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MISSING CASES OF HEAVY MENSTRUAL BLEEDING WHEN INVESTIGATING THE ETIOLOGY OF IRON DEFICIENCY

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Abstract

Due to incorrect answers to simple questions like "Do you have heavy menstrual bleeding?", heavy menstrual bleeding, the most prevalent cause of iron deficiency in women, is underdiagnosed. In this retrospective and cross-sectional study, menstruating female patients who applied to the iron deficiency outpatient clinic between April and September 2021 were analyzed. Scores on the picture bleeding assessment chart (PBAC) and complaints of heavy menstrual bleeding were recorded. The chi-square test and confusion matrix were conducted. There were 157 patients in the sample. There were 82 patients who said they did not have heavy menstrual bleeding, while 75 patients said they did ($\chi^2(1) = 19.7$, $p < 0.001$). Sixty percent of patients who did not report significant bleeding had a PBAC score greater than 100, with a median score of 184. The Chi-square test revealed a significant difference between complaints of heavy menstrual bleeding (yes/no) and PBAC (normal/high). The negative predictive value was calculated to be 40.2, while the false miss rate was 59.8%. Six out of ten patients who are investigated for iron deficiency and whose primary cause is heavy menstrual bleeding may be overlooked by this query. In such etiologic investigations, much more objective methodologies, such as PBAC, should be applied.

Key words: anemia, approach, etiology, heavy menstrual bleeding, iron deficiency, pictorial bleeding assessment chart

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Introduction. Iron deficiency (ID) is the most prevalent micronutrient deficit in the world [1]. Although the exact global prevalence of ID is unknown, it is estimated to be at least twice that of iron deficiency anemia (IDA), which is believed to affect approximately 1.2 billion people [2].

Parasitic infections appear to be the most prevalent cause of ID in developing and/or low-income countries, whereas menstrual and gastrointestinal blood losses are the most prevalent causes in industrialized nations [3]. The leading cause of ID in women from affluent nations is monthly losses that exceed physiological limitations and are also known as "heavy menstrual bleeding (HMB)" [4].

ID and its subsequent iron deficiency anemia (IDA) are currently underdiagnosed and undertreated among women of childbearing age, despite the high prevalence of HMB in around 30% of all women and its impact on quality of life [5].

Added to all of this, a very essential feature is that women's knowledge of the severity of HMB may be poor. In diagnosing HMB, patients represent one side of the coin, while the low awareness of HMB among health care providers represents the other [6]. Furthermore, if HMB is stated by a patient, healthcare providers may view it as "a typical aspect of being a woman" [7].

Typically, patients are admitted or referred to specialized medical fields such as internal medicine, family medicine, hematology, gastroenterology or obstetrics and gynecology to investigate the underlying etiology of iron deficiency (ID) or iron deficiency anemia (IDA). In practice, the presence of HMB is frequently detected by merely asking the patient if she is bleeding heavily. However, when a physician takes a patient's medical history, the patient's "no" response to the query "Do you have heavy menstrual bleeding?" for any reason and/or unawareness will likely result in the incorrect exclusion of the most common cause of ID/IDA in menstruating women.

The most precise procedure would be to collect and measure all pads and tampons used during menstruation, but this is impractical and laborious. Instead, numerous pictorial blood loss assessment charts (PBAC) have been developed, which can be used to estimate the quantity of blood loss by asking patients to identify images [8]. Other than Obstetrics and Gynecology, PBAC is not widely known. Awareness and application of the PBAC approach by all specialties coping with iron deficiency has the potential to eliminate unnecessary requests for consultation.

The purpose of this study is to demonstrate the importance and necessity of using PBAC rather than merely asking "Do you have heavy menstrual bleeding?" when investigating the etiology of ID/IDA in female patients presenting to clinics. In this research, it will be essential to identify potential cases of heavy menstrual bleeding (HMB) in individuals with iron deficiency (ID) who do not report experiencing HMB symptoms.

Materials and method. ***Institutional review board statement.*** The study was conducted in accordance with the Declaration of Helsinki, and approved

by the Ethics Committee of Ordu University (protocol code: 2023/30 and date of approval 01.20.2023).

Sample and patient selection. The research methodology was determined as a retrospective cross-sectional design. The sample for this research was composed of patients who applied to the Iron Deficiency Outpatient Clinic (IDOC) under the Department of Internal Medicine of Ordu University Training and Research Hospital, Ministry of Health, between April and September 2021. As part of the standard protocol at this clinic, female patients who are menstruating are routinely queried about the presence of heavy menstrual bleeding during their medical history intake. Subsequently, the PBAC scores of this population are calculated, regardless of whether or not HMB was reported.

The dataset comprised of female patients who were 18 years or older and had applied to the IDOC within the specified time frame. Patients who did not provide a binary response to the inquiry regarding the presence of heavy menstrual bleeding, those who were not evaluated using PBAC, and those who had undergone menopause were deemed as exclusionary criteria. Furthermore, individuals who fulfilled the pertinent criteria but exhibited a widespread absence of data were also eliminated from the dataset.

Data type and the final data set. Microsoft Excel was used to record the demographic data, medical history, pictorial bleeding assessment chart (PBAC) and hemogram, biochemical results of c-reactive protein (CRP), ferritin (FERR), iron, and iron binding capacity from the physical and digital patient files.

The IDOC uses the chart proposed by Hald and Lieng as PBAC [9]. This chart classifies the amount of menstrual period blood absorbed by pads and/or tampons into three distinct categories. The number of pads or tampons with evidence of light bleeding is multiplied by 1 (one), those with signs of moderate bleeding by 5 (five), and those with signs of hemorrhage filling the entire pad or tampon by 20 (twenty). After multiplying the bleeding findings by their respective coefficients, the resulting scores are added together to determine the PBAC score.

Ferritin readings exceeding 100 µg/L, TSAT values exceeding 45%, and high CRP values were eliminated from the data set. Those with elevated CRP but low ferritin levels were maintained in the data set. Once more, observations with missing parameters, particularly RDW-CV, FERR and TSAT values, were eliminated from the data set.

During the relevant time period, a total of 218 patients attempted the IDOC. After the design was formed in accordance with the study criteria, this number was finalized as 157.

Statistical analyses. The data were transferred from Microsoft Excel to the R programming language [10] and to the Jamovi application for statistical analysis [11].

A set of eight distinct variables was collected for a cohort of 157 patients. Age, hemoglobin (HGB), mean corpuscular volume (MCV), red blood cell distribution

width (RDW), transferrin saturation (TSAT), ferritin (FERR), PBAC and HMB status were the variables.

HMB status was a categorical "yes/no" variable, whereas other variables contained continuous data. A new categorical variable (PBAC-Class) was added to the dataset by classifying PBAC data as "normal" if less than or equal to 100 points and "high" if over 100 points.

According to the occurrence of HMB, independent variables were separated into two groups and compared. The chi-square test was used to analyze categorical variables. The confusion matrix ratios were then determined by comparing the presence of HMB to the PBAC score.

In conjunction with the confusionMatrix function of the R caret package, the following analyses are performed: Accuracy (Acc); Mcnemar's Test; sensitivity; specificity; positive predictive value; negative predictive value. Although the McNemar's test is a statistical test frequently applied to paired nominal data, it has also been suggested for comparing classification accuracies in overall [12]. This test is calculated alongside the aforementioned tests using the confussionMatrix function of the R caret package.

In addition to the confusion matrix rates stated previously, the false omission rate (FOR) will also be determined. FOR is the proportion of false negatives to all negatives (false negatives and true negatives). Alternatively, FOR is merely the difference between 1 and the negative predictive value (NPV). The NPV measures the accuracy with which negatives are predicted, whereas the FOR indicates how frequently the prediction of negatives is incorrect and, consequently, how frequently the test is inaccurately deemed negative. In this study, FOR will be used to ascertain how frequently patients who reported no HMB were incorrect when investigating the cause of ID/IDA.

Results. In Table 1, descriptive statistics are summarized. As emphasized in the patient selection section, typical results were obtained as a consequence of using data from iron-deficient patients. Except for age, no significant difference was

T a b l e 1

Descriptive statistics of continuous data

Variables	n	Mdn	Min	Max
AGE (years)	157	40	20	57
HGB (g/dL)	157	11.40	5.500	14.3
MCV (fL)	157	80.08	59.137	93.9
TSAT (%)	157	8.64	2.226	41.9
FERR (mcg/L)	157	8.56	0.570	96.9
PBAC (score)	157	174	3	819

Abbreviations: HGB – hemoglobin; MCV – mean corpuscular volume; TSAT – transferrin saturation; FERR – ferritin; PBAC – pictorial bleeding assessment chart; n – number of patients; Mdn – median; Min – minimum; Max – maximum

Table 2

Statistics characterizing the PBAC normal (≤ 100) and high (> 100) categories for 82 patients who reported no HMB

	n	Mdn	Min	Max
Normal PBAC	33	59	6	98
High PBAC	49	184	104	394

Abbreviations: PBAC – pictorial bleeding assessment chart; HMB – heavy menstrual bleeding; n – number of patients; Mdn – median; Min – minimum; Max – maximum

observed between those with and without HMB complaints regarding continuous variables.

Out of 157 patients, 75 (48%) responded yes to the HMB complaint, compared to 82 (52%) who responded adversely. There were 117 patients (75%) with a high PBAC score (> 100) and 40 patients (25%) with a normal PBAC score (≤ 100).

The data of patients who stated they did not have HMB were analyzed more thoroughly (Table 2). Consequently, the number of patients with a PBAC score above 100 among those who reported not having HMB was determined to be 49 (60%). Again, the median PBAC score for patients with PBAC > 100 in the related subgroup was 184.

Moreover, the mean values of fundamental biochemical parameters for ID/IDA, namely hemoglobin (HGB), mean corpuscular volume (MCV), transferrin saturation (TSAT), and ferritin, were determined for a sample of 49 patients who showed high levels of PBAC but did not report HMB. The mean values for HGB, MCV, TSAT, and ferritin were found to be 11.4 ± 1.76 g/dL, 79.5 ± 7.8 fL, $11.2 \pm 7.25\%$, and 13.0 ± 15.32 mcg/L, respectively.

Two categorical variables, the existence of HMB (yes/no) and the PBAC-Class (normal/high), were matched using the chi-square test, and a contingency table was generated (Table 3). The chi-square test revealed a statistically significant difference between the groups (χ^2 value 19.7, df $= 1$, $p < 0.001$).

Once more, the "confusionMatrix" function of the caret package in R was used to calculate the confusion matrix ratios between two categorical data. According to these findings, the accuracy was 64.3%, the sensitivity was 58.1%, the specificity was 82.5%, and the negative predictive value was 40.2% (Mcnemar's test $p < 0.001$). In addition to this function, manual calculations revealed that the false negative rate was 41.8% and the negative likelihood ratio was 50.6%. It is noteworthy that the majority of the 82 patients who reported no HMB had a high PBAC score ($n = 49$, false omission rate $= 59.8\%$) (Fig. 1).

Discussion. In this study, an investigation was undertaken to determine whether it would be more accurate to evaluate patients applying for the diagnosis and treatment of iron deficiency with PBAC in order to conclude that HMB does

Table 3

The contingency table is based on two categorical variables: the presence of HMB complaints and a normal or high PBAC score

	PBAC		
HMB Complaint	Normal	High	Total
No	33	49	82
% within row	40.2	59.8	100
% within column	82.5	41.9	52.2
% of total	21.0	31.2	52.2
Yes	7	68	75
% within row	9.3	90.7	100
% within column	17.5	58.1	47.8
% of total	4.5	43.3	47.8
Total	40	117	157
% within row	25.5	74.5	100.0
% within column	100	100.0	100.0
% of total	25.5	74.5	100.0

Abbreviations: HMB – heavy menstrual bleeding; PBAC – pictorial bleeding assessment chart

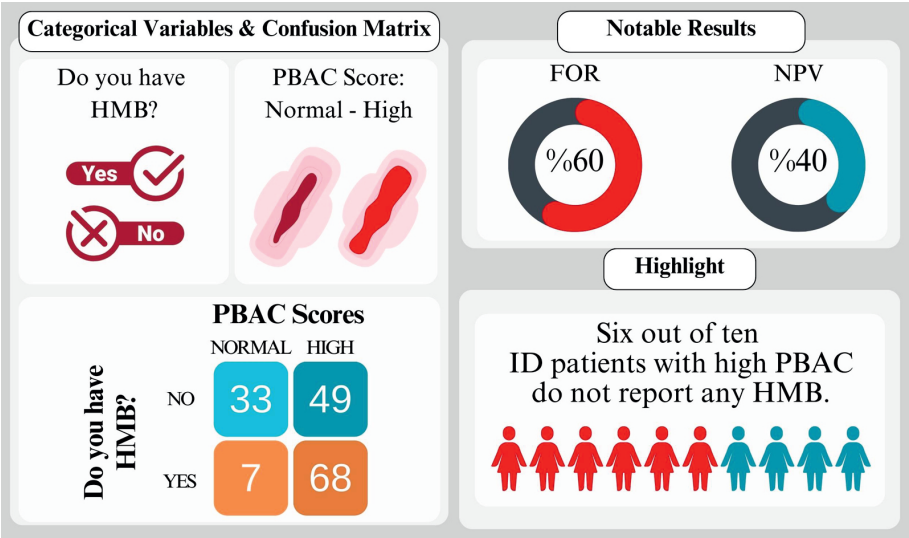


Fig. 1. A graphical representation of the confusion matrix results comparing the predictive value of the question "Do you have heavy menstrual bleeding?" to the PBAC score when investigating the presence of HMB in patients with ID. Abbreviations: HMB – heavy menstrual bleeding; PBAC – pictorial bleeding assessment chart; FOR – false omission rate; NPV – negative predictive value

not exist. The validity of the patient's "yes/no" responses to the question "Do you experience heavy menstrual bleeding?" has been investigated.

Undoubtedly, the most notable outcome observed in the contingency table and confusion matrix rates pertained to the false omission rate (FOR). The dis-

covery of a nearly 60% incidence rate holds significant implications for medical practitioners, particularly those specializing in the pertinent field tasked with exploring the etiology of ID/IDA. A false omission rate of 59.8% indicates that HMB, which is presumed to be absent by the patient, is actually the underlying cause of 6 out of 10 ID/IDA patients.

When screening an illness, predictive values are more relevant than sensitivity and specificity [13]. Therefore, the researcher or the clinician should not be misled by the great specificity of the HMB statement. In this investigation, it was determined that the negative predictive value, which also verifies this research hypothesis, was exceptionally low (40.2%). Therefore, the presence of HMB should be determined by the PBAC evaluation and not by the present/absent declarations of the patient.

The literature contains important findings concerning the consciousness of HMB or, additionally, the presence of opinions pertaining to the inability to alleviate HMB. For example, 48% of participants in a survey of more than 6000 individuals stated that they did not "never" or "very well" know about HMB, while only 39% of those affected believe there is no treatment available [14].

Even more, the difficulty in diagnosing HMB is not only due to women's lack of awareness. Although patients are aware of their HMB, "taboos" and/or societal reasons may force them to conceal it [15].

A cohort of 94 adolescent patients, with a mean age of was examined in a study [16]. Out of the total participants, 34 were diagnosed with HMB using PBAC criteria. In contrast, 11 of the patients who were diagnosed with HMB did not report experiencing menorrhagia. The study in question did not disclose the rate of false omissions; however, it can be calculated that the rate is 15.9% based on the presented data. The rate observed in our study is approximately four times lower than the aforementioned result. The dissimilarity observed in this discovery could potentially be attributed to the variance in age between the two studies.

The literature lacks inclusion of findings pertaining to false omission rates in studies. Nonetheless, despite the fact that negative predictive value findings are uncommon, some studies have been published. Calculating FOR is simple with 1-NPV. The FOR findings of PBAC, calculated over NPV, have been discovered at varying frequencies in various studies. The prevalence of the phenomenon under investigation was reported as 13.8% in one study [17], 15.1% in another [18], and 40% in a third study [19]. Lastly, there is no doubt that invasive procedures such as hysteroscopy will have a significantly low false omission rate of 6% with regard to not missing the underlying cause of HMB [20].

The study has a number of limitations. First, the PBAC scores of the patients were gathered retrospectively and calculated according to the patients' general menstrual habits. A prospective study examining the number of tampons used during menstrual periods spanning three to six months will yield superior results. As discussed in the preceding section, another limitation is that the patient's

perception of normal/high menstrual bleeding may result in incorrect responses to questions. At last, the size of the sample remained comparatively limited.

Conclusion. HMB plays an important role in the diagnosis and treatment of ID/IDA. Other causes of ID/IDA in female patients should not be investigated without first ruling out HMB. Patients and healthcare providers may ignore HMB due to their lack of awareness. Due to the diagnostic challenges and/or barriers associated with HMB, evaluating the amount of bleeding with PBAC is an important technique to make subjective data – albeit semi-quantitative – objective and/or to identify true HMB cases underlying suspect complaints. Thus, HMB that patients do not or cannot reveal will be discovered, and ID/IDA will be accurately diagnosed, treated, and followed up.

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