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Anemia at hospital admission and its relation to outcomes in patients with heart failure (from the polish cohort of 2 European Society of Cardiology Heart Failure Registries)

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Anemia is a commonly observed co-morbidity in heart failure (HF). The aim of the study was to assess prevalence, risk factors for, and effect of anemia on short- and long-term outcomes in HF. The study included 1,394 Caucasian patients hospitalized for HF, with known hemoglobin concentration on hospital admission, participating in 2 HF registries of the European Society of Cardiology (Pilot and Long-Term). Anemia was defined as hemoglobin concentration of <13 g/dl for men and <12 g/dl for women. Primary end points were (1) all-cause death at 1 year and (2) a composite of all-cause death and rehospitalization for HF at 1 year. Secondary end points included inter alia death during index hospitalization. In addition, we investigated the effect of changes in hemoglobin concentration during hospitalization on prognosis. Anemia occurred in 33% of patients. Predictors of anemia included older age, diabetes, greater New York Heart Association class at hospital admission and kidney disease. During 1-year follow-up, 21% of anemic and 13% of nonanemic patients died (p <0.0001). Combined primary end point occurred in 45% of anemic and in 33% of nonanemic patients (p <0.0001). Anemia was strongly predictive of all the prespecified clinical end points in univariate analyses but not in multivariate analyses. Changes in hemoglobin concentration during hospitalization had no effect on 1-year outcomes. In conclusion, anemia was present in 1/3 of patients with HF. Mild-to-moderate anemia seems more a marker of older age, worse clinical condition, and a higher co-morbidity burden, rather than an independent risk factor in HF.

Identification and prevention of risk factors for heart failure (HF) decompensation constitute the fundamentals of comprehensive care in HF.[1, 2, 3] Although anemia is a commonly observed co-morbidity in HF, associated with significantly worse prognosis, there is no certain explanation on how it affects mortality, provokes HF exacerbations, and influences the course of hospitalization.[4, 5, 6, 7, 8, 9] There are encouraging reports on the effectiveness of iron therapy in reducing HF symptoms; however, there are no favorable results in terms of mortality in HF.[10, 11, 12, 13] Thus, clinical implications of anemia in HF remain to be established. The aim of this study was to evaluate the prevalence of anemia in patients hospitalized for HF, compare baseline characteristics and course of index hospitalization of anemic and nonanemic HF patients, and determine the impact of anemia on short- and long-term outcomes in HF. Additional objectives of the analysis were to assess risk factors for anemia in HF patients and to evaluate changes in hemoglobin concentration during hospitalization and their prognostic significance in HF.

Methods

The study is based on 2 prospective, multicenter, observational surveys of patients with HF, conducted by the European Society of Cardiology (ESC). The first, ESC-HF Pilot Survey, which has already been completed, was conducted from October 2009 to May 2010 in 136 European cardiology centers, including 29 centers from Poland.[14] The second, ESC-HF Long-Term Registry, is a 3-phase study, conducted in 211 European cardiology centers, including 35 centers from Poland.[15] In the ESC-HF Pilot Survey and during phase I of the ESC-HF Long-Term Registry (lasting from May 2011 to April 2013), patients were enrolled on 1 specific day of the week for 12 consecutive months in each of the participating centers. In phase II and phase III (still on-going) of the ESC-HF Long-Term Registry, patients are enrolled during 5 days per trimester. The current analysis included Polish participants of the ESC-HF Pilot Survey and of phase I of the ESC-HF Long-Term Registry.

The surveys included both ambulatory and hospitalized HF patients, who were aged over 18 years. There were no specific exclusion criteria. Local ethics committees approved the surveys in accordance with the regulations of each participating country. All patients were provided with detailed information on the registries and signed informed written consent.

The current analysis included only patients admitted to hospital for new-onset or worsening HF, in whom data on hemoglobin concentration on hospital admission were available.

Patients were divided into 2 groups (anemic and nonanemic) according to hemoglobin concentration on admission. Following the World Health Organization criteria, anemia was defined as hemoglobin concentration of <13 g/dl for men and <12 g/dl for women. Severe anemia was defined as hemoglobin level <9 g/dl. Anemic and nonanemic patients were compared with regard to baseline characteristics, course of index hospitalization, diagnostic tests results, implemented treatment, in-hospital outcomes (death during hospitalization, length of hospital stay, time in intensive cardiac care unit [ICCU]) and 1-year outcomes (all-cause death and death or rehospitalization for decompensated HF).

The primary end points were (1) all-cause death at 1 year and (2) a composite of all-cause death and hospital readmissions for decompensated HF at 1 year. Secondary end points included (1) death during index hospitalization, (2) hospital stay >7 days, (3) time in ICCU >3 days, and (4) a worse clinical status (New York Heart Association [NYHA] class III or IV) at hospital discharge.

The main goal of the study was to determine whether anemia at hospital admission was predictive of the primary and the secondary end points in patients with HF. In addition, we assessed, whether changes in hemoglobin concentration during index hospitalization were related to 1-year outcomes (all-cause death and death or rehospitalization for decompensated HF). Increase and decrease in hemoglobin concentration were defined as changes of ≥1 g/dl during index hospitalization. Finally, we sought to identify risk factors for anemia at admission in hospitalized HF patients.

Statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, Illinois) and SAS 9.2 (SAS Institute Inc., Cary, North Carolina) software. Normally distributed continuous variables were presented as mean value and SD, whereas for ordinal variables and nonnormally distributed continuous variables, median value and interquartile range were given. Significance of differences between the 2 groups was determined by Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous and ordinal variables. Cox proportional hazards regression model was used to identify predictors of the primary end points, as well as to assess association of hemoglobin changes during index hospitalization and 1-year outcomes. To determine the predictors of the remaining secondary end points, univariate and multivariate logistic regressions were performed. Multivariate analyses included all variables found to be statistically significant in univariate analyses, maintaining adequate events per predictor variable values.[16] The list of all variables included in univariate analyses (both in Cox proportional hazards analyses and in logistic regression analyses) is provided in Supplementary Table S1. Kaplan-Meier curves were developed for both primary end points. For all tests, p value below 0.05 was considered significant. All tests were 2 tailed.

Results

Figure 1 shows the flow chart of patient selection for the present study. Finally, the study group included 1,394 Caucasian patients. Median hemoglobin concentration at hospital admission was 13.4 g/dl (interquartile range: 12.0 to 14.5 g/dl). Anemia at hospital admission was present in 466 of the 1,394 patients (33%). Severe anemia was reported in 28 patients (2%). Comparison of clinical characteristics and course of index hospitalization of anemic and nonanemic patients is presented in Tables 1 and 2.

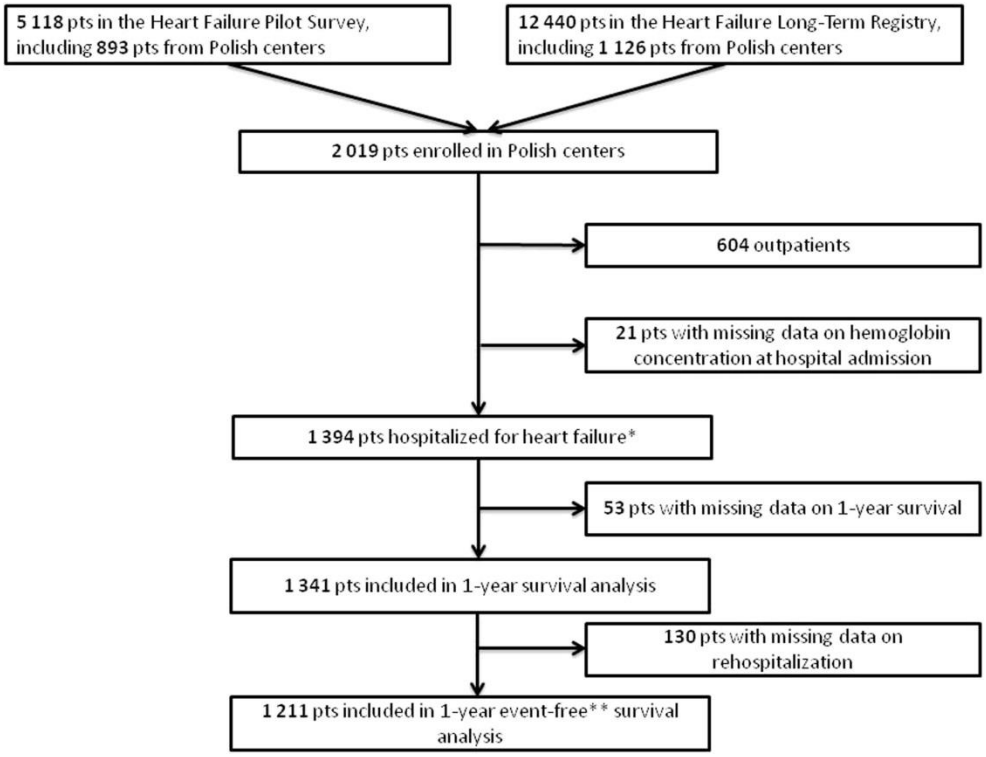

Figure 1. Flow chart of patient enrollment in the current analysis. *included in the comparative analysis of anemic and nonanemic patients and in the analyses of in-hospital outcomes. **death or rehospitalization for heart failure. pts = patients.

Table 1. Baseline characteristics, clinical, and laboratory status at hospital admission of anemic and nonanemic patients

Variable	Non-anemic *(n=928)*	Anemic *(n=466)*	*P*-value
Baseline characteristics			
Age (years)	67.6 (58.0-77.0)	73.0 (64.2-81.0)	**<0.0001**
Men	599 (65%)	319 (69%)	0.15
Body mass index (kg/m^2)	28.0 (25.0-31.3); n=885	26.8 (24.4-30.8); n=432	**0.003**
Current left ventricular ejection fraction (%)	36 (25-50); n=814	37 (25-50); n=398	0.45
Previous heart failure hospitalization	473/927 (51%)	288/464 (62%)	**<0.0001**
Idiopathic dilated cardiomyopathy	133 (15%)	41 (9%)	**0.003**
Ischemic etiology of heart failure	513 (55%)	293 (63%)	**0.01**
Prior percutaneous coronary intervention or coronary artery bypass grafting	296 (32%)	177/465 (38%)	**0.02**
Valve disease etiology of heart failure	109 (12%)	67 (14%)	0.17
Moderate or severe aortic stenosis	61/830 (7%)	39/403 (10%)	0.18
Moderate or severe aortic regurgitation	53/830 (6%)	46/403 (11%)	**0.003**
Moderate or severe mitral regurgitation	412/828 (50%)	210/404 (52%)	0.47
Moderate or severe tricuspid regurgitation	274/827 (33%)	181/404 (45%)	**<0.0001**
Hypertension	629/926 (68%)	330 (71%)	0.30
History of atrial fibrillation	376/926 (41%)	232 (50%)	**0.001**
Peripheral artery disease	101/927 (11%)	77/465 (17%)	**0.004**
Diabetes	296 (32%)	198 (43%)	**<0.0001**
Chronic kidney disease	161 (17%)	132/464 (28%)	**<0.0001**
Chronic obstructive pulmonary disease	142 (15%)	119/464 (26%)	**<0.0001**
Prior stroke or transient ischemic attack	95 (10%)	51/464 (11%)	0.71
3 or more non-cardiac comorbidities[a]	60 (7%)	54/464 (12%)	**0.001**
Current or former smoking	519/915 (57%)	251/455 (55%)	0.60
Alcohol usage	515/899 (57%)	236/448 (53%)	0.12
Previous pharmacotherapy			
Diuretic	598/912 (66%)	316/449 (70%)	0.09
Aldosterone antagonist	409/907 (45%)	197/450 (44%)	0.69
Angiotensin converting enzyme inhibitor	574/908 (63%)	275/449 (61%)	0.51
Angiotensin receptor blocker	87/906 (10%)	28/448 (6%)	**0.04**
β-blocker	677/908 (75%)	334/449 (74%)	0.95
Statin	490/910 (54%)	252/447 (56%)	0.39
Anticoagulant	270/911 (30%)	156/448 (35%)	0.054
Antiplatelet	476/909 (52%)	248/448 (55%)	0.33
Clinical status at admission			
Cardiogenic shock	22/890 (3%)	12/448 (3%)	0.86
Heart rate (b.p.m.)	80 (70-100); n=927	80 (70-100); n=464	0.75
Systolic blood pressure (mmHg)	130 (112-147); n=926	130 (110-140); n=465	0.17
NYHA class I	6/924 (1%)	4/463 (1%)	0.74
NYHA class II	249/924 (27%)	76/463 (16%)	**<0.0001**
NYHA class III	425/924 (46%)	221/463 (48%)	0.57
NYHA class IV	244/924 (26%)	162/463 (35%)	**0.001**
Ventricular fibrillation or ventricular tachycardia as a cause of admission	87/925 (9%)	21 (5%)	**0.001**
Acute coronary syndrome as a cause of heart failure decompensation	184/926 (20%)	88/465 (19%)	0.72
Atrial fibrillation as a cause of heart failure decompensation	235/927 (25%)	115 (25%)	0.79
Infection as a cause of heart failure decompensation	85/924 (9%)	85 (18%)	**<0.0001**

Table 1. Baseline characteristics, clinical, and laboratory status at hospital admission of anemic and nonanemic patients

Variable	Non-anemic *(n=928)*	Anemic *(n=466)*	*P*-value
Laboratory findings at admission			
Hemoglobin (g/dl)	14.1 (13.4-15.0)	11.5 (10.5-12.1)	**<0.0001**
Serum creatinine (mg/dl)	1.04 (0.89-1.29); n=908	1.21 (0.99-1.64); n=462	**<0.0001**
Estimated glomerular filtration rate (ml/min/1.73m^2)	66.8 (52.3-86.3); n=908	56.2 (40.3-75.8); n=462	**<0.0001**
Serum sodium (mmol/l)	139 (137-141); n=925	138 (135-141); n=463	**0.03**

Categorical data are presented as number of patients and percentages. Continuous variables are shown as a median and interquartile range. p Values are given for differences between the groups. Bolded text indicates p values <0.05.
∗ Included diabetes, stroke or transient ischemic attack, peripheral artery disease, chronic obstructive pulmonary disease, and chronic kidney disease.

Table 2. Clinical course of index hospitalization, in-hospital, and long-term outcomes of anemic and nonanemic patients

Variable	Non-anemic *(n=928)*	Anemic *(n=466)*	*P*-value
Management during index hospitalization			
Inotropic support	97/925 (11%)	73/464 (16%)	**0.01**
Intravenous diuretics	580/925 (63%)	357/464 (77%)	**<0.0001**
Intravenous nitrates	116/925 (13%)	78/463 (17%)	**0.03**
Percutaneous coronary intervention / coronary artery bypass grafting during hospitalization	127/925 (14%)	51/465 (11%)	0.15
Status at discharge*			
Heart rate (b.p.m.)	70 (65-80); n=900	70 (66-80); n=436	0.14
Systolic blood pressure (mmHg)	120 (110-130); n=906	120 (105-130); n=441	0.10
NYHA class I	60/909 (7%)	31/442 (7%)	0.82
NYHA class II	597/909 (66%)	242/442 (55%)	**<0.0001**
NYHA class III	238/909 (26%)	162/442 (37%)	**<0.0001**
NYHA class IV	14/909 (2%)	7/442 (2%)	1.00
Hemoglobin (g/dl)	13.8 (12.9-14.9); n=534	11.4 (10.5-12.4); n=305	**<0.0001**
Serum creatinine (mg/dl)	1.05 (0.90-1.30); n=639	1.20 (0.97-1.67); n=334	**<0.0001**
Serum sodium (mmol/l)	139 (136-141); n=683	138 (136-141); n=357	**0.04**
Pharmacotherapy at discharge*			
Diuretic	762/907 (84%)	391/443 (88%)	**0.04**
Aldosterone antagonist	618/906 (68%)	268/443 (61%)	**0.01**
Angiotensin converting enzyme inhibitor	700/908 (77%)	313/443 (71%)	**0.01**
Angiotensin receptor blocker	96/906 (11%)	34/442 (8%)	0.10
β-blocker	824/908 (91%)	390/443 (88%)	0.13
Statin	627/908 (69%)	301/443 (68%)	0.71

Table 2. Clinical course of index hospitalization, in-hospital, and long-term outcomes of anemic and nonanemic patients

Variable	Non-anemic *(n=928)*	Anemic *(n=466)*	*P*-value
Anticoagulant	371/907 (41%)	205/443 (46%)	0.07
Antiplatelet	590/908 (65%)	292/443 (66%)	0.76
In-hospital outcome			
Hospitalization length (days)	7 (4-10)	8 (5-13)	**<0.0001**
Time in Intensive Cardiac Care Unit (days)	0 (0-3); n=895	1 (0-6); n=447	**<0.0001**
Death during hospitalization	19 (2%)	23 (5%)	**0.004**
1-year outcome†			
Death	118/898 (13%)	95/443 (21%)	**<0.0001**
Death or rehospitalization	266/803 (33%)	183/408 (45%)	**<0.0001**

Categorical data are presented as number of patients and percentages. Continuous variables are shown as a median and interquartile range. p Values are given for differences between the groups. Bolded text indicates p values <0.05.
∗ In patients who survived to hospital discharge.
† Including patients who died during index hospitalization.

In the study group, independent predictors of anemia at hospital admission included older age, diabetes, greater NYHA class at admission, and kidney disease.

Data on 1-year survival were available for 1,341 patients. A total of 213 patients (16%) died during 1-year follow-up: 21% of the anemic and 13% of the nonanemic groups (Table 2). Kaplan-Meier curves for death at 1 year are presented in Figure 2. Predictors of death at 1 year are listed in Table 3.

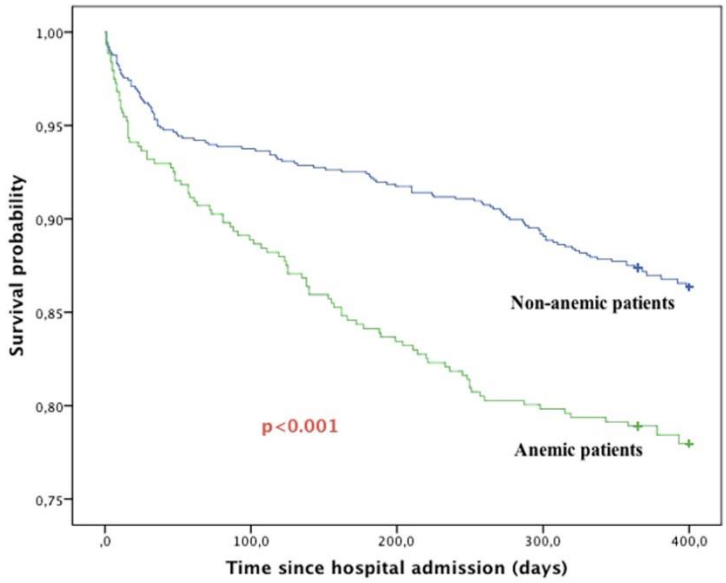

Figure 2. Kaplan-Meier curves for all-cause death at 1 year.

Table 3. Univariate and multivariate analyses of predictors of death at 1 year

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Anemia at admission	**1.74 (1.33-2.28)**	**<0.0001**	0.91 (0.72-1.44)	0.91
Age (per 10 years)	**1.04 (1.03-1.05)**	**<0.0001**	**1.03 (1.02-1.05)**	**<0.0001**
Current left ventricular ejection fraction (per 5%)	**0.98 (0.97-0.99)**	**0.001**	**0.97 (0.96-0.98)**	**<0.0001**
Peripheral artery disease	**1.50 (1.05-2.15)**	**0.03**	1.48 (0.98-2.25)	0.064
Chronic kidney disease	**1.87 (1.40-2.49)**	**<0.0001**	1.40 (0.98-2.00)	0.063
NYHA class at admission (per 1 class)	**2.33 (1.90-2.86)**	**<0.0001**	**1.74 (1.32-2.29)**	**<0.0001**
Serum sodium at admission (per 1 mmol/l)	**0.91 (0.89-0.93)**	**<0.0001**	**0.93 (0.90-0.96)**	**<0.0001**
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker at discharge	**0.32 (0.24-0.43)**	**<0.0001**	**0.57 (0.38-0.83)**	**0.004**
β-blocker at discharge	**0.30 (0.22-0.40)**	**<0.0001**	**0.55 (0.36-0.84)**	**0.01**

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the primary end point in the multivariate model. Other variables predictive of the primary end point in univariate analyses included body mass index, heart rate and systolic blood pressure at admission, history of atrial fibrillation, chronic obstructive pulmonary disease, diabetes and alcohol usage, infection as a cause of heart failure decompensation, moderate or severe mitral regurgitation, moderate or severe tricuspid regurgitation, serum creatinine at admission, statin, and antiplatelet treatment at discharge, all of them were also included in the multivariate model but did not prove independent predictors of death at 1 year.
Bolded text indicates p values <0.05.
CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.

Data on hospital readmissions for decompensated HF at 1 year were available for 1,211 patients. A total of 449 patients (37%) died or were readmitted for HF during 1-year follow-up: 45% of the anemic and 33% of the nonanemic groups (Table 2). Kaplan-Meier curves for death or rehospitalization for HF at 1 year are presented in Figure 3. Predictors of death or rehospitalization for HF at 1 year are presented in Table 4.

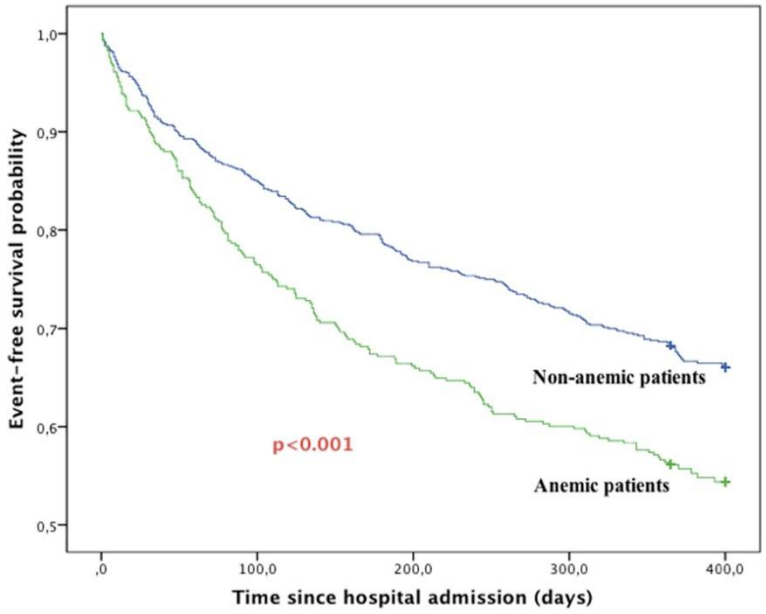

Figure 3. Kaplan-Meier curves for all-cause death or rehospitalization for heart failure at 1 year.

Table 4. Univariate and multivariate analyses of predictors of death or rehospitalization for heart failure at 1 year

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Anemia at admission	**1.50 (1.25-1.81)**	**<0.0001**	1.11 (0.89-1.40)	0.35
Age (per 10 years)	**1.01 (1.01-1.02)**	**0.001**	**1.01 (1.003-1.02)**	**0.04**
Current left ventricular ejection fraction (per 5%)	**0.98 (0.98-0.99)**	**<0.0001**	**0.98 (0.98-0.99)**	**<0.0001**
History of heart failure hospitalization	**1.40 (1.16-1.69)**	**0.001**	1.25 (0.996-1.58)	0.053
Diabetes	**1.32 (1.10-1.60)**	**0.004**	**1.27 (1.02-1.58)**	**0.03**
Chronic kidney disease	**1.60 (1.31-1.96)**	**<0.0001**	1.24 (0.97-1.59)	0.085
Alcohol usage	**0.73 (0.60-0.88)**	**0.001**	**0.78 (0.63-0.98)**	**0.03**
NYHA class at admission (per 1 class)	**1.82 (1.59-2.08)**	**<0.0001**	**1.40 (1.18-1.66)**	**<0.0001**
Serum sodium at admission (per 1 mmol/l)	**0.95 (0.93-0.96)**	**<0.0001**	**0.97 (0.95-0.99)**	**0.002**
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker at discharge	**0.48 (0.39-0.59)**	**<0.0001**	**0.69 (0.53-0.90)**	**0.01**
β-blocker at discharge	**0.52 (0.41-0.66)**	**<0.0001**	**0.72 (0.52-0.98)**	**0.04**

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the primary end point in the multivariate model. Other variables predictive of the primary end point in univariate analyses included heart rate and systolic blood pressure at admission, history of coronary artery disease, atrial fibrillation and chronic obstructive pulmonary disease, infection as a cause of heart failure decompensation, moderate or severe tricuspid regurgitation, serum creatinine at admission, statin, and antiplatelet treatment at discharge, all of them were also included in the multivariate model but did not prove independent predictors of death or rehospitalization for heart failure at 1 year.
Bolded text indicates p values <0.05.
CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.

Anemia was found to be strongly predictive of both primary end points only in univariate analyses, without statistical significance in multivariate analyses (Tables 3 and 4).

With regard to the analysis of the secondary end points, in the study group of 1,394 patients, 42 patients (3%) died during index hospitalization: 5% of the anemic and 2% of the nonanemic groups (Table 2). Predictors of death during hospitalization are listed in Table 5.

Table 5. Univariate and multivariate analyses of predictors of death during hospitalization

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Anemia at admission	**2.48 (1.34-4.61)**	**0.004**	1.93 (0.86-4.35)	0.11
Age (per 10 years)	**1.04 (1.01-1.07)**	**0.01**	**1.04 (1.01-1.08)**	**0.02**
Current left ventricular ejection fraction (per 5%)	**0.95 (0.92-0.98)**	**0.001**	**0.95 (0.92-0.99)**	**0.004**
Systolic blood pressure at admission (per 10 mmHg)	**0.97 (0.96-0.98)**	**<0.0001**	**0.99 (0.97-0.999)**	**0.04**
Heart rate at admission (per 10 b.p.m.)	**1.02 (1.01-1.03)**	**0.003**	**1.02 (1.01-1.03)**	**0.01**
NYHA class at admission (per 1 class)	**5.80 (3.07-10.94)**	**<0.0001**	**3.41 (1.60-7.25)**	**0.001**
Serum sodium at admission (per 1 mmol/l)	**0.88 (0.83-0.92)**	**<0.0001**	**0.88 (0.83-0.94)**	**<0.0001**
Serum creatinine at admission (per 1 mg/dl)	**1.44 (1.13-1.85)**	**0.004**	**1.41 (1.04-1.91)**	**0.03**

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the secondary end point in the multivariate model. Other variables predictive of the secondary end point in univariate analyses included acute coronary syndrome as a cause of heart failure decompensation, moderate or severe mitral regurgitation, and moderate or severe tricuspid regurgitation, all of them were also included in the multivariate model but did not prove independent predictors of death during hospitalization.
Bolded text indicates p values <0.05.
CI = confidence interval; NYHA = New York Heart Association; OR = odds ratio.

Hospital stay >7 days was reported in 603 patients (43% of the study group), including 221 of the 466 anemic patients (47%) and 382 of the 928 nonanemic patients (41%; p = 0.007). Time in ICCU >3 days was reported in 343 patients (26% of the 1,342 patients with data on ICCU stay), including 135 of 447 anemic patients (30%) and 208 of 895 nonanemic patients (23%; p = 0.003). At hospital discharge, anemic patients more often were in NYHA class III or IV compared with nonanemic patients (p <0.0001; Table 2).

Anemia was found to be predictive of all the aforementioned secondary end points only in univariate analyses, without statistical significance in multivariate analyses.

Data on hemoglobin concentration at both hospital admission and hospital discharge were available for 871 patients. During index hospitalization, hemoglobin concentration increased (by ≥ 1 g/dl) in 132 patients (15%), decreased (by ≥ 1 g/dl) in 183 patients (21%) and remained unchanged in 556 patients (64%). Changes in hemoglobin concentration during hospitalization had no effect on 1-year outcomes.

Discussion

Prevalence of anemia in patients with HF ranges from 5% to 70% in different studies, depending on anemia definition and patient characteristics.[5, 9] In our study, prevalence of anemia (33%) was similar to the frequencies observed in a meta-analysis by Groenveld et al and in the Swedish HF Registry.[6, 17] Lower prevalence of anemia (approximately 23% to 25%) was reported in 2 randomized clinical trials; however, recruited HF participants were significantly younger.[18, 19] In most randomized clinical trials, severe anemia is an exclusion criterion, which makes it difficult to precisely assess this group of patients.[18, 20]

There is a variety of pathogenetic pathways of anemia development in HF.[7, 18, 21, 22, 23, 24] In our analysis, independent risk factors for anemia included older age, diabetes, higher NYHA functional class at hospital admission, and kidney disease. In addition, anemic patients had significantly lower body mass index and were characterized by a higher cardiac and noncardiac co-morbidity burden, which might be partly explained by their older age. Due to decreased erythropoiesis, advanced chronic kidney disease leads to anemia.[22] In advanced HF, anemia may also result from iron deficiency due to malabsorption, nutritional deficiencies, and impaired metabolism and from subclinical inflammation associated with bone marrow depression (anemia of chronic disorders).[7, 8, 18] Furthermore, in hospitalized patients with severe HF, increased plasma volume and hemodilution may explain a higher prevalence of anemia.[7, 18]

The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) study and the IN-CHF Registry have demonstrated that anemic patients are less likely to receive guideline-recommended HF therapy, including β blockers and angiotensin-converting enzyme inhibitors.[21, 25] In our study, at hospital discharge, angiotensin-converting enzyme inhibitors and aldosterone antagonists were significantly less often prescribed to anemic patients. This might have been due to worse renal function in anemic patients and might also add to worse 1-year outcomes observed in anemic patients.

A meta-analysis of randomized clinical trials has shown that there is a strong association between anemia and adverse outcomes in HF.[6] However, it is unclear that how anemia affects mortality and morbidity and whether it is indeed an independent risk factor or only a marker of worse clinical condition and a mediator of increased risk.[18, 20, 21]

The results of our study suggest that although anemia is a strong marker of unfavorable prognosis in HF, it is not an independent risk factor for adverse outcomes. This may be dictated by the fact that most predictors of anemia, such as older age, higher NYHA class at hospital admission, kidney disease, and diabetes overlaped with predictors of clinical endpoints. Likewise, the same risk factors for anemia were identified in the Swedish HF Registry, IN-CHF Registry (Italian Registry of Congestive Heart Failure), and Val-HeFT (Valsartan in Heart Failure Trial) trial.[17, 18, 25]

In our study, mean age of the entire population (68 years) and the anemic cohort (73 years) was consistent with those of patients studied in the Swedish HF Registry and the EVEREST trial.[17, 21] In contrast, in the randomized Val-HeFT trial and in the IN-CHF Registry, anemic HF patients were younger (66 and 67 years, respectively); in those patients, anemia was associated with increased morbidity and mortality.[17, 25] In the Swedish HF Registry, the influence of anemia on mortality was significantly greater in younger patients and in those with more stable HF.[17] In the ATTEND (Acute Decompensated Heart Failure Syndromes) registry, there was no association between anemia on hospital admission and all-cause mortality in elderly patients.[9]

Similarly, to the relation between anemia and 1-year outcomes in our study, in-hospital mortality rate was not influenced by anemia in multivariate analysis, despite a significant association in univariate analysis (with an odds ratio of almost 2.5). This indicates that although anemia itself may not be a direct cause of unfavorable in-hospital outcome, HF patients with concomitant anemia constitute a high-risk group and might therefore require more intensive monitoring.

The results of our study imply that the previously observed relation between anemia and worse prognosis in HF is secondary to its association with older age, higher prevalence of cardiac and noncardiac comorbidities, and less frequent implementation of HF-modifying treatment. Reliability of our results is supported by the fact that other proved risk factors for in-hospital and long-term mortalities maintained statistical significance in multivariate analyses of the primary and the secondary end points.[1, 2, 3, 26, 27, 28]

Recently, studies on the impact of anemia correction in HF have been undertaken. In the IRON-HF (Randomized Trial to Assess the Effects of Iron Supplementation in Heart Failure Patients With Anemia) and FAIR-HF (Ferric carboxymaltose Assessment in patients with IRon deficiency and chronic Heart Failure) trials, HF patients with iron deficiency treated with intravenous iron experienced an improvement in quality of life, exercise tolerance, and NYHA functional class.[10, 11] Moreover, in the CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) trial, intravenous iron therapy was associated with a significant reduction in rehospitalizations for worsening HF and with an insignificant reduction of mortality.[12] However, it needs to be emphasized that inclusion criterion in these trials was iron deficiency, and not anemia itself, as the studies included both anemic and nonanemic patients. Iron deficiency may lead to anemia but also to muscle dysfunction without anemia.[1] Thus, the beneficial effects of iron therapy in HF probably result from mechanisms other than merely correction of anemia. Furthermore, in a meta-analysis on erythropoiesis stimulating therapy (with darbepoetin or erythropoietin) for mild and moderate anemia in chronic HF, this treatment did not reduce all-cause mortality and rehospitalizations.[20] This could also be a confirmation that anemia is merely a marker of a worse clinical status, including the presence of iron deficiency. Thus, it seems that alignment of hemoglobin level itself should not be a goal of HF treatment.

The limitations of our study derive mainly from general drawbacks of registries, including incompleteness of data (e.g., data on 1-year survival and hospital readmissions). The scope of data collected in the registries was preestablished by their coordinators. Data on the underlying causes of anemia, parameters of iron deficiency, and information on possible iron supplementation were not available.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.03.035.

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