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A systematic analysis of the patients with anemia in a university clinic

Duman Tuba-T, Aktas Gulali, M-Atak Burcin, Kocak M-Zahid, Savli Haluk

Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey

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KEYWORDS

Anemia etiology.
iron deficiency anemia.
MCV.
RDW.
Transferrin saturation.

Abstract :

Objectives. In this retrospective study, we aimed to present etiologies of anemia in patients treated in internal medicine clinic.

Methods. Anemia patients' characteristics and laboratory parameters were obtained from patients' files and database of our clinic. Patients were divided into two groups; iron deficiency anemia and mixed or other causes of anemia groups.

Results. Common anemia etiology in iron deficiency anemia group were gastrointestinal loss (42%), menstrual loss (45%), and in mixed or other causes of anemia group were malabsorption (37.3%), nutritional insufficiency (17.6%). Hb level was significantly and positively correlated with RBC, Htc, MCV, serum iron, transferrin saturation and negatively correlated with RDW in iron deficiency anemia group. Hb level was significantly and positively correlated with RBC, Htc, WBC and negatively correlated with RDW in mixed or other causes of anemia group. Neither of ferritin, PLT, vitamin B_{12} and folate levels were correlated with Hb level in study population.

Conclusions. We suggest that transferrin saturation and serum iron are more valuable than serum ferritin level in determination of the iron deficiency anemia. In addition, MCV, RBC and RDW could be useful in differentiating of sole iron deficiency anemia from mixed or other causes of anemias.

PALABRAS CLAVE

Etiología de la anemia.
Anemia por deficiencia de hierro.
MCV.
RDW.

Un análisis sistemático de los pacientes con anemia en una clínica universitaria

Resumen:

Objetivos. En este estudio retrospectivo, el objetivo fue presentar las etiologías de la anemia en pacientes tratados en el servicio de Medicina Interna.

Métodos. Las características de los pacientes con anemia y los parámetros de laboratorio empleados se obtuvieron de los archivos de pacientes y de la base de datos de nuestra clínica.

Corresponding author: draliaktas@yahoo.com (Gulali Aktas).

Saturación de transferrina.

Los pacientes fueron divididos en dos grupos; anemia por deficiencia de hierro y por causas mixtas, y grupos de otras causas de anemia.
Resultados. la etiología común de la anemia en el grupo con anemia por deficiencia de hierro fue la pérdida gastrointestinal (42%), la pérdida menstrual (45%) y en el grupo mixto u otras causas de anemia la malabsorción (37.3%), la insuficiencia nutricional (17.6%). El nivel de Hb se correlacionó de manera significativa y positiva con RBC, Htc, MCV, hierro sérico, saturación de transferrina y se correlacionó negativamente con RDW en el grupo de anemia por deficiencia de hierro. El nivel de Hb se correlacionó de manera significativa y positiva con RBC, Htc, WBC y se correlacionó negativamente con RDW en un grupo mixto u otras causas de anemia. Ninguno de los niveles de ferritina, PLT, vitamina B_{12} y folato se correlacionaron con el nivel de Hb en la población del estudio.
Conclusiones. Sugerimos que la saturación de transferrina y el hierro sérico son más útiles que el nivel de ferritina sérica en la determinación de la anemia por deficiencia de hierro. Además, MCV, RBC y RDW podrían ser útiles para diferenciar la anemia por deficiencia de hierro única de causas mixtas u otras de anemias.

Introduction

Decrease in hemoglobin (Hb), hematocrit (Htc) and erythrocyte concentration below reference values is considered as anemia[1]. One of every four of world's population is diagnosed with anemia in a period of their life[2-5]. Since anemia may cause functional impairment, fall, injuries and reduced quality of life, it is considered as a mendable contributor of all-cause mortality in geriatric population[6,7].

Hemoglobin is assigned in the oxygen supplementation of the body. Reduction in hemoglobin or in red cell mass may lead to anemia. Causes of anemia include; acute and chronic hemorrhage, deprived nutrition, decreased erythrocyte life span, mutations in hemoglobin genes, infection and chronic inflammatory processes that alter iron metabolism. The most common cause of anemia is iron deficiency anemia. Anemia is more frequent in pediatric age, advanced age, women and subjects with chronic conditions.

Anemia is classified as either acute or chronic depending on the duration of onset. Hemorrhage from trauma, vascular rupture, acute gastrointestinal blood loss, genitourinary bleeding, aplastic crisis in hemoglobinopathies and microangiopathic hemolytic anemia are the main causes of acute anemia[8-10]. Increased destruction (i. e. hemolytic anemia) or decreased production (i.e. iron deficiency anemia, megaloblastik anemia) of erythrocytes cause chronic anemia. The most common cause of chronic anemia is iron deficiency[2,9,11]. Iron deficiency develops either with insufficient intake or increased loss of iron. Anemia develops eventually in cases with low oral iron intake along with normal amount of iron loss and in cases with increased iron loss along without increased amount of oral iron intake. While iron deficiency anemia is associated with microcytosis, certain anemia types, such as, vitamin B_{12} deficiency are associated with macrocytic anemia.

History of patients with anemia should include hematemesis, hemoptysis, hematuria, hematochezia, and melena, menstruation in women, recent interventions or surgery, dietary habits and medications that could be related with anemia; such as, acetyl salicylate, non-steroidal anti-inflammatory drugs, phenytoin, sulfa containing drugs, and chemotherapeutics[2,9,11]. Although chronic anemia is not associated with alerting symptoms, hypotension, tachycardia, and tachypnea may be present in acute anemia[12,13]. Main determinants of the manifestation of anemia are severity of the anemia, age of the patient and comorbidities that accompany to anemia[8].

In this retrospective study, we aimed to present etiologies of anemia in patients treated in internal medicine clinic of Abant Izzet Baysal University Hospital, as well as, age, gender distribution, comorbidities, clinical findings, established diagnosis and treatment of the cases with anemia.

Methods

Study Design

In this study, we enrolled the patients with anemia that admitted to our outpatient internal medicine clinic between May 2017 and April 2018. These patients include both the patients whom were referred to our clinic from other clinics for establishing the cause of anemia and the patients incidentally defined as anemic while they were admitted to our clinic for another complaint. Exclusion criteria were age younger than 18 years and pregnant women. Anemic subjects that received any treatment or transfusion for anemia before admission to our clinic were also excluded.

Patients were grouped into two as follows; subjects with iron deficiency anemia and subjects with mixed or with other causes of anemia.

Age, gender, systolic and diastolic blood pressure, drug usage, comorbidities, presence of hepatosplenomegaly, characteristics of menstrual cycles and presence of menopause in women, endoscopic diagnoses (if present), presence of fecal occult blood or hematuria were obtained

from patients' files and database of our clinic. Underlying cause of anemia etiologies were noted.

Result of peripheral blood smear, celiac disease markers were also recorded. White blood cell count (WBC), erythrocyte count (RBC), hemoglobin (Hb), Hematocrit (Htc), mean erythrocyte volume (MCV), erythrocyte distribution width (RDW), platelet count (PLT) in hemogram test results and iron, iron binding capacity, ferritin, transferrin saturation, vitamin B_{12}, folic acid, urea and creatinine levels in serum biochemistry tests results were also obtained and recorded. If present Hb electrophoresis tests were transcripted. The initial test results of hemogram and serum biochemistry at the time of admission before received any treatment were used in the study.

Statistical Analysis

Data was analyzed with SPSS software (SPSS 15.0 for Windows, IBM Co, Chicago, IL, USA). Distribution of variables in study groups were conducted with Kolmogorov- Smirnov test. Variables with normal distribution were compared with independent samples t test and expressed as mean ± standard deviation. Variables without normal distribution were compared with Mann Whitney U test and expressed as median (interquartile range [IQR]). Categorical variables were conducted with chi-square test and expressed as percentage. Pearson correlation analyze test was used to observe correlation among study parameters. A p value lower than 0.05 was considered as statistically significant.

Results

After applying of the exclusion criteria, a total of 151 subjects; 100 patients in iron deficiency anemia group and 51 patients in mixed or other causes of anemia group, were enrolled to the study. In mixed or other causes of anemia group; 6 (11.8%) had anemia of chronic disease, 8 (15.7%) had vitamin B_{12} deficiency anemia, 1 (2%) had folic acid deficiency anemia, 2 (3.9%) had thalassemia, 22 (43.1%) had vitamin B_{12} and iron deficiency anemia, 6 (11.8%) had anemia of chronic disease and iron deficiency, 2 (3.9%) had anemia of chronic disease and vitamin B_{12} deficiency, 4 (7.8%) had other hematologic causes of anemia.

Age of iron deficiency anemia and mixed or other causes of anemia groups were 46.9 ± 19 years and 53 ± 20.2 years, respectively. The age difference between study groups was not statistically significant (p=0.08).

Eighty six of 100 (86%) in iron deficiency anemia group and 41 of 51 (80.4%) in mixed or other causes of anemia group were women. Gender was not statistically different among study groups (p=0.37).

Systolic blood pressure (p=0.66), diastolic blood pressure (p=0.58), WBC (p=0.57), Hb (p=0.81), Htc (p=0.44), PLT (p=0.11), folate (p=0.09), urea (p=0.20) and creatinine (p=0.53) levels in iron deficiency anemia group were similar to those in mixed or other causes of anemia group. While MCV of iron deficiency anemia group was 74 ± 9 fL, MCV of mixed or other causes of anemia group was 82 ± 15 fL. The MCV difference between study groups was statistically significant (p<0.001). RBC of iron deficiency anemia and mixed or other causes of anemia groups were 4.2 (0.61) M/mm^3 and 4.1 (1) M/mm^3, respectively (p=0.02). RDW of iron deficiency anemia and mixed or other causes of anemia groups were 19.6 (4)% and 17 (4.3)%, respectively (p=0.001).

As expected, serum iron (22 (17.5) µg/dL in iron deficiency anemia group vs 40 (43) µg/dL, in mixed or other causes of anemia group, p=0.009), ferritin (5.7 (5.8) µg/L in iron deficiency anemia group vs 14 (88) µg/L, in mixed or other causes of anemia group, p=0.001) and transferrin saturation (5 (4) % in iron deficiency anemia group vs 11 (14) % in mixed or other causes of anemia group, p<0.001) were significantly lower and total iron binding capacity (421 (75)% in iron deficiency anemia group vs 344 (174) % in mixed or other causes of anemia group, p<0.001) was significantly higher in iron deficiency anemia group compared to mixed or other causes of anemia group.

Serum vitamin B_{12} levels of iron deficiency anemia and mixed or other causes of anemia groups were 346 (191) ng/L and 186 (99) ng/L, respectively (p<0.001). Laboratory data of the study population is summarized in table I.

Forty five (45%) patients in iron deficiency anemia and 28 (55%) patients in mixed or other causes of anemia groups have comorbidities, such as, hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, thyroid conditions, malignancy and inflammatory bowel diseases (p=0.25).

In iron deficiency anemia group, 4 (4%) were on antiaggregant, 6 (6%) were on anticoagulant, 3 (3%) were on non-steroidal anti-inflammatory drug, 2 (2%) were on antiaggregant and anticoagulant treatment, while 85 (85%) had no drug usage. In mixed or other causes of anemia group 2 (3.9%) were on antiaggregant, 1 (2%) were on anticoagulant, 1 (2%) were on non-steroidal anti-inflammatory drug, 1 (2%) were on antiaggregant and anticoagulant treatment, while 46 (90.2%) had no drug usage. Rate of drug usage was not significantly different between study groups (p=0.84).

Four (4%) in iron deficiency anemia and 3 (5.9%) in mixed or other causes of anemia group had hepatosplenomegaly (p=0.60).

Fecal occult blood was positive in 14 (14%) in iron deficiency anemia and in 5 (9.8%) in mixed or other causes of anemia group (p=0.46).

Fourteen (14%) in iron deficiency anemia and none in mixed or other causes of anemia group had hematuria (p=0.005).

After establishment of the cause of anemia in our clinic, eighty three (83%) subjects received oral iron supplements, 4 (4%) patients received intravenous iron, 9 (9%) patients received erythrocyte suspension infusion, 2 (2%) patients received oral iron and vitamin B_{12} and 2 (2%) patients received oral iron and folate supplements in iron deficiency anemia group. Seventeen (33%) received oral iron supplements, 1 (2%) received intravenous iron, 5 (9.8%) received erythrocyte suspension infusion, and 6 (11.8%) received vitamin B_{12} supplements, 1 (2%)

Table I
General Characteristics and Laboratory Data of Study Population

	Iron deficiency anemia	Mixed or other causes of anemia	p
Women (n, %)	86 (86)	41 (80.4)	0.37
Men (n, %)	14 (14)	10 (19.6)	0.37
	Mean ±SD		
Age (years)	46.88 (19.25)		0.08
MCV (fL)	73.91 (8.88)		<0.001
PLT (k/mm^3)	286630 (83527.85)		0.11
	Median (interquartile range)		
Systolic blood pressure (mmHg)	120 (20)		0.66
Diastolic blood pressure (mmHg)	70 (20)		0.58
WBC (k/mm^3)	6.320 (2.4)		0.57
RBC (M/mm^3)	4.21 (0.61)		0.02
Hb (g/dL)	10.3 (1.68)		0.81
Htc (%)	32.15 (4.98)		0.44
RDW (%)	19.55 (3.97)		0.001
Serum iron (µg/dL)	22 (17.5)		0.009
Total iron binding capacity (µg/dL)	420.5 (74.75)		<0.001
Ferritin (µg/L)	5.68 (5.75)		0.001
Transferrin saturation (%)	0.0504 (0.04)		<0.001
Vitamin B_{12} (ng/L)	345.5 (190.75)		<0.001
Folate (µg/L)	6.1 (3.75)		0.09
Urea (mg/dL)	24.5 (15.75)		0.20
Creatinine (mg/dL)	0.7 (0.15)		0.53

received folate supplements and 16 (3.4%) received oral iron plus vitamin B_{12} supplements in mixed or other causes of anemia group.

Underlying causes of anemia in iron deficiency anemia group include; gastrointestinal loss in 42 (42%), urinary loss in 2 (2%), menstrual loss in 45 (45%), malabsorption in 3 (3%), nutritional insufficiency in 7 (7%) and nosebleed in 1 (1%). Underlying causes of anemia in mixed or other causes of anemia group include; gastrointestinal loss in 8 (15.7%), menstrual loss in 4 (7.8%), malabsorption in 19 (37.3%), nutritional insufficiency in 9 (17.6%), malignancy in 5 (9.8%) and unidentified in 6 (11.8%).

In correlation analysis, Hb level was significantly and positively correlated with RBC (r=0.42, p<0.001), Htc (r=0.92, p<0.001), MCV (r=0.47, p<0.001), serum iron (r=0.60, p<0.001), transferrin saturation (r=0.54, p<0.001), and negatively correlated with RDW (r=-0.34, p=0.001) in iron deficiency anemia group. Figure 1 shows the correlation between Hb and study parameters in iron deficiency anemia group. On the other hand, Hb level was significantly and positively correlated with RBC (r=0.35, p=0.01), Htc (r=0.90, p<0.001), WBC (r=0.31, p=0.03), and negatively correlated with RDW (r=-0.64, p<0.001) in mixed or other causes of anemia group. Figure 2 shows the correlation between Hb and study parameters in mixed or other causes of anemia group. Neither of ferritin, PLT, vitamin B_{12} and folate levels were correlated with Hb level in study population.

Discussion

Main outcomes of present study are; (1) RDW was negatively correlated with Hb levels in all types of anemia, (2) putting Htc aside, serum iron and transferrin saturation are the most relevant parameters that positively correlated with Hb in iron deficiency anemia, (3) putting Htc aside, WBC and RBC are the most relevant parameters that positively correlated with Hb in mixed or other causes of anemia group, (4) there are no significant difference between anemia groups in terms of gender, age, comorbidities, drug usage and hepatosplenomegaly, and (5)

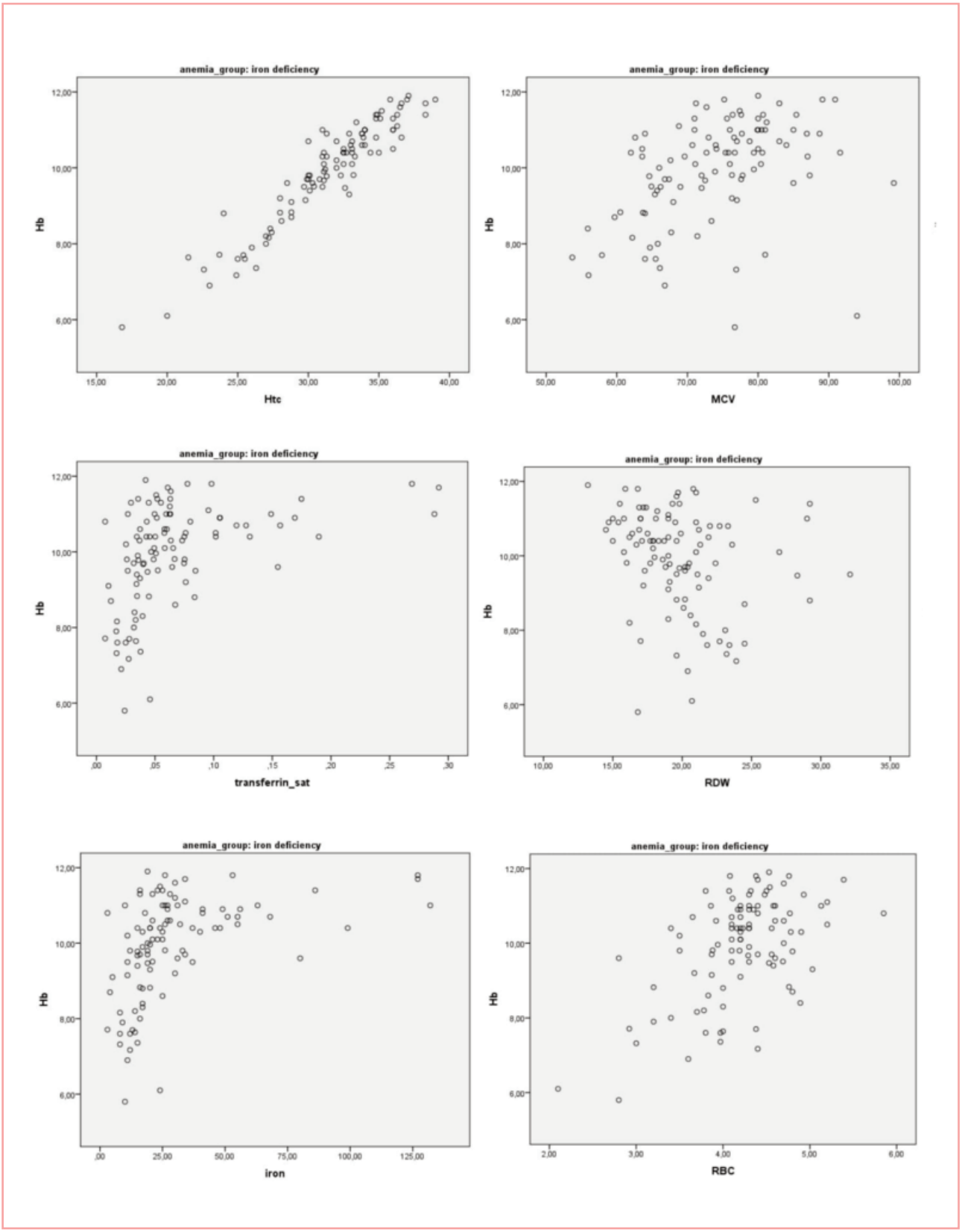

Figure 1. Correlation between Hb and study parameters in iron deficiency anemia group.

MCV and RBC are significantly lower and RDW is significantly higher in patients with iron deficiency anemia compared to those in mixed or other causes of anemia group.

As the intake of dietary iron decreases, while losses from the body remain constant, the level in the storage pool decreases. Healthy women and men have 500 mg 1000 mg of iron store, respectively, therefore anemia manifest earlier in women than in men after nutrition became iron deficient[14]. For these reasons, and because premenopausal women lose significant amount of iron

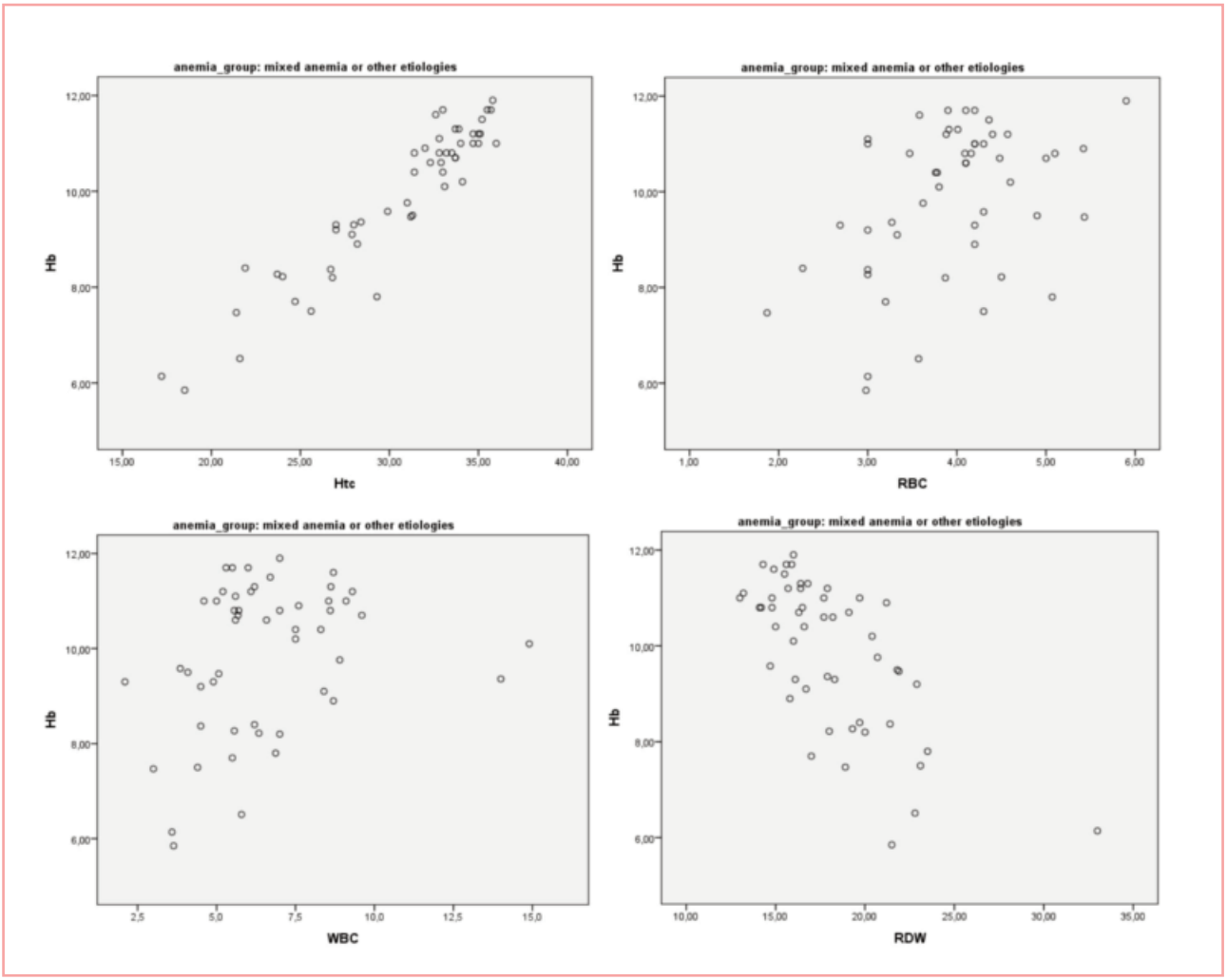

Figure 2. Correlation between Hb and study parameters in mixed or other causes of anemia group.

during menstruation, iron deficiency anemia is more common in women compared to men, in general population[15]. Indeed, 86% of the subjects with iron deficiency anemia were women and 16% were men in present report. Of 86 women in iron deficiency anemia group, 60 (70%) were women at childbearing age and 20 (30%) were postmenopausal women.

Diagnosis of iron deficiency anemia depends on reduction in ferritin and transferrin saturation along with decreased Hb and Htc values[16]. Transferrin saturation is a measure of the transported iron and of available iron to process in bone marrow; and lower levels than 15-20% represents iron deficiency[17]. In accordance with literature knowledge, transferrin saturation of iron deficiency anemia patients was lower than both transferrin saturation of subjects with mixed or other causes of anemia and the lower limit of normal population in our study. Moreover, it was strongly correlated with the degree of anemia regarded by Hb level in iron deficiency patients. This finding was previously suggested by a study from India[18].

Ferritin is a protein in human that act as a storage for iron. Plasma ferritin levels are increased as the body iron increases and vice versa. It is reported as the most important indice of iron deficiency anemia[19]. However, inflammatory conditions cause and increase in ferritin levels independent of iron store[20]. For instance, the minimum and maximum ferritin levels in iron deficiency anemia patients in our report was 1.4 and 207, respectively. Therefore its usefulness in iron deficiency anemia is limited. Accordingly, serum level of ferritin in iron deficiency anemia group was not different from the ferritin levels of the patients with other causes of anemia in present study. In addition, serum ferritin was not correlated with Hb level in study population. We think lack of correlation between ferritin and hemoglobin could be a consequence of increased ferritin levels as an acute phase reaction.

The RDW refers the size variability of circulating erythrocytes. Elevation in RDW is reported in iron deficiency anemia. Authors suggested that RDW had a high sensitivity in detecting iron deficiency anemia[18]. In another study, it has been reported that as the anemia classified from mild to severe, RDW value was increased[21]. About 83% of the patients with iron deficiency anemia had elevated RDW levels in a study from Asia[22]. Similar to the literature knowledge, RDW of iron deficiency patients were increased and even higher than that of the patients with mixed or other causes of anemia in present report. Since RDW also elevates in other conditions, such as, vi-

tamin B_{12} deficiency, RDW of patients with mixed or other causes of anemia were also higher than reference range of RDW. Therefore, elevated RDW could not be considered as unique for iron deficiency anemia.

The MCV refers the size of circulating erythrocytes. It decreases in iron deficiency anemia. In contrast, elevated MCV is a common feature of macrocytic anemias, e. g., vitamin B_{12} and folate deficiency anemias. About 92 % of the subjects with iron deficiency anemia had decreased MCV and 63% of patients with vitamin B_{12} deficiency anemia had increased MCV in a study in literature[22]. MCV of iron deficiency anemia patients were significantly lower than that of the subjects with mixed or other causes of anemia in our study.

Relatively small study population is a limitation of present study. Heterogeneous anemia etiology of the patients in mixed or other causes of anemia group in present study could be another limitation. However, our study provides valuable information about anemia patients treated in a tertiary referral hospital, such as, greater diagnostic value of transferrin saturation and serum iron compared to serum ferritin in establishing of the iron deficiency anemia diagnosis.

In conclusion, we suggest that transferrin saturation and serum iron are more valuable than serum ferritin level in determination of the iron deficiency anemia. In addition, MCV, RBC and RDW could be useful in differentiating of sole iron deficiency anemia from mixed or other causes of anemias.

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