

Prevalence of Anemia and its Association with Parameters of Rheumatoid Arthritis Patients: A Study from the Moroccan Quest - RA Data

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Abstract

Objective: To evaluate the prevalence of anemia in patients with rheumatoid arthritis (RA) and analyze its relationship with parameters of disease activity from the QUEST-RA Moroccan data.

Methods: Moroccan QUEST-RA (Quantitative Standard Monitoring Patients with RA), was inspired from Finnish QUEST-RA and is a national multicentric cross-sectional study of patients with RA (according to the 1987 ACR criteria). Patients were divided into two groups: a group with anemia and a group without anemia according to the criteria of the World Health Organization. The parameters of disease activity were assessed by patient and physician visual analog scale (VAS: 0-100 mm), erythrocyte sedimentation rate (ESR), C- Reactive protein (CRP) and DAS-28 ESR (Disease activity score in 28 joints).

Results: 1129 patients with RA were eligible. The mean age of patients was 48.8 ± 12.7 years with female predominance (87.3%). The median disease duration was 6 years (3-12), the mean of DAS28 ESR was 4.94 ± 1.68 . The prevalence of anemia was 28.8%. In univariate analysis, there was an association between the presence of anemia, the patient activity assessment, physician activity assessment, ESR, CRP, DAS28 ESR, HAQ. Moreover, there was no association between anemia and the presence of comorbidities (ulcer; myocardial infarction, vascular pathology...). In multivariate analysis, only persisted an association between anemia ESR, CRP and HAQ.

Conclusion: This study suggests that the prevalence of anemia was common and appeared to be independently associated with disease activity. Further studies are needed.

Keywords: Rheumatoid arthritis; Disease activity; Anemia; QUEST-RA

Introduction

One of the most frequent extra-articular organ manifestations in Rheumatoid Arthritis (RA) is anemia [1]. As anemia in RA patients may result in severe symptoms and worsening of other disease manifestations (e.g. arteriosclerosis), the influence on RA course of might be profound.

A systematic search of the scientific literature estimated the prevalence of anemia in rheumatoid arthritis between 33% and 60% [2]. In a large cohort of 2120 consecutive patients with RA, the estimated lifetime prevalence of anemia (Hb <12 g/dl) was 51%, 34% in men and 58% in women. At lower cutpoints (Hb <11 g/dl) the prevalence is 20% in men and 33% in women [3].

The aetiology of anemia in RA is complex. Anemia of inflammation (AI) and iron deficiency anemia, alone or in combination are the most frequent forms of anemia in RA. Changes in iron metabolism are the leading causes of anemia in RA patients and mainly induced by the altered synthesis and function of hepcidin and ferroportin. The typical changes of iron metabolism and hepcidin synthesis in RA are induced by proinflammatory cytokines, primarily interleukin-6 [1].

Studies suggest that increases in Haemoglobin level is significantly associated with positive changes in quality of life for patients with Rheumatoid Arthritis and anaemia [2]. Large-scale studies that demonstrate the importance of anaemia screening and treatment in this population are lacking [4].

Similar studies have been conducted in Europe and the United States of America, but there is no study of this kind in North Africa or in the Arabic countries. This has lead us to study the prevalence of anemia and its association with parameters of Rheumatoid Arthritis in Moroccan population and to compare it with the results obtained in different countries that have another lifestyle. This study using data from the Moroccan QUEST-RA (Multicentric Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis), was conducted to determine the prevalence of anemia in patients with RA, and to assess the link between Hb levels and specific aspects of RA, including disease severity, activity and comorbidities.

Materials and Methods

Data source and study population

Moroccan QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis), inspired from the Finnish QUEST-RA, includes data on 1129 patients with Rheumatoid

Arthritis, according to the 1987 American College of Rheumatology criteria [5], from private practice and academic sites. Data obtained during the period between January 2008 and December 2010. The Moroccan QUEST-RA data collection program was designed to collect information on patients characteristics, Rheumatoid Arthritis aspects, including disease severity and activity, associated comorbidities, laboratory measures and radiographs, treatment including disease modifying anti-rheumatic drugs (DMARDs), corticosteroids and biologics.

Hemoglobin levels

Patients were divided into 2 groups based on presence or absence of anemia, which was defined as Hb level <13 g/dl in males and Hb level <12 g/dl in females, based on WHO criteria for anemia [6].

Baseline information

Baseline information was collected from questionnaires that were completed by rheumatologists during consultations.

Informations included: Patients characteristics: age, gender, smoking, work, Body Mass Index (BMI), Rheumatoid arthritis therapies, including, corticosteroids, methotrexate, biotherapy. Identification of comorbidities: comorbidities were recorded as present or absent, further details on individual comorbid severity were not collected. Comorbidities that have been researched are: cardiovascular disease: myocardial infarction (MI), coronary artery disease (CAD), stroke, high blood pressure; gastrointestinal disease: peptic ulcer, diabete mellitus, renal comorbidities, vasculitis.

Disease characteristics: fatigue, morning stiffness, functional disability assessed by the Health Assessment Questionnaire (HAQ), patient and physician activity assessment of Rheumatoid Arthritis by the visual analog scale (VAS: 0-100 mm), the Disease Activity Score in 28 joints (DAS 28 ESR).

Laboratory analysis and radiographic evaluation: Hemoglobin concentration was determined in patients, Biomarkers of inflammation were measured: C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) status, Radiographic evaluation mainly of erosions.

Statistical analysis: Data and statistical analysis was done using the Statistical Package for Social Science (SPSS) version 18.

Descriptive Statistics included the mean and Standard Deviation (SD) for quantitative variables, and effective and percentage for categorical variables.

Comparisons of baseline characteristics by the presence or absence of anemia were performed using a Student t test for quantitative variables, and Pearson's chi 2 test for categorical variables.

The relation of hemoglobin concentration to patients characteristics, disease characteristics, comorbidities, laboratory analysis and radiographic evaluation, was tested using an univariate and multivariate regression models.

The univariate analysis was used to explore the relationship between Hemoglobin status and each individual variable. While the multivariate analysis was used to examine the relationship of Hemoglobin status with all variables simultaneously. We included in the multivariate analysis all variables with $p < 0.20$.

Odds ratio (OR) were reported with 95% confidence intervals (CI). The odds was considering statistically significant if the 95% CI for the OR did not include 1.

Results

Patients characteristics and comorbidities

Table 1 displays the patients characteristics and comorbidities of our population. A total of 1129 patients were included in the Moroccan Quest RA. 1032 of them had the value of hemoglobin. The anemia occurred in 297 patients and its prevalence was 28.8% for both sexes combined using the WHO definition (4), while 735 patients (71.2%) had a normal rate of Hemoglobin. The mean value of hemoglobin in the anemic group was 10.73 ± 5.57 g/l and in the nonanemic group was 12.87 ± 0.91 g/l.

We observed that there was no significant difference between both groups in the patients characteristics, except for age and Body Mass Index (BMI). Patients with anemia were more likely than those without anemia to be slightly younger (mean age 49 years versus 46 years, $p < 0.001$) and to have a low body mass index (BMI) (mean BMI 26 versus 25, $p < 0.001$).

There was no significant difference between both groups in the history of Rheumatoid arthritis therapies. Cardiovascular, gastrointestinal, renal comorbidities and vasculitis were not associated with anemia in our study.

Variables	Normal Hb Group n=735		Low Hb Group n=297		P
	n	n%	n	n%	
Age in years, mean \pm SD	699	49 \pm 12.25	281	46 \pm 13.96	<0.001
Female gender	691	605(87.5%)	275	239(80.9%)	0.78
Work	735	84(11.42%)	297	52(17.5%)	0.009
Smoking	699	53(7.58%)	284	17(5.98%)	0.37
BMI, mean \pm SD	695	26.37 \pm 4.57	280	25.4 \pm 4.82	<0.001
Cardiovascular comorbidities					
-Coronary artery disease	734	6(0.81%)	296	1(0.33%)	0.39

-Myocardial infarction	734	2(0.27%)	296	0(0%)	0.36
-stroke	734	7 (0.95%)	296	2(0.67%)	0.66
-High blood pressure	734	102 (13.89%)	296	40(13.5%)	0.87
Gastrointestinal comorbidities					
-Peptic ulcer	734	18(2.45%)	296	7(2.36%)	0.93
Renal comorbidities	734	5(0.68%)	296	3(1.01%)	0.58
Vasculitis	733	7 (0.95%)	296	3(1.01%)	0.93
Diabetes	729	70(9.6%)	295	16(5.4%)	0.029
Corticosteroids	734	653(88%)	296	258 (87.16%)	0.41
Methotrexate	735	625 (85.03%)	297	245(82.5%)	0.3
Biotherapy	735	30 (4.08%)	297	10 (3.36%)	0.59
Hb: Hemoglobin; SD: Standard Deviation, BMI: Body Mass Index.					

Table 1: Patients characteristics (n=1129) and comorbidities according to Haemoglobin status.

Disease variables: The disease variables in both anemic and non-anemic group are given in Table 2.

Rheumatoid Arthritis patients with low hemoglobin levels displayed significantly greater disease activity and functional disability. Increased disease activity was characterized by higher patient and

physician disease activity and DAS 28 ESR, higher CRP and ESR levels ($p < 0.05$ for all). A greater degree of functional disability, measured by Health Assessment Questionnaire (HAQ) was reported in the low hemoglobin group (1.4 versus 0.9, $p < 0.001$) (Table 2).

Variable	Normal Hb Group		Low Hb Group		P
	n	n(%)	n	n(%)	
Patient assessment of activity disease	716	35.64 ± 24.74	289	47.95 ± 25.5	<0.001
Physician assessment of activity disease	722	36.96 ± 29.68	295	49.28 ± 25.5	<0.001
Morning joint stiffness	730	705(96.57%)	295	282(95.6%)	0.45
Fatigue, mean ± SD	712	39.79 ± 26.07	289	51.76 ± 26.45	<0.001
HAQ, mean ± SD	733	0.95 ± 0.77	297	1.44 ± 0.81	<0.001
DAS 28 ESR, mean ± SD	712	4.7 ± 1.69	293	5.45 ± 1.55	<0.001
Erosion	694	533(76.80%)	284	229(80.6%)	0.19
FR positive	698	503(72.06%)	285	213(74.73%)	0.39
AntiCCP positive	735	206(28.02%)	297	68 (22.89%)	0.09
CRP, mean ± SD	467	19.15 ± 20.04	218	33.93 ± 36.81	<0.001
ESR, mean ± SD	725	32.94 ± 21.77	294	49.28 ± 29.67	<0.001
HB, mean ± SD	735	12.87 ± 0.91	297	10.73 ± 5.57	<0.001
SD: Standard deviation; HAQ: Health Assessment Questionnaire; DAS 28 ESR: Disease activity score in 28 joints; FR: rheumatoid factor; AntiCCP: Anticyclic citrullinated peptide; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin					

Table 2: Disease variables in anemic and non-anemic groups.

Univariate analyses, showed that the markers of disease activity and functional disability were associated with low Hb levels: Patient activity disease (OR: 1.02; 95% CI: 1.01-1.02), Physician activity disease (OR: 1.01; 95%CI:1.01-1.02), DAS28 ESR (OR:1.31; 95% CI:

1.2-1.43), ESR (OR: 1.02; 95% CI:1.01-1.03), CRP (OR: 1.02; 95% CI: 1.01-1.02), Fatigue (OR:1.01, 95% CI:1.01-1.02), HAQ (OR: 2.09, 95% CI:1.75-2.48) (For all $p < 0.001$) (Table 3).

Variables	Multivariate analysis		
	OR	95% CI	P
Age	0.97	0.96-0.99	0.002
Work	1.25	0.76-2.07	0.37
BMI	0.97	0.93-1.01	0.23
Diabetes	0.47	0.21-1.05	0.06
Patient assessment of activity disease	1	0.99-1.02	0.29
Physician assessment of activity disease	1	0.98-1.02	0.7
Fatigue	0.99	0.98-1	0.51
HAQ	1.46	1.04-2.06	0.02
DAS28 ESR	1	0.84-1.19	0.97
Erosion	-	-	-
AntiCCP	-	-	-
CRP	1	1-1.01	0.04
ESR	1.01	1-1.02	0.01

OR: Odds Ratio; CI: Confidence intervals; BMI: Body Mass Index; HAQ: Health Assessment Questionnaire; DAS 28 ESR: Disease Activity Score of 28 joints; AntiCCP: Anticyclic citrullinated peptide; CRP: C reactive protein; ESR: Erythrocyte Sedimentation Rate.

Table 3: Univariate and multivariate analysis on the association between the probability of low hemoglobin levels and comorbidities and disease characteristics.

Associations between markers of disease activity, functional disability and hemoglobin levels were explored using a multivariate analysis. ESR (OR: 1.01; 95% CI: 1-1.02), CRP (OR: 1; 95% CI: 1-1.01), HAQ (OR: 1.46; 95% CI: 1.04-2.06) were predictive of low hemoglobin levels. (For all $p < 0.05$) (Table 3).

Discussion

This study revealed that anemia was present in 28.8% of Rheumatoid Arthritis patients. The prevalence of anemia varied between studies in the literature.

Furst [7], found that approximately 17% of Rheumatoid Arthritis patients had low hemoglobin levels and met the WHO criteria [6] for anemia, this estimate was below the prevalence of anemia reported in other studies, which reflects the changes in treatment paradigms towards tighter control of disease activity; the majority of patients in his study received DMARD therapy (98%) including methotrexate (70%) and biologic agents (46%), for the treatment of Rheumatoid Arthritis.

In Borah [8] study, the prevalence of anemia was high 64.5%, consistent with a high disease activity, the DAS 28 ESR in the anemic group was 6.85 ± 0.64 .

Our results were near to those reported by Wolfe [3] and Santen [9], who found that anemia was present in 31.5% and 37.7% respectively.

The degree of anemia in Rheumatoid Arthritis is related to disease activity and inflammation. The improvement of disease activity by its treatment usually improves anemia [10].

Anemia in Rheumatoid Arthritis can be related to chronic disease or iron deficiency [11,12]. These aetiologies cannot be separated on the basis of the data available in the QUEST RA database. Iron deficiency of anemia of chronic disease was observed in 40% and anemia of chronic disease was observed in 60% of anemic subjects [13,14].

This reflects the fact that though anemia of chronic disease is the commonest type of anemia in RA [8].

Patients from anemic group have more severe disease activity than patients from non anemic group as reflected by acute phase reactants (CRP, ESR) and DAS 28 score. Our results are similar with previous studies [15-17]. Wolfe and colleagues reported similar findings in their prospective study involving 2120 RA patients who were seen at the Wichita Arthritis Center between 1974 and 2004. In their univariate analyses, ESR, CRP was all found to be predictors of anemia in patients with RA [3]. So the well-established relationship between inflammation and anemia was confirmed in this study by significant

associations between lower hemoglobin concentrations and higher DAS28 ESR, CRP and ESR. Inflammation in Rheumatoid arthritis is characterized by high circulating levels of interleukin 6 (IL6). IL6 stimulates the hepatic production of hepcidin, which is the main iron regulatory hormone [18]. This hormone causes inhibition of iron release from macrophages which generates iron sequestration, thus reducing the iron supply to erythropoiesis generating anemia [18].

Renal, gastrointestinal, cardiovascular comorbidities and vasculitis were examined, they were not predictive of low Hb level. Moller [19] showed that hemoglobin levels were not associated with renal or gastrointestinal comorbidity. Furst [7] found that only bleeding ulcers were predictive to low hemoglobin levels.

This study found that anemia is associated with functional disability. These data are consistent with those from previous studies that have raised concerns about the potential consequences of clinically significant anemia. Han et al. [20] documented that low levels of hemoglobin at baseline were associated with more severe physical disability and that an increase in hemoglobin after treatment was an independent contributor to the improvement of physical function.

Patients with low Hemoglobin levels reported a statistically higher percentage of subjective symptoms such as fatigue. Han et al. [20] showed that anemia is one of the factors associated with poor physical function in Rheumatoid Arthritis patients.

This study is limited by its retrospective study design, the lack of some information regarding biological markers of iron deficient erythropoiesis, such as the parameters of iron metabolism, and the history of use of the nonsteroidal antiinflammatory drugs.

Our findings suggest that anemic patients tend to have more severe disease as reflected by high disease activity score and HAQ, no relationship between comorbidities and the level of hemoglobin. The screening of anemia should be a part of RA management program and to establish an appropriate treatment. Additional large-scale studies on prevalence and anemia-related outcomes are needed to establish the importance of anemia screening and treatment in RA.

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