ORIGINAL ARTICLE

Clinical Determinants and Prognostic Value of Hemoglobin in Hospitalized Patients With Systolic Heart Failure

Belén Redondo-Bermejo,[a] Domingo A. Pascual-Figal,[a] José A. Hurtado-Martínez,[a] Jorge Montserrat-Coll,[b] Pablo Peñafiel-Verdú,[a] Francisco Pastor-Pérez,[a] José A. Giner-Caro,[a] and Mariano Valdés-Chávarri[a]

[a]Servicio de Cardiología, Unidad de Insuficiencia Cardiaca, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
[b]Servicio de Hematología, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Introduction and objectives. Anemia is a common finding in outpatients with heart failure (HF) and is associated with increased mortality. The aims of this study were to identify determinants of the hemoglobin level in a large group of hospitalized patients with systolic HF and to investigate the medium-term prognostic value of the hemoglobin level.

Methods. The study included 460 consecutive patients (age 68.3 [12.3] years, 74% male) who were hospitalized with a diagnosis of HF and left ventricular systolic dysfunction (i.e., a left ventricular ejection fraction <45%). At hospital discharge, biochemical and hematological parameters were measured and clinical and echocardiographic variables were recorded. Patients were followed up for 16.8[9.7] months.

Results. Anemia, as defined by World Health Organization criteria, was present in 189 (41.1%) patients. The following independent determinants of the hemoglobin level were identified: age (relative risk [RR]=1.035, 95% CI, 1.011–1.060; *P*=.004), female sex (RR=1.843, 95% CI, 1.083–3.135; *P*=.024), diabetes mellitus (RR=1.413, 95% CI, 1.087–1.838; *P*=.010), plasma urea level (RR=1.013, 95% CI, 1.005–1.022; *P*=.001), and loop diuretic use (RR=2.801, 95% CI, 1.463–5.364; *P*=.002). A decrease in hemoglobin level was associated with increased risks of death (RR per g/dL=1.232, 95% CI, 1.103–1.375; *P*<.001) and death or HF readmission (RR per g/dL=1.152, 95% CI, 1.058–1.255; *P*<.001), but not with readmission for non-fatal HF (RR per g/dL=1.081, 95% CI, 0.962–1.215; *P*=.265). Blood transfusion during hospitalization did not alter the increased risk of death (RR=2.19, 95% CI 1.40–3.41; *P*=.001).

Conclusions. In hospitalized patients with systolic HF, the hemoglobin level at hospital discharge was an independent predictor of death in the medium term, but not of readmission for non-fatal HF. The main determinants of the hemoglobin level were age, sex, renal function, diabetes, and the need for diuretics.

Key words: *Heart failure. Anemia. Hemoglobin. Prognosis.*

Determinantes clínicos y valor pronóstico de la hemoglobina en pacientes hospitalizados con insuficiencia cardiaca sistólica

Introducción y objetivos. En pacientes ambulatorios con insuficiencia cardiaca, la anemia es frecuente y se asocia con un aumento de la mortalidad. Estudiamos los determinantes del valor de hemoglobina y su valor pronóstico a medio plazo en una población amplia de pacientes hospitalizados con IC sistólica.

Métodos. Se incluyó a 460 pacientes consecutivos (68,3 ± 12,3 años, 74% varones) hospitalizados con el diagnóstico de insuficiencia cardiaca y disfunción sistólica (fracción de eyección del ventrículo izquierdo [FEVI] < 45%). En el momento del alta hospitalaria se realizaron las determinaciones bioquímicas y hematológicas y se recogieron las variables clínicas y ecocardiográficas. Los pacientes fueron seguidos durante 16,8 ± 9,7 meses.

Resultados. Un total de 189 (41,1%) pacientes presentaban anemia (según la definición de la Organización Mundial de la Salud). Los determinantes independientes del valor de hemoglobina fueron la edad (riesgo relativo [RR] = 1,035; intervalo de confianza [IC] del 95%, 1,011-1,060; p = 0,004), el sexo femenino (RR = 1,843; IC del 95%, 1,083-3,135; p = 0,024), diabetes mellitus (RR = 1,413; IC del 95%, 1,087-1,838; p = 0,010), urea plasmática (RR = 1,013; IC del 95%, 1,005-1,022; p = 0,001) y diuréticos del asa (RR = 2,801; IC del 995%, 1,463-5,364; p = 0,002). Un menor valor de hemoglobina se asoció con un mayor riesgo de muerte evento (RR = 1,232; IC del 95%, 1,103-1,375; p < 0,001) y del evento combinado de muerte o reingreso por insuficiencia cardiaca (RR = 1,152; IC del 95%, 1,058-1,255; p < 0,001), pero no de reingreso por insuficiencia cardiaca no fatal (RR = 1,081; IC del 95%, 0,962-1,215; p = 0,265). La transfusión de hematíes durante el ingreso no modificó el incremento del riesgo de muerte (RR = 2,19; IC del 95%, 1,40-3,41, p = 0,001).

Correspondence: Dr. D.A. Pascual.
Servicio de Cardiología. Unidad de Insuficiencia Cardiaca. Hospital Universitario Virgen de la Arrixaca.
Benabia, 7. 30110 Murcia. España.
E-mail: dapascual@servicam.com

Received August 10, 2006.
Accepted for publication March 1, 2007.

Conclusiones. En pacientes hospitalizados con IC sistólica, el valor de hemoglobina en el momento del alta es un predictor independiente de mortalidad a medio plazo, pero no de reingresos por IC no fatal. Sus principales determinantes fueron la edad, el sexo, la función renal, la diabetes y la necesidad de diuréticos.

Palabras clave: *Insuficiencia cardiaca. Anemia. Hemoglobina. Pronóstico.*

ABBREVIATIONS

LVEF: left ventricular ejection fraction
CHF: congestive heart failure
NYHA: New York Heart Association
RR: relative risk

INTRODUCTION

Congestive heart failure (CHF) is a serious public health problem that affects nearly 1% of the population older than 40 years and around 10% older than 70 years.[1] Currently, more is spent on CHF than any other cardiovascular disease in industrialized countries (2% of the health budget) and is the leading cause of hospitalization in adults >60 years; 75% of expenditures are due to hospitalization.[2] Despite therapeutic progress, patients hospitalized for CHF form one of the subgroups with the worst prognosis: nearly 45% will be hospitalized again at least once in the following 12 months and the risk of death or rehospitalization ranges between 30% and 60% depending on the population.[3,4] Thus, the factors determining evolution have to be identified in patients hospitalized for CHF, and whose correction could lead to clinical improvement.

Anemia is a frequent comorbidity in patients with chronic CHF, with a prevalence of 10% to 50% depending on the population and definition used.[5-12] The cause of anemia in CHF is not well-understood and seems to be multifactorial, being promoted by the hemodynamic and inflammatory changes that occur during chronic CHF and influenced by the treatment administered and renal function.[11-14] It has been associated with worse functional class and increased readmission, and mortality rates.[8-11,15]

Our aim was to assess, in a broad homogeneous population of hospitalized patients with systolic CHF, whether the hemoglobin concentration at discharge can help to predict the risk of complications during follow-up in the medium term and to study the clinical determinants of hemoglobin concentrations, and the effect of in-hospital transfusion.

METHODS

Study Population

The study included 460 consecutive patients diagnosed with CHF and left ventricular systolic dysfunction, admitted to the cardiology department of a tertiary university hospital from January 2002 to April 2004. Primary or secondary CHF was diagnosed and established according to the current clinical guidelines.[16,17] All patients underwent echocardiography (Sonos 5500, Hewlett-Packard) at admission, once the acute phase had passed (at least 72 hours after admission) and before discharge. Systolic dysfunction was defined as left ventricular ejection fraction (LVEF) <45%, measured by the Simpson biplane method. The following parameters were also recorded at that time: maximum E wave and A wave velocity, E/A relationship, left ventricular end-diastolic and end-systolic volumes, posterior wall diameter, left ventricular septum diameter, left atrial diameter, and pulmonary artery systolic pressure when tricuspid valve regurgitation was detected.

At hospital discharge, biochemical and hematological parameters were measured and baseline clinical variables recorded: age, sex, diabetes, hypertension, smoking habit, hypercholesterolemia, New York Heart Association (NYHA) functional class, etiology of cardiomyopathy, previous admissions for heart failure, heart rhythm, branch block, medication at discharge, and red blood cell transfusions during hospital stay.

Laboratory Parameters

Before discharge and after 10 minutes rest, blood samples were collected and immediately processed to measure hematological and biochemical parameters. Hemoglobin and hematocrit concentrations were measured using the automated blood analyzer XE-2100 (Symex, Kobe, Japan), and biochemical parameters were measured with a Roche/Hitachi Modular analyzer (Roche diagnosis, Mannheim, Germany). Anemia was defined according to World Health Organization criteria (hemoglobin <13 g/dL in men and <12 g/dL in women). Renal function was assessed through creatinine and urea concentrations, glomerular filtration rate (GFR) — as calculated using the simplified Modification of Diet in Renal Disease equation[18] (mL/min/1.73 m^2, $186.3 \times [\text{plasma creatinine}]^{-1.154} \times [\text{age}]^{-0.203}$) (the correction factor for women was ×0.742)- and creatinine clearance (CCr) according to the Cockroft-Gault formula. The following were also recorded: plasma sodium, uric acid, lipid profile, C-reactive protein, albumin, total protein, and fibrinogen.

Events and Follow-Up

The main event assessed was death from any cause. Furthermore, readmission for CHF and the combination

of death or readmission for CHF were recorded as secondary events. The patients who had undergone elective cardiac transplantation were censored at the transplantation date. Follow-up was conducted by personal interview in the outpatient ward, reviewing hospital registries, telephone contact, and reviewing official mortality records. The cause of death was recorded as cardiovascular or non-cardiovascular when this was known. Mean follow-up was 16.8 (9.7) months.

Statistical Analysis

Normally distributed quantitative variables were expressed as mean (standard deviation [SD]) and those with a skewed distribution were expressed as medians (semiquartile range). Discrete variables are presented as frequencies (percentage). Patients were divided into quartiles according to hemoglobin concentrations. The between-quartiles differences for the different clinical variables were established according to linear trend via ANOVA and linear association by χ^2 tests. If the variables with $P<.1$ were found in the quartile with the lowest hemoglobin concentration, then they were included in the logistic regression analysis for the study of independent determinants. The Kaplan-Meier method was used to measure event-free survival and the log-rank test for between-quartiles comparison. The Cox proportional risk model was used for the univariate analysis of predictors of events. This included age, sex, NYHA functional class, smoking habit, previous admission for heart failure, creatinine, urea, GFR, CCr, β-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin-II

TABLE 1. **Baseline Clinical Characteristics***

Hemoglobin, g/dL	Quartile 1 (<11.8) (n=118)	Quartile 2 (11.8-13.0) (n=114)	Quartile 3 (13.0-14.4) (n=113)	Quartile 4 (>14.4) (n=115)	*P*
Age, years	74.2 (11.4)	72.3 (16.3)	67.5 (18.3)	65.2 (19.3)	<.001
BMI	27.8 (4.1)	27.3 (3.6)	28.0 (4.3)	27.8 (3.4)	.664
Men	72 (61.0)	75 (65.8)	96 (85.0)	97 (84.3)	<.001
Diabetes mellitus	59 (50.0)	39 (34.2)	38 (33.6)	32 (27.8)	.001
Arterial hypertension	72 (61.0)	59 (51.8)	66 (58.4)	53 (46.1)	.064
Hypercholesterolemia	40 (36.4)	36 (31.6)	51 (45.1)	30 (26.1)	.372
Smoking habit	11 (9.3)	16 (14.0)	31 (27.4)	36 (31.3)	<.001
NYHA III or IV	78 (67.8)	68 (61.3)	51 (45.5)	54 (47.8)	<.001
Previous hospitalization for CHF	26 (22.0)	33 (28.9)	30 (26.5)	21 (13.3)	.448
Chronic lung disease	19 (16.1)	14 (12.3)	21 (18.6)	27 (23.5)	.075
Cerebrovascular disease	14 (11.9)	18 (15.8)	15 (13.3)	12 (10.4)	.632
Peripheral vascular disease	11 (9.3)	10 (8.8)	5 (4.4)	4 (3.5)	.749
Atrial fibrillation	24 (20.3)	22 (19.3)	26 (23.0)	26 (22.6)	.539
Complete bundle branch block	35 (29.7)	30 (26.3)	29 (25.7)	24 (20.9)	.136
Etiology					
Ischemic	75 (63.6)	62 (54.4)	62 (54.9)	66 (57.4)	.373
Dilated idiopathic	21 (17.8)	27 (23.7)	27 (23.9)	30 (26.1)	.148
Valvular	15 (12.7)	11 (9.6)	8 (7.1)	5 (4.3)	.017
Hypertensive	4 (3.4)	10 (8.8)	11 (9.7)	8 (7.0)	.271
Treatment					
ACE inhibitors/ARA-II	101 (85.6)	101 (88.6)	95 (84.1)	105 (91.3)	.358
β-blockers	63 (53.4)	70 (61.4)	75 (66.4)	71 (61.7)	.137
Antiplatelet agents	88 (74.6)	76 (66.7)	77 (68.1)	81 (70.4)	.557
Anticoagulant therapy	25 (21.2)	36 (31.6)	37 (32.7)	35 (30.4)	.121
Loop diuretics	97 (82.2)	80 (70.2)	71 (62.8)	68 (59.1)	<.001
Digoxin	35 (29.7)	34 (29.8)	43 (38.1)	34 (29.6)	.683
Spironolactone	30 (25.4)	40 (35.1)	30 (36.5)	31 (27.0)	.849
Statins	57 (48.3)	55 (48.2)	65 (57.5)	61 (53.0)	.260

*ARA-II indicates angiotensin-II receptor antagonists; ACE inhibitors, angiotensin-converting enzyme inhibitors; NYHA, New York Heart Association. Values are expressed as median [semiquartile range] and n (%).

TABLE 2. **Baseline Analytical and Echocardiographic Parameters***

Hemoglobin, g/dL	Quartile 1 (<11.8) (n=118)	Quartile 2 (11.8-13) (n=114)	Quartile 3 (13-14.4) (n=113)	Quartile 4 (>14.4) (n=115)	*P*
Laboratory					
Hemoglobin, g/dL	10.6 (0.9)	12.5 (0.3)	13.7 (0.4)	15.3 (0.7)	
Hematocrit, %	32.5 (2.9)	37.5 (1.5)	40.1 (1.9)	45.5 (2.4)	
Serum creatinine, mg/dL	1.5 (0.6)	1.1 (0.3)	1.2 (0.5)	1.2 (0.4)	.007
Urea, mg/dL	57.5 (48.3)	45.0 (26.0)	53.0 (28.5)	45.0 (22.0)	<.001
GFR, mL/min/1.73 m^2	53.1 (29.1)	60.3 (23.1)	62.2 (24.7)	64.4 (24.1)	<.001
Creatinine clearance	42.3 (20.0)	47.7 (17.9)	48.5 (23.5)	51.8 (23.6)	.001
Uric acid	7.4 (3.7)	7.0 (2.6)	7.5 (2.9)	7.2 (2.7)	.323
Echocardiography					
LVEF, %	32.0 (15.0)	30.0 (13.0)	33.0 (14.5)	35.0 (12.0)	.946
LVEDV, mL	144.9 (67.0)	136 (68.7)	143.0 (79.0)	128.0 (46.5)	.330
Left atrium, mm	46.4 (12.0)	43.0 (11.0)	46.0 (9.5)	44.0 (7.5)	.425
E/A Index	1.2 (0.6)	1.0 (0.4)	0.8 (0.5)	1.0 (0.7)	.735

*LVEF indicates left ventricular ejection volume; GFR, glomerular filtrate rate; LVEDV, left ventricular end-diastolic volume.
Values are expressed as mean (standard deviation) and median (semiquartile range).

receptor antagonists (ARA-II), and LVEF. The variables that reached a value of *P*<.1 in the univariate analysis were included in the Cox multivariate analysis. Relative risk (RR) and 95% confidence intervals (95% CI) are shown. A *P* value less than .05 was considered significant. All statistical analyses was conducted using the SPSS v. 12.0 statistical package (SPSS Inc., Chicago, Ill, USA).

RESULTS

Study Population

The study included 460 consecutive patients discharged with a diagnosis of CHF. Table 1 and Table 2 show their clinical characteristics at discharge. Mean age was 68.3 (12.3) years (interval, 19-93 years), 74% were men, with high cardiovascular risk in relation to diabetes mellitus (36%), hypertension (54%), and hypercholesterolemia (35%). At discharge, 55% were in NYHA functional class III-IV, LVEF was 31.6% (7.7) and the main etiology was ischemic (56%). A total of 21% had atrial fibrillation and 26% presented complete branch block in the electrocardiogram. At discharge, 87% of the patients received treatment with ACE inhibitors/ARA-II, 61% β-blockers, 69% loop diuretics, 32% digoxin, and 29% spironolactone.

Determinants of Hemoglobin Concentration

At discharge, the mean hemoglobin concentration in the total population was 13.0 (1.8) mg/dL and hematocrit was 39.1 (5.3). A total of 189 (41%) patients presented anemia defined according to the World Health Organization (WHO) criteria and adjusted for sex. A total of 46 patients (10%) received a red blood cell transfusion. Table 1 shows the baseline clinical characteristics distributed by hemoglobin quartiles. The hemoglobin concentrations were lower in women and when there was greater cardiovascular risk as defined by older age and a higher prevalence of diabetes and hypertension. In contrast, a smoking habit was associated with greater concentrations of hemoglobin. Low hemoglobin concentrations were associated with worse functional class, a higher prevalence of NYHA functional class III-IV, and a greater need for loop diuretics at discharge. There was no significant association between the etiology of heart disease, pharmacological treatment, and electrocardiogram findings, and hemoglobin concentrations.

Table 2 shows the distribution of the biochemical and echocardiographic parameters. The lowest concentrations of hemoglobin were associated with greater deterioration of renal function measured by urea concentrations, GFR, and CCr, which were more significant than raw creatinine concentrations. There were no differences between hemoglobin concentrations and cardiac function parameters as assessed by echocardiography, and thus, the LVEF remained similar under different hemoglobin concentrations. The independent determinants in the quartile with the lowest value of hemoglobin were age (RR=1.035; 95% CI, 1.011-1.060; *P*=.004), female sex (RR=1.843; 95% CI, 1.083-3.135; *P*=.024), diabetes mellitus (RR=1.413; 95% CI, 1.087-1.838; *P*=.010), plasma urea level (RR=1.013; 95% CI, 1.005-1.022; *P*=.001), and loop diuretics (RR=2.801; 95% CI, 1.463-5.364; *P*=.002).

Prognosis and Hemoglobin

A total of 81 patients (17.6%) died during follow-up. Using the Kaplan-Meier method, the 18-month survival rate was 83.0%, with a mean survival time of 37.7 (0.9)

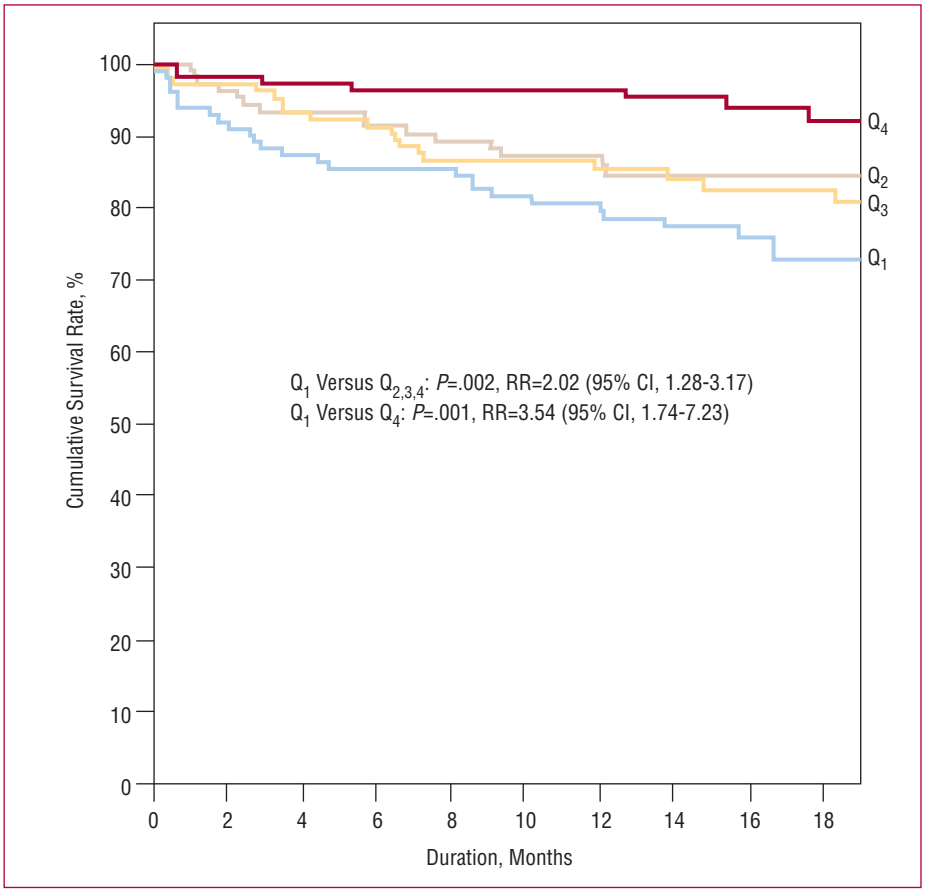

Figura 1. Kaplan-Meier survival curves for death, according to quartiles of hemoglobin concentrations and relative risk associated with quartile 1 (g/dL, Q indicates quartile; Q_1<11.8; Q_2 11.8-13.0; Q_3 13.0-14.4; Q_4>14.4).

months (95% CI, 35.8-39.6 months). Six patients were censored due to need for cardiac transplantation. A total of 65 (14.4%) patients were readmitted for non-fatal CHF and the survival rate free from readmission due to non-fatal CHF was 72.3% at 18 months.

The lowest hemoglobin concentrations were associated with a greater risk of death (by g/dL, RR=1.232; 95% CI, 1.103-1.375; *P*<.001) and the composite of death or readmission due to CHF (by g/dL, RR=1.152; 95% CI, 1.058-1.255; *P*<.001), but were not associated with readmission due to non-fatal CHF when measured in isolation (by g/dL, RR=1.081; 95% CI, 0.962-1.215; *P*=.265). The Kaplan-Meier survival analysis by quartiles of hemoglobin showed significantly lower survival free from all-cause death (Figure 1), and composite events (Figure 2). However, the probability of readmission due to non-fatal decompensated CHF did not differ between the different quartiles (Figure 3). Of the 62 patients where the direct cause of death was known, in 14 (22.6%) patients non-cardiovascular mortality contributed a similar percentage to the last quartile as to the remaining quartiles (23.8% and 22.0%, respectively, *P*=.868).

Cox univariate analysis identified the following as predictors of mortality in the study population (Table 3): age, female sex, worse NYHA functional class, previous admissions due to CHF, low LVEF, loop diuretic use, lack of treatment with ACE inhibitors/ARA-II or β-blockers and poor renal faction as assessed by plasma creatine and plasma urea concentrations, and GFR. After adjusting for these in the Cox multiple regression model, the hemoglobin concentration was an independent predictor of mortality and its decrease was associated with a significant increase in risk of death (by g/dL, RR=1.163; 95% CI, 1.024-1.321; *P*=.020) In the analysis by quartiles, after adjusting for the remaining predictors of mortality, the last quartile was associated with an increased risk of death (RR=1.920; 95% CI, 1.213-3.040; *P*<.001) which was maintained when including in the quartile those patients who had received a red blood cell transfusion transfusion (RR=2.19; 95% CI, 1.40-3.41; *P*=.001) (Figure 4). Thus, the patients who received transfusions and had hemoglobin concentrations higher than the last quartile at discharge had a mortality of 26%, similar to the 29% mortality in patients in the last quartile who had not recived a transfusion (*P*=.73). This was significantly above the 13% in patients who did not receive a transfusion and who had a hemoglobin concentration above the last quartile (*P*<.001). However, when survival free of readmission due to decompensated nonfatal CHF was analyzed, the hemoglobin

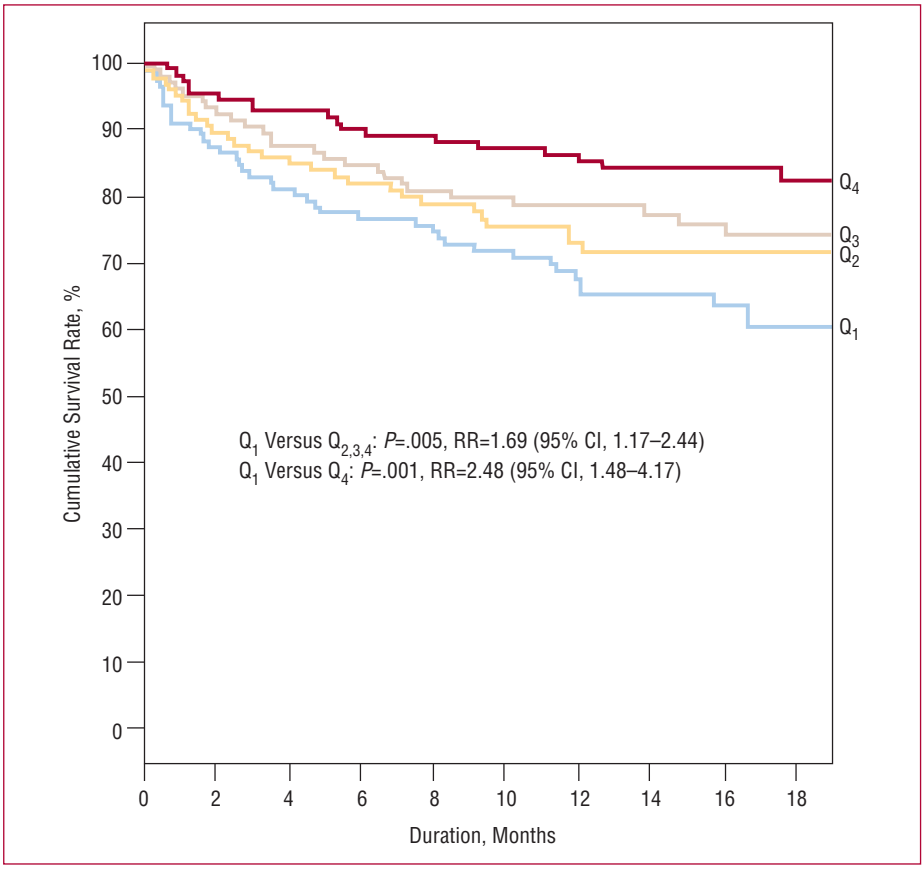

Figure 2. Kaplan-Meier survival curves for death or hospital readmission due to CHF, according to quartiles of hemoglobin concentrations and relative risk associated with quartile 1 (g/dL, Q indicates quartile; Q_1<11.8; Q_2 11.8-13.0; Q_3 13.0-14.4; Q_4>14.4).

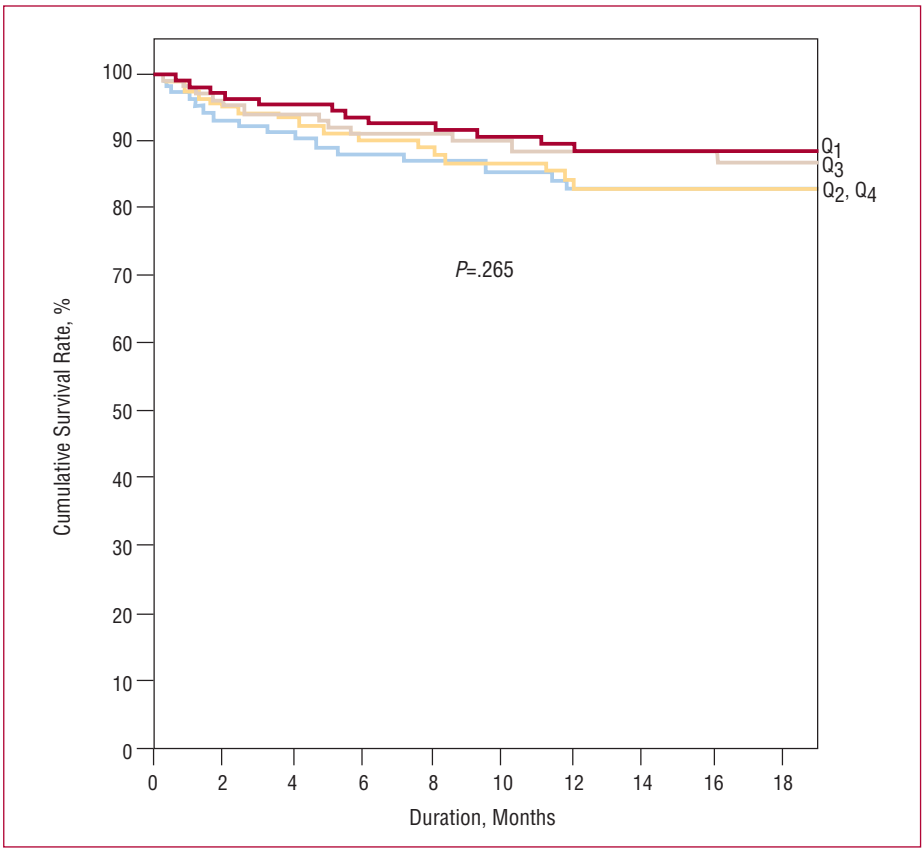

Figure 3. Kaplan-Meier survival curves for hospital readmission due to non-fatal heart failure, according to quartiles of hemoglobin concentrations (g/dL, Q indicates quartile; Q_1<11.8; Q_2 11.8-13.0; Q_3 13.0-14.4; Q_4>14.4).

TABLE 3. **Univariate and Multivariate Analysis of Mortality***

	Univariate		Multivariate	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age	1.056 (1.032-1.082)	<.001	1.042 (1.015-1.069)	.002
Male	0.436 (0.278-0.684)	<.001	0.480 (0.296-0.777)	.003
NYHA	1.357 (1.090-1.689)	.006	–	.253
Previous admission due to CHF	1.728 (1.087-2.748)	.021	–	.124
Hemoglobin, mg/dL	0.812 (0.727-0.907)	<.001	0.860 (0.757-0.977)	.020
ACE inhibitors/ARA-II	0.515 (0.297-0.892)	.018	0.484 (0.263-0.893)	.020
β-blockers	0.558 (0.358-0.871)	.010	–	.510
Loop diuretics	1.824 (1.053-3.163)	.032	–	.605
Creatinine	1.221 (1.020-1.463)	.030	–	.139
Urea	1.011 (1.005-1.017)	.001	1.007 (1.000-1.013)	.055
GFR, mL/min/1.73 m^2	0.978 (0.967-0.989)	<.001	–	.724
LVEF	0.980 (0.954-1.007)	.149	0.961 (0.933-0.989)	.007

*ARA-II indicates angiotensin-II receptor antagonists; LVEF, left ventricular ejection volume; CHF, congestive heart failure; ACE inhibitors, angiotensin-converting enzyme inhibitors; NYHA, New York Heart Association; GFR, glomerular filtrate rate.

concentration (*P*=.065) and lower quartile (*P*=.190) did not reach significance.

DISCUSSION

This study evaluated hemoglobin concentrations in a broad population of patients hospitalized for systolic heart failure. We found that: *a)* hemoglobin concentrations are basically determined by age, sex, renal function, diabetes, and diuretic use; *b)* decreased hemoglobin concentrations involves increased all-cause risk of death that is independent of other clinical variables and that is not modified by the patient having undergone red blood cell transfusion during hospitalization; and *c)* in contrast, these concentrations do not affect the risk of rehospitalization due to non-fatal heart failure.

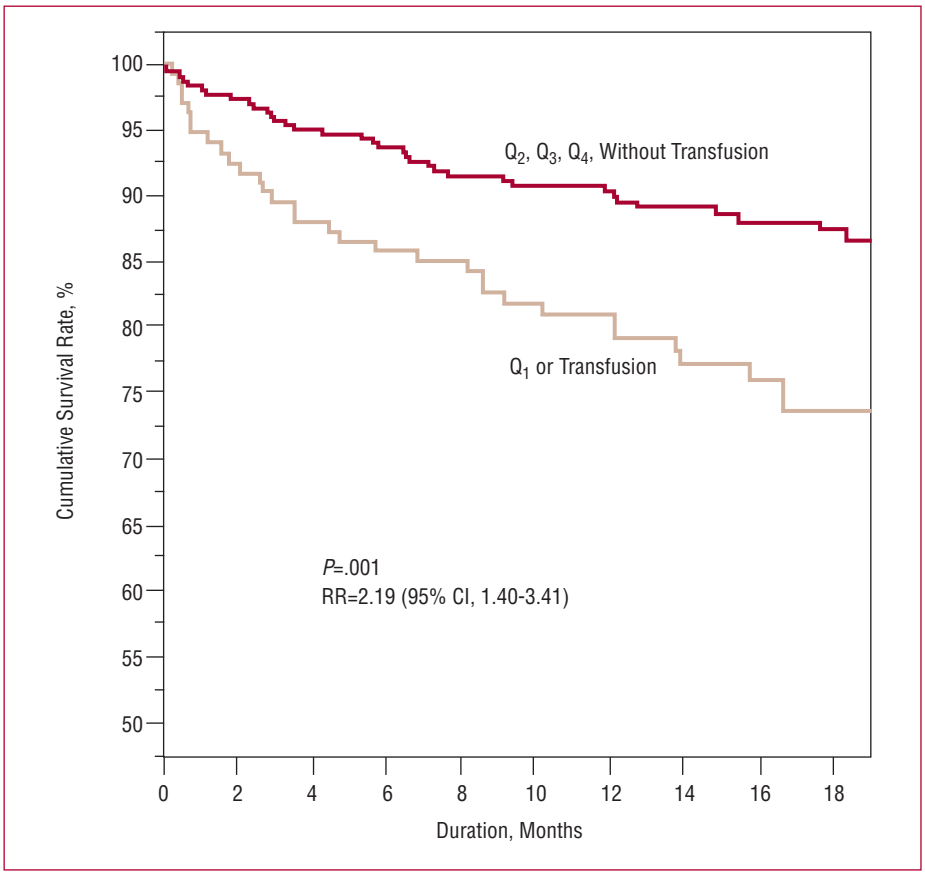

Figure 4. Kaplan-Meier survival curves for death showing quartile Q_1 (<11.8 g/dL) or red blood cell transfusion at admission (red line) versus the remaining population (Q_2, Q_3, Q_4, without transfusion; brown line).

Prevalence and Determinants

Anemia is a common finding in patients with heart failure. Its prevalence varies depending on the definition used and the population evaluated.[5-9] Published studies have evaluated ambulatory populations with chronic CHF and most have reported a prevalence of 20%-30%. In contrast to these studies, our population included patients who had been hospitalized and then discharged after a decompensation episode, and where the hemoglobin concentration was measured at discharge as a possible biological marker of risk of complications. We observed a prevalence of 41% in this population, which is higher than that reported in ambulatory populations and that could indicate greater associated clinical deterioration. Thus, a study on patients with advanced CHF before transplantation reported a prevalence of up to 61%.[12] Greater hypervolemia may contribute to greater reductions in hemoglobin concentrations in these patients.[12]

In our population, the hemoglobin concentration was associated with known physiological variables, such as age and female sex. The association with diabetes and hypercholesterolemia would be explained by the greater degree of systemic inflammation that these involve, with increases in cytokines and tumor necrosis factor-alpha, and the consequent development of resistance to the action of erythropoietin.[13,14,19] Deterioration in renal function is a documented determinant of lower concentrations of hemoglobin, due to a reduction in the physiological response of erythropoietin to anemia.[8,20,21] In the present study, there were significant correlations between all the parameters of renal function analyzed, although urea concentrations had the greatest independent value in the final model, indicating greater renal hypoperfusion. At the same time, the association with a greater need for diuretics would indicate greater congestion and hypervolemia, and also greater hemodilution.[12,22] Such hypoperfusion and congestion is indicated by the association between lower hemoglobin concentrations and worse NYHA functional class, a finding common to multiple studies.[8,9,11,21,23,24] Taken together, these findings support the hypothesis that hemoglobin concentration is a marker of the severity of CHF.

It has been reported that chronic anemia increases cardiac output, promotes left ventricular hypertrophy and ischemic heart disease, and contributes to left ventricular dilatation, and dysfunction.[25,26] However, we did not find a correlation between hemoglobin concentrations and the parameters of systolic or diastolic function. It has been suggested that ACE inhibitors could inhibit the proliferation of hematopoietic cells and increase the risk of anemia.[9,23] We did not observe this association in our population, although the percentage of patients who did not receive ACE inhibitors was only 12.6%, which could have hindered this analysis.

Our findings indicate that a decrease in hemoglobin concentrations is an indicator of the severity of heart failure, due to its correlation with functional class, the need for diuretics, and greater deterioration in renal function, aggravated by variables such as age, female sex, and diabetes. As previously described, it would include multiple contributory mechanisms including systemic inflammation, bad intestinal absorption, renal dysfunction, bone marrow depression, and hemodilution, that are more clearly manifested in advanced stages of CHF.[12,14,15,27]

Prognosis

In the present study, the hemoglobin concentration was inversely associated with increased risk of death, which in the analysis only reached independent significance in the lower quartile. It is noteworthy that this increase in risk was maintained when we added the patients with hemoglobin concentrations in the higher quartiles, but who had undergone blood transfusion at admission, which indicates that this risk does not change despite transfusion. No study has analyzed this aspect up to the time of writing. The prognostic value of anemia has been mainly studied in ambulatory populations with chronic CHF,[8-11,15,21,23,24] whereas our work, like other Spanish series, shows that after hospital admission due to CHF, a low hemoglobin concentration is a risk marker of death in the long-term.[28,29] In contrast to the study by Grigorian-Shamogian et al,[28] which analyzed the presence of anemia (as defined by WHO) at the time of hospital admission and focused on total mortality, our work evaluated hemoglobin concentrations at the time of discharge and contributes new information on the cause of death and hospital readmission. Recently, Sánchez-Torrijos et al[29] also showed that anemia at discharge is a predictor of long-term mortality, cardiac or otherwise, although these authors used an independent cut-off value for sex (<12 g/dL) arbitrarily selected as diagnostic of anemia. In their study, as in previous ones, anemia, as defined, was associated with a higher readmission rate for CHF, with no difference between fatal and non-fatal CHF.[10,11,24] In our study, low hemoglobin concentrations were not associated with a greater risk of readmission for non-fatal CHF. Thus, our work indicates that anemia is a marker for severity and risk of death, but not for simple decompensated CHF.

Possible pathogenic links between hemoglobin concentrations and mortality have been suggested, involving an increase in cardiac output, ischemia, and myocardial stress, thereby promoting chronic volume overload, tissue hypoxia, and peripheral vasodilatation.[26] To date, it has not been made clear whether a low hemoglobin concentration plays a causal role or is simply a marker of non-modifiable risk per se. Previous studies have shown that treatment with erythropoietin or intravenous iron improves the functional situation and

even systolic function parameters.[30,31] However, changes in prognosis in relation to mortality would have to demonstrated to establish a pathogenic link. The association with other classical risk factors, such as functional deterioration (NYHA functional class), severe congestion (need for diuretics), worse renal function, diabetes mellitus, and older age, indicates that anemia can be a marker of severity and CHF progression. However, its independent prognostic value indicates that it has a deleterious effect in itself. The main limitation of the present study is its exploratory character; thus, its findings should be confirmed in other cohorts and, in particular, on the basis of intervention studies investigating whether the correction of anemia has any prognostic benefit.

CONCLUSIONS

In patients hospitalized for CHF with systolic dysfunction, a low hemoglobin concentration is an independent marker of severity and risk of death, but not of readmission for non-fatal CHF. Furthermore, this risk is not modified by red blood cell transfusion at admission. Anemia is frequent in these patients and is determined by physiological variables, old age, and female sex, and also by diabetes and the severity of CHF as defined by worse renal function, greater functional deterioration, and greater need for diuretics.

REFERENCES

1. Rodríguez-Artalejo F, Banegas B Jr, Guallar-Castillon P. Epidemiología de la insuficiencia cardiaca. Rev Esp Cardiol. 2004; 57:163-70.
2. Rich MW, Nease RF. Cost-effectiveness analysis in clinical practice: the case of heart failure. Arch Intern Med. 1999;159:1690-700.
3. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med. 1995;333:1190-5.
4. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. Am J Med. 2001;110:378-84.
5. Komajda M. Prevalence of anemia in patients with chronic heart failure and their clinical characteristics. J Card Fail. 2004;10:S1-S4.
6. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. J Card Fail. 2005;11:91-8.
7. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002;39:1780-6.
8. al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38:955-62.
9. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003;107:223-5.
10. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110:149-54.
11. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation. 2006;113:986-94.
12. Androne AS, Katz SD, Lund L, laManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107:226-9.
13. Horl WH, Ertl G. Anaemia and the heart. Eur J Clin Invest. 2005;35:20-5.
14. Okonko DO, Anker SD. Anemia in chronic heart failure: pathogenetic mechanisms. J Card Fail. 2004;10:S5-S9.
15. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol. 2003;41:1933-9.
16. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001;22:1527-60.
17. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26:1115-40.
18. O'Meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA. The Modification of Diet in Renal Disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. Eur J Heart Fail. 2006;8:63-7.
19. Iversen PO, Woldbaek PR, Tonnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol. 2002;282:R166-R72.
20. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation. 2005;112:1121-7.
21. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002;39:1780-6.
22. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation. 2005;112:1121-7.
23. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2005;45:391-9.
24. Lupon J, Urrutia A, González B, Herreros J, Altimir S, Coll R, et al. Significado pronóstico de los valores de hemoglobina en pacientes con insuficiencia cardiaca. Rev Esp Cardiol. 2005;58:48-53.
25. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis. 1996;28:53-61.
26. Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant. 2000;15:14-8.
27. Felker GM, Adams KF Jr, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol. 2004;44:959-66.
28. Grigorian-Shamagian L, Varela-Román A, Mazón-Ramos P, Pedreira-Pérez M, Rigueiro-Veloso P, González-Juanatey JR. Anemia como nuevo predictor de la mortalidad de pacientes hospitalizados por insuficiencia cardiaca congestiva. Med Clin (Barc). 2005;625:647-52.

29. Sánchez-Torrijos J, Gudin-Uriel M, Nadal-Barangué M, Jacas-Osborn V, Trigo-Bautista A, Jiménez-Alcala M, et al. Valor pronóstico de las cifras de hemoglobina en el momento del alta en pacientes hospitalizados por insuficiencia cardiaca. Rev Esp Cardiol. 2006;59:1276-82.
30. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001;37:1775-80.
31. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003;107:294-9.