

Research Article

Biochemical, Metabolic, Cardiovascular, and Histopathological Predictors of Anemia Severity and Treatment Response in Women with Heavy Menstrual Bleeding: A Prospective Cohort Study

Fareeha Karamat Cheema^{1*}, Lubna Aslam², Tariq Hussain³, Waqar Ahmed⁴, Hamid Nawaz Khokhar⁵, Aneeqa Shahid⁶

^{1*}Assistant Professor, Department of Biochemistry, Gujranwala Medical College, Gujranwala, Pakistan.

²Associate Professor, Department of Obstetrics and Gynecology, Postgraduate Medical Institute (PGMI)/Ameer-Ud-Din Medical College (AMC) / Lahore General Hospital (LGH), Lahore, Pakistan.

³Associate Professor, Department of Biochemistry, Bakhtawar Amin Medical and Dental College, Multan, Pakistan.

⁴Consultant Cardiologist, Department of Cardiology, Khatam-un-Nabiyeen Trust (Regd.) Hospital, Sargodha, Punjab, Pakistan.

⁵Assistant Professor, Department of Pathology, Sahara Medical College, Narowal, Pakistan.

⁶Assistant Professor, Department of Biochemistry, Aziz Fatima Medical and Dental College, West Canal Road, Faisalabad, Pakistan.

Corresponding Author: Dr. Fareeha Karamat Cheema

Email: dr.fareehacheema@yahoo.com

Received: 19.06.26, Revised: 14.07.26, Accepted: 18.08.26

ABSTRACT

Background: Heavy menstrual bleeding (HMB) is a major cause of iron-deficiency anemia in reproductive-aged women, but anemia severity and treatment response may also be influenced by metabolic, inflammatory, cardiovascular, and endometrial factors.

Methods: This prospective cohort study included 130 women with HMB and anemia recruited from the Department of Biochemistry, Gujranwala Medical College, Gujranwala, and Lahore General Hospital, Lahore, Pakistan, from January 2025 to January 2026. Hematological indices, ferritin, transferrin saturation, C-reactive protein (CRP), metabolic parameters, HOMA-IR, cardiovascular measurements, menstrual blood loss, and clinically indicated endometrial histopathology were assessed. Participants were reassessed after 12 weeks. Treatment response was defined as hemoglobin improvement ≥ 2.0 g/dL or achievement of hemoglobin ≥ 12.0 g/dL.

Results: Mild, moderate, and severe anemia occurred in 25.4%, 55.4%, and 19.2% of participants, respectively. Greater anemia severity was independently associated with higher PBAC score, lower ferritin, CRP > 5 mg/L, HOMA-IR ≥ 2.5 , and increased resting heart rate. At 12 weeks, 92 women (70.8%) achieved hematological response. Ferritin < 10 ng/mL, elevated CRP, insulin resistance, persistent PBAC ≥ 150 , and endometrial hyperplasia predicted non-response. The combined model showed strong discrimination for severe anemia (AUC 0.90) and good discrimination for treatment non-response (AUC 0.84).

Conclusion: HMB-associated anemia is influenced by interconnected hematological, metabolic, inflammatory, cardiovascular, and endometrial factors. Multidomain assessment may improve early risk stratification and treatment planning.

Keywords: Heavy Menstrual Bleeding, Iron-Deficiency Anemia, Ferritin; Insulin Resistance, C-Reactive Protein, Endometrial Histopathology, Treatment Response.

INTRODUCTION

Heavy menstrual bleeding (HMB) is an important manifestation of abnormal uterine bleeding (AUB) and a major cause of iron deficiency and iron-deficiency anemia among women of reproductive age¹. HMB is currently defined according to its adverse effect on a woman's physical, emotional, social, and material quality of life rather than solely by an

objectively measured volume of menstrual blood loss. The International Federation of Gynecology and Obstetrics (FIGO) recommends systematic evaluation of AUB using the PALM-COEIN classification, incorporating structural causes polyp, adenomyosis, leiomyoma, and malignancy/hyperplasia—and nonstructural causes including coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic

causes, and conditions not otherwise classified. Among the different patterns of AUB, HMB is particularly strongly associated with progressive iron depletion and anemia^{2,3}.

During repeated losses of periods, iron stores can become depleted, which results in a decrease in the production of red blood cells and eventually a decrease in the amount of hemoglobin in the blood⁴. Women with HMB may consequently experience fatigue, weakness, exercise intolerance, dizziness, impaired concentration, palpitations, and reduced quality of life. Hemoglobin is still the primary indicator of anaemia severity, but it is a limited measure of iron status. Additional information about the degree and severity of the iron depletion can be obtained from serum ferritin, serum iron, total iron-binding capacity, transferrin saturation, mean corpuscular volume, and red-cell distribution width. Importantly, ferritin is also an acute-phase reactant, so it is important to have an acute-phase assessment when evaluating iron status at the same time. Yet, iron deficiency related to HMB is still under-recognized and under-treated in many women^{5,6}.

The severity of anemia in women with HMB may not, however, be explained by menstrual blood loss and iron deficiency alone. Metabolic derangements such as obesity, insulin resistance, dysglycemia, and dyslipidemia may help in the development of abnormal endometrial function via effects on the metabolism of estrogens, hyperinsulinemia, chronic low-grade inflammation, and alterations in ovulation⁷. Endometrial proliferative abnormalities and endometrial hyperplasia are also well-known risk factors for obesity and metabolic dysfunction. An increase in BMI, diabetes, and hypertension have been linked to clinically significant endometrial lesions in women who present with AUB. Based on these observations, it is suggested that the metabolic parameters may have an impact on the mechanism of persistent uterine bleeding and on the recovery from anemia⁸⁻¹⁰.

Important adaptations to the cardiovascular system occur with anemia. Decreases in blood oxygen-carrying capacity will lead to increases in heart rate and cardiac output to maintain tissue oxygen delivery¹¹. Women may, therefore, be clinically more likely to exhibit tachycardia, orthostatic change, palpitation, hypotension, or an increase in shock index due to greater blood loss. Previous clinical observations in women presenting with AUB have demonstrated that the combination of

tachycardia and hypotension is associated with moderate-to-severe anemia, indicating that readily obtainable cardiovascular parameters may complement laboratory measurements when assessing disease severity¹².

Histopathological evaluation provides an additional dimension in selected women with HMB because persistent or recurrent bleeding may reflect endometrial polyps, disordered proliferative endometrium, hyperplasia, inflammatory abnormalities, or other endometrial pathology¹³. Histopathological studies of AUB populations demonstrate considerable heterogeneity in underlying endometrial findings, while metabolic factors such as obesity and diabetes may further increase the likelihood of hyperplastic or neoplastic lesions. Structural and endometrial causes of persistent bleeding may also limit hematological recovery when iron replacement is provided without adequate control of the underlying source of blood loss¹⁴.

Most clinical assessment of HMB-associated anemia focuses primarily on hemoglobin, conventional iron indices, and gynecological etiology. Comparatively less attention has been given to the combined contribution of biochemical, metabolic, cardiovascular, and histopathological characteristics in predicting both baseline anemia severity and subsequent treatment response. A multidimensional approach could identify women at greater risk of severe anemia or inadequate hematological recovery and may support earlier intensification of iron replacement and treatment of persistent uterine bleeding^{15,16}.

Therefore, the present prospective cohort study aimed to evaluate biochemical, metabolic, cardiovascular, and histopathological predictors of anemia severity and treatment response in women with heavy menstrual bleeding. The study further examined whether integration of iron indices, inflammatory and metabolic markers, cardiovascular parameters, menstrual characteristics, and histopathological findings could improve clinical risk stratification compared with assessment based predominantly on hemoglobin concentration.

MATERIALS AND METHODS

Study Design and Setting

The study was a prospective cohort study carried out between January 2025 and January 2026 at Gujranwala Medical College, Gujranwala, Pakistan, and Lahore General Hospital (LGH), Lahore, Pakistan. A total of 130 women suffering from HMB and anemia were

consecutively enrolled and followed to assess baseline severity of anemia and hematological treatment response.

Study Population

Eligible women were those who presented with HMB and hemoglobin <12.0 g/dL in the age group 18-50 years. The individual was identified from clinical history, and HMB was quantified with the Pictorial Blood Assessment Chart (PBAC). Pregnancy, postpartum status, menopause, known hemoglobinopathy, chronic kidney or advanced liver disease, malignancy, active systemic infection, gastrointestinal bleeding, or recent blood transfusion were exclusion criteria.

Clinical and Gynecological Assessment

A structured proforma was used to elicit details of demographic features, parity, menstrual characteristics, clots passed, duration of HMB, medication history, and associated symptoms. Height, weight and BMI (body mass index) were measured. All patients who presented with abnormal uterine bleeding underwent pelvic ultrasonography and gynecological evaluation to determine the cause of the bleeding and categorize it as per the FIGO PALM-COEIN system.

Hematological and Biochemical Assessment

Venous blood samples were taken at baseline. Laboratory tests included complete blood count (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red-cell distribution width, leukocytes, and platelets). Iron status was evaluated by serum ferritin, serum iron, total iron-binding capacity, and transferrin saturation. As an inflammatory marker, C-reactive protein (CRP) was measured. Based on haemoglobin concentration, anaemia was divided into mild, moderate and severe.

Metabolic Assessment

Metabolic evaluation included fasting plasma glucose, fasting insulin, HbA1c, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as fasting insulin $\times$ fasting glucose/405. BMI and metabolic parameters were assessed for their association with anemia severity and treatment response.

Cardiovascular Assessment

Resting heart rate and systolic and diastolic blood pressure were recorded after at least five minutes of rest. Orthostatic heart-rate changes were assessed after standing. Shock index was calculated as heart rate divided by systolic blood pressure. Symptoms including palpitations, dizziness, exertional dyspnea, presyncope, and exercise intolerance were also documented.

Histopathological Assessment

Endometrial sampling was performed only when clinically indicated, including persistent or irregular bleeding, abnormal ultrasonographic findings, obesity, treatment failure, or other risk factors for endometrial pathology. Histopathological findings were categorized as normal cyclical endometrium, disordered proliferative endometrium, polyp-associated changes, endometrial hyperplasia without atypia, or inflammatory endometrial changes. Histopathological analyses were performed as subgroup analyses.

Treatment and Follow-up

Participants received iron replacement and cause-directed treatment for HMB according to clinical severity and gynecological findings. Oral or intravenous iron was administered as appropriate, while HMB was managed using medical, hormonal, or procedural treatment when indicated. Participants were reassessed after 12 weeks with repeat hemoglobin, red-cell indices, ferritin, transferrin saturation, PBAC score, and cardiovascular measurements.

Outcome Measures

The primary outcomes were baseline anemia severity and hematological treatment response at 12 weeks. Treatment response was defined as an increase in hemoglobin of ≥ 2.0 g/dL from baseline or achievement of hemoglobin ≥ 12.0 g/dL. Secondary outcomes included improvement in ferritin, transferrin saturation, menstrual blood loss, and cardiovascular parameters.

Statistical Analysis

Data were analyzed using SPSS version 27.0. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, while categorical variables were presented as frequencies and percentages. ANOVA, Kruskal-Wallis, chi-square, or Fisher's exact tests were used as appropriate. Multivariable ordinal logistic regression identified independent predictors of

increasing anemia severity, while binary logistic regression identified predictors of treatment non-response. Results were reported as adjusted odds ratios with 95% confidence intervals. Receiver-operating-characteristic analysis assessed predictive performance. A two-sided $p < 0.05$ was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the relevant institutional ethics committee. Written informed consent was obtained from all participants before enrollment.

RESULTS

Baseline Characteristics and Anemia Severity

A total of 130 women with heavy menstrual bleeding and anemia completed the study. The mean age was 36.4 ± 7.2 years, and the mean body mass index (BMI) was 27.9 ± 4.3 kg/m². Mild anemia was observed in 33 (25.4%) women, moderate anemia in 72 (55.4%), and severe anemia in 25 (19.2%).

Increasing anemia severity was accompanied by progressively greater menstrual blood loss. The mean Pictorial Blood Assessment Chart (PBAC) score increased from 177 ± 52 in

women with mild anemia to 337 ± 94 in those with severe anemia ($p < 0.001$). Hemoglobin declined from 11.3 ± 0.3 g/dL to 7.2 ± 0.5 g/dL, while mean corpuscular volume (MCV) decreased from 78.6 ± 5.2 fL to 67.8 ± 6.3 fL. Red-cell distribution width (RDW) increased significantly with increasing anemia severity (Table 1).

Iron depletion was more pronounced among women with severe anemia. Median serum ferritin decreased from 14.8 ng/mL in the mild group to 5.1 ng/mL in the severe group, while transferrin saturation (TSAT) decreased from $16.2 \pm 5.1\%$ to $7.1 \pm 3.1\%$ (both $p < 0.001$). Higher anemia severity was also associated with greater inflammatory and metabolic abnormalities. C-reactive protein (CRP), HOMA-IR, triglyceride concentration, and BMI increased progressively across anemia categories.

Cardiovascular compensation also became more pronounced with increasing anemia severity. Resting heart rate increased from 82 ± 8 beats/min in mild anemia to 101 ± 11 beats/min in severe anemia, while systolic blood pressure decreased from 118 ± 11 mmHg to 108 ± 13 mmHg. The shock index increased from 0.61 ± 0.08 to 0.82 ± 0.13 ($p < 0.001$) (Table 1).

Table 1. Baseline Characteristics According to Anemia Severity

Variable	Mild (n=33)	Moderate (n=72)	Severe (n=25)	p-value
Age, years	34.2 ± 7.4	36.2 ± 7.0	38.7 ± 6.4	0.031
BMI, kg/m ²	25.7 ± 3.6	28.0 ± 4.1	30.3 ± 4.4	<0.001
PBAC score	177 ± 52	252 ± 76	337 ± 94	<0.001
Hemoglobin, g/dL	11.3 ± 0.3	9.4 ± 0.8	7.2 ± 0.5	<0.001
MCV, fL	78.6 ± 5.2	72.9 ± 6.1	67.8 ± 6.3	<0.001
RDW, %	15.2 ± 1.8	17.4 ± 2.3	19.6 ± 2.5	<0.001
Ferritin, ng/mL	14.8 (10.7–20.2)	8.9 (5.9–13.0)	5.1 (3.4–7.8)	<0.001
TSAT, %	16.2 ± 5.1	10.8 ± 4.3	7.1 ± 3.1	<0.001
CRP, mg/L	2.4 (1.5–3.8)	3.9 (2.3–5.8)	6.1 (3.9–8.6)	<0.001
HOMA-IR	2.1 ± 0.9	2.7 ± 1.2	3.4 ± 1.4	<0.001
Triglycerides, mg/dL	128 ± 35	146 ± 42	165 ± 48	0.006
Resting heart rate, beats/min	82 ± 8	91 ± 10	101 ± 11	<0.001
Systolic blood pressure, mmHg	118 ± 11	115 ± 12	108 ± 13	0.004
Shock index	0.61 ± 0.08	0.69 ± 0.10	0.82 ± 0.13	<0.001

BMI represents body mass index, PBAC represents the Pictorial Blood Assessment Chart, MCV represents mean corpuscular volume, RDW represents red-cell distribution width, TSAT represents transferrin saturation, CRP represents C-reactive protein, and HOMA-IR represents the homeostatic model assessment of insulin resistance. Ferritin and

CRP values are presented as median with interquartile range, while the remaining continuous variables are presented as mean $\pm$ standard deviation.

Histopathological Findings

Endometrial histopathological findings were available for 84 women who underwent biopsy

based on clinical indications. Normal cyclical endometrium was the most common finding and was identified in 35 (41.7%) women. Disordered proliferative endometrium was present in 18 (21.4%), hyperplasia without atypia in 15 (17.9%), polyp-associated changes in 12 (14.3%), and inflammatory endometrial changes in 4 (4.8%). The prevalence of severe anemia differed significantly according to histopathological

pattern ($p=0.018$). Severe anemia was identified in 6 of 15 women (40.0%) with endometrial hyperplasia without atypia compared with only 3 of 35 (8.6%) women with normal cyclical endometrium. Moderate-to-severe anemia was also common among women with disordered proliferative and inflammatory endometrial changes (Table 2).

Table 2. Histopathological Findings According to Anemia Severity

Histopathological finding	Total n (%)	Mild anemia n (%)	Moderate anemia n (%)	Severe anemia n (%)
Normal cyclical endometrium	35 (41.7)	12 (34.3)	20 (57.1)	3 (8.6)
Disordered proliferative endometrium	18 (21.4)	3 (16.7)	11 (61.1)	4 (22.2)
Polyp-associated changes	12 (14.3)	3 (25.0)	7 (58.3)	2 (16.7)
Hyperplasia without atypia	15 (17.9)	2 (13.3)	7 (46.7)	6 (40.0)
Inflammatory endometrial changes	4 (4.8)	1 (25.0)	2 (50.0)	1 (25.0)

The overall association between histopathological pattern and anemia severity was statistically significant at $p=0.018$. The highest proportion of severe anemia occurred among women with endometrial hyperplasia without atypia.

Treatment Response at 12 Weeks

Significant hematological improvement was observed after 12 weeks of treatment. Mean hemoglobin increased from 9.1 ± 1.5 g/dL at baseline to 11.4 ± 1.3 g/dL at follow-up ($p<0.001$). MCV increased from 72.9 ± 6.7 fL to 80.8 ± 5.5 fL, while median serum ferritin

increased from 8.8 ng/mL to 31.5 ng/mL. TSAT increased from $10.8 \pm 5.2\%$ to $23.6 \pm 7.4\%$ (Table 3).

Menstrual blood loss also improved substantially. Median PBAC score decreased from 244 at baseline to 116 at 12 weeks ($p<0.001$). Cardiovascular parameters improved simultaneously, with resting heart rate decreasing from 91.2 ± 11.9 beats/min to 82.7 ± 8.8 beats/min, while the shock index decreased from 0.70 ± 0.12 to 0.62 ± 0.09 . Overall, 92 of 130 women (70.8%) achieved the predefined hematological response, whereas 38 (29.2%) were classified as non-responders.

Table 3. Changes in Hematological and Clinical Parameters at 12 Weeks

Parameter	Baseline	12 weeks	p-value
Hemoglobin, g/dL	9.1 ± 1.5	11.4 ± 1.3	<0.001
MCV, fL	72.9 ± 6.7	80.8 ± 5.5	<0.001
Ferritin, ng/mL	8.8 (5.3–14.1)	31.5 (20.4–46.8)	<0.001
TSAT, %	10.8 ± 5.2	23.6 ± 7.4	<0.001
PBAC score	244 (186–319)	116 (72–174)	<0.001
Resting heart rate, beats/min	91.2 ± 11.9	82.7 ± 8.8	<0.001
Shock index	0.70 ± 0.12	0.62 ± 0.09	<0.001

Ferritin and PBAC values are expressed as median with interquartile range, while other variables are presented as mean $\pm$ standard deviation. Significant improvement was observed across all evaluated hematological, menstrual, and cardiovascular parameters.

Independent Predictors of Anemia Severity

Multivariable ordinal logistic regression demonstrated that greater menstrual blood

loss, depleted iron stores, systemic inflammation, insulin resistance, and cardiovascular compensation were independently associated with increasing anemia severity.

Each 50-point increase in PBAC score was associated with a 47% increase in the odds of belonging to a more severe anemia category (adjusted odds ratio [aOR] 1.47, 95% CI 1.22–1.77; $p<0.001$). Each 5-ng/mL decrease in

ferritin was associated with a 68% increase in the odds of greater anemia severity (aOR 1.68, 95% CI 1.28–2.20; $p<0.001$).

CRP >5 mg/L was associated with more than twofold greater odds of increasing anemia severity (aOR 2.21, 95% CI 1.08–4.52; $p=0.030$), while HOMA-IR ≥ 2.5 was independently associated with approximately twofold greater odds (aOR 1.96, 95% CI 1.03–3.73; $p=0.041$). Each 10-beats/min increase in resting heart rate was associated with a 58% increase in the odds of greater anemia severity (aOR 1.58, 95% CI 1.18–2.12; $p=0.002$) (Table 4).

Predictors of Treatment Non-response

Women who failed to achieve hematological response had greater baseline iron depletion, higher inflammatory activity, greater insulin resistance, and more persistent menstrual

blood loss. Baseline ferritin <10 ng/mL independently predicted treatment non-response (aOR 2.41, 95% CI 1.12–5.21; $p=0.025$).

CRP >5 mg/L was associated with 2.53-fold higher odds of non-response (95% CI 1.12–5.71; $p=0.026$), while HOMA-IR ≥ 2.5 approximately doubled the odds of treatment failure (aOR 2.07, 95% CI 1.01–4.24; $p=0.047$).

Persistent PBAC ≥ 150 at 12 weeks showed the strongest association with inadequate hematological recovery, producing more than fourfold higher odds of treatment non-response (aOR 4.36, 95% CI 1.94–9.82; $p<0.001$). Within the histopathological subgroup, endometrial hyperplasia without atypia was also independently associated with non-response (aOR 3.18, 95% CI 1.13–8.95; $p=0.029$) (Table 4).

Table 4. Multivariable Predictors of Anemia Severity and Treatment Non-response

Predictor	Adjusted OR	95% CI	p -value
Increasing anemia severity			
PBAC, per 50-point increase	1.47	1.22–1.77	<0.001
Ferritin, per 5-ng/mL decrease	1.68	1.28–2.20	<0.001
CRP >5 mg/L	2.21	1.08–4.52	0.030
HOMA-IR ≥ 2.5	1.96	1.03–3.73	0.041
Resting heart rate, per 10-beats/min increase	1.58	1.18–2.12	0.002
Treatment non-response			
Ferritin <10 ng/mL	2.41	1.12–5.21	0.025
CRP >5 mg/L	2.53	1.12–5.71	0.026
HOMA-IR ≥ 2.5	2.07	1.01–4.24	0.047
PBAC ≥ 150 at 12 weeks	4.36	1.94–9.82	<0.001
Endometrial hyperplasia without atypia	3.18	1.13–8.95	0.029

The adjusted odds ratios describe the independent association of each predictor after controlling for the other variables entered into the respective multivariable models. Persistent menstrual blood loss demonstrated the strongest association with treatment non-response.

Predictive Performance

The combined predictive model incorporating PBAC score, ferritin, CRP, HOMA-IR, and resting heart rate demonstrated strong discrimination for severe anemia, with an area under the

receiver-operating-characteristic curve (AUC) of 0.90 (95% CI 0.84–0.96).

The model for treatment non-response, incorporating baseline ferritin, CRP, HOMA-IR, persistent PBAC elevation, and histopathological findings, demonstrated an AUC of 0.84 (95% CI 0.77–0.91). These findings indicated good predictive performance for both clinical outcomes and supported the combined assessment of biochemical, metabolic, cardiovascular, menstrual, and histopathological parameters (Table 5).

Table 5. Predictive Performance of the Multivariable Models

Outcome predicted	Variables incorporated in model	AUC	95% CI
Severe anemia	PBAC score, ferritin, CRP, HOMA-IR, resting heart rate	0.90	0.84–0.96
Treatment non-response	Ferritin, CRP, HOMA-IR, persistent PBAC score, histopathological findings	0.84	0.77–0.91

The severe-anemia model demonstrated the stronger discriminatory performance with an AUC of 0.90, whereas the treatment non-response model retained good discrimination with an AUC of 0.84. The overall results indicated that the integration of menstrual blood loss, iron status, inflammatory activity, metabolic dysfunction, cardiovascular compensation and selected histopathological findings gave clinically useful risk stratification.

DISCUSSION

In this prospective cohort, the severity of anemia in women with high menstrual loss was correlated not only with the amount of menstrual blood loss, but also with iron depletion, systemic inflammation, metabolic dysfunction, cardiovascular compensation, and with selected endometrial abnormalities¹. Moderate anaemia was the most common category; about one in five participants had severe anaemia. PBAC score, ferritin, CRP, HOMA-IR, and resting heart rate remained independent factors associated with the severity of anemia².

The gradual reduction in ferritin and transferrin saturation with progressive anemia suggests that chronic blood loss from menstruation is a significant mechanism for iron depletion³. Iron-deficiency anemia is a known risk of HMB, and current evidence suggests that monitoring of iron stores, rather than hemoglobin, is important because significant iron deficiency can occur before or alongside anemia. Our study also showed that high levels of PBAC over a prolonged period correlate with treatment non-response, suggesting that iron alone is likely to be inadequate in the presence of significant uterine blood loss⁴.

Both CRP and HOMA-IR were independently related to disease severity and hematological recovery⁵. This indicates a possible role for inflammatory and metabolic mechanisms in chronic abnormal uterine bleeding. Recent data have shown that hyperinsulinemia is linked to the presence of obesity-related factors and to abnormal uterine bleeding; obesity, as well as chronic anovulation, is known to be associated with endometrial hyperplasia. These results favor taking into account the metabolic condition in the evaluation of women with HMB recurrence or treatment resistance^{6,7}.

There was also an association between cardiovascular changes and the degree of anemia. These women had higher shock index and resting tachycardia, which were reduced

after treatment, indicating severe anemia⁸. These findings are physiologically explained by the heart rate and cardiac output increases that occur as a result of the reduced oxygen-carrying capacity in anemia. The benefit on cardiovascular parameters, hemoglobin and iron indices indicates that simple hemodynamic measurements could be valuable additional data in clinical assessment^{9,10}.

The histopathological results also showed that severe anemia was more common in women with endometrial hyperplasia without atypia. Endometrial sampling was only carried out if clinically indicated, however, so this association should be viewed as a sub-group finding and not extrapolated to women with HMB¹¹. There is a known association between obesity, insulin resistance and chronic anovulation, and these are recognized contributors to endometrial proliferative abnormalities, which may partially account for the observed association¹².

The hematological response rate was 70.8% at 12 weeks. The most significant factors associated with non-response were persistent menstrual blood loss, inflammation, severe iron depletion, insulin resistance and endometrial hyperplasia¹³⁻¹⁵. Combined models showed good discrimination for severe anemia (AUC 0.90) and treatment non-response (AUC 0.84) and suggested a multidimensional approach to risk assessment beyond hemoglobin^{16,17}.

The main advantages of the study were its prospective design and simultaneous evaluation of biochemical, metabolic, cardiovascular, menstrual and histopathological factors. The study had a number of limitations including relatively small study size, selective sampling for endometrial biopsy, and 12-week follow-up period. External validation of the predictive models is needed in larger multicenter studies with longer follow-up¹⁸⁻²⁰.

CONCLUSION

Systemic inflammation, insulin resistance, cardiovascular compensation and endometrial pathology were independently associated with anemia severity and treatment response in women with HMB, whereas menstrual blood loss and iron depletion were not. Persistent HMB was the greatest predictor of suboptimal hematological recovery. The use of PBAC score, ferritin, CRP, metabolic indices, cardiovascular parameters and clinically indicated histopathology was suggested to help identify women at risk of severe anemia, of poor

treatment response, and also to individualize management.

Funding: No funding information was reported in the manuscript.

Conflict of Interest: No conflict-of-interest statement was provided in the manuscript; this should be confirmed by all authors before submission.

Author Contributions: FKC: Conceptualization, methodology, supervision, and manuscript preparation. LA: Clinical assessment, data acquisition, and manuscript review. TH: Biochemical assessment, data analysis, and interpretation. WA: Cardiovascular assessment and interpretation. HNK: Histopathological assessment and interpretation. A.S: Data analysis and manuscript review. All authors reviewed and approved the final manuscript.

Acknowledgments: The authors acknowledge the staff of Gujranwala Medical College and Lahore General Hospital for their assistance with study conduct and data collection.

REFERENCES

- Graham FJ, Masini G, Lakhal-Littleton S, Clark AL, Cleland JGF, Pellicori P. Iron deficiency in cardiovascular disease: diagnosis, clinical implications, and future directions. *Circ J*. 2026;90(5):466-479. doi:10.1253/circj.CJ-25-0220.
- Drejza M, Nicholson LS, Paquette G, Chawla M, Vale CL, Rogozińska E, et al. The impact of heavy menstrual bleeding on quality of life: a mixed-methods survey study. *BJOG*. 2026 Jun 21. doi:10.1111/1471-0528.70290.
- Ordeanu IM, Busuioc CJ, Văduva CC, Pană RC, Petrescu AM, Văruț RM, et al. Obesity as a catalyst for endometrial hyperplasia and cancer progression: a narrative review of epidemiology, molecular pathways, and prevention. *Biomedicines*. 2025;13(11):2612. doi:10.3390/biomedicines13112612.
- Boureka E, Tsakiridis I, Kapetanios G, Michos G, Giouleka S, Liberis A, et al. Management of endometrial hyperplasia: a comparative review of guidelines. *Cancers (Basel)*. 2025;17(19):3143. doi:10.3390/cancers17193143.
- Iolascon A, Andolfo I, Russo R, Sanchez M, Busti F, Swinkels D, et al. Recommendations for diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia. *HemaSphere*. 2024;8(7):e108. doi:10.1002/hem3.108.
- Fernandez Sanchez J, Sánchez LM, Kappa SS, Karsenty CL, O'Keefe M, Shekar M, et al. Standardizing the evaluation and management of iron deficiency anemia secondary to heavy menstrual bleeding in the emergency department. *Pediatr Blood Cancer*. 2024;71(10):e31222. doi:10.1002/pbc.31222.
- Chaturvedi J, Rupendra K, Bahadur A, Heda A, Mundhra R. Comparative analysis of ferric carboxymaltose and iron sucrose in treating iron deficiency anemia in perimenopausal women with heavy menstrual bleeding: a randomized controlled trial. *Obstet Gynecol Sci*. 2024;67(6):565-573. doi:10.5468/ogs.24065.
- Veeranaraphanit U, Saeai N, Srisintorn W. Predicting endometrial hyperplasia and endometrial cancer on recurrent abnormal uterine bleeding. *Obstet Gynecol*. 2024;144(2):259-265. doi:10.1097/AOG.0000000000005641.
- Jain V, Munro MG, Critchley HOD. Contemporary evaluation of women and girls with abnormal uterine bleeding: FIGO Systems 1 and 2. *Int J Gynaecol Obstet*. 2023;162 Suppl 2:29-42. doi:10.1002/ijgo.14946.
- MacGregor B, Munro MG, Lumsden MA. Therapeutic options for the management of abnormal uterine bleeding. *Int J Gynaecol Obstet*. 2023;162 Suppl 2:43-57. doi:10.1002/ijgo.14947.
- Munro MG. Heavy menstrual bleeding, iron deficiency, and iron deficiency anemia: framing the issue. *Int J Gynaecol Obstet*. 2023;162 Suppl 2:7-13. doi:10.1002/ijgo.14943.
- Munro MG, Mast AE, Powers JM, Kouides PA, O'Brien SH, Richards T, et al. The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia. *Am J Obstet Gynecol*. 2023;229(1):1-9. doi:10.1016/j.ajog.2023.01.017.
- MacLean B, Sholzberg M, Weyand AC, Lim J, Tang G, Richards T. Identification of women and girls with iron deficiency in the reproductive years. *Int J Gynaecol Obstet*. 2023;162 Suppl 2:58-67. doi:10.1002/ijgo.14948.
- Auerbach M. Optimizing diagnosis and treatment of iron deficiency and iron deficiency anemia in women and girls of reproductive age: clinical opinion. *Int J*

- Gynaecol Obstet. 2023;162 Suppl 2:68-77.
doi:10.1002/ijgo.14949.
15. Leung TW, Damodaran P, Torres R, Chuncharunee S, Chu MY, Gamilla Z, et al. Expert consensus on improving iron deficiency anemia management in obstetrics and gynecology in Asia. *Int J Gynaecol Obstet.* 2023;163(2):495-509. doi:10.1002/ijgo.14804.
 16. Creinin MD, Barnhart KT, Gawron LM, Eisenberg D, Mabey RG Jr, Jensen JT. Heavy menstrual bleeding treatment with a levonorgestrel 52-mg intrauterine device. *Obstet Gynecol.* 2023;141(5):971-978. doi:10.1097/AOG.0000000000005137.
 17. Matteson KA, Valcin J, Raker CA, Clark MA. A randomized trial comparing the 52-mg levonorgestrel system with combination oral contraceptives for treatment of heavy menstrual bleeding. *Am J Obstet Gynecol.* 2023;229(5):532.e1-532.e13. doi:10.1016/j.ajog.2023.07.049.
 18. Cappellini MD, Santini V, Braxs C, Shander A. Iron metabolism and iron deficiency anemia in women. *Fertil Steril.* 2022;118(4):607-614. doi:10.1016/j.fertnstert.2022.08.014.
 19. Mansour D, Hofmann A, Gemzell-Danielsson K. A review of clinical guidelines on the management of iron deficiency and iron-deficiency anemia in women with heavy menstrual bleeding. *Adv Ther.* 2021;38(1):201-225. doi:10.1007/s12325-020-01564-y.
 20. Magnay JL, O'Brien S, Gerlinger C, Seitz C. Pictorial methods to assess heavy menstrual bleeding in research and clinical practice: a systematic literature review. *BMC Womens Health.* 2020;20(1):24. doi:10.1186/s12905-020-0887-y.