

ORIGINAL PAPER

Characteristics of Anemia in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an inflammatory, chronic and systemic disease that primarily affects the synovial joints. Anemia is a common extra-articular manifestation in the absence of an effective treatment. The main mechanisms involved include shortening the lifespan of erythrocytes, inadequate bone marrow and abnormalities in iron metabolism. Eighty-eight patients over 18 years with definite diagnosis of rheumatoid were included in this study. The prevalence, respectively the characteristics of anemia were analyzed, together with demographic data, the type of symptoms, the type of comorbidities, the hematological indices and treatments. The mean age of the study population was 65.31 ± 12.57 years. Treat to target was achieved in one third of the patients (36.4%). The prevalence of anemia was 55% with higher prevalence in males (57%) than females (50%). Anemia was associated with higher disease activity ($p=0.036$). Out of the anemic patients, 7.14% had megaloblastic anemia, 40.48% had anemia of chronic disease and 21.43% suffered from iron deficiency anemia. Microcytic normochromic and normocytic hypochromic patterns can have mixed causes, belonging to both iron-pathophysiological processes and chronic inflammation. The prevalence of anemia at the 1-year check-up was 29.44% and the percentage of patients who achieved treat-to-target goals increased from 36.40% to 40.90%. The majority (48.80%) did not prove to have anemia neither at admission nor at follow-up. The results of the study suggest that anemic patients tend to have a higher level of RA activity, therefore screening for anemic syndrome should be part of the management of these patients, in an effort to establish the best therapeutic conduct.

Keywords: anemia, rheumatoid arthritis, DAS28-CRP.

Rezumat

Poliartrita reumatoidă (PR) este o boală inflamatorie, cronică și sistemică care afectează în primul rând sinoviala articulară. Anemia este o manifestare extraarticulară frecventă în absența unui tratament eficient. Principalele mecanisme implicate includ scurtarea duratei de viață a eritrocitelor, formarea osoasă medulară inadecvată și anomalii în metabolismul fierului. Optzeci și opt de pacienți cu diagnostic cert de PR și cu vârstă peste 18 ani au fost incluși în studiu. Au fost analizate prevalența, respectiv caracteristicile anemiei, împreună cu datele demografice, manifestările clinice, comorbiditățile, indicii hematologici și abordarea terapeutică. Vârsta medie a populației studiate a fost de $65,31 \pm 12,57$ ani. Tinta terapeutică a fost atinsă la o treime dintre pacienți (36,4%). Prevalența anemiei a fost de 55%, cu o prevalență mai mare în rândul bărbaților (57%) comparativ cu femeile (50%). Anemia s-a asociat cu activitatea crescută a bolii ($p=0,036$). Dintre pacienții anemici, 7,14% prezentau anemie megaloblastică, 40,48% anemie de boală cronică, iar 21,43% sufereau de anemie feriprivă. Modelele microcitare-normocromice și normocitare-hipocromice pot avea cauze mixte, aparținând atât deprinderii de fier, cât și inflamației cronice. Prevalența anemiei la controlul de 1 an a fost de 29,44%, iar procentul de pacienți care și-au atins obiectivele de tratament la țintă au crescut de la 36,40% la 40,90%. Aproape jumătate dintre pacienți (48,80%) nu au prezentat

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anemie nici la includerea în studiu, nici la urmărirea în dinamică. Rezultatele studiului sugerează că pacienții anemici tind să aibă un nivel mai ridicat de activitate a RA, prin urmare screening-ul pentru sindrom anemic ar trebui să facă parte din managementul acestor pacienți, în efortul de a stabili cea mai bună conduită terapeutică.

Cuvinte cheie: anemie, poliartrită reumatoidă, DAS28-CRP.

INTRODUCTION

Patients with rheumatoid arthritis (RA) may have a wide range of hematologic abnormalities. Common manifestations among patients with active disease may be anemia, thrombocytosis, and leukocytosis. The types of anemia with the highest prevalence among these patients include anemia of chronic disease (ACD) and iron deficiency anemia (IDA)^{1,2}.

Anemia, previously frequent among patients with RA, has become less common since the 1990s, probably due to the introduction of new therapies. B. Möller et al observed that the prevalence of anemia decreased between 2001 and 2007³. A study published in 2014, which included 89 patients with RA, reported an estimated prevalence of 46%⁴.

ACD mainly reflects a reduction in bone marrow erythropoiesis. A number of factors seem to contribute to this hypo-proliferative state in RA: hepcidin-induced changes in iron metabolism, inability to increase erythropoiesis in response to anemia, a relative decrease in erythropoietin (EPO) production, and decreased survival time of red blood cells⁵. Tumor necrosis factor alpha (TNF-alpha) and TNF receptor gene polymorphisms may be particularly important in the pathogenesis of RA, contributing to the inhibition of erythropoietin production⁶.

Iron deficiency is often caused by chronic blood loss, commonly seen in gastritis (induced by nonsteroidal anti-inflammatory drugs), peptic ulcer, or gastroesophageal reflux due to diaphragmatic hernia. Most cases IDA are asymptomatic. Patients with RA occasionally have IDA associated with ACD. When this happens, the hemoglobin level usually drops below 9.5g/dL^{7,8}.

Megaloblastic anemia secondary to folic acid deficiency, vitamin B12 deficiency, treatment with methotrexate or azathioprine, or secondary to concomitant chronic liver disease is found in some patients with RA, but is less common than ACD or IDA^{1,9}.

PATIENTS, MATERIALS & METHODS

It is a cross-sectional retrospective observational study carried out at the Department of Internal Medicine

and Rheumatology of Hospital "Dr I. Cantacuzino", Bucharest and conducted between 01.01.2018-01.05.2019.

Eighty-eight patients with definite diagnosis of rheumatoid arthritis according to the 2010 American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) Classification Criteria with age over 18 years old were included in this study. The patients hospitalized for pathological entities other than RA and patients known with hereditary types of anemia were excluded.

The prevalence, respectively the characteristics of anemia were analyzed, together with demographic data, the type of symptoms (tender and swollen joints, morning stiffness, fatigability and weight loss), the type of comorbidities, the hematological indices and the treatments administered at the time of hospitalization.

Complete blood counts, iron profile, serum ferritin levels, inflammatory biomarkers represented by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were performed. Disease activity was quantified by using the DAS28-CRP score as follows: a score below 2.6 corresponds to remission, 2.6-3.2 corresponds to low disease activity, 3.2-5.1 is associated with moderate disease activity and above 5.1 with high disease activity. Each patient had two check-ups: the initial evaluation and the 1-year follow-up

Anemia was defined in this study, according to the World Health Organization (WHO), as hemoglobin of 12 g/dL or less for women and 13 g/dL or less for men.

Data was analyzed using IBM SPSS version 27, and p value <0.05 was considered significant.

RESULTS

Initial evaluation

The predominance of the subjects was clearly female (68.2%), with a gender ratio of 2: 1. The mean age of the study population was 65.31 ± 12.57 years.

80.68% of the patients included in the study had comorbidities, of which the most common were hypertension (60.23%), osteoporosis (27.27%), ischemic heart disease (23.86%), peripheral vascular disease (22.72%), diabetes mellitus type II (15.9%).

At the time of hospitalization, 82.95% were under treatment with at least one conventional synthetic disease-modifying anti-rheumatic drug (DMARDs) (the most common was Methotrexate-58.44% followed by Leflunomide- 36.36%), and 55.68% were under biological therapy (Rituximab the most frequent-42.86% followed by Etanercept in 18.37 % of the cases and Tocilizumab- 16.33%). Two-thirds of the patients were taking non-steroidal anti-inflammatory drugs (NSAIDs) and one third of the participants were on corticosteroid treatment.

The duration of the disease among the patients in the study group had a mean value of 10.42 ± 9.16 years.

The most common symptoms reported by patients were morning stiffness (84.1%), with a mean duration of 77.31 ± 48 minutes and fatigue (46.6%).

Regarding the disease activity, objectified by the DAS28-CRP score, in order of frequency, 43.2% of the patients had moderate activity of the disease, 21.6% were in remission, 20.5% high activity and 14.8% low activity, so treat to target was achieved in almost one third of the patients (36.4%)

The prevalence of anemia in this study was 55% with higher prevalence in males (57%) than females (50%). The hematocrit (Ht) level was below normal in 40.91% of participants.

To determine the cause of anemia, 22.73% of patients underwent upper gastrointestinal endoscopy, while 15.91% of them underwent colonoscopy. Among the endoscopically investigated patients, the most common pathological findings of the superior tract were: gastritis (30%), gastric ulcers (15%), gastric hyperemia (10%) and hiatal hernia (5%). Colonic polyps (42.86%), signs of colitis (35.71%), and angiodysplasia (7.14%) were the most frequent results among the patients who underwent colonoscopy.

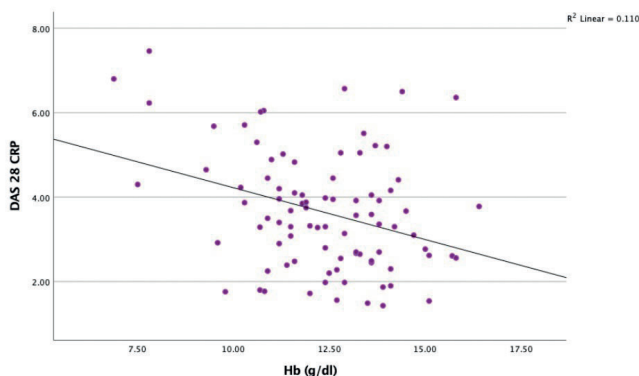


Figure 1. The tendency of low hemoglobin values to be associated with higher DAS28-CRP scores

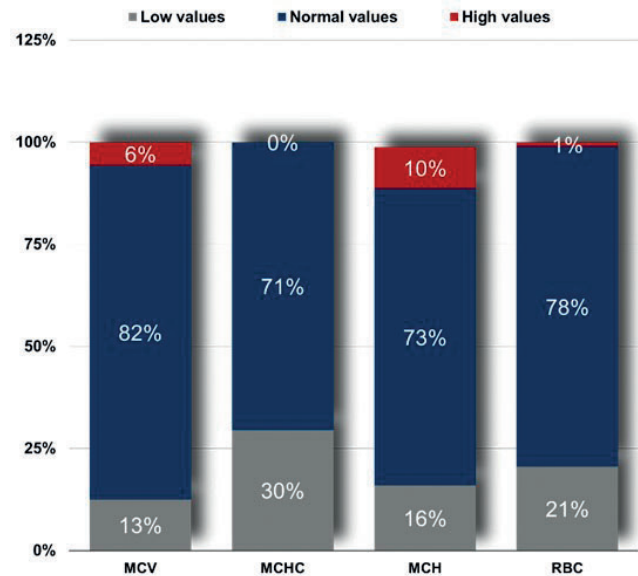


Figure 2. Distribution of erythrocyte indices among the study group (n=88)

Patients with low hemoglobin levels at admission tend to have higher DAS28-CRP scores, suggesting that the activity of RA may be higher in the case of association with anemic syndrome.

For a better understanding of the hematological status of patients at the admission in hospital, the investigative effort also focused on evaluating the statistics of red blood cell indices among the participants in this study. The red blood cell count (RBC), the mean corpuscular volume (MCV), the mean corpuscular hemoglobin (MCH) and the mean corpuscular hemoglobin concentration (MCHC) were analyzed.

Regarding the RBC, the majority of patients had values within the normal limits (78.4%), compared to those that were below the normal limit (20.5%). 1.1% of patients had high RBC values.

81.8% of the participants had MCV within the commonly allowed limits, 12.5% had lower levels, while 5.7% demonstrated a MCV that exceeds the upper limit considered normal.

The MCHC levels divided the studied group into two distinct groups, those that showed values below the lower limit (29.5%) and those that did not show deviations from the normal limits (70.5%).

The MCH was within normal limits in 72.7% of patients, 10.2% had higher MCH, while 15.9% had lower values.

A significant percentage of the study group had higher CRP (94.3%) and ESR (47.7%) than normal.

Further, we divided the study group into 2 subgroups

Table 1. The characteristics of the group of study at the initial admission

SD - standard deviation

P - Statistical significance

* - statistically significant result

Variable	Normal Hb level group n=46			Low Hb level group n=42			P value
	Cuantum	Percent (n=46)	Percent of total (n=88)	Cuantum	Percent (n=42)	Percent of total (n=88)	
Age, mean $\pm$ SD (years)	66,60 $\pm$ 12,80			63,95 $\pm$ 12,31			0,3260
Age at diagnosis, medie $\pm$ SD (years)	52,20 $\pm$ 16,20			56,26 $\pm$ 16,18			0,2430
Female gender	30	65,20%	34,09%	30	71,40%	34,09%	0,6480
Fatigability	17	36,95%	18,31%	24	57,14%	27,27%	0,0866
Weight loss	11	23,90%	12,50%	13	31,00%	14,77%	0,0482
Morning stiffness, mean $\pm$ SD (minutes)	64,21 $\pm$ 39,40			91,14 $\pm$ 52,76			0,009*

that we compared - subgroup of patients with normal hemoglobin levels and those with anemia.

Studying the characteristics of each group of patients, the mean age of the anemic group was lower (63.95 ± 12.31 years) than the group of those with hemoglobin within normal limits (66.6 ± 12.8 years). In addition, the mean age at diagnosis in anemic patients was higher (56.26 ± 16.18 years) than in non-anemic patients (52.20 ± 16.20 years). The female gender was more predominant among the anemic patients (71.40% vs 65.2%).

Fatigue and weight loss were more common in patients with anemia. The mean duration of morning stiffness was significantly higher ($p = 0.009$) in the group of anemic patients (91.14 ± 52.76 minutes) compared to that found in non-anemic participants (64.21 ± 39.40 minutes).

A higher prevalence of comorbidities was observed in the subgroup of patients with anemia, the only statistically significant association being with congestive heart failure (4.30% of the non-anemic group versus 19.00% of the anemic group, $p=0.0431$). 19.60% of patients with normal hemoglobin levels had ischemic heart disease compared to 28.60% of those with anemia. 54.30% of patients without anemia suffered

from hypertension, in distinction to 66.70% of those with anemia. Peripheral vascular disease was present in 17.40% of patients without anemia and in 28.60% of patients with anemic syndrome. Type II diabetes was more common among anemic patients (19.00% versus 13.00%).

NSAIDs and DMARDs were used in similar percentages in the two subgroups. Glucocorticoid treatment was more common among patients with anemia (42.90% versus 34.80%). The use of biological therapy was similar between the two groups (58.7% anemia versus 52.4% without anemia), Etanercept being the most frequently used biological agent ($p=0.0314$) in the non-anemic group. The use of folic acid had a frequency comparable to that of methotrexate, reaching 54.30% in non-anemic group, respectively 42.90% among the anemic group. As expected, iron treatment was of greatest importance in the anemic group (14.3% versus 0%, $p=0.0097$). Vitamin B12 was used in a minority of cases (4.8% in anemic patients, 2.2% in the non-anemic group)

Disease activity (DAS28-CRP) was higher in the anemic subgroup ($p=0.036$). In addition, the mean levels of ESR and CRP were higher in the anemic group (CRP: 14.65 ± 24 mg/dl; ESR: 26 ± 26.57 mm/1h) in comparison to those found among in non-anemic subjects (CRP: 13.17 ± 24.66 mg/dl; ESR: 22.53 ± 15.58 mm/1h).

Regarding erythrocyte indices, Hemoglobin, Ht, MCH, MCHC were lower in patients who presented with anemia ($p<0.001$). In addition, iron levels were lower in this subgroup ($p=0.0042$).

With reference to the type of anemia, the normochromic, normocytic type was the most common (40.48%). The hypochromic, normocytic and the hypochromic microcytic pattern were observed in fewer cases, quantifying a percentage of 28.57%, respectively 21.43%. The least common anemic types were normochromic macrocytic (megaloblastic), in proportion of 7.14% and normochromic microcytic anemia, in proportion of 2.38%.

Regarding the pathophysiological mechanism of anemia, the most common anemia was the one associated with chronic inflammation, the normochromic normocytic one (40.48%), while IDA (pure microcytic hypochromic) had a lower prevalence (21.43%). Microcytic normochromic (2.38%) and normocytic hypochromic (28.57%) patterns can have mixed causes, belonging to both iron-pathophysiological processes and chronic inflammation.

Patients with normocytic anemia had a higher mean hemoglobin level than the other two (11.73 ± 0.64 g/dl) [Pversus microcytic group <0.001 *; Pversus megaloblastic group=0.103].

66.7% of the patients with megaloblastic anemia received Methotrexate in combination with folic acid and the disease activity was higher compared to the other groups studied, suggested by the mean DAS28-CRP score of 7.52 ± 1.39 at admission [Pversus normocytic group=0.031 *; Pversus microcytic group=0.057].

1-year follow-up

Remission (DAS28-CRP score below 2.6) was achieved at 1-year follow-up by 27.3% of the study participants and 13.6% were in the low activity disease category (score between 2.6 and 3.2), so one year later the treat to target goal was achieved in 40.9% of the patients and the control of the disease activity was improved. Most of the patients had moderate and high activity disease. 38.6% were in the moderate activity disease category (DAS28-CRP score between 3.2 and 5.1), while 20.5% had a DAS28-CRP above 5.1 corresponding to a high disease activity.

Figures 3. and 4. describe the evolution of the disease activity and the hemoglobin level in the study group, between the two admissions. The green color reflects the status of the patients who were initially non-anemic, and the red color represents those who had anemic syndrome at first hospital admission. The mean level of hemoglobin in the initial anemic group had an increase between the two moments and was associated with a decrease in the disease activity (DAS28-CRP). In contrast, the patients initially considered non-anemic had a constant evolution between the two evaluations, with similar hemoglobin levels and mean DAS28 score.

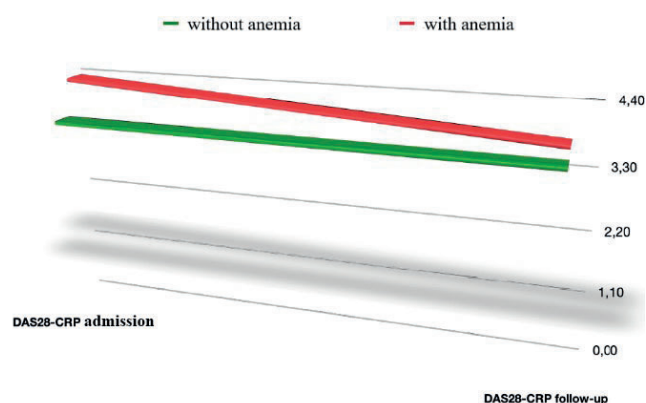


Figure 3. Evolution of mean DAS28-CRP between the initial admission and follow-up

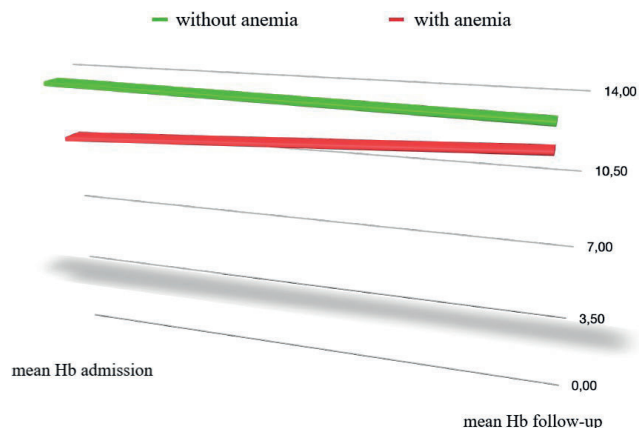


Figure 4. Evolution of mean hemoglobin between the initial admission and follow-up

The prevalence of anemia at the 1-year check-up was 29.44% with higher predominance in females (21.59% of the study group) than in males (7.95%). Most of the patients (70.46%) had normal hemoglobin levels at the one-year follow-up, and the distribution by gender suggests, once again, the predominance of females (46.59%) compared to the percentage of male patients with normal hemoglobin level (23.87%).

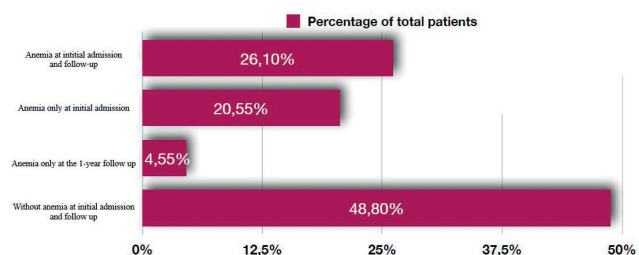


Figure 5. Distribution of anemia at the initial admission and 1-year follow-up

Studying the prevalence of the anemic syndrome between the two check-ups, it was found that 26.10% of the entire study group was assessed as anemic, both at the time of first admission and at the time of the 1-year follow-up. The percentage of those who were initially classified as anemic, but later had normal hemoglobin levels, was 20.55%, while the proportion of those who developed anemia within a year was only 4.55 %. Those who did not prove to have anemia neither at admission nor at follow-up represented the majority (48.80%).

Depending on the MCV level, we formed three subgroups (normocytic subgroup, microcytic subgroup and megaloblastic subgroup) and we analyzed them. Therefore, the most important results obtained were:

- The average hemoglobin level was higher in the normocytic subgroup ($p < 0.001$),
- Higher improvement of the anemic syndrome at the follow-up examination was observed in the normocytic subgroup ($p < 0.05$),
- The activity of the disease at the initial admission was higher in the macrocytic subgroup compared to the other subgroups (P versus normocytic group = 0.031; P versus microcytic group = 0.057)
- Iron levels were the lowest in the microcytic subgroup
- The majority of patients in the microcytic subgroup used NSAIDs (86.4%). This can explain the multitude of endoscopic lesions discovered in these cases (13.5% gastritis, 4.5% gastric ulcer).
- Iron treatment was most common in the microcytic subgroup, while methotrexate and folic acid were predominant in the microcytic subgroup.

DISCUSSION

In our study, the prevalence of anemia was 55%, taking as the cut-off value hemoglobin of 12 g/dL or less for women and 13 g/dL or less for men, according to WHO¹⁰. In the literature, it varies from one study to another. Hajar T., et al.¹¹ estimated its prevalence in patients with rheumatoid arthritis at 28.8%, S. Agrawal et al.¹² reported a prevalence of 47.5% while Ganna S.⁴ observed a prevalence of 64%.

Higher disease activity was observed among the patients with anemia ($p = 0.036$). Hajar T., et. al.¹⁰, Wolfe et. al.¹³ and R. Arul et al reported similar findings. Therefore, the symptoms (fatigue, weight loss, morning stiffness) were more severe in these patients¹⁴.

ACD was the most common type of anemia (40.48%), followed by IDA (21.43%) and megaloblastic anemia (7.14%), different from S.Agrawal et al.¹² who concluded that the first two anemic patterns had a similar proportion.

The activity of the disease at the initial admission was higher in the macrocytic subgroup compared to the other subgroups (P versus normocytic group=0.031; P versus microcytic group=0.057).

26.10% of the entire study group was assessed as anemic, both at the time of first admission and at the time of the 1-year follow-up. In 20.55% of patients, the anemic status improved, while 4.55% of them developed anemia within a year. The majority (48.80%)

did not prove to have anemia neither at admission nor at follow-up.

At the time of follow-up investigations, hemoglobin levels and inflammatory status showed improvements in all three subgroups of patients. Decreased clinical and biological activity of the disease was observed, data comparable to those found in other studies^{12,15}.

CONCLUSIONS

The prevalence of anemia was around 55%, anemia of chronic disease being the most common type (40.48%).

At the time of the 1-year follow-up, improvements in both hemoglobin levels and disease activity were observed. The prevalence of anemia decreased from 55% at initial admission to 29.44% one year later, and the percentage of patients who achieved treat-to-target goals increased from 36.40% to 40.90%.

The results of the study suggest that anemic patients tend to have a higher level of RA activity, therefore, screening for anemic syndrome should be part of the management of these patients, in an effort to establish the best therapeutic conduct.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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