Anemia and Heart Failure: A Community Study
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ABSTRACT
PURPOSE: Anemia is an important comorbidity in heart failure and has been associated with increased mortality. The goals of this study were to define the prevalence of anemia in a community population with heart failure, examine trends in prevalence over time, and evaluate the role of anemia in patients with heart failure with preserved and reduced ejection fraction.

METHODS: Two cohorts of Olmsted County residents with heart failure were examined. The retrospective cohort included incident heart failure cases from 1979 to 2002 (n = 11063). The prospective cohort included active heart failure cases from 2003 to 2006 (n = 677). Clinical characteristics were collected. Anemia was defined by World Health Organization criteria.

RESULTS: The prevalence of anemia was 40% in the retrospective cohort and 53% in the prospective cohort. Anemia prevalence increased by an estimated 16% between 1979 and 2002 (P < .008) and was higher in those with preserved (≥50%) versus reduced (<50%) ejection fraction (58% vs 48%, respectively, P < .001) from 2003 to 2006. Anemia was associated with a large increase in the risk of death (P < .001 both cohorts). The relationship between mortality and hemoglobin followed a J-shaped curve, with increased mortality with hemoglobin levels less than 14 mg/dL and greater than 16 mg/dL. In the prospective cohort, after adjustment for clinical characteristics, the hazard ratios (95% confidence interval) for death were 3.07 (1.26-6.82) in those with a hemoglobin level of 16 mg/dL or more and 2.39 (1.37-4.27) in those with a hemoglobin level less than 10 mg/dL, using hemoglobin 14 to 16 mg/dL as the referent.

CONCLUSION: In the community, half of patients with heart failure are anemic, and the prevalence of anemia has increased over time. Anemia is more prevalent in heart failure with preserved ejection fraction and is associated with a large increase in mortality.

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More than 5 million Americans are currently living with heart failure, constituting a major public health problem. As heart failure treatments advance, there has been associated improvement in survival, but overall prognosis remains poor. Recently, the role of anemia in heart failure has become a focus of interest as a possible target for therapeutic intervention.

Anemia is seemingly common among patients with heart failure in the United States, with an estimated prevalence ranging from 23% to 48%. However, previous studies cannot be readily generalized because they pertain mostly to patients with systolic dysfunction, had incomplete ejection fraction ascertainment, or were performed using clinical trial populations. In addition, varied definitions for anemia have been used including physician’s diagnosis, hematocrit less than 30% to 37%, hemoglobin less than 12.0 mg/dL, and the World Health Organization (WHO) definition (hemoglobin < 12 mg/dL in women and < 13 mg/dL in men). Whether the prevalence of anemia has changed over time is unknown.

Previous studies have demonstrated that anemia is associated with increased morbidity and mortality. However, a recent study noted that patients with elevated hemoglobin levels (≥17 mg/dL) were at increased mortality risk compared with those with hemoglobin levels of 13.0 to 13.9 mg/dL and at a risk similar to those with hemoglobin levels
of 11.0 to 11.9 mg/dL. These findings have not been replicated and require further examination.

The present study was designed to address these gaps in knowledge by ascertaining the prevalence of anemia in community patients with heart failure. We aimed at assessing whether there has been a change in prevalence over time and determining whether anemia and hemoglobin level are associated with mortality in community patients with heart failure with a wide range of ejection fraction and heart failure severity.

**MATERIALS AND METHODS**

**Study Design and Setting**

This is a population-based study conducted in Olmsted County, Minnesota, using the resources of the Rochester Epidemiology Project. According to the US Census Bureau (www.census.gov), the 2005 Olmsted County population is estimated at 135,189, the majority of whom are white (90.2%) and 50.8% of whom are women.

We used 2 complementary study designs in this analysis: a retrospective cohort including patients with incident heart failure diagnosed from 1979 to 2002 and a prospective cohort enrolling patients with active heart failure from 2003 to 2006. The retrospective cohort allows the examination of trends in the prevalence of anemia over more than 2 decades and captures patients with heart failure at the time of diagnosis. The prospective cohort represents a contemporary heart failure population, contains complete echocardiographic data, and provides information on heart failure severity, including biomarker data and New York Heart Association (NYHA) functional class, lacking from previous studies. Investigations were approved by the appropriate institutional review board.

This type of research is feasible in Olmsted County because medical care is provided by few providers, including Mayo Clinic, Olmsted Medical Center, and a few private practitioners. Each institution’s records are easily retrievable because Mayo Clinic maintains extensive indices that, through the Rochester Epidemiology Project, are extended to the records of other care providers to county residents. The result is the linkage of medical records from all sources of care through a centralized system.

**Heart Failure Retrospective Cohort (1979-2002): Patient Identification**

Olmsted County residents with a possible heart failure diagnosis were identified by International Classification of Diseases, Ninth Revision code 428 (heart failure). Codes are primarily assigned on the basis of physician diagnoses during outpatient visits or at hospital discharge. From all patients with International Classification of Diseases, Ninth Revision code 428, a subset was randomly selected for case validation and data abstraction. Validation occurred using methods previously described and described here in brief. Experienced nurse abstractors blinded to study hypotheses reviewed records to ensure each met Framingham criteria and had a physician’s diagnosis of heart failure. When this method was used previously, missing data were minimal and Framingham criteria could be applied in 98% of cases. The inter-abstractor agreement was 100%, indicating these methods of classification are highly reproducible.

**Heart Failure Prospective Cohort (2003-2006): Patient Identification and Recruitment**

After a clinical visit, details are transcribed and appear in the electronic medical record within 24 hours. Natural language processing of the electronic text is used to identify potential heart failure cases. Nurse abstractors then review the cases to confirm heart failure diagnosis using Framingham criteria and collect additional data. All patients with active heart failure were identified from 2003 to 2006, including both incident and prevalent heart failure cases. Patients were prospectively recruited into the study, which includes a blood draw and echocardiogram. Hospitalized patients were contacted during hospitalization, and outpatients were contacted at their next clinic appointment.

**Data Collection: Retrospective and Prospective Cohorts**

**Laboratory Data.** Hemoglobin closest to heart failure diagnosis was used. Hemoglobin values within 1 year of heart failure diagnosis were available for 97% and more than 99% of patients in the retrospective and prospective cohorts, respectively. Anemia was defined by WHO criteria (hemoglobin < 13 mg/dL in men and < 12 mg/dL in women).

Creatinine clearance was calculated on the basis of the last creatinine value (within 30 days of heart failure diagnosis) using the Cockroft Gault equation. Brain natriuretic peptide (BNP) was measured on enrollment in the prospective cohort by a 2-site immunoenzymatic sandwich assay on the Dxi 800 automated immunoassay system (Beckman Instruments, Chaska, Minn) in the Immunochemical Core Laboratory of Mayo Clinic, Rochester, Minn.

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**CLINICAL SIGNIFICANCE**

- More than half of community patients with heart failure are anemic, and anemia prevalence is increasing over time.
- Patients with heart failure with preserved ejection fraction have a higher prevalence of anemia than those with reduced ejection fraction.
- Anemia is associated with a large increase in mortality in patients with heart failure with preserved and reduced ejection fraction.
Echocardiography. Echocardiograms were obtained and analyzed at the Mayo Clinic Echocardiography laboratory according to the American Society of Echocardiography guidelines.\textsuperscript{20} Left ventricular ejection fraction was measured using M-mode, quantitative, and semiquantitative methods as previously described and validated\textsuperscript{21} with excellent correlation between the methods. Ejection fraction values were averaged when multiple measurements were performed. Patients with an ejection fraction of 50% or more were classified as having preserved ejection fraction, whereas those with an ejection fraction less than 50% were classified as having reduced ejection fraction.\textsuperscript{15} All patients in the prospective cohort had complete echocardiographic data. Echocardiograms were not consistently performed in the retrospective cohort, and data were not included in analysis.

Additional Patient Data. Research nurses collected baseline characteristics from the medical record. Physician’s diagnosis defined previous coronary artery disease, chronic obstructive pulmonary disease, and malignancy. Hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or use of antihypertensive medications.\textsuperscript{22} Smoking status was classified as “ever” or “never.” Diabetes mellitus was defined using the American Diabetes Association criteria.\textsuperscript{23} Body mass index (BMI) was calculated using patient weight at the time of heart failure diagnosis and earliest adult height. NYHA functional class was assessed using standard definitions.

Mortality Follow-Up. We relied on passive surveillance of the medical record via the Rochester Epidemiology Project. In addition to deaths noted in clinical care, death certificates for Olmsted County residents are obtained annually, the Mayo Clinic registration office records all obituaries and local death notices, and death data are obtained from the State of Minnesota Department of Vital and Health Statistics annually.\textsuperscript{16}

Statistical Analysis
Baseline characteristics are represented as frequencies or mean values with standard deviations. Differences in baseline characteristics comparing the 2 cohorts and by anemia status were analyzed using a $t$ test for continuous variables and chi-square test for categoric variables. Year-specific prevalence rates of anemia, diabetes, hypertension, mean creatinine clearance, age, and BMI were calculated. Changes in prevalence over time were calculated using generalized linear models.

Subjects were divided into groups on the basis of hemoglobin level (<10, 10.0-11.9, 12.0-13.9, 14-15.9, $\geq$16.0 mg/dL). Survival was assessed using Kaplan-Meier methods with censoring at the time of last follow-up. Cox proportional hazard regression analysis was performed to assess both the unadjusted and adjusted hazard ratios (HRs) by hemoglobin group, using a hemoglobin level of 14.0 to 15.9 mg/dL as the referent. The proportional hazard assumption using the Schoenfeld residuals was valid in both cohorts. Data were more than 99% complete with the exception of smoking status (n = 13 missing retrospective), creatinine clearance (n = 58 missing retrospective, n = 29 missing prospective), and BNP (n = 51 missing prospective). A $P$ value of less than .05 was used as the level of significance. Analyses were performed using SAS Version 8.02 (SAS Institute Inc, Cary NC) and JMP Version 6.0 (SAS Institute Inc).

RESULTS

Patient Populations
There were 1063 patients with heart failure in the retrospective cohort and 677 patients in the prospective cohort. Age and sex distributions in both cohorts were similar. The prospective cohort had an increased proportion of patients with higher BMI, hypertension, diabetes, coronary artery disease, smoking, chronic obstructive pulmonary disease, and malignancy ($P < .001$ for all).

Prevalence of Anemia and Associated Characteristics

Retrospective Cohort. The prevalence of anemia was 40% and increased over time (Figure 1), with an estimated increase of 0.67% annually. This equates to an estimated 16% increase from 1979 to 2002. During the same period, the mean age remained stable ($P = .13$), whereas mean creatinine clearance increased ($P < .001$). However, the frequency of other comorbidities, including hypertension ($P < .001$), diabetes mellitus ($P = .026$), and mean BMI ($P = .001$), increased over time.

Prospective Cohort. The prevalence of anemia in the prospective cohort was 53% from 2003 to 2006, which is

![Figure 1](image-url) Time trends in the prevalence of anemia. Trends in the prevalence of anemia by year of heart failure diagnosis were examined from 1979 to 2002.
consistent with the prevalence predicted by data from the retrospective cohort. Patients with preserved ejection fraction had an increased prevalence of anemia (58%) compared with patients with reduced ejection fraction (48%, \( P < .001 \)).

In both cohorts, anemia was associated with decreased creatinine clearance and coronary artery disease (Table 1). In the retrospective cohort, patients with anemia were older, and a similar trend was observed in the prospective cohort. Prospective cohort data indicated that anemia was associated with higher BNP.

**Anemia, Hemoglobin, and Mortality**

In the retrospective cohort, 917 of 1063 patients (86%) with heart failure died after a mean follow-up of 5.3 ± 4.8 years. In the prospective cohort, after a mean follow-up of 21 ± 13 months, 241 of 677 patients (36%) had died. The estimated 2-year mortality (95% confidence interval [CI]) was 30% (27%-33%) and 33% (29%-37%) in the retrospective and prospective cohorts, respectively. Mortality was higher in those with anemia in both cohorts (\( P < .001 \); Figure 2A and B). In the prospective cohort, 2-year mortality (95% CI) was 41% (36%-47%) in those with anemia compared with 24% (19%-29%) in those without anemia. The results were similar in the retrospective cohort.

Although anemic patients with heart failure had higher mortality, the association between hemoglobin and mortality followed a J-shaped curve in both cohorts (Figure 2C and D). An increase in 2-year mortality was noted with hemoglobin less than 14.0 mg/dL or greater than 16.0 mg/dL. For example, in the prospective cohort estimated 2-year mortality (95% CI) was 30% (6%-48%) with hemoglobin levels 16 mg/dL or more, 19% (11%-26%) with hemoglobin levels 14.0 to 15.9 mg/dL, 28% (21%-34%) with hemoglobin levels 12.0 to 13.9 mg/dL, 41% (34%-48%) with hemoglobin levels 10.0 to 11.9 mg/dL, and 49% (35%-59%) with hemoglobin levels less than 10 mg/dL.

Cox proportional hazard regression further documented that mortality was higher with hemoglobin less than 14 mg/dL or greater than 16 mg/dL in both cohorts. After adjustment for the clinical characteristics in the prospective cohort, the HRs (95% CI) for death were 2.40 (0.99-5.23) with hemoglobin levels 16.0 mg/dL or more, 1.41 (0.89-2.31) with hemoglobin levels 12.0 to 13.9 mg/dL, 1.99 (1.27-3.25) with hemoglobin levels 10.0 to 11.9 mg/dL, and 2.37 (1.39-4.11) with hemoglobin levels less than 10.0 mg/dL using hemoglobin 14.0 to 15.9 mg/dL as the referent (Figure 3). A similar J-shaped mortality curve was demonstrated in the retrospective cohort using the same model (Figure 3). Adjustment for year of diagnosis did not significantly change results.

By using the additional data available in the prospective cohort, we further adjusted for ejection fraction, NYHA functional class, and BNP. HRs were similar for those with hemoglobin levels less than 14.0 mg/dL, whereas in those with hemoglobin levels 16 mg/dL or more, the HR (95% CI) increased to 3.07 (1.26-6.82) (Figure 3). There was no interaction between hemoglobin and ejection fraction in the prospective cohort (\( P = .76 \) interaction term).

**DISCUSSION**

In community patients with heart failure, the prevalence of anemia is high and increasing over time. Currently, anemia is present in more than half of patients with heart failure and...
is considerably more prevalent in those with preserved ejection fraction. Anemia is associated with a large increase in mortality independently of known clinical characteristics. The relationship between hemoglobin and mortality is not linear, because both reduced (<14 mg/dL) and elevated (≥16 mg/dL) hemoglobin are associated with increased mortality.

Prevalence of Anemia

Previous studies demonstrated an estimated prevalence of anemia in patients with heart failure from 23% to 48%. In a general elderly population (National Health and Nutrition Examination Survey) with age and sex distributions similar to those in our study, the prevalence of anemia was 10.6% in those aged 65 years or more (mean age 74.9 years, 56.6% were female). The present study extends previous reports by demonstrating that the burden of anemia in patients with heart failure is substantial, with more than half anemic by WHO criteria in recent years. This prevalence is higher than previously reported, likely reflecting the unselected population represented in our community cohorts in contrast with the highly selective nature of trial participants and in studies limited to those with reduced ejection fraction. Further, the prevalence of anemia increased markedly over time, and this steady increase cannot be readily explained by changes in age and renal function. As observed herein and consistent with previous studies, the prevalence of anemia increases with age. However, no temporal change in mean age at heart failure diagnosis was detected. In addition, despite the known correlation between anemia and chronic kidney disease in heart failure, in this cohort the mean creatinine clearance increased over time.

One possible contributor could be the increase in patients with heart failure with preserved ejection fraction. Previous data have been conflicting on whether the prevalence of anemia differs by ejection fraction, with studies demonstrating prevalence is higher, lower, and the same in patients with preserved versus reduced ejection fraction. Our data from 2003 to 2006 performed in an unselected population with heart failure with complete ejection fraction ascertainment demonstrate that the prevalence of anemia is higher in those with preserved versus reduced ejection fraction. Owan et al recently reported that the proportion of patients with heart failure with preserved ejection fraction is increasing over time. Given this proportionate increase in patients with heart failure with preserved ejection fraction, and an increased prevalence of anemia in those with preserved ejection fraction, it is plausible that this shift in case mix is contributing to the increased prevalence of anemia in community patients with heart failure. Because the pathogenesis of anemia in heart failure has not been fully elucidated, further work is needed to define the mechanisms of anemia in heart failure.
Anemia, Hemoglobin, and Association with Outcomes

Anemia and low hemoglobin have been associated with adverse outcomes in several clinical studies.3-13 However, it becomes difficult to establish a causal relationship between anemia and mortality when studies include prevalent heart failure cases. By using our retrospective cohort with only incident heart failure cases, we demonstrated that anemia and low hemoglobin at the time of heart failure diagnosis are associated with increased mortality. A previous study had demonstrated that patients with elevated hemoglobin levels also are at increased mortality risk.10 Our study supports these findings and extends them by demonstrating that adjusting for ejection fraction, NYHA functional class, and BNP did not attenuate this association.

Whether to treat anemia in patients with heart failure remains controversial. Few studies to date have randomized patients to treatment with erythropoietin or darbepoetin with or without intravenous iron therapy versus placebo and evaluated outcomes. The results have been promising, with trials demonstrating an improvement in peak oxygen consumption,29 exercise duration,29 NYHA functional class,30 and health-related quality of life31 in patients treated with erythropoietin,29 erythropoietin + iron,30 or darbepoetin31 compared with placebo. Concerns have been raised about the safety of treating patients with these agents29 because of potential thrombotic complications. However, because of the promising results, a larger phase III trial evaluating treatment of anemic patients with heart failure with darbepoetin is under way. Given the high burden of anemia in heart failure, if treatment improves outcomes, the impact could be great.

Strengths and Limitations

Some limitations should be acknowledged to aid in data interpretation. First, despite its growing diversity, Olmsted County remains largely white, so generalization of these data to other racial and ethnic groups should be cautious. Second, information on anemia cause, including ferritin and transferrin levels, was not available for analysis. Finally, the consent rate for the prospective cohort was 69% during the study period, which is similar to rates reported in other community studies of cardiovascular disease.32 This study has several strengths. First, we examined the role of anemia in heart failure in a large unsel ected community population. Second, our retrospective cohort included only incident heart failure cases and spanned more than 20 years. Third, our prospective cohort had complete ejection fraction ascertainment and included data on heart failure severity.

CONCLUSIONS

More than half of community patients with heart failure are currently anemic and the prevalence is increasing over time. Patients with heart failure with preserved ejection fraction have an increased prevalence of anemia compared with patients with reduced ejection fraction. Anemia is associated with increased mortality, but hemoglobin follows a J-shaped curve, with increased mortality at both low and very high hemoglobin levels. Further work is needed to investigate the increasing prevalence of anemia in heart failure and to determine whether treatment improves outcomes.

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References


20. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-1463.


