Mortality in Heart Failure with Worsening Anemia: A National Study

Howard S. Oster MD PhD[1], Michal Benderly PhD[2], Michael Hoffman MD[1], Eytan Cohen MD[3], Avraham Shotan MD[4] and Moshe Mittelman MD[1]

[1]Department of Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]Israel Society for the Prevention of Heart Attacks, Sheba Medical Center, Tel Hashomer, Israel
[3]Recanati Center for Medicine and Research, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[4]Heart Institute, Hillel Yaffe Medical Center, Hadera, Israel
All affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Anemia is common in heart failure (HF), but there is controversy regarding its contribution to morbidity and mortality.

Objective: To examine the association of mild and severe anemia with acute HF severity and mortality.

Methods: Data were prospectively collected for patients admitted to all departments of medicine and cardiology throughout the country during 2 months in 2003 as part of the Heart Failure Survey in Israel. Anemia was defined as hemoglobin (Hb) < 12 g/dl for women and < 13 g/dl for men; Hb < 10 g/dl was considered severe anemia. Mortality data were obtained from the Israel population registry. Median follow-up was 33.6 months.

Results: Of 4102 HF patients, 2332 had acute HF and available hemoglobin data. Anemia was common (55%) and correlated with worse baseline HF. Most signs and symptoms of acute HF were similar among all groups, but mortality was greater in anemic patients. Mortality rates at 6 months were 14.9%, 23.7% and 26.3% for patients with no anemia, mild anemia and severe anemia, respectively ($P < 0.0001$), and 22.2%, 33.6% and 39.9% at one year, respectively ($P < 0.0001$). Compared to patients without anemia, multivariable adjusted hazard ratio was 1.35 for mild anemia and 1.50 for severe anemia (95% confidence interval 1.20–1.52 and 1.27–1.77 respectively).

Conclusions: Anemia is common in patients with acute HF and is associated with increased mortality correlated with the degree of anemia.

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KEY WORDS: heart failure (HF), anemia, morbidity, mortality, Heart Failure Survey in Israel (HFSIS), New York Heart Association (NYHA) class

Heart failure is common and is a frequent reason for hospitalization [1]. Its prevalence is approximately 2% in the general population and 15% among patients older than 80 [2]. In recent years several reports have suggested that anemia is common in patients with HF and that its severity is associated with increased morbidity and mortality [3,4]. However, the prevalence of anemia in patients with HF varies widely among reports, ranging from 10% [5] to 61% [6], and the degree to which the severity of anemia is associated with increased morbidity and mortality of HF is controversial.

The Heart Failure Survey in Israel (HFSIS) 2003 was a large prospective nationwide survey that included all patients admitted with the diagnosis of HF during a 2 month period. Our aim was to investigate the relationship between anemia and mortality in a large cohort of ethnically diverse patients hospitalized for acute HF and to assess how this association varies with anemia severity.

PATIENTS AND METHODS

HFSIS 2003 has been described previously [7]. Briefly, this was a national survey including all consecutive patients admitted to 96 departments of internal medicine and 25 cardiology wards during March–April 2003. Detailed data on patient characteristics, hospital course, management during hospitalization, prehospital and discharge medications, and diagnoses were collected and recorded on structured forms by trained coordinating physicians in each participating medical center. Mortality data were obtained from the Israel population registry. Median follow-up was 33.6 months (interquartile range 9.2–57.1). The survey comprised 4102 HF patients of whom 2336 were hospitalized with acute HF. (For the 412 patients who had more than one admission during the survey period only the first hospitalization was included.) Data on hemoglobin were available for all but 4 of these 2336 patients. The current report focuses on this subset of 2332 patients. Anemia was defined according to the World Health Organization criteria [8] as Hb < 13 g/dl for men and < 12 g/dl for women. Among anemic patients, Hb ≥

HF = heart failure
HFSIS = Heart Failure Survey in Israel
Hb = hemoglobin

10 g/dl was classified as mild. Severe anemia was defined as Hb < 10 g/dl for both men and women owing to the widely practiced guidelines to transfuse patients with acute coronary syndromes with Hb < 10 g/dl (or hematocrit < 30) [9].

VARIABLE DEFINITION

- *Hypertension* was defined as blood pressure > 140/90 mmHg, or if hypertension was reported on admission, discharge, or as etiology of HF
- *Renal insufficiency* was defined as creatinine > 1.5 mg/dl or if renal failure was reported as an admission or discharge diagnosis or as a precipitating factor of HF. Glomerular filtration rate was calculated using the MDRD (modification of diet in renal disease) estimation
- *Dyslipidemia* was defined if reported as a cardiovascular risk factor or if any of the following criteria were met: total cholesterol > 200 mg/dl, low density lipoprotein-cholesterol > 130 mg/dl, high density lipoprotein-cholesterol < 40 mg/dl, or triglycerides > 150 mg/dl.

STATISTICAL ANALYSIS

Data were analyzed using the SAS® software version 8.2 (SAS institute, Cary, NC, USA). Characteristics by anemia status are presented as frequencies or mean ± SD unless otherwise specified, and compared by chi-square tests for categorical variables, analysis of variance for normally distributed continuous variables, or by the non-parametric Kruskal-Wallis test for all other variables.

P measures the statistical significance of the comparison of variables among the three groups. Trend in proportions (denoted the *P* trend) was assessed by the Mantel-Haenzel chi-square test. Linear trend in mean of blood pressure and laboratory tests was performed applying the CONTRAST statement with the SAS GLM procedure. The cumulative probability of mortality by anemia groups was calculated with the Kaplan-Meier method. Curves were compared using the log-rank test.

Age and multivariate adjusted hazard ratios were obtained using the Cox proportional hazard model. The proportional hazard assumption was ascertained by running a model including anemia groups and a time-dependent explanatory variable for each group to test the assumption of a no time-dependent effect. No significant deviation from the proportional hazard assumption was detected.

The predictive ability of each model was evaluated using a *C*-statistic corresponding to the area under-a-receiver operating characteristics curve [10]. *C*-statistics ranged between 0.6 for the age-adjusted model and 0.7 for the multivariate models. Variable selection was based on clinical judgment and univariate association with mortality. Use of medication in the models refers to discharge recommendation for those who survived their hospital stay, or medication before admission for those who died in the hospital.

RESULTS

DEMOGRAPHICS

Among the 2332 patients who were admitted for first-time or acute exacerbation of HF, more than half (1288, 55%) were anemic, and most of the anemic patients had mild anemia (994, 77%) [Table 1]. On average, the anemic patients were 2 years older than the non-anemic patients ($P < 0.0001$). The proportion of men was similar among anemic and non-anemic patients. Severe anemia was more prevalent among women than among men [Table 1].

CO-MORBIDITIES

Patients with anemia were more likely to have diabetes mellitus [Table 1]. Renal insufficiency was more prevalent among anemic patients, particularly those with severe anemia, and GFR was inversely associated with anemia and its severity. Dyslipidemia demonstrated an inverse correlation with the presence and severity of anemia. There was no significant correlation with hypertension or coronary artery disease.

On admission, patients with anemia had a lower heart rate ($P = 0.04$) and a lower diastolic blood pressure ($P < 0.0001$) compared to those without anemia. Systolic blood pressure

GFR = glomerular filtration rate

Table 1. Characteristics of 2332 patients hospitalized for acute HF, grouped by anemia severity

	No anemia (n=1044)	Mild anemia (n=994)	Severe anemia (n=294)	*P* value	*P* trend
Men	558 (53.4%)	596 (60.0%)	136 (46.3%)	‹ 0.0001	0.67
Age (yr, mean ± SD)	72.5 ± 12.9	74.8 ± 11.4	74.9 ± 11.2	‹ 0.0001	0.002
History of					
Diabetes	474 (45.4%)	565 (56.8%)	166 (56.5%)	‹ 0.0001	‹ 0.0001
Renal insufficiency	294 (28.2%)	493 (49.6%)	183 (62.2%)	‹ 0.0001	‹ 0.0001
Hypertension	794 (76.1%)	762 (76.7%)	225 (76.5%)	0.95	0.79
CAD	843 (80.7%)	830 (83.5%)	238 (81.0%)	0.24	0.45
Dyslipidemia	641 (61.4%)	573 (57.6%)	142 (48.3%)	0.0003	0.0001
Blood pressure* (mmHg, mean ± SD)					
Systolic	145.3 ± 32.9	142.1 ± 32.2	146.5 ± 33.)	0.03	0.52
Diastolic	81.4 ± 17.2	76.7 ± 16.3	75.4 ± 16.9	‹ 0.0001	‹ 0.0001
Heart rate* (mean ± SD)	87.5 ± 21.7	85.2 ± 21.2	85.1 ± 20.2	0.04	0.10
Smoking, current	161 (15.4%)	83 (8.4%)	11 (3.7%)	‹ 0.0001	‹ 0.0001
Laboratory (mean ± SD)					
Sodium (mEq/L)	138.3 ± 9.5	139.2 ± 39.4	137.9 ± 4.9	0.65	0.82
Glucose (mg/dl)	168.7 ± 87.5	169.4 ± 95.8	160.9 ± 85.3	0.35	0.20
GFR (ml/min/1.73 m²)	63.6 ± 21.2	54.7 ± 29.8	47.7 ± 43.4	‹ 0.0001	‹ 0.0001
TC (mg/dl)	186 ± 53	170 ± 59	165 ± 48	‹ 0.0001	‹ 0.0001

* Measured on admission

Values presented are No. (%), unless otherwise specified

CAD = coronary artery disease, TC = total cholesterol, GFR = glomerular filtration rate, SD = standard deviation

Table 2. Severity of HF, grouped by anemia severity

	No anemia	Mild anemia	Severe anemia	*P* value	*P* trend
Indicators of baseline severity					
Median number of prior hospitalizations	1	1	2	‹ 0.0001	‹ 0.0001
NYHA class III or class IV	417 (41%)	458 (47%)	153 (53%)	0.0003	‹ 0.0001
Indicators of acute severity					
Dyspnea	836 (80.1%)	828 (83.3%)	246 (83.7%)	0.12	0.06
Fatigue	246 (23.6%)	254 (25.6%)	92 (31.3%)	0.03	0.01
Peripheral edema	213 (20.4%)	282 (28.4%)	96 (32.7%)	‹ 0.0001	‹ 0.0001
Pulmonary edema	333 (31.9%)	337 (33.9%)	109 (37.1%)	0.23	0.09
Shock	26 (2.5%)	23 (2.3)	7 (2.4%)	1.0	0.84
Syncope	22 (2.1%)	20 (2.0%)	7 (2.4%)	0.93	0.87
Arrhythmia	63 (6.0%)	64 (6.4%)	12 (4.1%)	0.32	0.42

Values presented are No. (%)

Table 3. All-cause mortality, grouped by anemia severity

	No anemia	Mild anemia	Severe anemia	*P* value	*P* trend
In-hospital	47 (4.5%)	58 (5.9%)	25 (8.6%)	0.024	0.008
30 day	73 (7.0%)	92 (9.3%)	35 (11.9%)	0.019	0.005
6 month	155 (14.9%)	235 (23.7)	77 (26.3%)	‹ 0.0001	‹ 0.0001
1 year	230 (22.2%)	333 (33.6%)	117 (39.9%)	‹ 0.0001	‹ 0.0001
Total*	552 (52.9%)	710 (71.4%)	212 (72.1%)	‹ 0.0001	‹0.0001
HR (95%CI) adjusted for					
Age	Reference	1.52 (1.36–1.69)	1.71 (1.46–2.00)		
Model 1†	Reference	1.35 (1.20–1.52)	1.50 (1.27–1.77)		
Model 2‡	Reference	1.32 (1.17–1.48)	1.42 (1.20–1.67)		

* Median follow-up time 33.6 months (interquartile range 9.2–57.1)

† Adjusted for age, gender, diabetes, hypertension, renal insufficiency, ischemic heart disease, NYHA class, systolic blood pressure (continuous), current smoking

‡ Adjusted for variables included in model 1 and medication use (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, aspirin) , serum Na level and dyslipidemia

HR = hazard ratio, CI = confidence interval

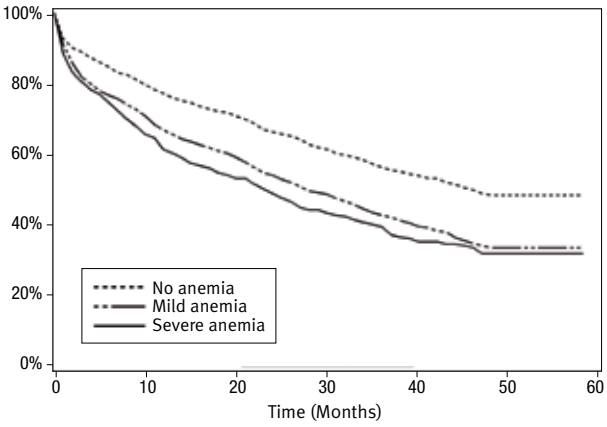
was lowest among patients with mild anemia ($P = 0.03$, without significant trend), but these mild anemia patients had also received more antihypertensive drugs than patients in the other groups (data not shown). Fewer anemic patients smoked compared with non-anemic patients, but there was no association between anemia and past smoking status.

HF SEVERITY

Table 2 examines the severity of the HF, both prior to and during hospitalization for the acute episode, by anemia status. Severity of the acute episode was indicated by symptoms and findings recorded upon admission. The number of prior hospitalizations rose from a median of 1 for non-anemic patients to 2 for severe anemia patients ($P > 0.0001$). Only 41% of the non-anemic patients had significant functional limitation (New York Heart Association class III/IV) prior to the index exacerbation, compared with 47% and 53% of the mildly and severely anemic patients, respectively.

Fatigue and peripheral edema increased significantly with increasing severity of anemia. There were no significant differences in pulmonary edema, shock, syncope or arrhythmia across anemia groups.

Figure 1. Age-adjusted Kaplan-Meyer survival curve for the three groups vs. time. Median follow-up time was 33.6 months (interquartile range 9.2–57.1). Note that from early on, mild and severe anemia behave similarly



EJECTION FRACTION

EF data were available for 1717 patients in the study. Of those patients, 54% were anemic and 46% were not. There was a slight trend where increased EF was associated with a greater percentage of patients with anemia (e.g., 56% of patients with EF > 50% were anemic, while 54% of the patients with EF < 30% were anemic), but this trend was not statistically significant ($P = 0.66$).

MORTALITY

For all points in time, increasingly severe anemia was associated with increased mortality [Table 3]. During hospital stay of varying length, mortality was lowest among anemia-free patients and highest among those with severe anemia (P trend = 0.008). A similar significant trend was observed at one year, with rates of 22.2%, 33.6% and 39.9% for anemia-free, mild anemia and severe anemia, respectively (P and P trend < 0.0001).

MULTIVARIABLE ADJUSTED MORTALITY RISK

The age-adjusted cumulative probability of survival is presented in Figure 1. Age-adjusted mortality hazard associated with anemia was higher than hazard in anemia-free patients

EF = ejection fraction

(52% higher in mildly anemic and 71% higher in severely anemic patients) [Table 3]. With additional adjustment for gender, diabetes, hypertension, renal insufficiency, coronary heart disease, NYHA class, systolic blood pressure (continuous), and current smoking status (model 1), the hazard ratio was attenuated to 1.35 and 1.50 for mild and severe anemia, respectively [Table 3]. Further adjustment for medication use, sodium level and dyslipidemia (model 2) yielded a HR of similar magnitude [Table 3]. When anemia classification in model one was replaced by hemoglobin as a continuous variable, an increase of 1 g/dl was associated with HR = 0.91 (95% confidence interval 0.89–0.94). In both models, male gender, diabetes, renal insufficiency, and NYHA class III or IV demonstrated a significant contribution to mortality, but higher systolic blood pressure was found to have a "protective" association (model 2: HR = 0.85, 95%CI 0.80–0.90). In the second model, use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was protective (HR = 0.84, 95%CI 0.75–0.94), while aspirin usage was only borderline protective (HR = 0.90, 95%CI 0.81–1.01).

DISCUSSION

In a large cohort of patients hospitalized for acute HF, anemia was very common. The prevalence of anemia in HF patients varies greatly in the literature, which can be explained partially by differences in the definition of anemia and the criteria for inclusion or exclusion of patients [11]. In the vast majority of patients in our study hemoglobin was above 10 g/dl, which is consistent with other reports [5]. Our finding that anemic patients were older than non-anemic patients is supported by a number of other studies [11,12]. There was no significant correlation between EF and anemia.

As expected, a diagnosis of renal insufficiency and a lower calculated GFR were more prevalent among anemic patients. Diabetes too was more prevalent among anemic patients, and this may also be related to nephropathy. While anemia (especially due to hemorrhage) can cause acute renal failure, it is more likely that the renal failure preceded the anemia because the failing kidney produces less erythropoietin. Although renal insufficiency and anemia are not independent entities [13], they each have an independent role in HF [14]. If at least some patients suffer from anemia because of their renal insufficiency, treatment with erythropoietin may improve their outcome.

Three aspects of clinical HF severity were assessed in relation to anemia: baseline severity before admission, severity of the acute HF itself, and mortality during and after the hospitalization period. Note that more than half the severely anemic patients were found to be in NYHA class III or IV at baseline before being admitted to hospital. They also had more prior admissions than the other groups. Despite the differences in baseline HF severity, once the acute HF event began, the distribution of symptoms and physical findings was similar in all hemoglobin groups.

Our data demonstrate that anemic patients, mild and severe, had consistently increased mortality throughout the follow-up period compared to anemia-free patients, which was consistent (albeit with a slight attenuation) after age adjustment as well as other multivariable adjustments. The mortality of the two anemia groups was similar.

Over the past several years an increasing number of studies have examined the relationship between anemia and HF, with several of these studies showing either no association between anemia and mortality in HF patients [15,16] or an association only in subgroups of the population: men [17] or patients younger than 75 years old [18]. Almost all the larger studies (> 1000 patients), however, demonstrated such an association [3,5,12,19-21]. One exception is the study of more than 50,000 patients by Kosiborod et al. [6], who found that once adjusted for multiple variables, there was no relationship between anemia and mortality. Similar to our study, they examined patients admitted to the hospital with HF, and the reason for the differing results is unclear.

A number of the large studies compared not only anemia but the various levels of hemoglobin and their impact upon mortality in HF, with differing conclusions [5,6,12,19,20]. We found that mortality is increased even with mild anemia. Similarly, Horwich and co-authors [12] found a clear linear relationship between Hb level and mortality among patients with advanced heart failure (NHYA class III or IV). This association extended into Hb values, which are not considered to be anemia by the WHO criteria used in our study. In addition to the differences among the studies in the definition of anemia, there are differences in the setting of the studies and the condition of the patients. For example, some studies examined patients with chronic stable HF in an ambulatory setting. Such differences hamper direct comparison among studies.

The "protective" association of hypertension with mortality can be explained by reduced tissue perfusion due to lower systolic blood pressure which, as the failure progresses, leads eventually to multi-organ failure and death. This finding is also consistent with other studies [22].

This study has limitations. It cannot provide information regarding a causal relationship between anemia and any risk factor as they were measured at the same time. One could postulate that anemia causes decreased oxygen-carrying capacity, forcing the heart to compensate with increased stroke volume and heart rate. This high output may in turn cause the failed heart to fail further [13]. Worsening heart failure can also cause worsening anemia by several possible mechanisms, including

NYHA = New York Heart Association
HR = hazard ratio

WHO = World Health Organization

renal dysfunction and neurohormonal and pro-inflammatory cytokine activation [13]. On the other hand, anemia may just be a marker for more severe HF.

If anemia were a cause of more severe HF and greater mortality, one would expect that correcting the anemia would improve the outcomes. A randomized controlled trial of 32 patients with NYHA class III and IV demonstrated that erythropoietin treatment reduced hospitalizations, increased left ventricular ejection fraction, reduced HF class, reduced the required dose of intravenous furosemide, and slowed the decline of GFR [23]. Subsequent studies demonstrated similar results in other subgroups of HF patients. The benefits of long-term treatment are unclear, especially in light of more recent information that excessive erythropoietin-induced raising of Hb may be deleterious [24], and that blood transfusions may only be beneficial in the short term [25]. It does, however, hint that the anemia may at least play a role in causing the worse baseline HF and the increased mortality in these patients, and that its correction may improve outcomes.

In summary, this multicenter national study of patients with HF demonstrates that anemia is common in these patients. It demonstrates that the anemic patients have worse renal function and more severe baseline HF. Although by most parameters the severity of their HF exacerbation is similar, they have a significantly higher mortality than non-anemic patients. Even patients with mild anemia experience this poor outcome and surprisingly have a mortality that approaches that of the severely anemic patients. Well-designed randomized control trials are needed to determine whether ameliorating the anemia with blood products or with erythropoietin improves long-term quality of life and survival.

Corresponding author:
Dr. M. Mittelman and Dr. H.S. Oster
Dept. of Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
Phone: (972-3) 697-3366
Fax: (972-3) 697-4855
email: moshemt@tlvmc.gov.il, howardo@tlvmc.gov.il

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"I paint objects as I think them, not as I see them"

Pablo Picasso (1881-1973), Spanish painter, sculptor, printmaker, ceramicist, and stage designer considered one of the greatest and most influential artists of the 20th century