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Coexistence of multiple causes in patients with iron deficiency

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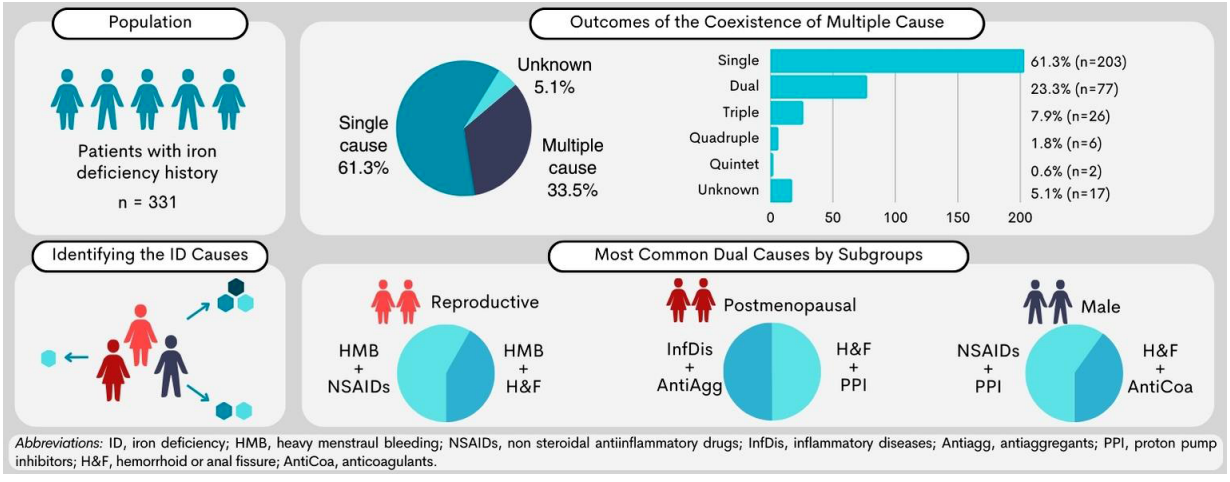
Abstract. – OBJECTIVE: The etiology of disorders may be attributable to multiple causal factors simultaneously. This study sought to investigate how frequently, and which causes coexist in patients with iron deficiency.

PATIENTS AND METHODS: All patients who applied to the Iron Deficiency Outpatient Clinic between January and December 2021 were included in this cross-sectional study. The causes of iron deficiency were extracted from patient files. Analyses were conducted on the entire population as well as three subgroups: women of reproductive age, postmenopausal women, and males. Numbers and frequencies of causes of iron deficiency were calculated. The subgroups were compared using the Jamovi software.

RESULTS: The study sample comprised a total of 331 patients. Women of reproductive age were the majority of patients admitted to the clinic (86.7%, n=287). Men represented 6.3% of the sample (n=21), and postmenopausal women accounted for 7.0% (n=23). The mean ages were 37.6±9.05, 49.2±15.49 and 57.8±10.84 years, respectively. The overall sample's rate of multiple iron deficiency causes coexisting was 33.5% (n=111) and the subgroups showed similar frequencies for the coexistence of multiple causes. Statistically, the number of simultaneous multiple causes varied between subgroups (χ^2=118, df=10, p<0.001). Heavy menstrual bleeding and nonsteroidal anti-inflammatory drug use were the most common dual causes of multiple coexisting conditions (n=46, 41.4%). In terms of the number of causes, the coexistence of two causes of iron deficiency in women was notable, whereas the coexistence of three causes in males was remarkable. Furthermore, it has been found that some patients have up to five coexisting causes of iron deficiency.

CONCLUSIONS: Some iron deficiency causes may coexist, and this must be taken into account for the effective management of iron deficiency.

Key Words:
Anemia, Coexistence, Etiology, Iron deficiency, Multiple causes.



Graphical Abstract. Between January and December 2021, the Iron Deficiency Outpatient Clinic identified the causes of 331 iron deficiency patients. Patients' coexisting causes of iron deficiency and rates were examined. The whole sample had 33.5% (n=111) coexistence of multiple iron deficiency causes, and subgroups (reproductive age women, postmenopausal women, men) had similar frequencies. Different subgroups had different numbers of concurrent causes ($p < 0.001$). There are up to five different causes that can concurrently contribute to iron deficiency. Reasons underlying multiple iron deficiency causes varied between subgroups.

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Introduction

Iron deficiency (ID) is the most prevalent micronutrient deficiency worldwide[1], and the anemia it induces is the most prevalent type of anemia worldwide[2]. Iron deficiency anemia (IDA) is just one of the effects of iron deficiency (ID). Therefore, it is estimated that ID is more prevalent than IDA.

To diagnose iron deficiency, serum ferritin levels below 30 mcg/dL are needed[3]. Ferritin levels must be below 100 mcg/L for chronic inflammatory conditions. If ferritin is between 100 and 300 mcg/dL in chronic inflammatory disorders, transferrin saturation is evaluated, and iron deficiency is considered if it is below 20%[4]. When this micronutrient deficiency is combined with low hemoglobin[5] (<13 g/dL in men, <12 g/dL in women, and <11 g/dL in pregnant women), it is known as iron deficiency anemia.

ID may result from a variety of physiopathologic causes. In general, the etiology of ID can be categorized as blood loss, malabsorption, increased need, inadequate intake, and chronic diseases. Under these main categories, it is seen that various factors contributing to genitourinary and gastrointestinal bleeding primarily result in iron deficiency[6].

Typically, the etiology of disorders or diseases can be attributed to one or more causative factors. This phenomenon can arise either as a singular outcome of multifactorial events[7] or as a consequence of polypathology or the coexistence of several etiologies[8]. The concurrent coexistence of various causes is also a possible concern for patients with iron deficiency[9], and it has been documented[10] that this situation is commonly observed.

The coexistence of numerous causes in ID patients is not well-documented in the literature. Nonetheless, it is evident that the presence of multiple causes will have a direct impact on the management, treatment, and follow-up of ID[11].

Hence, the primary objective of this research endeavor was to investigate the occurrence of several causative factors among patients seeking medical care at the clinic and receiving a diagnosis of iron deficiency (ID), with the intention of ascertaining the relative prevalence of these factors.

Patients and Methods

Study Design and Patient Selection

The sample of this retrospective cross-sectional study was comprised of all patients who applied to the Iron Deficiency Outpatient Clinic of Ordu University Training and Research Hospital between January 2021 and December 2021 for a total of one year. The Iron Deficiency Outpatient Clinic at our hospital primarily admits patients who have been diagnosed with ID; consequently, the vast majority of patients who present to the outpatient clinic either have ID in their medical history or are currently suffering from it.

Patients referred to and admitted in our outpatient clinic had ferritin levels below 30 mcg/L either at the time of admission or in their recent medical history. If there is a background of chronic disease, the levels should be <100 mcg/L or between 100-300 mcg/L and transferrin saturation should be below 20%. Aside from that, the patients cannot be accepted to the outpatient clinic for iron deficiency.

Identifying and Noting the Etiologic Causes of Iron Deficiency

Patients over 18 years old were included, while pregnant patients and those with incomplete data were excluded from the study.

The study documented the causes of iron deficiency, the initial symptoms reported by patients, their documented medical history, prescriptions, bleeding scores calculated for menstrual women, and diagnoses established from basic testing. Advanced investigation outcomes, such as endoscopic approaches and imaging techniques, were not included.

In addition, patients with elevated ferritin and transferrin saturation or a lack of these variables were not excluded from the dataset in order to prevent an inordinate loss of data. In patients presenting with a history of iron deficiency, these elevated values are frequently attributable to inflammatory events, a recent history of iron replacement, satiety at the time of the biochemistry examination, and/or the use of oral iron preparations prior to the relevant tests. Cases containing these anomalies were kept in the dataset because they do not impact the primary topic of this article, which is the etiology of multiple ID. As stated previously, all patients with a history of ID are referred to this clinic.

Data Type

Microsoft Excel was used for collecting demographic data, medical history from physical and digital patient files. The data set also included bleeding assessment chart (PBAC) scores com-

puted specifically for menstruating women. In the outpatient clinic, the method proposed by Hald and Lieng[12] is used among bleeding scoring charts. Patients with a score of 100 or higher were categorized as having heavy menstrual bleeding (HMB).

Statistical Analysis

The collected data were initially analyzed on the entire sample in accordance with the study's objectives. Then, assessments were conducted in three subgroups. The subgroups were categorized in the following format: group 1 consisted of women of reproductive age, group 2 included postmenopausal women, and group 3 comprised men. The data were analyzed with the Jamovi[13] program (version 2.4.8).

As the basis for a statistical analysis, descriptive statistics were calculated first, followed by the proportions of conditions, disorders, and diseases that caused ID. Using the Chi-square test, these rates and the presence of associated causes were compared between the groups. A *p*-value lower than 0.05 was considered statistically significant.

Results

Descriptive Statistics

During the relevant time period, the clinic admitted 342 patients. Three of these patients were excluded from the dataset due to a lack of data, and seven were due to pregnancy. The final set of data included 331 cases. Table I provides descriptive information regarding the numbers and ages of the patient groups. During a one-year period, the majority of patients admitted to the clinic were women of reproductive age (86.7%, n=287). Postmenopausal women were admitted at a rate of 7.0%, while men were admitted at a rate of 6.3%.

Iron Deficiency Causes and Their Frequency

According to the data obtained from patient files, a total of seventeen distinct causes contributing to iron deficiency were observed. Due to the fact that hemorrhoids and anal fissures belong to a group of diseases that can be misinterpreted by patients, these two causes were grouped together. Due to the small number of patients who underwent bariatric or bowel surgery that was observed in the data, these two histories were recorded as a singular cause. As a result, fifteen distinct conditions were considered iron deficiency causes.

When the results for the causes of ID are analyzed, it is discovered that various causes are represented in varying proportions both overall and by group. The quantities and percentages of identified causes of illness are shown in Table II.

Coexistence and Rates of Multiple Causes

Following the determination of the quantity and percentages of the different causes contributing to iron deficiency, an analysis was conducted to assess the frequency of patients experiencing multiple causes of iron deficiency. Table III displays the numbers and percentages of patients afflicted with multiple causes of iron deficiency.

Within the entirety of the sample, it was observed that 111 out of 331 individuals, accounting for 33.5%, exhibited the presence of multiple causes. Consequently, the prevalence for multiple causes was shown to range from 30.4% to 38.1% across all groups. In this context, the groups showed similar frequencies for the coexistence of multiple causes (c^2=0.296, df=2, p=0.862).

Out of the entire patient population, a total of 17 individuals (5.1%) were unable to have the cause of their iron deficiency determined through anamnesis, examination, or simple tests upon their initial admission.

Table I. The table of age distribution by group.

Group number	Groups' names	N	Pct	M	SD
1	Reproductive age women	287	86.7%	37.6	9.05
2	Postmenopausal women	23	7.0%	57.8	10.84
3	Men	21	6.3%	49.2	15.49
	Total	331	100%	39.7	11.2

n, number; Pct, percentage; M, mean; SD, standard deviation.

Table II. The number and frequency of the causes of ID in three patient groups. The numbers and frequencies of ID causes within the relevant patient groups are shown. In the final column, the quantity and frequency of the relevant ID cause among all patients are presented.

Causes	Reproductive age women		Postmenopausal women		Men		Total	
	N	%	N	%	N	%	N	%
Heavy menstrual bleeding	195	63.1	0	0	0	0	195	58.9
Inflammatory diseases	13	4.5	7	30.4	1	4.8	21	6.3
Chronic heart failure	0	0	2	8.7	1	4.8	3	0.9
Inflammatory bowel disease	3	1.0	1	4.3	0	0	4	1.2
Anticoagulant use	3	1.0	2	8.7	2	9.5	7	2.1
Antiaggregant use	3	1.0	2	8.7	4	19.0	9	2.7
NSAIDs	63	22.0	3	13.0	6	28.6	72	21.7
PPI	12	4.2	2	8.7	3	14.3	17	5.1
Frequent blood donation	1	0.3	0	0	2	9.5	3	0.9
Peptic ulcer	8	2.8	0	0	1	4.8	9	2.7
Helicobacter pylori	2	0.7	1	4.3	0	0	3	0.9
Bleeding disorders	4	1.4	0	0	0	0	4	1.2
Hemorrhoid or anal fissure	42	14.6	2	8.7	3	14.3	47	14.2
Bariatric or bowel surgery	2	0.7	0	0	1	4.8	3	0.9
Celiac disease	1	0.3	0	0	0	0	1	0.3

NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Additionally, the number of causes of iron deficiency was determined for each group (Table IV). Consequently, within the entire sample, dual causes exhibited greater prominence in relation to multiple causes, while within the male subgroup, triple causes were more frequently observed. There were significant differences found in the number of cases of multiple causes of disease among different groups (c^2=118, df=10, p<0.001).

The phenomenon of multiple causes coexisting was frequently interpreted as a manifestation of dual causality (n=77, 23.3%). When evaluating the entire sample, the most common dual cause was the presence of HMB and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (n=46, 41.1%). Additionally, cases with multiple iron deficiency causes included not only dual causes, but also triple, quadruple, and quintuple causes.

The rates of coexistence of dual causes in subgroups were also calculated. In Figure 1, the most prevalent dual causes among the groups are shown graphically. In the coexistence of multiple causes of iron deficiency, the presence of HMB, the presence of hemorrhoid or anal fissure (H&F), and the usage of NSAIDs were shown to be the most contributing factors when all causes were included.

Table III. Number and percentage of patients with multiple iron deficiency causes.

Groups		Presence of multipl etiologies		Total
		-	+	
1	Observed	191	96	287
	% within row	66.6%	33.4%	100.0%
2	Observed	16	7	23
	% within row	69.6%	30.4%	100.0%
3	Observed	13	8	21
	% within row	61.9%	38.1%	100.0%
Total	Observed	220	111	331
	% within row	66.5%	33.5%	100.0%

Groups: Group 1, women of reproductive age; Group 2, postmenopausal women; Group 3, men.

Table IV. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

Groups		Number of causes						Total
		0	1	2	3	4	5	
1	Observed	1	190	69	19	6	2	287
	% within row	0.3%	66.2%	24.0%	6.6%	2.1%	0.7%	100.0%
2	Observed	7	9	5	2	0	0	23
	% within row	30.4%	39.1%	21.7%	8.7%	0.0%	0.0%	100.0%
3	Observed	9	4	3	5	0	0	21
	% within row	42.9%	19.0%	14.3%	23.8%	0.0%	0.0%	100.0%
Total	Observed	17	203	77	26	6	2	331
	% within row	5.1%	61.3%	23.3%	7.9%	1.8%	0.6%	100.0%

Groups: Group 1, women of reproductive age; Group 2, postmenopausal women; Group 3, men.

Discussion

Although the coexistence of multiple causes in the etiology of iron deficiency is known clinically and theoretically and mentioned in the scientific literature[14-16], it has not been statistically analyzed. Therefore, the results obtained in this study regarding the coexistence of multiple causes in adult patients with iron deficiency seem to be the first contribution to the literature in this regard. In a singular study[17] conducted in the field of pediatrics, it was shown that the prevalence

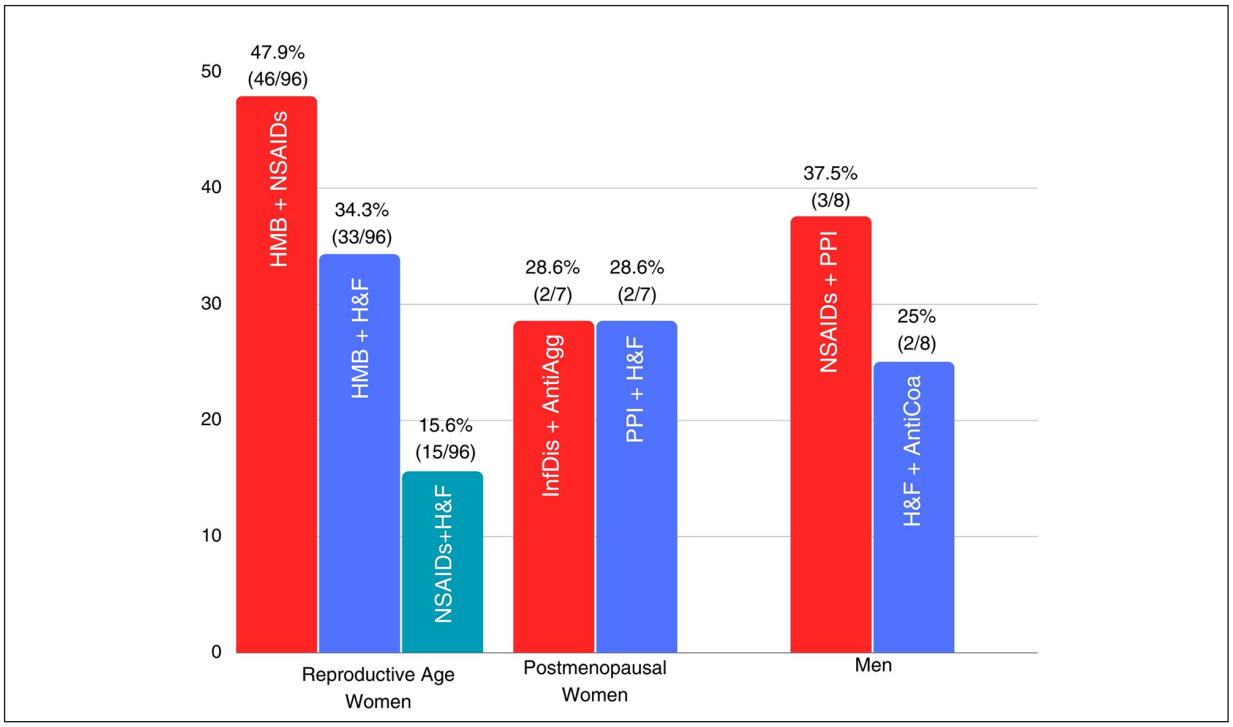

Figure 1. The most prevalent forms within subgroups of dual causes. In the group of women of reproductive age (n=96) with multiple causes, 46 patients (47.9%) had both HMB and NSAIDs use, 33 patients (34.3%) had both HMB and hemorrhoids/fissures, and 15 patients had both HMB and hemorrhoids/fissures. In the group of postmenopausal women with multiple causes (n=7), two patients (28.6%) had inflammatory disease and PPI use, and two patients (28.6%) had PPI use and hemorrhoids/fissure. NSAID and PPI use was present in 3 (37.5%) and anticoagulation and hemorrhoids/fissures in 2 (37.5%) of the 8 men with multiple causes. HMB, heavy menstrual bleeding; PPI, proton-pump inhibitor usage; InfDis, inflammatory diseases; AntiCoa, anticoagulant usage; AntiAgg, antiaggregant usage; NSAIDs, non-steroidal anti-inflammatory drugs; H&F, hemorrhoid or anal fissure.

of multiple causes among patients aged 11 to 18 years was found to be 7%. This is considerably lower than the numbers found in our research. Increasing comorbidity with age appears to be related to this[18].

The study yielded novel findings indicating that an important percentage (33.5%) of iron deficiency patients, regardless of age or gender, exhibited multiple etiological causes. In subgroup analyses, the prevalence rates were determined to be 33.4% for women in the reproductive age group, 30.4% for postmenopausal women, and 38.1% for men. In this regard, male patients had the highest prevalence of multiple iron deficiency causes. While the presence of two etiologic causes stood out in terms of the number of iron deficiency causes, the presence of three iron deficiency etiologic causes in this group of male patients drew attention in terms of the number of multiple causes.

Iron loss is a normal phenomenon in reproductive-age women. However, excessive hemorrhaging causes iron deficiency and/or iron deficiency anemia that is more pronounced/severe. This identifies HMB as the most prevalent cause of iron deficiency in this patient population[19]. The findings of this study indicate that HMB was the primary factor contributing to iron deficiency in a majority of cases, particularly among young women who were more prone to experiencing iron deficiency.

In contrast, the use of NSAIDs emerged as the most prevalent cause of iron deficiency other than HMB, when multiple causes were taken into account. In fact, it is estimated that NSAID use accounts for roughly 15% of all IDA cases worldwide[20]. According to reports[21], NSAID use is the most prevalent cause of IDA, particularly in men and postmenopausal women. Except for postmenopausal women, NSAID use was the most prevalent contributor to dual iron deficiency in this study's two subgroups. The high use of NSAIDs in women of reproductive age is related to the prevalence of painful diseases (such as migraine, fibromyalgia, and dysmenorrhea) that are more prevalent in women[22], as well as the fact that women experience pain more than men due to neuroimmune, hormonal, psychological, and sociocultural differences[23]. Studies[24,25] have shown that women use analgesics more frequently than males due to all of these factors. The other noteworthy finding in this context is the simultaneous presence of both HMB and NSAIDs, with one of these substances being suggested as a therapeutic intervention for the other[26].

This study examined the frequency of hemorrhoids and anal fissures as major disorders contributing to the coexistence of multiple causes in postmenopausal women. While this particular etiological factor was strong within specific subgroups, its existence was not apparent when numerous causes were considered. These two anorectal disorders, which exhibit similar symptoms and can be easily mistaken for one another[27], are the primary contributors to lower gastrointestinal hemorrhage[28]. Nevertheless, notwithstanding the high occurrence rate, it has been documented[29] that over half of all individuals with hemorrhoids do not exhibit any symptoms. This might have restricted its role in multiple causes.

Finally, it was observed that the rate of triple cause was particularly high among males. This may be due to the medications used to treat coronary artery disease and cerebrovascular illnesses, which are more prevalent in men and lead to multiple drug use, having a higher iron deficiency potential[30]. Hence, this study found that the coexistence of multiple causes for iron deficiency was caused by not just two different factors but, in some patients, by three, four, or even five distinct causes. Undoubtedly, the fact that iron deficiency can be concurrently caused by multiple causes may result in a new chapter of iron replacement therapy failures[31].

Limitations

The etiology of iron deficiency in this investigation was ascertained through the collection of anamnestic data during the initial patient encounter. Therefore, the conclusive etiological findings derived from additional investigations, such as endoscopic examinations, were not incorporated. On the other hand, dietary habits are a significant aspect to consider when discussing iron deficiency. This etiologic factor was not considered in this analysis. Nevertheless, when focusing solely on the consumption of tea, it becomes evident that this particular beverage could play a substantial role in predicting the etiology of iron deficiency, given its widespread consumption in Turkey[32]. This would classify it as a classic instance of the coexistence of multiple causal entities.

Conclusions

The coexistence of multiple causes in individuals with iron deficiency seems to impact a considerable number of the respective patient

groups. The follow-up and treatment of iron deficiency is a matter of significance and may necessitate a thorough examination of the underlying causes in these individuals. It should be remembered that some iron deficiency causes may be prevalent and coexist in the relevant age and gender categories.

Conflict of Interest
The author declares that he has no conflict of interests.

Funding
This study did not receive any financial support.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ordu University (Approval Date: 15.09.2023, No.: 2023/237).

Informed Consent
Not applicable.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the author on reasonable request.

Authors' Contribution
The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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