

# Anemia and Renal Function in Patients with Rheumatoid Arthritis

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**ABSTRACT.** *Objective.* Treatments are now available that can improve the anemia of chronic illnesses such as rheumatoid arthritis (RA). Despite recognition that anemia is common in RA and that renal function may be impaired and affect hemoglobin levels, there are almost no quantitative comparative data regarding the prevalence of anemia or decreased renal function in RA.

*Methods.* We studied a prospectively acquired clinical database of 2120 patients with RA who had 26,221 hemoglobin determinations, and a control population of 7124 patients with noninflammatory rheumatic disorders (NIRD) who had 12,086 determinations.

*Results.* Using the World Health Organization definition, anemia occurred in 31.5% of patients with RA, and followed a U-shaped distribution that had minimal prevalence around 60 years of age. Anemia prevalence in men was 30.4% and in women 32.0%. Anemia occurred in 11.1% at hemoglobin < 11 g/dl and 3.4% at hemoglobin < 10 g/dl. After erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) was the strongest predictor of anemia, followed by estimated creatinine clearance. Adjusted for age and sex, estimated creatinine clearance was 9.8 (95% CI 7.5 to 12.1) ml/min lower in patients with RA than in those with NIRD.

*Conclusion.* Anemia occurs in 31.5% of RA patients, 3 times the rate in the general population. However, severe chronic anemia (hemoglobin < 10 g/dl) is rare (3.4%). In addition, renal function is impaired in patients with RA compared with NIRD. Renal function has a small effect on the anemia of RA, and ESR and CRP have slightly greater effects. (J Rheumatol 2006;33:1516–22)

## Key Indexing Terms:

ANEMIA RHEUMATOID ARTHRITIS RENAL DISEASE CREATININE CLEARANCE

Hemoglobin is measured repeatedly in patients with rheumatoid arthritis (RA), and anemia is a common concomitant of RA. Surprisingly, there are few published data concerning the prevalence of anemia in RA. In a recent review of anemia in RA (2004), Wilson, *et al* found 623 patients in 9 reports whose sample sizes ranged from 10 to 136<sup>1</sup>. The definitions of anemia were not always given and often disagreed, and selection problems occurred in many of the cited studies. They concluded that the prevalence of mild anemia ranged from 33% to 60% and that positive correlations existed between RA symptoms and anemia. Standard textbooks provide no quantitative information about the prevalence of anemia, indicating only that normocytic anemias occur in the majority of patients<sup>2</sup> and/or that anemia correlates qualitatively with disease activity<sup>3</sup>.

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However, it would be useful to know more about anemia, particularly because severe anemia might contribute independently to the burden of RA and might be treatable with erythropoietin<sup>4–8</sup>, although the practical value of this therapy in RA is uncertain<sup>4</sup>. In addition, it would be useful to understand the role that age, sex, and renal function play in anemia, and whether RA patients are different from others with respect to renal function and anemia. Finally, while it is simply given that RA disease activity is associated with anemia, the quantitative associations have not been described. It is impossible to understand the relationship between anemia and clinical and outcome variables without quantitative data.

In our current report we used 26,221 hemoglobin determinations in 2120 consecutive RA patients assessed over a 30-year period and also 12,086 determinations in 7124 consecutive patients with noninflammatory rheumatic disorders (NIRD) to determine prevalence, incidence, and correlates of anemia, with special attention to patients with RA.

## MATERIALS AND METHODS

All patients in our report were seen by the first author for clinical care at the Wichita Arthritis Center between 1974 and 2004. Data from every clinic visit were recorded contemporaneously and are included. This data set has been described<sup>9,10</sup>. There were 2120 consecutive patients with RA who contributed 26,221 hemoglobin determinations. As a comparison group we used 7124 consecutive patients with NIRD, such as osteoarthritis, back pain syndromes, fibromyalgia, etc. These patients contributed 12,086 hemoglobin determinations. For the full data set, 15,713 creatinine values, 36,184 erythrocyte sedimentation rates (ESR) performed by the Westergren method, and 8343 C-

reactive protein (CRP) measurements were available. Creatinine was measured at initial visits, at followup visits from RA patients receiving methotrexate (MTX), and when clinically indicated for monitoring purposes. Blood samples for creatinine, ESR, and CRP determination were obtained at the same time as blood for hemoglobin determination. Anemia was defined using the World Health Organization (WHO) definition: hemoglobin < 12 g/dl for women and < 13 g/dl for men<sup>11</sup>. In addition, we also examined alternative anemia definitions separately for each sex: hemoglobin < 13, < 12, < 11, and < 10 mg/dl.

We also obtained a visual analog scale (VAS) pain score, VAS patient global severity, and the Health Assessment Questionnaire (HAQ)<sup>12</sup> at each clinic visit. The Patient Activity Scale, a normalized average of pain, global, and HAQ (0–10), was also calculated<sup>13</sup>, and mood was measured using the Arthritis Impact Measurement Scales anxiety and depression scales<sup>14,15</sup>. Physical measures included a modified Ritchie tender joint count<sup>16</sup> and grip strength<sup>17</sup>.

Patients with RA satisfied the American College of Rheumatology (formally the American Rheumatism Association) criteria for RA in effect at the time of patient's diagnosis<sup>18,19</sup>.

Creatinine clearance was calculated according to the method of Cockcroft:  $[(140 - \text{age (yrs)}) * \text{weight (kg)}] / [72 * \text{serum Cr (mg/dl)}]$  (multiplied by 0.85 for women)<sup>20</sup>. This method has been validated in RA by Boers, *et al*<sup>21</sup>.

**Statistical analyses.** For longitudinal analyses, we used generalized estimating equations (GEE) and survival analyses. Where indicated, fractional polynomial regression analysis was applied to GEE, ordinary least-squares regression, or logistic regression. For clarity in presentation, figures are based on one randomly selected observation per patient. Similarly, univariable associations were described using Kendall's tau on randomly selected observations. Cross-sectional prevalence percentages were derived for observations that were inversely weighted by the number of clinical visits, and their confidence intervals were boot-strapped. Statistical significance was set at the 0.05 level. All analyses were performed using Stata version 9.1<sup>22</sup>.

## RESULTS

**Clinical and demographic characteristics.** Table 1 displays the demographic and clinical characteristics of the study patients with RA. As patients had multiple observations, the table shows the mean per-patient value for the cohort.

**The current and lifetime prevalence of anemia in RA.** The lifetime prevalence of anemia using the WHO definition was 57.0% (95% CI 54.0% to 59.1%) and was 53.8 (95% CI 49.8% to 57.8%) in men (Table 2). The lifetime prevalence of at least one hemoglobin determination < 12 g/dl (WHO definition in women) was 51.6% (95% CI 49.5% to 53.7%), with women at 58.3% (95% CI 55.8 to 60.8) and men at 34.5% (95% CI 30.6% to 38.3%). At lower cutpoints for anemia the lifetime prevalence falls. At a hemoglobin cutoff of 11 g/dl the lifetime prevalence was 29.8% (95% CI 27.8% to 31.7%); and at 10 g/dl the lifetime prevalence was 13.7% (95% CI 12.3% to 15.2%).

The cross-sectional or current prevalence of anemia was considerably lower. The current prevalence was 31.5% (95% CI 30.5% to 32.6%) for both sexes combined using the WHO definition, and was 30.4% (95% CI 28.0% to 32.8%) in men. At a cutoff of 12 g/dl (the WHO definition in women) the prevalence was 26.9% (95% CI 25.9% to 27.8%), with women at 32.0% (95% CI 30.6% to 33.4%) and men at 14.4% (95% CI 12.5% to 16.3%). At a cutoff of 11 g/dl the rate was 11.1% (95% CI 10.3% to 11.8%), and at a cutoff of 10 g/dl it

**Table 1.** Demographic and clinical characteristics of the 2120 clinic patients with RA. Data represent the mean per-patient values.

| Variable                             | Mean | SD   |
|--------------------------------------|------|------|
| Age, yrs                             | 58.1 | 14.2 |
| Male, %                              | 28.0 |      |
| Education, yrs                       |      |      |
| 0–8, %                               | 12.1 |      |
| 8–11, %                              | 9.0  |      |
| 12, %                                | 44.4 |      |
| 13–15, %                             | 18.6 |      |
| ≥ 16, %                              | 16.0 |      |
| Ethnic origin                        |      |      |
| White, not of Hispanic origin, %     | 93.2 |      |
| Black, not of Hispanic origin, %     | 3.1  |      |
| Asian or Pacific Islander, %         | 0.5  |      |
| American Indian or Alaskan Native, % | 0.6  |      |
| Hispanic, %                          | 2.4  |      |
| Other, %                             | 0.3  |      |
| Disease duration, yrs                | 10.0 | 9.3  |
| Tender joint count, 0–24             | 7.3  | 4.9  |
| Health Assessment Questionnaire, 0–3 | 1.3  | 0.7  |
| Pain, 0–10                           | 4.9  | 2.2  |
| Global severity, 0–10                | 4.6  | 2.0  |
| Patient activity score, 0–10         | 4.6  | 1.9  |
| Hemoglobin, g/dl                     | 12.8 | 1.4  |
| Erythrocyte sedimentation rate, mm/h | 33.1 | 21.5 |
| C-reactive protein, mg/dl            | 1.8  | 2.0  |

**Table 2.** Lifetime and current prevalence of anemia in RA by anemia classification and sex.

| Classification | Sex     | Prevalence (95% CI) |                   |
|----------------|---------|---------------------|-------------------|
|                |         | Current             | Lifetime          |
| WHO*           | Both    | 31.5 (30.5, 32.6)   | 57.0 (54.0, 59.1) |
| < 13 mg/dl     | Male*   | 30.4 (28.0, 32.8)   | 53.8 (49.8, 57.8) |
| < 12 mg/dl     | Both    | 26.9 (25.9, 27.8)   | 51.6 (49.5, 53.7) |
|                | Male    | 14.4 (12.5, 16.3)   | 34.5 (30.6, 38.3) |
|                | Female* | 32.0 (30.6, 33.4)   | 58.3 (55.8, 60.8) |
| < 11 mg/dl     | Both    | 11.1 (10.3, 11.8)   | 29.8 (27.8, 31.7) |
|                | Male    | 6.2 (5.0, 7.5)      | 20.5 (17.3, 23.8) |
|                | Female  | 13.0 (12.1, 14.0)   | 33.4 (31.0, 35.8) |
| < 10 mg/dl     | Both    | 3.4 (2.9, 3.9)      | 13.7 (12.3, 15.2) |
|                | Male    | 2.4 (1.6, 3.2)      | 9.1 (6.8, 11.4)   |
|                | Female  | 3.8 (3.3, 4.4)      | 15.5 (13.7, 17.4) |

\* WHO definition of anemia: hemoglobin < 12 g/dl (women) or < 13 g/dl (men).

was 3.4% (95% CI 2.9% to 3.9%). To describe anemia using other cutpoints, we provide a nomogram for interested readers based on a random observation from each RA patient (Figure 1).

Given the patient was not anemic at the first assessment, the estimated annual incidence of anemia for both sexes was 7.9% (95% CI 7.3% to 8.6%) using the WHO definition, 6.9% (95% CI 6.3% to 7.5%) for anemia with a hemoglobin < 12 g/dl, 3.3% (95% CI 3.0% to 3.6%) for < 11 g/dl, and 1.5% (95% CI 1.3% to 1.7%) for < 10 g/dl (Table 3).

**Predictors of hemoglobin levels and anemia in RA.** Figure 2

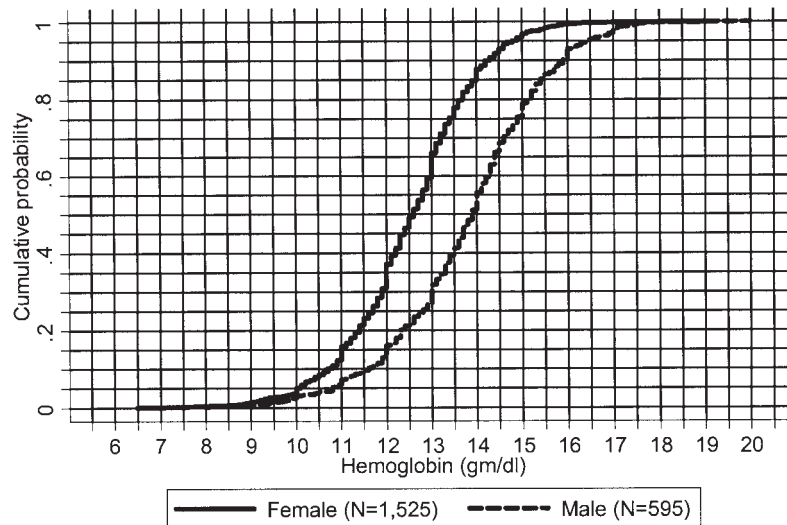


Figure 1. The cumulative distribution of hemoglobin levels in RA by sex.

Table 3. Annual incidence of anemia per 100 patient-years. Incidence determined excluded patients with anemia at first assessment.

| Classification | Sex     | Incidence (95% CI) |
|----------------|---------|--------------------|
| WHO*           | Both    | 7.9 (7.3 to 8.6)   |
| < 13 mg/dl     | Male*   | 7.8 (6.6 to 9.1)   |
| < 12 mg/dl     | Both    | 6.9 (6.3 to 7.5)   |
|                | Male    | 8.0 (7.3 to 8.8)   |
|                | Female* | 4.8 (4.0 to 5.7)   |
| < 11 mg/dl     | Both    | 3.3 (3.0 to 3.6)   |
|                | Male    | 3.5 (3.2 to 4.0)   |
|                | Female  | 2.6 (2.1 to 3.2)   |
| < 10 mg/dl     | Both    | 1.5 (1.3 to 1.7)   |
|                | Male    | 1.6 (1.4 to 1.9)   |
|                | Female  | 1.1 (0.8 to 1.5)   |

\* WHO definition of anemia: hemoglobin < 12 g/dl (women) or < 13 g/dl (men).

shows the age, sex, and estimated creatinine clearance adjusted relationship between acute phase reactants and level of hemoglobin. A 10-unit change in ESR resulted in a 0.28 (95% CI 0.24 to 0.33) g/dl change in hemoglobin, and a 1-unit change in CRP was associated with a 0.15 (95% CI 0.13 to 0.17) g/dl change. Age and hemoglobin were also associated (Figure 3A). For men, hemoglobin fell progressively from about 14.3 g/dl at age 40 to about 12.8 mg/dl by age 90. The pattern of association was different for women, with hemoglobin levels peaking at about age 58 years and being lower in younger and older women. Adjusted for age in a nonlinear GEE model, hemoglobin was 1.1 (95% CI 1.0 to 1.2) g/dl greater in men than in women. As might be expected anemia varied with age, and the greatest prevalence values were found in the elderly (Figure 3B).

A number of clinical variables were predictive of anemia, although the effects were often weak. Table 4 shows the relationship between WHO anemia and clinical variables, as

measured by Kendall's tau in univariable analyses. For CRP, which is not affected by red cell size, tau is 0.15 and the respective receiver-operating characteristic (ROC) area under the curve (AUC) is 0.66 (95% CI 0.61 to 0.70); this relationship is also shown in Figure 2. Of the clinical measures, grip strength had the strongest correlation with anemia.

**Renal function and anemia.** Figure 4 shows the relationship between renal function and anemia for RA and patients with NIRD. The figure is adjusted for age and sex. Overall, in an age and sex adjusted fractional polynomial model, hemoglobin levels were 0.80 (95% CI 0.71 to 0.89) g/dl lower in RA patients than in those with NIRD. Hemoglobin was weakly related to estimated creatinine clearance and decreased slightly with decreasing renal function, 0.04 (95% CI 0.2 to 0.5) g/dl per 10-unit change in creatinine clearance. As to the ability of various levels of anemia to be identified by estimated creatinine clearance, the AUC ROC curve in RA was 0.60 (95% CI 0.55 to 0.63) for WHO anemia, 0.62 (95% CI 0.58 to 0.65) for the 12 g/dl cut, 0.64 (95% CI 0.59 to 0.69) for the 11 g/dl cut, and 0.61 (95% CI 0.52 to 0.70) for the 10 g/dl cut.

**Creatinine clearance in RA vs NIRD.** The mean estimated creatinine clearance in RA was 83.0 (SD 40.6) versus 94.8 (SD 45.1) ml/min in NIRD. Adjusted for age and sex in a fractional polynomial model, estimated creatinine clearance was 9.8 (95% CI 7.5 to 12.1) ml/min lower in RA patients. Using a definition of impaired renal function of estimated creatinine clearance  $\leq$  60 ml/24 h, impaired renal function occurred in 30.3% of RA patients compared with 21.9% of NIRD. The age and sex adjusted relative risk of impaired renal function in RA compared with NIRD was 1.63 (95% CI 1.31 to 2.03).

## DISCUSSION

The data of our study provide new information on several issues of importance in RA. Severe anemia, or a hemoglobin

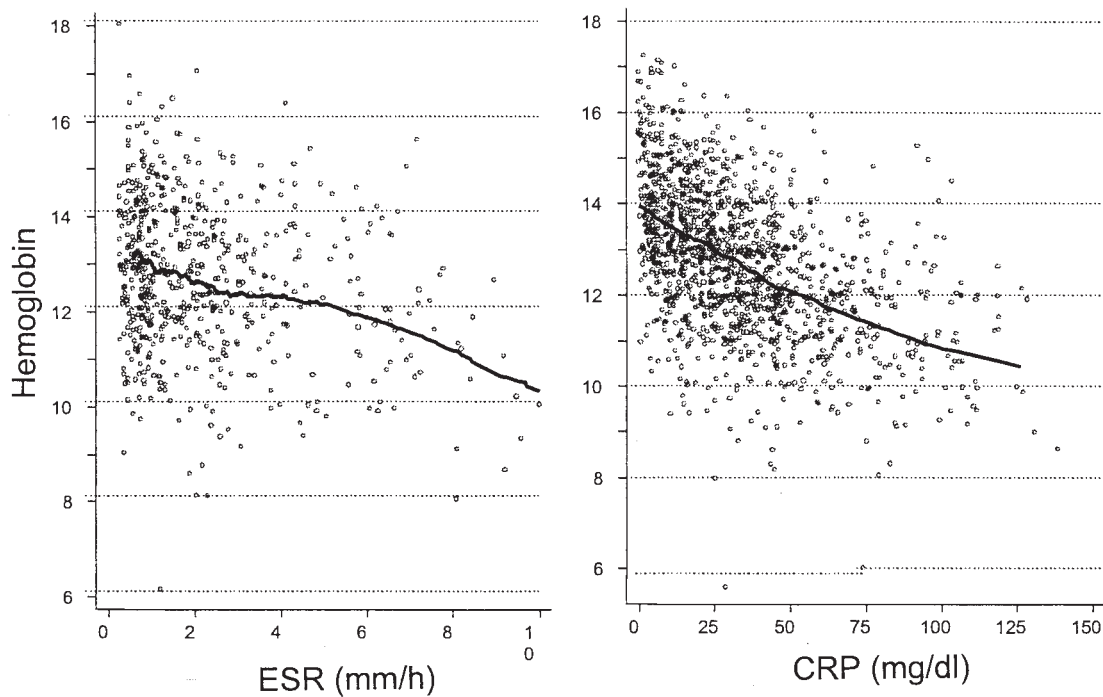


Figure 2. The relation between C-reactive protein (left panel) and erythrocyte sedimentation rate (right panel) and hemoglobin in patients with RA. Analyses are adjusted for age, sex, and estimated creatinine clearance.

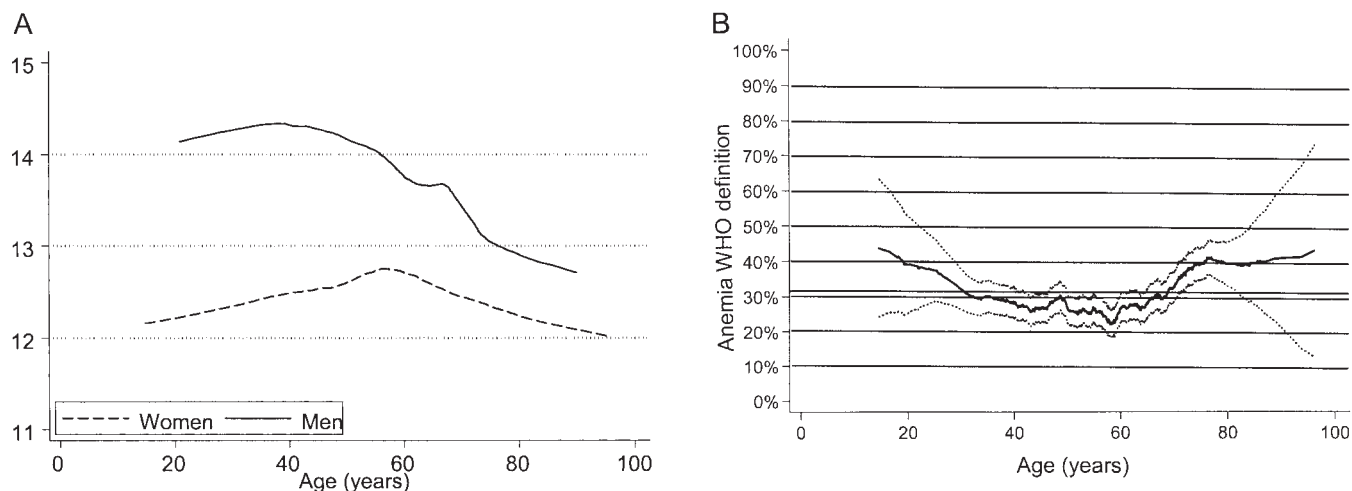


Figure 3. The relationship between hemoglobin and sex versus age (A) and anemia versus age (B) in patients with RA. Lines in (B) represent the predicted percentage with anemia and 95% confidence intervals, with the mean represented by a line at 31.5%.

level of less than 10 mg/dl, is found in about 3.4% of RA patients (Table 2). However, the lifetime prevalence of severe anemia is 13.7%. At the other end of the spectrum, mild anemia or WHO level of anemia (< 12 g/dl in women and < 13 g/dl in men) has a lifetime prevalence of 57.0% and a cross-sectional prevalence of 31.5% (Table 2 and Figure 1). Data from the NHANES III study indicated that 11.0% of men and 10.2% of women over the age of 65 were anemic according to

the WHO criteria<sup>23</sup>. Overall, the prevalence of anemia in NHANES-II was < 10%<sup>24</sup>, and other data regarding anemia in the general population are consistent overall<sup>23-27</sup>. By contrast (Figure 3), at least 30% of elderly RA patients were anemic, and the average rate of anemia across all ages was 31.5%. Therefore, the rate of anemia is tripled in RA patients compared with the general population.

Considering hemoglobin rather than anemia, the

Table 4. Relationship between clinical and laboratory variables and hemoglobin.

| Variable             | Kendall's tau | p       | 95% CI         |
|----------------------|---------------|---------|----------------|
| <b>Women</b>         |               |         |                |
| ESR                  | 0.19          | < 0.001 | 0.17 to 0.22   |
| CRP                  | 0.15          | < 0.001 | 0.11 to 0.19   |
| Grip strength        | -0.11         | < 0.001 | -0.13 to -0.08 |
| Creatinine clearance | -0.08         | < 0.001 | -0.12 to -0.05 |
| Tender joint count   | 0.07          | < 0.001 | 0.05 to 0.10   |
| HAQ                  | 0.06          | < 0.001 | 0.03 to 0.09   |
| Body mass index      | 0.06          | < 0.001 | -0.09 to -0.04 |
| Pain scale           | 0.05          | 0.001   | 0.02 to 0.08   |
| Patient global       | 0.05          | 0.001   | 0.02 to 0.07   |
| Depression           | 0.02          | 0.231   | -0.01 to 0.05  |
| Fatigue              | 0.00          | 0.966   | -0.03 to 0.04  |
| <b>Men</b>           |               |         |                |
| ESR                  | 0.15          | < 0.001 | 0.12 to 0.19   |
| CRP                  | 0.11          | < 0.001 | 0.06 to 0.17   |
| Grip strength        | -0.06         | < 0.001 | -0.09 to -0.03 |
| Creatinine clearance | -0.09         | < 0.001 | -0.13 to -0.04 |
| Tender joint count   | 0.04          | 0.015   | 0.01 to 0.07   |
| HAQ                  | 0.05          | 0.007   | 0.01 to 0.09   |
| Body mass index      | 0.03          | 0.091   | -0.06 to -0.00 |
| Pain scale           | 0.04          | 0.073   | 0.00 to 0.08   |
| Patient global       | 0.05          | 0.004   | 0.02 to 0.09   |
| Depression           | 0.05          | 0.012   | 0.01 to 0.08   |
| Fatigue              | 0.05          | 0.061   | 0.00 to 0.10   |

NHANES-III study of 8506 women and 7645 men found mean hemoglobin levels of 13.1 g/dl (SD 1.2) and 14.9 g/dl (SD 1.3), respectively<sup>28</sup>. Adjusted to the same age (age 48 yrs), RA patients in our current study had predicted hemoglobin levels of 12.6 (95% CI 12.5 to 12.7) g/dl and 13.7 (95% CI 13.6 to 13.8) g/dl, a difference of 0.5 g/dl and 1.2 g/dl, respectively. Using the NIRD controls of our current study,

hemoglobin was 0.80 (95% CI 0.71 to 0.89) g/dl lower in the RA patients.

We evaluated several potential and often overlapping predictive factors: role of renal function, role of RA, and role of inflammation. Other causes, which include bleeding, iron deficiency, pernicious anemia, and similar diseases, were not evaluated in this study because data to distinguish them were not available. As shown in Figure 4, hemoglobin decreases as a function of loss of renal function. The rate of loss shown here is similar to that reported in the NHANES-II study<sup>28</sup>. We also noted that clinical predictors were related to lower hemoglobin levels. Acute phase reactants in RA were more strongly related to hemoglobin than other predictors: a 10-unit change in ESR was associated with a 0.28 (95% CI 0.24 to 0.33) unit change in hemoglobin, and a 1-unit change in CRP was associated with a 0.15 (95% CI 0.13 to 0.17) unit change. Overall, as noted above, patients with RA had hemoglobin values that were 0.80 (95% CI 0.71 to 0.89) g/dl lower than patients with NIRD. Other clinical variables were predictive of anemia, but their effect was weaker than the association with CRP. All of this is to be expected, given the features of the anemia of chronic inflammation.

How much anemia can be attributed to disease activity in the RA population? To attempt to get some idea about this, we predicted in a statistical model the prevalence of WHO anemia given that ESR was 10 mm/h or CRP was 0.6 or HAQ was 0. In comparison with the observed prevalence of 33.5% in the regression model, the respective adjusted prevalences were 17%, 27%, and 20%. These predicted prevalences are still greater than noted in the population studies (~< 10%). Although such data may be of interest, caution should be used in extrapolating from these statistical models to clinical rheumatology.

We also found that patients with RA had impaired renal

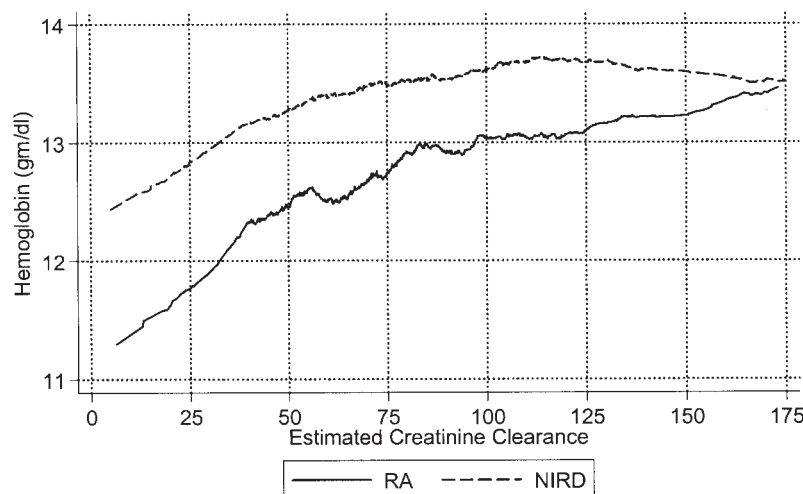


Figure 4. The relation between hemoglobin and estimated creatinine clearance in 1311 patients with RA and 2131 with noninflammatory rheumatic disorders (NIRD). Graphs are adjusted for age and sex. Hemoglobin is 0.80 (95% CI 0.71 to 0.89) g/dl lower in patients with RA in analyses adjusted for age, sex, and estimated creatinine clearance.

function compared with those with NIRD, with an estimated creatinine clearance that was about 10 ml/min lower. Using an estimated creatinine clearance of 60 ml/24 h as impaired, the age and sex adjusted relative risk of impaired renal function in RA compared with NIRD was 1.6 (95% CI 1.3 to 2.0). In a comprehensive review, Boers has documented the range of renal abnormalities in RA<sup>29</sup>. Despite many analytic studies on the nature of the renal problem, we found no other comparative data regarding estimated creatinine clearance in RA<sup>29,30</sup>. To consider whether the use of nonsteroidal antiinflammatory drugs (NSAID) or NSAID and angiotensin-converting enzyme (ACE) inhibitors might be more common in RA and therefore explain decreased renal function we explored the use of the agents in patients with RA and NIRD in the National Data Bank for Rheumatic Diseases (NDB)<sup>31</sup>, as reliable data on such drug use were not available in the current data set. Among 12,962 RA and 4192 non-RA patients in the NDB seen before the era of tumor necrosis factor inhibitors, RA patients were less likely to be taking NSAID alone [odds ratio (OR) 0.73, 95% CI 0.67 to 0.80] or NSAID and ACE inhibitors (OR 0.63, 95% CI 0.55 to 0.72).

It is difficult to measure loss of quality of life (QOL) caused by anemia because functional status forms the basis of commonly used QOL utility scales. Therefore, statistical models would have to hold disease activity (function) constant while measuring the effect of hemoglobin difference, assumptions that are contrary to clinical reality except in the case of treatment with erythropoietin. However, it is possible to estimate the maximum effect of hemoglobin change. Persons who satisfy WHO anemia criteria have HAQ scores that are 0.18 units higher than those not anemic. Extrapolating from data from the NDB<sup>31</sup>, a difference of this degree would change the EuroQol-based utility score by 0.03 units or an improvement of 12%. Therefore we can estimate that the effect of correction of WHO level anemia would change the QOL utility score by 0 to 0.03 units. Peeters, *et al* conducted a clinical trial of erythropoietin in RA to determine the degrees of improvement in QOL utilities<sup>4</sup>. Using a rating scale, QOL improved significantly compared with placebo treatment, but no improvement was seen using the standard-gamble method. Compared with the Disease Activity Scale<sup>32</sup> contribution to utility improvement of 21% in the rating scale, the explained variance for hemoglobin was 3%.

In summary, renal function is impaired in patients with RA, with the estimated creatinine clearance about 10 ml/h lower in RA than in NIRD. Severe chronic anemia (hemoglobin < 10 g/dl) is rare (3.4%), but mild chronic anemia is common, occurring in 35.3% compared with rates of < 10% in the general population. Renal function has a small effect on the anemia of RA, and ESR and CRP have slightly greater effects.

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