Prevalence of low hemoglobin levels and associations with other disease parameters in rheumatoid arthritis patients: Evidence from the CORRONA registry

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Abstract

Objective

To estimate the prevalence of low hemoglobin (Hb) levels in a large US cohort of patients with rheumatoid arthritis (RA) and examine the relationship between Hb levels and RA severity, associated comorbidities, and quality-of-life parameters by cross-sectional analysis of data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry.

Methods

The study population comprised patients with RA ≥18 years of age and clinical information recorded in the CORRONA registry between October 1, 2001 and February 1, 2007. Patients were separated into low (Hb <13 g/dl for men; <12 g/dl for women) and normal Hb groups (Hb ≥13 g/dl for men; ≥12 g/dl for women). Hb levels were calculated from recorded hematocrit values.

Results

Of the 10,397 study patients, 1734 (16.7%) had low Hb levels and 8663 (83.3%) had normal Hb levels. More patients in the low Hb group had a history of comorbid cardiovascular disease, diabetes, and gastrointestinal disease. The low Hb group exhibited greater disease severity and activity ($p<0.05$) as reported by patients and rheumatologists. In multivariate analyses, RA severity ([odds ratio] OR 1.24; 95% confidence interval [CI]: 1.07-1.44) and ESR (OR 1.04; 95% CI: 1.03-1.05), and comorbid bleeding ulcers (OR 2.04; 95% CI: 1.01-4.12) were predictive of low Hb levels.

Conclusion

Despite changes in treatment paradigms, low Hb levels remain prevalent in RA patients. This analysis suggests that low Hb levels may be associated with RA disease severity and the presence of certain comorbidities.

Key words

Rheumatoid arthritis, anemia, disease activity, quality of life.

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Introduction

Anemia is prevalent among individuals with certain chronic conditions including rheumatoid arthritis (RA), chronic kidney disease (CKD), inflammatory bowel disease, cardiovascular disease (CVD), human immunodeficiency virus (HIV) infection, and cancer (1-5). Prior small-scale studies have estimated the prevalence of anemia in RA at between 33% and 60% (5). A recent prospective trial involving over 2000 patients with RA found that anemia (World Health Organization [WHO] classification: hemoglobin (Hb) <12 g/dl in women and <13 g/dl in men) was present in 31.5% of patients, while the lifetime prevalence of anemia was estimated to be 57% (6). In patients with RA, anemia develops as a result of long-standing disease (anemia of chronic disease [ACD]) although other conditions such as iron deficiency may also be contributing factors (7, 8). Although the pathogenesis of ACD is not fully understood, several mechanisms have been proposed, including abnormalities of iron absorption (9) and release from macrophages (10) as well as malfunction of the cytokine network (11-16), all of which can result in inadequate erythropoiesis.

There is conclusive evidence to show that the presence of anemia in patients with chronic illnesses such as CKD, cancer, and HIV is associated with a substantial negative impact on morbidity, mortality, and quality-of-life (QOL) outcomes (2, 17, 18). While a few studies have also found similar associations between anemia and poor outcomes in patients with RA (6, 19), large-scale studies that demonstrate the importance of anemia screening and treatment in this patient population are lacking (20). This cross-sectional analysis, using data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry (21-23), was conducted to determine the frequency and degree of low Hb in patients with RA, and to assess the relationship between Hb levels and specific aspects of RA, including disease severity and activity, associated comorbidities, patient characteristics, and QOL parameters.

Materials and methods

Data source

CORRONA is an independent registry of patients who have RA, osteoarthritis (OA), psoriatic arthritis (PsA), and/or osteoporosis and are under the care of a rheumatologist in the United States. At present, the registry includes information on more than 11,000 patients with RA from 91 private practice or academic sites. The CORRONA data collection program is designed to systematically collect and document information on treatment patterns as well as the effectiveness and safety of medications, including: disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), biologics, and any other drugs used in the management of RA, OA, osteoporosis, and PsA. Approval for the CORRONA registry was obtained from the respective institutional review boards of participating academic sites and a central private institutional review board for patients from private practice sites. Further details on the CORRONA registry have been described elsewhere (21-24).

Study population

The study population constituted patients ≥18 years of age with a diagnosis of RA, at least one recorded hematocrit value, and updated clinical information obtained during the study period between October 1, 2001 and February 1, 2007.

Hemoglobin classification

As CORRONA collects only hematocrit values, Hb concentrations were derived by multiplying the hematocrit values recorded at the first visit by a factor of 0.34 as previously defined (25). Patients were then categorized into 2 groups, the low Hb group for patients with a Hb level <13g/dl for men and Hb <12 g/dl for women and the normal Hb group for patients with a Hb level ≥13 g/dl for men and Hb ≥12 g/dl for women, based on WHO criteria for anemia (26).

Clinical data

Data were collected prospectively and were based on patient and physician questionnaires that were administered

during routine clinical visits (requested every 3 to 6 months), selected laboratory data (laboratory measurements were within 2 weeks of the clinical assessment), and a rheumatological physical exam. The patient questionnaire encompassed demographic characteristics, a review of systems, completion of a modified Health Assessment Questionnaire (mHAQ), and an evaluation of the disease status incorporating an assessment of pain using the visual analog scale (VAS 0–100 mm), and assessment of the presence of morning stiffness, fatigue, depression, and patient activity. The data collected by the physician included disease-specific data using American College of Rheumatology (ACR) core criteria, American Rheumatism Association (ARA) assessments, Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints (DAS28) criteria, and RA disease severity on a 5-point ordinal scale and data on diagnostic laboratory measures including hematocrit and serum creatinine levels, rheumatoid factor (RF), cyclic citrullinated peptide (CCP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and radiographic evidence of erosion and joint space narrowing. The physician questionnaires also captured patient comorbidity data, including the presence or absence of CVD (coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), and stroke), diabetes, and gastrointestinal (GI) disease (bleeding ulcer, gastroesophageal reflux disease (GERD), dyspepsia, or other GI diseases defined by the use of a proton pump inhibitor or gastroprotective agent).

Table I. Demographic characteristics.

Characteristic	Low Hb Group n=1734		Normal Hb Group n=8663	
	n	n (%)	n	n (%)
Female	1734	1288 (74.3)	8628	6486 (75.2)
Age in years, mean ± SD	1690	62.6 ± 14.6	8460	58.4 ± 13.3*
Race				
Caucasian	1701	1370 (80.5)	8503	7299 (85.8)*
African American	1701	146 (8.6)	8503	329 (3.9)*
Hispanic	1701	105 (6.2)	8503	581 (6.8)
Asian	1701	37 (2.2)	8503	119 (1.4)*
Cardiovascular disease				
CAD	1734	124 (7.2)	8663	403 (4.7)*
MI	1734	93 (5.4)	8663	284 (3.3)*
CHF	1734	32 (1.8)	8663	81 (0.9)*
Stroke	1734	57 (3.3)	8663	178 (2.1)*
GI disease				
Bleeding ulcer	1734	59 (3.4)	8663	229 (2.6)
GERD	1734	282 (16.3)	8663	1524 (17.6)
Dyspepsia	1734	113 (6.5)	8663	606 (7.0)
Other GI disease	1734	673 (38.8)	8663	2814 (32.5)*
Diabetes mellitus	1734	195 (11.2)	8663	544 (6.3)*
Hb in g/dl (initial level), mean ± SD	1734	11.4± 1.0	8663	13.9 ± 1.2*
Hb in g/dl (6 month level), mean ± SD	660	12.0 ± 1.2	3307	13.7 ± 1.2

Hb: hemoglobin; SD: standard deviation; CAD: coronary artery disease; MI: myocardial infarction; CHF: congestive heart failure; GERD: gastroesophageal reflux disease; GI: gastrointestinal. Where N represents the number of patients with recorded data in the CORRONA registry and n (%) represents the number of patients with a positive status for a specific characteristic.
*$p<0.05$ for the difference between low and normal Hb groups.

Statistical analysis

The percentage of patients, mean values, and standard deviations were calculated from baseline visit, defined as the first visit where the hematocrit value was recorded for each patient in the study. The statistical significance of categorical and continuous variables between the low and normal Hb level groups was determined using the independent two-sample Student's *t*-test. Univariate and multivariate regression models were used to assess the magnitude of impact of each variable including demographic characteristics, disease severity and activity, cardiovascular status (CAD, MI, CHF, and stroke), diabetes, GI disease, outcomes of laboratory tests (creatinine, CRP, ESR, and RF), and patient-reported outcomes on Hb status. The univariate models were used to examine the relationship between Hb status and each individual independent variable, while the multivariate models were used to evaluate the relationships of Hb status with all independent variables simultaneously (to determine the effect of low Hb levels on a given variable after adjusting for the effect of all other variables in the model). The univariate and multivariate models were used to examine the effect of race-specific analysis, and the sensitivity of the models was investigated using expanded scales for the ordinal measures. A sub-analysis of the data generated two distinct models which explored the association between disease markers and QOL measures and low Hb levels. The sample size for all models was restricted to patients with complete data for all relevant variables. Odds ratios (ORs) were reported with 95% confidence intervals (CIs) associated with each outcome and the significance determined by the Chi-Square test. The odds of having low Hb levels associated with an outcome was considered statistically significant ($p<0.05$) if the 95% CI for the OR did not include 1.0. The standard error of the OR estimates from the multiple observations contributed by the same patient was corrected by introducing a clustering effect in the model fitting process. All analyses were performed using STATA 9.0 (StataCorp LP, College Stations, TX).

Results

Patient characteristics

There was a total of 15,014 patients in the CORRONA registry as of February 1, 2007. Of these, 10,397 patients with RA and recorded hematocrit

Table II. Markers of disease severity and activity.

Variable	Low Hb Group n=1734		Normal Hb Group n=8663	
	n	n (%)	n	n (%)
RA disease activity, mean ± SD	1724	30.4 ± 23.2	8614	23.7 ± 20.4*
RA disease severity, mean ± SD	1714	2.9 ± 1.1	8551	2.6 ± 1.0*
CDAI, mean ± SD	1590	17.4 ± 14.0	8098	13.9 ± 12.4*
DAS28, mean ± SD	1716	5.9 ± 6.5	8567	4.7 ± 5.7*
mHAQ, mean ± SD	1685	0.5 ± 0.5	8475	0.3 ± 0.4*
Exercise (daily or ≥ 1 times per week)	1650	1044 (63.3)	8327	5736 (68.9)*
Morning joint stiffness	1640	1185 (72.3)	8326	5885 (70.7)
Fatigue (8 weeks)	1734	455 (26.2)	8663	2040 (23.5)*
Depression (8 weeks)	1734	300 (17.3)	8663	1472 (17.0)
Currently working	888	577 (65.0)	5414	3984 (73.6)*
ARA Functional Class 1	1690	556 (32.9)	8540	3741 (43.8)*
ARA Functional Class 2	1690	764 (45.2)	8540	3829 (44.8)
ARA Functional Classes 3 & 4	1690	370 (21.9)	8540	970 (11.4)*
Erosion	954	517 (54.2)	4989	2502 (50.2)*
Joint space narrowing	975	625 (64.1)	5077	3049 (60.1)*
RF positive	1155	816 (70.6)	5675	4127 (72.7)
CCP positive	172	112 (65.1)	871	553 (63.5)
Creatinine in mg/dl, mean ± SD	1354	1.0 ± 0.5	6914	0.9 ± 0.4*
CRP in mg/l, mean ± SD	565	5.8 ± 13.8	2731	2.5 ± 7.6*
ESR in mm/hr, mean ± SD	1030	41.3 ± 29.1	4943	21.7 ± 18.9*

Hb: hemoglobin; RA: rheumatoid arthritis; SD: standard deviation; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; mHAQ: Modified Health Assessment Questionnaire; ARA: American Rheumatism Association; RF: rheumatic factor; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. Where N represents the number of patients with recorded data in the CORRONA registry and n (%) represents the number of patients with a positive status for a specific variable.
*p<0.05 for the difference between low and normal Hb groups.

levels between October 1, 2001 and February 1, 2007, met the diagnostic criteria and were included in this study; 1734 patients (16.7%) had low Hb levels (mean Hb: 12.0±1.2 g/dl in men, 11.3±0.7 g/dl in women) and 8663 patients (83.3%) had normal Hb levels (mean Hb: 14.8±1.0 g/dl in men, 13.6±1.0 g/dl in women). There were 37 (0.4%) severely anemic patients (Hb ≤9 g/dl) in the study population, and therefore there were insufficient patients with severe anemia to conduct a statistically valid sub-group analysis. Table I displays demographic characteristics of the study patients with RA stratified by Hb level. The overall demographic characteristics for the patients in the low and normal Hb groups were similar, with the exception of age and race. Patients in the low Hb group were slightly older than those in the normal Hb group (mean age 63 years *vs*. 58 years, p<0.05). The low Hb group had a higher percentage of African Americans (8.6% *vs*. 3.9%) and Asians (2.2% *vs*. 1.4%) and a lower percentage of Caucasians (80.5% *vs*. 85.6%) compared with the normal Hb group (all p<0.05). More patients in the low Hb group had a history of CVD, diabetes, and certain GI diseases than those in the normal Hb group (p<0.05; Table I).

Relationship between Hb levels and RA disease

Physician questionnaire results

The differences between the low and normal Hb groups in the markers of RA disease severity and activity are presented in Table II. In general, RA patients with low Hb levels displayed significantly greater disease severity and activity. Increased disease activity was characterized by higher CDAI score and DAS28, higher CRP and ESR levels, and higher rates of erosion and joint space narrowing in the low versus normal Hb groups (p<0.05 for all). A greater degree of RA disease severity, measured on a 5-point ordinal scale, was reported in the low versus normal Hb groups, and the percentage of patients with low Hb levels in ACR functional classes 3 and 4 was doubled (21.9% *vs*. 11.4%, p<0.05).

Univariate analyses showed that in patients with RA, a history of the following comorbidities was associated with low Hb levels: myocardial infarction (OR 2.24; 95% CI: 1.08–4.66), CHF (OR 4.38; 95% CI: 1.36–14.11), stroke (OR 3.17; 95% CI: 1.05–9.56), diabetes (OR 1.72; 95% CI: 1.06–2.81), and bleeding ulcers (OR 2.54 95% CI: 1.33–4.87). RA disease severity (OR 1.31; 95% CI: 1.15–1.49) and activity (OR 1.01; 95% CI: 1.01–1.02), DAS28 (OR 1.29; 95% CI: 1.19–1.40), CDAI (OR 1.01; 95% CI: 1.00–1.02), ESR (OR 1.04; 95% CI: 1.03–1.04), and CRP levels (OR 1.03; 95% CI: 1.02–1.04) were also predictive of low Hb levels.

Associations between comorbidities, RA disease parameters, and Hb levels were also explored using a multivariate analysis. In patients with RA, a history of comorbid bleeding ulcers (OR 2.04; 95% CI: 1.01-4.12) was predictive of low Hb levels (Fig. 1A). RA severity (OR 1.24; 95% CI: 1.07-1.44) and increased ESR (OR 1.04; 95% CI: 1.03-1.05) were also predictive of low Hb levels; body mass index (BMI) and dyspepsia were found to be inversely related to anemia in this analysis (Fig. 1B).

Patient questionnaire results

Patients in the low Hb group reported significantly higher mean mHAQ scores and a higher rate of fatigue compared with the normal Hb group (Table II). There were no between group differences in the percentage of patients who reported morning joint stiffness. Approximately 74% of patients with normal Hb levels reported that they were currently employed compared with 65% in the low Hb group (p<0.05). The percentage of patients who reported routine exercise (daily or ≥1 times per week) was also greater in the normal versus low Hb groups (69% *vs*. 63%; p<0.05).

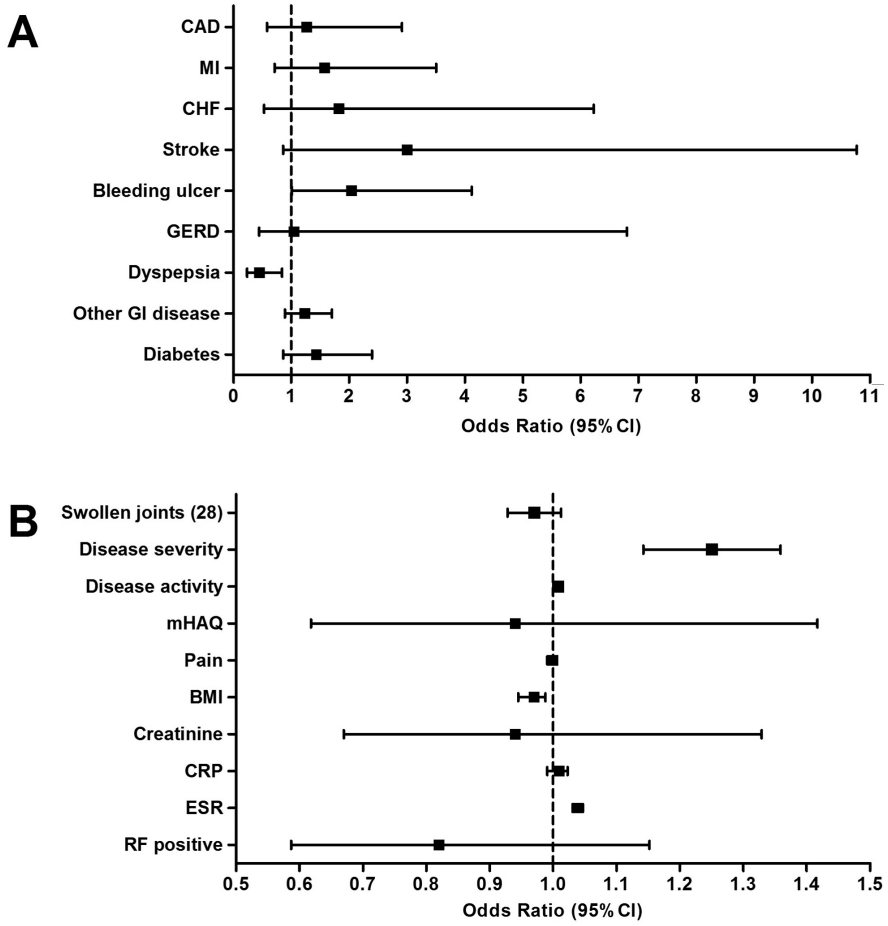

Fig. 1. Multivariate analysis on the association between the probability of low hemoglobin levels and (A) comorbidities and (B) diagnostic indicators of rheumatoid arthritis.
All variables, including demographic characteristics, disease severity and activity, cardiovascular status (CAD, MI, CHF, and stroke) diabetes, GI disease, outcomes of laboratory tests (creatinine, CRP, ESR, and RF), and patient-reported outcomes were incorporated into the model in a stepwise fashion. CAD: coronary artery disease; MI: myocardial infarction; CHF: congestive heart failure; GERD: gastroesophageal reflux disease; GI: gastrointestinal; CI: confidence interval; mHAQ: Modified Health Assessment Questionnaire; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor.

Univariate and multivariate analyses were performed to explore a possible association between mHAQ, fatigue, depression, exercise, employment status, and Hb levels. In the univariate analyses, mHAQ scores (OR 1.50; 95% CI: 1.12-2.02) and pain (OR 1.01; 95% CI: 1.00-1.01) were found to be predictive of low Hb levels. In the multivariate analyses, none of these covariates were found to be associated with low Hb levels.

Discussion

This study represents the largest examination of the prevalence of anemia in RA patients in the United States to date. Approximately 17% of RA patients in this analysis had low Hb levels and met the WHO criteria for anemia (Hb level <13 g/dl for men and Hb <12 g/dl for women). While this estimate falls well below the prevalence of anemia reported in other studies (5), it reflects the changes in treatment paradigms towards tighter control of disease activity; the majority of patients in our study received DMARD therapy (98%), including methotrexate (70%) and biologic agents (46%), for the treatment of RA. Concurrent illnesses such as CVD, GI disease, or diabetes were more prevalent in RA patients with low Hb levels compared to those with normal Hb levels.

Low Hb levels in these patients may be related to blood loss or ACD, and these etiologies cannot be separated on the basis of the data available in the CORRONA database. However, other studies have shown ACD to be present in up to 70% of RA patients who are anemic, suggesting that the low Hb levels observed in the CORRONA patients may be the result of ACD (14). The presence of ACD in patients with chronic infections, certain malignancies, and chronic inflammatory diseases has been shown to adversely affect morbidity and mortality outcomes (2, 17, 18). A significant correlation has also been noted between longstanding anemia and disease severity in patients with chronic illnesses such as CKD (18). Our findings suggest that the same may be true for patients with RA. In this study, the percentage of patients in the low Hb group in ACR functional classes 3 and 4 was doubled compared with the normal Hb group. The low Hb group also exhibited a significantly greater degree of disease activity as marked by statistically higher CDAI and DAS28 scores compared with the normal Hb group. The acute phase reactants ESR and CRP, which are commonly elevated in patients with RA and anemia (27), were approximately twice as high in patients with low versus normal Hb levels, suggesting a greater degree of disease activity in the low Hb group. Serum creatinine levels were also higher in the low versus normal Hb groups (1.0 mg/dl *vs*. 0.9 mg/dl). While this difference in creatinine levels is relatively small, it amounts to a difference in the estimated creatinine clearance of approximately 10 ml/min. 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, and estimated creatinine clearance were all found to be predictors of anemia in patients with RA. Renal function was determined to have a small effect on anemia while ESR and CRP had slightly greater effects on anemia in patients with RA (6).

In our study, patient-reported outcomes were statistically more favorable in the normal Hb group; more patients in this group reported that they were currently working compared with the low

Hb group. Patients with low Hb levels reported a slightly but statistically higher mean mHAQ score and a higher percentage of subjective symptoms such as fatigue. These results suggest that certain measures of RA disease severity and activity may be associated with low Hb levels. The multivariate analysis showed that some parameters, such as RA severity and ESR, were predictive of low Hb levels. Other parameters, including the average CDAI, DAS28, and mHAQ scores, CRP and serum creatinine levels, as well as rates of erosion and joint space narrowing, were greater in the low Hb group compared with the normal Hb group; however, these parameters were not found to be predictive of low Hb levels in the multivariate analysis. These real-world observations indicate that further hypothesis-driven trials are necessary to define these relationships. A number of comorbidities were also examined in the multivariate analysis; however, only bleeding ulcers were found to be predictive of low Hb levels. The inverse relationship between dyspepsia and anemia may be an example of bias by indication; for example, dyspepsia may not have been recorded in patients with RA who had dyspepsia with bleeding and anemia, if dyspepsia was treated with proton pump inhibitors and antacids.

Anemia is more prevalent in African Americans than in the Caucasian population in some diseases, such as CKD (28). However, there have been few studies that have examined the prevalence of anemia in patients with RA by race. In our study there was a higher percentage of Caucasian patients with RA and low Hb levels than African Americans, and a similar proportion of patients was reported by Wolfe and colleagues (6). Multivariate analyses of the population excluding African Americans compared with the total study population resulted in the same covariates, except for the comorbidity bleeding ulcer, being associated with low Hb levels.

The complete multivariate model that included all disease markers, comorbidities, and QOL measures revealed no further significant covariates. However, two separate exploratory models, one using disease markers and another using QOL as the independent variables, did suggest significant association between pain (VAS) and disease activity and low Hb levels (data not shown).

This study does have certain limitations. This cross-sectional analysis examines correlations between Hb levels and the variables recorded in the CORRONA registry and causal relationships cannot be readily extrapolated from these data. Complete information on all study parameters was not available for all of the 10,397 patients that were included in the analysis; some disease parameters such as CRP, ESR, as well as erosion and joint space narrowing were only assessed in a smaller proportion of the total study population. Also, the anti-CCP test was only assessed in a minority of patients as it is a relatively new diagnostic test that is not ordered routinely on patients with established RA diagnoses. Another potential limitation is that Hb levels were not measured directly, but were derived from recorded hematocrit values. This may have had a small effect on the estimate of anemia prevalence in this study population; however, it is unlikely that any variation in these measures would have substantially affected the outcomes reported. Also, although the CORRONA database captures detailed clinical, demographic, and laboratory data on RA patients, it is possible that all the potential determinants of anemia may not have been captured. Some of the measures used here also have limitations. The RA severity score was a physician-derived 5-point ordinal scale which has face validity but has not been formally validated. The mHAQ, while frequently used and easy to administer, has floor effects, making the lower scores less responsive to change. Finally, the patients in this cohort have relatively low disease activity when compared with typical patients entered in randomized controlled trials. Observational studies of this magnitude that capture data from very large numbers of patients from 35 states within the United States are unlikely to be skewed significantly; nevertheless, this possibility does exist. Our patients also have comorbidities and overall disease severity measures that would exclude them from typical randomized controlled trials.

Despite these limitations, the findings of this study clearly show that low Hb levels remain prevalent in RA patients. These findings also suggest that disease severity and activity, as reported by both patients and physicians utilizing a wide array of outcomes, may be associated with low Hb levels. Adequate treatment of anemia has been associated with attenuation of RA symptoms such as joint swelling and an improvement in grip strength and energy levels. Increased Hb levels have also been associated with significant improvements in QOL parameters in patients with RA (5, 6, 19). Clinicians should be aware of the importance of monitoring Hb levels in patients with RA, and incorporate routine anemia screening as part of their RA management program to identify patients who may benefit from closer follow-up and implementation of alternate or modified treatment strategies. The precise link between anemia and multiple comorbidities and RA disease outcomes deserves further study.

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