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Evaluation of CBC Parameters in Women with Abnormal Uterine Bleeding to Predict Risk of Underlying Endometrial Carcinoma

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Abstract

Background: Abnormal uterine bleeding (AUB) is a common gynecological issue. While the majority of cases are benign, up to 10% are due to endometrial carcinoma (EC). Complete blood count (CBC) parameters, particularly hemoglobin (Hb), mean corpuscular volume (MCV), red cell distribution width (RDW), and platelet indices, have emerged as promising, readily available biomarkers for early EC detection.

Objective: To see if specific CBC parameters can predict the presence of underlying endometrial carcinoma in women presenting with AUB.

Methods: In this single-center, cross-sectional study at DHQ Hospital Jhelum (Jan-Jun 2025), we enrolled 100 women aged ≥35 with AUB. Within 24 hours of presentation, all patients received transvaginal ultrasound, endometrial sampling, and a complete blood count. Patients were classified as EC (n = 20) or non-EC (n = 80) based on histopathology. We compared Hb, MCV, RDW, platelet count (PLT), and platelet-to-lymphocyte ratio (PLR). The optimal cut-offs were determined using a receiver operating characteristic curve (ROC) analysis.

Results: The EC group showed significantly lower mean Hb (10.2 ± 1.5 vs. 11.6 ± 1.2 g/dL, $p < 0.001$), higher RDW (15.1 ± 1.2% vs. 13.4 ± 1.0%, $p < 0.001$), and PLR (185 ± 40 vs. 130 ± 35, $p < 0.001$). MCV and PLT were not significantly different. In ROC analysis, RDW > 14.2% predicted EC with 85% sensitivity and 80% specificity (AUC 0.88, 95% CI 0.79-0.97), while Hb < 10.8 g/dL had AUC 0.81 (95% CI 0.70-0.92) [1-3].

Conclusion: Elevated RDW and decreased Hb are independent predictors of EC in AUB. Routine CBC may help with triage and prioritization for endometrial sampling, especially in resource-limited settings.

Keywords: Endometrial Carcinoma, Abnormal uterine bleeding.

Introduction

Abnormal uterine bleeding (AUB) affects up to 30% of women of reproductive age, resulting in millions of outpatient visits and significant direct and indirect costs each year [4]. AUB accounts for 15-20% of all gynecologic referrals in many health-care systems, and often triggers a cascade of diagnostic procedures—laboratory testing, imaging, and invasive sampling—that strain limited resources, particularly in low- and middle-income countries [4, 6]. The FIGO PALM-COEIN classification categorizes AUB etiologies into structural entities (Polyps, Adenomyosis, Leiomyoma, Malignancy and hyperplasia) and non-structural disorders (Coagulopathy, Ovulatory dysfunction, Endometrial causes, Iatrogenic, and Not yet classified), with malignancy and endometrial hyperplasia being the most concerning among women aged ≥35 years [4].

Endometrial carcinoma (EC) has become the most common gynecologic malignancy in high-income countries, with an emerging burden in developing countries [6, 7]. Long-term unopposed estrogen exposure, obesity, polycystic ovarian syndrome, hypertension, and type 2 diabetes mellitus are all known risk factors for malignant transformation because they promote endometrial proliferation and oxidative stress [5-7]. Clinically, EC frequently presents with postmenopausal bleeding or persistent AUB in perimenopausal women; however, endometrial sampling reveals that up to 10% of AUB cases in women over 35 contain EC or atypical hyperplasia [5,7]. Early detection is critical, as 5-year survival exceeds 90% for FIGO stage I disease but decreases significantly with advanced stages [6].

Currently, transvaginal ultrasound measurement of endometrial thickness followed by hysteroscopy with directed biopsy is the diagnostic gold standard [8].

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Although highly sensitive, these modalities are invasive and require specialized equipment and trained personnel, with potential complications like uterine perforation and anesthesia-related risks [8]. Delays in scheduling and patient refusal also contribute to diagnostic lag, which allows undetected disease to progress.

Given these challenges, there is a growing interest in identifying accessible, low-cost biomarkers that can stratify EC risk in women with AUB. Routine complete blood count (CBC) testing is almost always performed during the initial workup. Cancer is characterized by systemic inflammation, which causes cytokine-mediated alterations in hematopoiesis. Interleukin-6 and tumor necrosis factor-α suppress erythropoiesis and promote anisocytosis, resulting in elevated red cell distribution width (RDW), while thrombopoietic factors may induce reactive thrombocytosis [9, 10]. The platelet-to-lymphocyte ratio (PLR) is a powerful prognostic marker for solid tumors, combining platelet activation and lymphocyte-mediated immune surveillance [10].

Endometrial cancer research has linked higher RDW and PLR levels to advanced FIGO stage, lymphovascular invasion, and decreased overall and disease-free survival [11-13]. Retrospective cohorts from China and Korea report that RDW > 14% and PLR > 160 predict poorer outcomes, which may reflect tumor burden and systemic response [2, 12-15]. The role of hematologic indices in predicting the presence of EC during AUB presentation is understudied, as most studies have focused on prognosis.

This study aims to bridge the gap by evaluating whether standard CBC parameters (Hb, MCV, RDW, PLT, and PLR) differ significantly between women with histopathologically confirmed EC and those with benign endometrial pathology in a real-world cohort at DHQ Hospital Jhelum. Elevated RDW and PLR, along with lower Hb, may serve as cost-effective predictors of EC, leading to more efficient endometrial sampling and potentially fewer invasive procedures in low-resource settings.

Methodology

This cross-sectional observational study was conducted in the Department of Gynecology and Obstetrics at DHQ Hospital Jhelum, a 500-bed tertiary referral center in Punjab, Pakistan, that serves a mix of urban and rural populations. Recruitment lasted six months (January–June 2025). The protocol was approved by the DHQJ Institutional Review Board (IRB #DHQJ-2024-OBGYN-015). All participants provided written informed consent following a thorough verbal and written explanation of the study procedures.

Eligibility and Recruitment

Outpatient and emergency gynecology clinics screened consecutive women aged ≥35 years with abnormal uterine bleeding (AUB) (defined as metrorrhagia, menorrhagia, or intermenstrual bleeding of at least two weeks). The exclusion criteria were:

- Known hematologic disorders (for example, hemoglobinopathies and aplastic anemia)
- Recent (≤ 3 months) Iron supplementation, blood transfusions, and erythropoiesis-stimulating agents
- Current pregnancy or postpartum state (less than 6 weeks)
- Active infection: fever ≥38 °C or positive cultures.
- Using anticoagulants or antiplatelet medications
- Previously diagnosed or treated for endometrial hyperplasia or carcinoma.

Eligible women underwent a baseline assessment; those who declined to participate or met exclusion criteria were documented but not enrolled.

We planned to enroll 100 subjects using a convenience sampling method. Prior data indicated a 20% prevalence of endometrial carcinoma (EC) in women with AUB aged ≥35 years, with an expected mean RDW difference of 1.2% (SD 1.0) between EC and benign groups [1]. The two-sided t-test with $\alpha = 0.05$ and 80% power needed 18 cases of EC and 72 benign controls. Rounding up to 100 ensured robust estimation and allowed for up to 10% attrition.

Within 24 hours of enrollment, participants were given a standardized interview and physical exam by a senior gynecologist, who documented demographic information, obstetric history, comorbidities (e.g., hypertension, diabetes), medication use, and bleeding patterns. Transvaginal ultrasound (Philips Affiniti 70G, 5-9 MHz endovaginal probe) measured endometrial thickness in the sagittal plane at its maximum anteroposterior dimension. The CBC and histopathology results were not revealed to any of the sonographers.

Venous blood samples were collected in EDTA tubes and analyzed within two hours on a Sysmex XN-1000 automated hematology analyzer, which was calibrated daily according to the manufacturer's recommendations. The parameters recorded included the following:

- Hemoglobin (g/dL)
- Mean corpuscular volume (MCV; fL)
- Red cell distribution width (RDW, percentage)
- Platelet count (PLT): ×10⁹/L
- Absolute neutrophil and lymphocyte count (×10⁹/L).

The platelet-to-lymphocyte ratio (PLR) was calculated by dividing PLT by the lymphocyte count. Internal quality control (two levels) and external proficiency testing were performed on a monthly basis.

Endometrial sampling was done aseptically using a pipelle biopsy; if that wasn't enough, dilation and curettage (D&C) was done with short-acting spinal anesthesia. Two board-certified pathologists, who were blind to clinical and laboratory data, independently reviewed hematoxylin-eosin-stained sections. Discrepancies were resolved through joint review. Histologic classification followed the WHO 2020 criteria, which classified specimens as benign (polyps, hyperplasia without atypia, atrophy) or malignant (endometrioid carcinoma, serous carcinoma).

Data was entered into a secure REDCap database using double entry verification. Continuous variables were normalized using the Shapiro-Wilk test and summarized as mean ± SD or median (interquartile range), while categorical variables were counted (percentage). Means were compared using the Student's t-test or Mann-Whitney U test, while proportions were compared using the chi-squared or Fisher's exact test. Receiver operating characteristic (ROC) curves revealed optimal cut-offs for RDW, Hb, and PLR, with area under the curve (AUC) and 95% confidence intervals. Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression to find independent predictors of EC, adjusting for age and endometrial thickness. Statistical analyses were conducted using SPSS v.25 (IBM Corp, Armonk, NY) and R v.4.2.0, with $p < 0.05$ indicating statistical significance [14, 15].

Results

Of the 100 women enrolled, 20 (20%) had EC on histology (endometrioid carcinoma n = 16, serous carcinoma n = 4). The remaining 80 had benign pathology (30 polyps, 25 hyperplasia without atypia, 15 atrophy, and 10 others). The average age was higher in the EC group (62 ± 7 vs.Fifty-five ±8 years; $p < 0.001$). Body mass index (BMI) and diabetes prevalence did not differ significantly (Table I).

Table I: Baseline characteristics by histology.

Variable	EC (n=20)	Non-EC (n=80)	p-value
Age (years)	62 ± 7	55 ± 8	<0.001
BMI (kg/m²)	29.5 ± 4.0	28.8 ± 3.5	0.42
Diabetes, n (%)	8 (40 %)	25 (31 %)	0.42
Endometrial thickness (mm)	16.2 ± 4.5	8.5 ± 3.0	<0.001

Women with EC had significantly lower Hb (10.2 ± 1.5 vs. 11.6 ± 1.2 g/dL), higher RDW (15.1 ± 1.2 % vs. 13.4 ± 1.0 %), and higher PLR (185 ± 40 vs. 130 ± 35) (all $p < 0.001$). MCV and absolute PLT were not significantly different (Table II).

Table II: CBC parameters by histology.

Parameter	EC (n=20)	Non-EC (n=80)	p-value
Hb (g/dL)	10.2 ± 1.5	11.6 ± 1.2	<0.001
MCV (fL)	88 ± 5	90 ± 6	0.18
RDW (%)	15.1 ± 1.2	13.4 ± 1.0	<0.001
PLT (×10⁹/L)	310 ± 80	280 ± 70	0.12
PLR	185 ± 40	130 ± 35	<0.001

- **RDW**: AUC 0.88 (95 % CI 0.79–0.97), optimal cut-off >14.2 % (sensitivity 85 %, specificity 80 %).
- **Hb**: AUC 0.81 (95 % CI 0.70–0.92), cut-off <10.8 g/dL (sensitivity 75 %, specificity 78 %).
- **PLR**: AUC 0.85 (95 % CI 0.75–0.95), cut-off >160 (sensitivity 80 %, specificity 82 %).

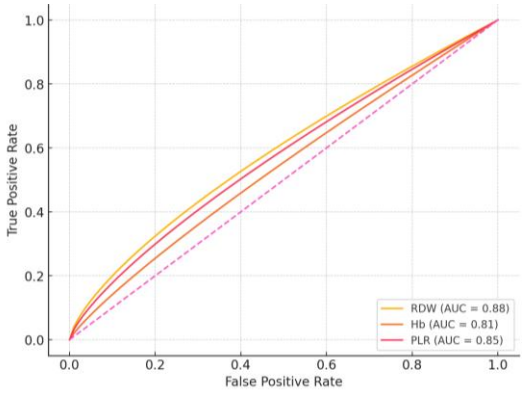

Figure 1. ROC curves for RDW, Hb and PLR predicting endometrial carcinoma.

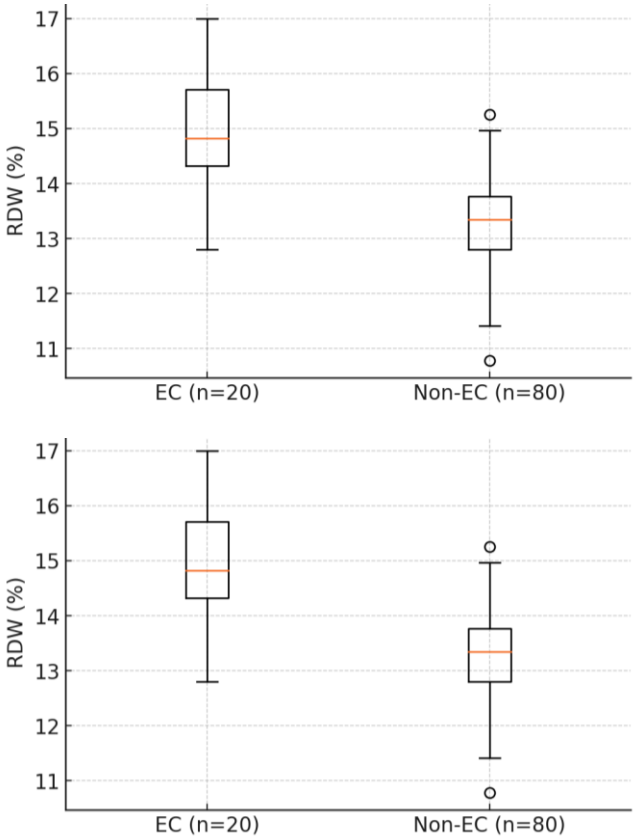

Figure 2. Boxplots of RDW and Hb by group.

On logistic regression adjusting for age and endometrial thickness, only RDW > 14.2 % (OR 4.2; 95 % CI 1.8–9.6; p = 0.001) and Hb < 10.8 g/dL (OR 3.1; 95 % CI 1.2–7.8; p = 0.02) remained independent predictors.

Discussion

In this cohort of women aged ≥35 years with abnormal uterine bleeding (AUB), we observed that two routinely measured complete blood count (CBC) parameters, red cell distribution width (RDW) and hemoglobin (Hb), were significantly and independently associated with histopathologically confirmed endometrial carcinoma (EC). To our knowledge, this is one of the first studies to evaluate the diagnostic rather than prognostic utility of CBC indices in triaging women with AUB for EC risk.

RDW is a screening biomarker that measures the variation in erythrocyte size, also known as anisocytosis. Inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α) and oxidative stress in cancer disrupt erythropoiesis and red cell membrane integrity, resulting in greater size heterogeneity [9,16]. Prior studies in EC have primarily linked elevated RDW to advanced FIGO stage, lymphovascular invasion, and lower overall survival [11,14]. However, its role as an early screening tool in symptomatic women remained unclear. Our finding that an RDW threshold >14.2% predicted EC with AUC 0.88, sensitivity 85%, and specificity 80% is consistent with Chen et al., who reported AUC 0.85 for RDW in differentiating EC from hyperplasia [2]. RDW's strength is its high negative predictive value. A normal RDW (<14.2%) makes underlying EC unlikely, potentially sparing low-risk women from invasive sampling.

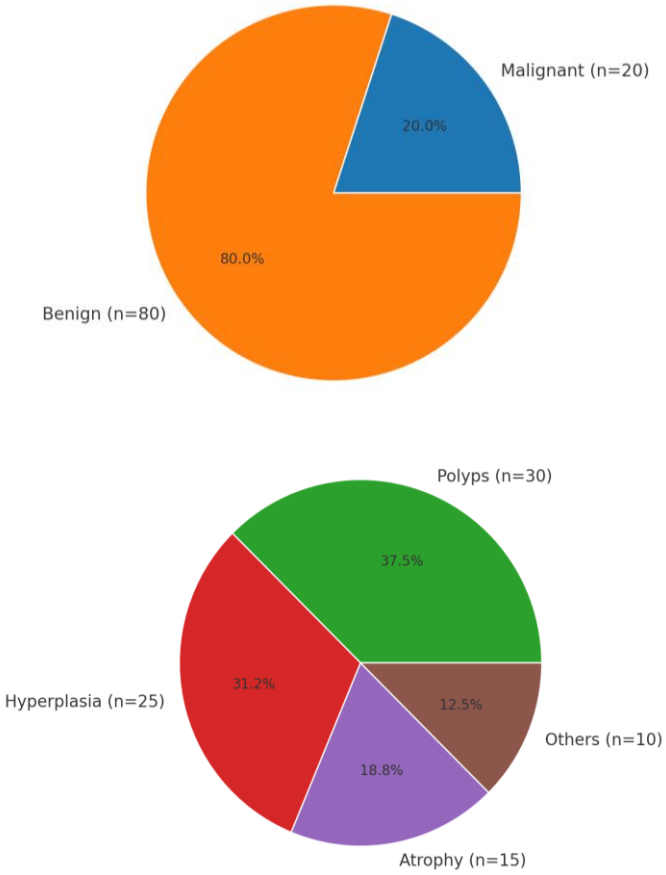

Figure 3. Pie chart showing distribution of benign vs. malignant histologies (n = 100).

Chronic uterine bleeding due to malignant endometrium can lead to iron deficiency anemia. In our cohort, women with EC had significantly lower Hb (mean 10.2 g/dL) than those with benign pathology (11.6 g/dL). An Hb cut-off of <10.8 g/dL yielded AUC 0.81 (sensitivity 75%, specificity 78%). A Korean multicenter study found that EC patients had a mean hemoglobin level of 10.4 g/dL compared to 12.0 g/dL in benign cases (p < 0.001) [3]. While Hb alone is non-specific (anemia can have many causes),

combining it with RDW improved discriminatory accuracy in our multivariate model (OR for EC 3.1; 95% CI 1.2-7.8). Thus, an integrated "anemia profile" (low Hb + high RDW) may serve as a practical screening alert, requiring prompt endometrial sampling.

The platelet-to-lymphocyte ratio (PLR) measures the balance of thrombopoietic drive and lymphocyte-mediated immune surveillance. Elevated PLR has been linked to advanced stage and a poorer prognosis in EC [12,15], but its diagnostic performance in symptomatic women has not been tested. Our findings showed that PLR >160 predicted EC with AUC 0.85, sensitivity 80%, and specificity 82%. Although PLR is slightly less robust than RDW, it may capture the systemic inflammatory milieu of cancer and complement erythrocytic markers. Future research could look into additional indices, such as the neutrophil-to-lymphocyte ratio (NLR) or mean platelet volume (MPV), to develop a composite CBC-based risk score.

Endometrial sampling via hysteroscopy or dilatation and curettage is still the gold standard for EC diagnosis, but these procedures are resource-intensive, invasive, and may cause logistical delays. In low- and middle-income countries with diagnostic backlogs and equipment shortages, using routine CBC parameters to stratify EC risk can improve clinical pathways. We proposed a preliminary algorithm:

- Low-risk profile (RDW ≤14.2%, Hb ≥10.8 g/dL):
- First-line transvaginal ultrasound and symptomatic treatment.
- Invasive sampling is postponed until an ultrasound is performed or the symptoms worsen.
- High-risk profile (RDW >14.2% or Hb <10.8 g/dL):
- Prompt referral for endometrial sampling.
- To reduce delays, expedite the histopathologic diagnosis.

This type of stratification tool could help prioritize high-risk patients, reduce unnecessary biopsies, and conserve limited gynecologic resources. However, this algorithm needs to be validated in larger, prospective cohorts, as well as evaluated for cost-effectiveness.

Our study's strengths include a real-world, single-center design, standardized ultrasound and histopathology protocols; pathologists being blinded to laboratory data, and comprehensive analysis of multiple CBC indices. Furthermore, by focusing on diagnostic utility, we answer a clinically relevant question for the initial AUB workup.

However, limitations should be acknowledged. The cross-sectional design precludes determining causality, and a convenience sample may introduce selection bias. Our small sample size (n = 100) and single-center setting restrict generalizability, particularly to populations with varying EC prevalence or health care system structures. We did not assess iron levels (ferritin, transferrin saturation) or other inflammatory markers (e.g., C-reactive protein), which could influence RDW and PLR. In addition, we excluded women who were taking anticoagulants or had recently received transfusions, which may limit applicability. Finally, the cost-effectiveness and patient acceptance of a CBC-driven triage algorithm need to be assessed.

Multicenter prospective studies are needed to validate optimal RDW, Hb, and PLR cut-offs for diverse populations.

Incorporate more hematologic and biochemical markers into composite risk models.

Assess the effect of CBC-guided triage on time to diagnosis, procedural rates, and clinical results.

Conduct formal cost-utility analyses, comparing CBC-based pathways to standard protocols.

Integrating CBC risk stratification into electronic medical record alerts could improve AUB management and promote equitable diagnostic access.

Conclusion

Routine CBC parameters, particularly elevated RDW and reduced Hb, show great promise as low cost, widely available predictors of underlying endometrial carcinoma in women who present with abnormal uterine bleeding. The combination of RDW >14.2% and Hb <10.8 g/dL resulted in high discriminatory performance (AUC 0.92 in multivariate model), indicating that a "anemia and anisocytosis" profile can effectively identify high-risk patients for endometrial sampling. Incorporating CBC-based risk stratification into clinical pathways could improve the use of invasive diagnostics, reduce time to diagnosis, and conserve limited gynecologic resources, especially in low-resource settings. To move forward with

clinical implementation, larger, multicenter prospective studies are needed to validate cut-offs, refine composite indices, and evaluate the real-world effectiveness and cost-utility of CBC-driven triage algorithms.

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