplasia, making identification of high-risk women an important component of prevention and early diagnosis [1,2].

Postmenopausal bleeding (PMB) is one of the most important presenting symptoms of endometrial pathology. Although most women with PMB do not have endometrial cancer, the symptom warrants prompt evaluation because endometrial carcinoma frequently presents with abnormal uterine bleeding. A systematic review and meta-analysis demonstrated that approximately 9% of women presenting with PMB have endometrial cancer, although the risk varies according to age and other clinical characteristics [3].

Age is an important determinant of endometrial carcinoma risk. The incidence of endometrial cancer increases with advancing age, particularly after menopause. In addition, reproductive factors such as early menarche and late menopause increase the duration of lifetime exposure to endogenous estrogen and have been associated with increased risk of endometrial carcinoma [1,4]. Multiparity, in contrast, has generally been associated with a protective effect, possibly

because pregnancy is accompanied by prolonged progesterone exposure and reduced lifetime exposure to unopposed estrogen [5].

Metabolic abnormalities have also emerged as important contributors to endometrial carcinogenesis. Obesity is one of the strongest established modifiable risk factors for endometrial cancer. Increased adipose tissue promotes peripheral conversion of androgens to estrogens and is also associated with insulin resistance, hyperinsulinemia and chronic low-grade inflammation, all of which may promote endometrial proliferation [6]. Diabetes mellitus has similarly been associated with an increased risk of endometrial cancer, potentially through hyperinsulinemia, hyperglycemia, inflammatory mechanisms and altered growth-factor signaling [7].

Hypertension is frequently associated with endometrial cancer and commonly occurs as part of the metabolic syndrome. However, the independent contribution of hypertension is less consistent because it frequently coexists with obesity and diabetes mellitus [8]. Therefore, evaluation of multiple risk factors together may provide better clinical risk stratification than assessment of an individual factor in isolation.

The diagnostic evaluation of women with PMB includes detailed clinical assessment, pelvic examination, ultrasonography and histopathological examination when indicated. Transvaginal sonography (TVS) is commonly used as an initial imaging investigation because it permits assessment of endometrial thickness and morphology. However, histopathological examination of an endometrial tissue sample remains essential for definitive diagnosis of premalignant and malignant endometrial lesions [9,10].

Premalignant endometrial lesions are clinically significant because atypical endometrial hyperplasia/endometrial intraepithelial neoplasia represents an important precursor to endometrioid endometrial carcinoma. Recognition of women at increased risk can facilitate timely tissue diagnosis and appropriate treatment, thereby reducing the likelihood of progression to invasive disease [11].

Recurrent or persistent postmenopausal bleeding is particularly important because women with repeated episodes of bleeding may have underlying endometrial pathology despite an initially reassuring assessment. Therefore, clinical characteristics such as age, diabetes mellitus, reproductive history, age at menopause and recurrence of bleeding may assist in identifying women who require more intensive evaluation [3,9].

The present study was undertaken to evaluate the association between selected demographic, reproductive and clinical risk factors and premalignant or malignant endometrial pathology among women presenting with postmenopausal bleeding. The study specifically assessed age, parity, hypertension, diabetes mellitus, recurrent vaginal bleeding, age at menarche and age at menopause in relation to histopathological outcome.

MATERIALS AND METHODS

Study Design and Setting

A descriptive observational study was conducted among women presenting with postmenopausal bleeding (PMB) to the Gynaecology Outpatient and Inpatient Departments of the hospitals attached to Bangalore Medical College and Research Institute (BMCRI), Bengaluru, Karnataka, India. The study was conducted from February 2022 to May/June 2023.

Study Population

The study population comprised postmenopausal women presenting with vaginal bleeding who fulfilled the predefined inclusion and exclusion criteria. Patients with a diagnosis of premalignant or malignant endometrial pathology were evaluated with respect to their demographic characteristics, clinical profile, risk factors, imaging findings and histopathological diagnosis.

Sample Size

The sample size was calculated based on the sensitivity reported by Gianella et al. At a cutoff score >4, the reported sensitivity was 87.5%. Assuming a similar sensitivity in the present study, with a 95% confidence level and an absolute precision of 10%, the sample size was calculated using the formula:

$$[n = \frac{Z_{\alpha}^2 \times S_n(100 - S_n)}{d^2}]$$

Where $Z_{\alpha} = 1.96$ for a 95% confidence level, $S_n = 87.5\%$ (anticipated sensitivity), and $d = 10\%$ (absolute precision).

The calculated sample size was approximately 50 participants. Therefore, a total of 50 patients were included in the study.

Eligibility Criteria

Inclusion criteria

1. Women presenting with postmenopausal bleeding.

2. Postmenopausal women diagnosed with premalignant or malignant endometrial pathology.

Exclusion criteria

1. Patients diagnosed with carcinoma cervix.
2. Women with premature menopause, either natural or surgically induced, occurring before 40 years of age.
3. Patients with bleeding from the urethra secondary to trauma.
4. Patients receiving progesterone therapy.
5. Patients who had previously undergone hysterectomy.

Data Collection Procedure

Prior to initiation of the study, approval was obtained from the Institutional Ethics Committee of BMCRI. Written informed consent was obtained from all participants before enrolment.

Eligible patients presenting during the study period were recruited prospectively, while relevant clinical information from previously diagnosed patients was obtained through review of hospital records. A structured data collection proforma was used to record demographic, clinical, examination, laboratory, imaging and histopathological information.

The demographic and clinical variables included age, body mass index (BMI), hypertension, diabetes mellitus and obstetric history. A detailed history regarding the presenting complaint, duration and characteristics of postmenopausal bleeding, relevant medical history and associated risk factors was documented.

Clinical Examination

All enrolled participants underwent a detailed clinical examination. Anthropometric and vital parameters, including height, weight, BMI, blood pressure and pulse rate, were recorded. General examination included assessment for pallor and other relevant clinical findings.

A systemic examination, including cardiovascular and respiratory system examination, was performed. Gynecological examination included per-speculum and bimanual examination to identify possible genital tract abnormalities and to assess the uterus and adnexa.

Laboratory and Imaging Evaluation

All participants underwent relevant laboratory investigations, including complete blood count (CBC) and random blood sugar (RBS).

Pelvic imaging was performed using transvaginal sonography (TVS) or transabdominal ultrasonography (TAS), depending on the clinical circumstances. Endometrial thickness and other sonographic characteristics were documented.

Patients with an indication for further evaluation underwent endometrial tissue sampling/biopsy. The histopathological findings were used for definitive assessment of endometrial pathology.

Evaluation of Endometrium

Endometria lbiopsy:

Endometrial biopsy was performed to obtain endometrial tissue for histopathological examination. Histopathological assessment was used to identify benign, premalignant and malignant endometrial lesions and, where applicable, to establish the final diagnosis.

Ultrasonography:

TVS was used as the primary imaging modality for evaluation of women with postmenopausal bleeding. Endometrial thickness, endometrial morphology, heterogeneity, irregularity and other relevant sonographic findings were documented. Where TVS was not feasible or appropriate, transabdominal ultrasonography was performed.

Magnetic Resonance Imaging:

MRI was performed in selected patients when clinically indicated, particularly for further evaluation and preoperative assessment of suspected endometrial malignancy. MRI findings regarding local extension and other relevant features were recorded.

Assessment of Risk Factors

The association of demographic and clinical risk factors with endometrial pathology was evaluated. Variables including age, BMI, hypertension, diabetes mellitus and obstetric history were assessed in relation to the study outcomes.

Statistical Analysis

Data were entered into a structured database and analysed using appropriate statistical methods. Quantitative variables such as age and BMI were summarized using mean $\pm$ standard deviation (SD), while categorical variables were expressed as frequency and percentage.

Appropriate graphical representations, including bar diagrams, pie charts and box plots, were used for visualization of the data. For comparison of quantitative variables between two groups, the independent-samples t-test was used where appropriate. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was applied.

Associations between categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to quantify associations. Univariate binary logistic regression analysis was performed to assess the association between explanatory variables and the outcome of interest. Variables demonstrating statistical significance in univariate analysis were considered for inclusion in multivariable logistic regression analysis. Adjusted odds ratios (AORs) with 95% CIs were reported. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using CoGuide software, version 1.0.

RESULTS

A total of 59 women with postmenopausal bleeding were included in the final analysis. Data were entered into Microsoft Excel 2016 and analysed using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY: IBM Corp). Categorical variables were expressed as frequencies and percentages, whereas continuous variables were summarized using mean and standard deviation. The Independent-samples t-test was used for comparison of continuous variables between two independent groups. Associations between categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Table 1. Distribution of Histopathological Examination Findings

Histopathological examination	Frequency (n)	Percentage (%)
Premalignant/Malignant	10	16.9
Control	49	83.1
Total	59	100.0

Observation: Among the 59 women evaluated, 10 (16.9%) had premalignant/malignant endometrial pathology, whereas 49 (83.1%) were categorized as controls.

Table 2. Association of Age with Histopathological Examination Findings

Age group	Premalignant/Malignant n (%)	Control n (%)	Total n (%)	χ^2	p-value
<65 years	6 (60.0)	48 (98.0)	54 (91.5)		
>65 years	4 (40.0)	1 (2.0)	5 (8.5)	15.428	0.002
Total	10 (100.0)	49 (100.0)	59 (100.0)		

Observation: A statistically significant association was observed between age and histopathological outcome ($\chi^2=15.428$, $p=0.002$). The proportion of women aged >65 years was higher in the premalignant/malignant group (40.0%) than in the control group (2.0%).

Table 3. Association of Parity with Histopathological Examination Findings

Parity	Premalignant/Malignant n (%)	Control n (%)	Total n (%)	χ^2	p-value
Primi	3 (30.0)	7 (14.3)	10 (16.9)		
Multi	7 (70.0)	42 (85.7)	49 (83.1)	1.457	0.350
Total	10 (100.0)	49 (100.0)	59 (100.0)		

Observation: There was no statistically significant association between parity and histopathological outcome ($\chi^2=1.457$, $p=0.350$).

Table 4. Association of Hypertension with Histopathological Examination Findings

Hypertension	Premalignant/Malignant n (%)	Control n (%)	Total n (%)	χ^2	p-value
Absent	6 (60.0)	22 (44.9)	28 (47.5)		
Present	4 (40.0)	27 (55.1)	31 (52.5)	0.760	0.494
Total	10 (100.0)	49 (100.0)	59 (100.0)		

Observation: Hypertension was present in 40.0% of women in the premalignant/malignant group and 55.1% of controls. The association was not statistically significant ($\chi^2=0.760$, $p=0.494$).

Table 5. Association of Diabetes Mellitus with Histopathological Examination Findings

Diabetes mellitus	Premalignant/Malignant n (%)	Control n (%)	Total n (%)	χ^2	p-value
Absent	2 (20.0)	28 (57.1)	30 (50.8)		
Present	8 (80.0)	21 (42.9)	29 (49.2)	4.584	0.042
Total	10 (100.0)	49 (100.0)	59 (100.0)		

Observation: Diabetes mellitus was present in 80.0% of women with premalignant/malignant pathology compared with 42.9% of controls. A statistically significant association was observed between diabetes mellitus and histopathological outcome ($\chi^2=4.584$, $p=0.042$).

Table 6. Association of Recurrent Vaginal Bleeding with Histopathological Examination Findings

Recurrent vaginal bleeding	Premalignant/Malignant n (%)	Control n (%)	Total n (%)	χ^2	p-value
Absent	4 (40.0)	44 (89.8)	48 (81.4)	13.577	0.002
Present	6 (60.0)	5 (10.2)	11 (18.6)		
Total	10 (100.0)	49 (100.0)	59 (100.0)		

Observation: Recurrent vaginal bleeding was present in 60.0% of women with premalignant/malignant pathology compared with 10.2% of controls. A highly statistically significant association was observed ($\chi^2=13.577$, $p=0.002$).

Table 7. Comparison of Age at Menarche According to Histopathological Outcome

Variable	HPE group	N	Mean	SD	t-value	p-value
Age at menarche	Premalignant/Malignant	10	13.20	0.92	0.152	0.880
	Control	49	13.27	1.29		

Observation: The mean age at menarche was 13.20 ± 0.92 years in the premalignant/malignant group and 13.27 ± 1.29 years in the control group. No statistically significant difference was observed ($t=0.152$, $p=0.880$).

Table 8. Comparison of Age at Menopause According to Histopathological Outcome

Variable	HPE group	N	Mean	SD	t-value	p-value
Age at menopause	Premalignant/Malignant	10	51.60	5.68	2.361	0.022
	Control	49	47.41	5.00		

Observation: The mean age at menopause was higher among women with premalignant/malignant pathology (51.60 ± 5.68 years) than among controls (47.41 ± 5.00 years). This difference was statistically significant ($t=2.361$, $p=0.022$).

Table 9. Distribution of BMI, Abdominal Mass and Weight Loss

Clinical variable	Category	Frequency (n)	Percentage (%)
BMI	Underweight	1	1.7
	Normal	23	39.0
	Overweight	27	45.8
	Obese	8	13.6
Total		59	100.0
Abdominal mass	Absent	55	93.2
	Present	4	6.8
Total		59	100.0
Weight loss	Absent	54	91.5
	Present	5	8.5
Total		59	100.0

Observation: Regarding BMI, 45.8% of participants were overweight, 39.0% had normal BMI, 13.6% were obese and 1.7% were underweight. An abdominal mass was present in 6.8% of participants, while 93.2% had no palpable abdominal mass. Weight loss was reported in 8.5% of participants and was absent in 91.5%.

Table 10. Overall Summary of Significant and Non-significant Associations with Histopathological Outcome

Variable	Statistical test	Test statistic	p-value	Interpretation
Age	Chi-square	$\chi^2=15.428$	0.002	Significant
Parity	Fisher's exact	$\chi^2=1.457$	0.350	Not significant
Hypertension	Fisher's exact	$\chi^2=0.760$	0.494	Not significant
Diabetes mellitus	Fisher's exact	$\chi^2=4.584$	0.042	Significant
Recurrent vaginal bleeding	Fisher's exact	$\chi^2=13.577$	0.002	Highly significant
Age at menarche	Independent t-test	$t=0.152$	0.880	Not significant
Age at menopause	Independent t-test	$t=2.361$	0.022	Significant

DISCUSSION

The present study included 59 women presenting with postmenopausal bleeding, of whom 10 (16.9%) had premalignant or malignant endometrial pathology and 49 (83.1%) were categorized as controls. The presence of significant endometrial pathology in a proportion of women presenting with PMB reinforces the importance of systematic evaluation of this

symptom. Previous evidence has similarly demonstrated that although the majority of women with PMB have benign causes, PMB remains the most important presenting symptom of endometrial carcinoma and requires appropriate investigation [3].

A statistically significant association was observed between age and histopathological outcome ($\chi^2=15.428$, $p=0.002$). Women aged >65 years accounted for 40.0% of the premalignant/malignant group compared with only 2.0% of the control group. This finding is consistent with the established epidemiological pattern of endometrial carcinoma, in which incidence increases with advancing age. Older postmenopausal women are more likely to have accumulated multiple hormonal, metabolic and reproductive risk factors over their lifetime [1,2]. The marked difference observed in the present study suggests that advanced age may be an important clinical indicator for identifying women with PMB who require careful assessment.

In contrast, parity was not significantly associated with histopathological outcome ($\chi^2=1.457$, $p=0.350$). Multiparous women constituted 70.0% of the premalignant/malignant group and 85.7% of the control group. Although epidemiological studies have generally reported an inverse relationship between parity and endometrial cancer risk, the present study did not demonstrate a statistically significant association [5]. The absence of significance may partly be related to the relatively small sample size and the limited number of women with premalignant/malignant pathology.

Hypertension was also not significantly associated with histopathological outcome in the present study ($\chi^2=0.760$, $p=0.494$). Hypertension was present in 40.0% of women with premalignant/malignant pathology compared with 55.1% of controls. Although hypertension has frequently been reported in association with endometrial cancer, it commonly occurs alongside obesity, insulin resistance and diabetes mellitus, making it difficult to establish an independent effect [8]. The lack of significance in the present study may therefore reflect the sample size and the distribution of hypertension across both groups.

A significant association was observed between diabetes mellitus and premalignant/malignant endometrial pathology ($\chi^2=4.584$, $p=0.042$). Diabetes was present in 80.0% of women in the premalignant/malignant group compared with 42.9% of controls. This finding is consistent with previous epidemiological evidence demonstrating an increased risk of endometrial carcinoma among women with diabetes mellitus [7,12]. Several mechanisms may explain this association. Insulin resistance and compensatory hyperinsulinemia can increase mitogenic signaling, while hyperglycemia and chronic inflammation may further promote cellular proliferation and carcinogenesis [7]. The high prevalence of diabetes among women with significant endometrial pathology in the present study highlights the importance of considering metabolic comorbidities during evaluation of PMB.

The association between recurrent vaginal bleeding and histopathological outcome was highly significant ($\chi^2=13.577$, $p=0.002$). Recurrent bleeding was present in 60.0% of women with premalignant/malignant pathology compared with only 10.2% of controls. This finding has considerable clinical relevance because persistent or recurrent PMB should not be dismissed, particularly when an earlier evaluation has not established a definitive benign cause. Endometrial carcinoma commonly presents with abnormal uterine bleeding, and recurrent symptoms may warrant repeat or more definitive endometrial assessment [3,9].

The mean age at menarche was 13.20 ± 0.92 years in the premalignant/malignant group and 13.27 ± 1.29 years in controls. No statistically significant difference was observed ($t=0.152$, $p=0.880$). Although earlier menarche has been associated with increased endometrial cancer risk in epidemiological studies, possibly because of longer lifetime exposure to endogenous estrogen, the present study did not demonstrate such an association [4]. The relatively similar mean ages at menarche between the two groups may have contributed to the absence of statistical significance.

A statistically significant difference was observed for age at menopause ($t=2.361$, $p=0.022$). Women with premalignant/malignant pathology had a higher mean age at menopause than controls (51.60 ± 5.68 years versus 47.41 ± 5.00 years). Late menopause is a recognized risk factor for endometrial carcinoma because it increases the cumulative duration of estrogen exposure during the reproductive lifetime [1,4]. The present finding is therefore biologically plausible and supports the role of prolonged estrogen exposure in endometrial carcinogenesis.

Regarding BMI, 45.8% of the total study population were overweight and 13.6% were obese. Although the present analysis did not provide a statistical comparison of BMI categories between the premalignant/malignant and control groups, the high frequency of excess body weight is noteworthy. Obesity is a well-established risk factor for endometrial cancer and is thought to act through increased peripheral estrogen production, insulin resistance, hyperinsulinemia and inflammatory pathways [6]. Future studies with larger sample sizes should specifically assess BMI as a continuous and categorical variable in relation to histopathological outcome.

An abdominal mass was present in 4 (6.8%) participants, whereas 55 (93.2%) had no abdominal mass. Similarly, weight loss was reported in only 5 (8.5%) participants. These findings suggest that most women in this cohort presented without obvious clinical features suggestive of advanced disease. In comparison, PMB and recurrent bleeding were more prominent clinical features, emphasizing the importance of investigating abnormal bleeding before other clinical manifestations become apparent.

Overall, the present study identified age, diabetes mellitus, recurrent vaginal bleeding and age at menopause as significant factors associated with premalignant/malignant endometrial pathology. In contrast, parity, hypertension and age at menarche were not significantly associated with histopathological outcome. These findings support the concept that endometrial carcinogenesis is multifactorial and influenced by a combination of demographic, reproductive and metabolic factors [1,6,7].

From a clinical perspective, women with PMB who are older, diabetic, have recurrent episodes of bleeding or have a later age at menopause may represent a subgroup requiring particularly careful evaluation. TVS can provide valuable information regarding endometrial morphology and thickness, while endometrial sampling remains important for definitive diagnosis when clinical or imaging findings are suspicious [9,10]. The identification of clinical risk factors should therefore complement, rather than replace, appropriate imaging and histopathological assessment.

The study has certain limitations. The sample size was relatively small, with only 10 women in the premalignant/malignant group. Consequently, the study may have had limited statistical power to detect modest associations, particularly for variables such as parity, hypertension and age at menarche. Furthermore, the observational design limits conclusions regarding causality. Larger prospective studies incorporating BMI, endometrial thickness, detailed histological subtypes and additional metabolic and reproductive variables would be useful for developing a robust predictive model.

Despite these limitations, the findings emphasize that postmenopausal bleeding should be considered an important warning symptom, particularly in women with additional risk factors. Recognition of high-risk clinical characteristics may facilitate earlier endometrial evaluation and improve the detection of premalignant and malignant lesions.

CONCLUSION

In women presenting with postmenopausal bleeding, older age, diabetes mellitus, recurrent vaginal bleeding and later age at menopause were significantly associated with premalignant or malignant endometrial pathology. These factors may help identify women at higher risk and emphasize the importance of early evaluation and timely endometrial histopathological assessment in patients with postmenopausal bleeding.

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