

Prognostic Value of Discharge Hemoglobin Level in Patients Hospitalized for Acute Heart Failure

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Introduction and objectives. Recent studies show that the prevalence of anemia in patients with heart failure is high and indicate that its presence leads to increased mortality and morbidity. Our aims were to determine the prevalence of anemia in patients hospitalized for heart failure and to study the long-term prognostic significance of anemia by evaluating its relationship with mortality (total and due to heart failure) and readmission for heart failure.

Methods. The study included 242 consecutive patients admitted to our cardiology department and discharged with a diagnosis of congestive heart failure. The Kaplan-Meier technique and Cox regression modeling were used to determine whether anemia is an independent predictor of death or readmission for heart failure. Anemia was defined as a hemoglobin level <12 g/dL. The mean follow-up period was 23.5 (10.9) months.

Results. Overall, 79 patients (32.6%) were anemic. During follow-up, 77 died (53 due to heart disease) and 117 were readmitted for heart failure. Multivariate analysis showed that anemia was an independent predictor of death (hazard ratio [HR]=1.85, 95% confidence interval [CI], 1.12-3.06), death due to heart disease (HR=1.88, 95% CI, 1.03-3.45), and readmission for heart failure (HR=1.87, 95% CI, 1.28-2.74).

Conclusions. The prevalence of anemia was high in patients hospitalized for heart failure. Moreover, a discharge hemoglobin level less than 12 g/dL was a predictor of all-cause death, cardiac death, and readmission for heart failure.

Key words: Hemoglobin. Heart failure. Prognosis.

Valor pronóstico de las cifras de hemoglobina en el momento del alta en pacientes hospitalizados por insuficiencia cardiaca

Introducción y objetivos. Estudios recientes muestran una elevada prevalencia de anemia en pacientes con insuficiencia cardiaca y señalan que su presencia condiciona un aumento de la morbimortalidad. El objetivo de nuestro estudio fue determinar la prevalencia de anemia en pacientes dados de alta con diagnóstico de insuficiencia cardiaca, estudiar su valor pronóstico a largo plazo y evaluar la relación entre anemia y mortalidad (total y cardiaca) y reingresos por nueva descompensación.

Métodos. Analizamos una serie de 242 pacientes ingresados en el servicio de cardiología y dados de alta con diagnóstico de insuficiencia cardiaca. Utilizamos el método de Kaplan-Meier y el modelo de regresión de Cox para el estudio de la anemia como predictor independiente de mortalidad y reingresos por insuficiencia cardiaca. Consideramos anemia una cifra de hemoglobina < 12 g/dl. El tiempo medio de seguimiento fue de 23,5 ± 10,9 meses.

Resultados. En total, 79 (32,6%) pacientes tenían anemia. Durante el seguimiento fallecieron 77 pacientes, 53 por causa cardiaca, y reingresaron por insuficiencia cardiaca 117 pacientes. En el análisis multivariable, la anemia resultó predictora de mortalidad total (*hazard ratio* [HR] = 1,85; intervalo de confianza [IC] del 95%, 1,12-3,06), mortalidad cardiaca (HR = 1,88; IC del 95%, 1,03-3,45) y reingreso por insuficiencia cardiaca (HR = 1,87; IC del 95%, 1,28-2,74).

Conclusiones. En nuestra serie de pacientes hospitalizados por insuficiencia cardiaca observamos una elevada prevalencia de anemia. Además, una cifra de hemoglobina en el momento del alta < 12 g/dl resultó predictora de mortalidad total, mortalidad cardiaca y reingreso por descompensación de la insuficiencia cardiaca.

Palabras clave: Hemoglobina. Insuficiencia cardiaca. Pronóstico.

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ABBREVIATIONS

ARA-II: angiotensin II receptor antagonists
 HR: hazard ratio
 CHF: congestive heart failure
 ACEI: angiotensin converting enzyme inhibitors

INTRODUCTION

Congestive heart failure (CHF) has become a high-priority health problem due to its increasing prevalence, the high rates of associated morbidity and mortality, and the healthcare costs associated with the disease.^{1,2} Although the role of anemia as a trigger for cardiac decompensation is well known, in recent years the study of anemia in patients with CHF has been the focus of increasing interest due to its high prevalence and prognostic implications.³

The prevalence of anemia in patients with CHF varies widely in different published studies, ranging from 4% to 55%.⁴⁻²⁰ This variability is explained by the different populations selected and by the absence of consensus on the definition of anemia.²¹

Recently, various observational studies found that the presence of anemia leads to a worse prognosis in patients with CHF.^{8-20,22-27} In addition, in some small intervention studies a beneficial effect of correction of anemia on quality of life was observed in patients with refractory CHF.²⁸⁻³⁰ However, available information is still limited regarding the relationship between anemia and prognosis in hospital case series involving patients with acute decompensation of CHF.

The aim of this study was to determine the prevalence of anemia in patients discharged following decompensation of CHF, to describe the factors associated with the presence of anemia, and to determine its long-term prognostic value.

METHODS

An observational study was undertaken in which discharge reports and patient histories were analyzed for 270 consecutive patients who were admitted to the cardiology ward of a tertiary hospital and discharged with diagnosis of CHF between January 2002 and February 2003. A total of 242 patients for whom hemoglobin level at discharge was available were included in the study. Data were collected on the following types of variables: demographic (age and sex), clinical (history of diabetes mellitus, hypertension, and atrial fibrillation, and type of heart disease), biochemical (creatinine), echocardiographic (ejection fraction), and treatment

related (treatment at admission with drugs linked to prognosis of CHF or development of anemia: angiotensin converting enzyme inhibitors [ACEI], angiotensin II receptor antagonists [ARA-II], loop diuretics, spironolactone, digoxin, antiplatelet drugs, oral anticoagulants, statins, and nitrates).

Patients were considered anemic if their hemoglobin level was below 12 g/dL. The mean follow-up period was 23.5 (10.9) months (median, 26.4 months). Follow-up was successfully performed by telephone interview and consultation of the records held by the cardiology and hospital admissions departments in 233 (96.3%) of the 242 patients. All-cause and cardiac mortality were recorded, and cardiac death was defined as that occurring through terminal CHF, fatal myocardial infarction, or sudden death. Two patients who received a heart transplant were recorded as cardiac deaths. We also recorded repeat hospital admission in any department (cardiology, internal medicine, short-stay unit) for decompensation of CHF.

Statistical Analysis

Continuous variables are shown as means (SD) and were compared by Student *t* test for independent samples. Qualitative variables are expressed as percentages and univariate comparisons were made using Pearson's χ^2 test. Incidence density was used as a measure of the incidence of events and the results shown as incidence per 100 patient-years. Multivariate analysis was performed by logistic regression to identify variables that were independently associated with the presence of anemia and the results are shown as the odds ratio (OR) with 95% confidence interval (CI). Kaplan-Meier survival curves were compared for anemic and nonanemic patients using a log-rank test. Cox regression analysis was used for multivariate analysis of survival and the results expressed as the hazard ratio (HR) with 95% CI. The variables included in the Cox regression model were those that were significant in the univariate analysis along with variables of known prognostic value in CHF (age, anemia, hypertension, sex, systolic function, atrial fibrillation, diabetes mellitus, creatinine, ACEI, β -blockers, and loop diuretics).

Statistical analysis was carried out using SPSS for Windows, version 12.0. $P < .05$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Population and Prevalence of Anemia

The mean age of the population was 72 (11) years (range, 38-92 years). Table 1 shows the baseline characteristics of the population and the treatment at discharge. Systolic dysfunction was present in 60% of

TABLE 1. Baseline Characteristics and Treatment at Discharge*

Variable	Overall Group	Anemia	No Anemia	P
Age, mean (SD), y	72 (11) (range, 38-92)	74.04	71.12	.051
Women	123 (50.8%)	65.8%	43.6%	.001
Diabetes mellitus	100 (41.7%)	57%	34.2%	.001
Hypertension	155 (61.5%)	65.4%	65%	NS
Atrial fibrillation	98 (40.8%)	31.6%	45.3%	.043
Serum creatinine, mean (SD), mg/dL	1.39 (0.71)	1.51 (0.87)	1.21 (0.59)	.006
Hemoglobin, g/dL	12.69 (1.9)	10.49 (1.05)	13.76 (1.16)	<.001
Preserved LVEF	97 (40.1%)	51.9%	34.4%	.009
Etiology				.089
Ischemic heart disease	112 (46.5%)	51.9%	43.8%	
Hypertensive heart disease	32 (13.3%)	12.7%	13.6%	
Valvular heart disease	41 (17%)	21.5%	14.8%	
Dilated cardiomyopathy	36 (14.9%)	6.3%	19.1%	
Other heart disease	20 (8.3%)	7.6%	8.6%	
Treatment				
ACEI	159 (65.7%)	50.6%	73%	.001
ARB-II	15 (6.2%)	7.6%	5.5%	NS
β -blockers	98 (40.5%)	31.6%	44.8%	.051
Loop diuretics	226 (95.4%)	97.5%	91.4%	.075
High doses of loop diuretics†	31 (12.8%)	20.3%	9.2%	.016
Digoxin	40 (16.5%)	7.6%	20.9%	.009
Spironolactone	44 (18.2%)	19%	17.8%	NS
Nitrates	79 (32.6%)	38%	30.1%	NS
Oral anticoagulation	89 (36.8%)	27.8%	41.1%	.048
Antiplatelet drugs	130 (53.7%)	54.4%	53.4%	NS
Statins	75 (31%)	34.2%	29.4%	NS

*Data are shown as number (%) and %, unless otherwise indicated.

LVEF: left ventricular ejection fraction; ACEI: angiotensin converting enzyme inhibitors; ARA-II: angiotensin II receptor antagonists; NS: not statistically significant.

† Doses of loop diuretics equivalent to greater than 80 mg furosemide.

patients, the most common etiology was ischemic heart disease, and 40% of the population had atrial fibrillation. The mean hemoglobin level at discharge was 12.69 (1.9) g/dL (range, 7-18.5 g/dL); 79 patients (32.6%) had hemoglobin levels below 12 g/dL.

Clinical Variables Associated With Anemia

As shown in Table 1, the population of anemic patients was older, contained a higher proportion of women, diabetics, and patients with preserved systolic function, displayed higher creatinine levels, and contained fewer patients treated with ACEI, digoxin, and oral anticoagulants, and more treated with diuretics.

Multivariate analysis by logistic regression showed the following variables as predictors of the presence of anemia: female sex (OR, 1.5; 95% CI, 1.1-1.7; $P=.001$), preserved systolic function (OR, 2.27; 95% CI, 1.2-4.3; $P=.011$), diabetes (OR, 2.13; 95% CI, 1.2-3.9; $P=.014$),

absence of atrial fibrillation (OR, 0.455; 95% CI, 0.24-0.88; $P=.02$), and the highest concentrations of creatinine (OR, 1.962; 95% CI, 1.27-3.03; $P=.002$).

Prognostic Value of Anemia

Mortality

After a mean follow-up period of 23.5 (10.9) months (median, 26.4 months), corresponding to 473.9 patient-years of follow-up, the rate of mortality for the overall group was 17.12 per 100 patient-years (77 deaths) and the rate of cardiac mortality was 11.78 per 100 patient-years (53 cases). Anemia was associated with higher rates for both all-cause mortality (28 per 100 patient-years in anemic patients vs 12.4 per 100 patient-years in nonanemic patients, $P<.01$) and cardiac mortality (19.89 per 100 patient-years in anemic patients vs 8.28 per 100 patient-years in nonanemic patients, $P<.01$). Hemoglobin

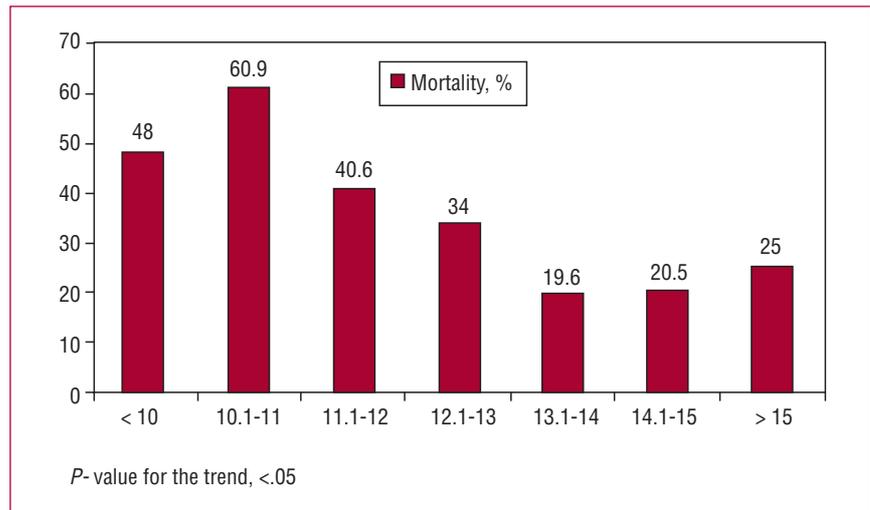


Figure 1. Distribution of all-cause mortality according to hemoglobin level.

levels were significantly lower in the group of patients who died during follow-up, both in the analysis of all-cause mortality (13.02 [1.8] g/dL in living patients vs 11.97 [1.9] g/dL in patients who died during follow-up, $P<.0001$) and cardiac mortality (12.9 [1.83] g/dL in living patients vs 11.91 [1.97] g/dL in patients who died during follow-up, $P=.001$). Figure 1 shows the distribution of all-cause mortality according to hemoglobin level.

As shown by the Kaplan-Meier survival curve (Figure 2A), mortality was significantly higher in the group containing anemic patients (log-rank test, 12.81; $P=.0003$). In the multivariate analysis, adjusted for age, hypertension, sex, systolic function, atrial fibrillation, diabetes mellitus, creatinine, and treatment with ACEI, β -blockers, and loop diuretics, anemia remained as a predictor of mortality

and caused a 1.85-fold increase in the risk of all-cause death ($P=.017$) and a 1.88-fold increase in the risk of cardiac death ($P=.04$) (Table 2). Treatment with high doses of diuretics and the absence of hypertension were also associated with all-cause and cardiac mortality. In addition, when hemoglobin level was analyzed as a quantitative variable, for each gram reduction in hemoglobin concentration a 20.5% increase was observed in the risk of death (HR, 0.795; 95% CI, 0.709-0.893).

We undertook a multivariate analysis of all-cause mortality in subsets of patients with preserved or depressed systolic function. Anemia was a predictor of all-cause mortality in both groups (HR, 2.27; 95% CI, 1.25-4.22 for systolic dysfunction—HR, 2.08; 95% CI, 1.03-4.22 for preserved systolic function).

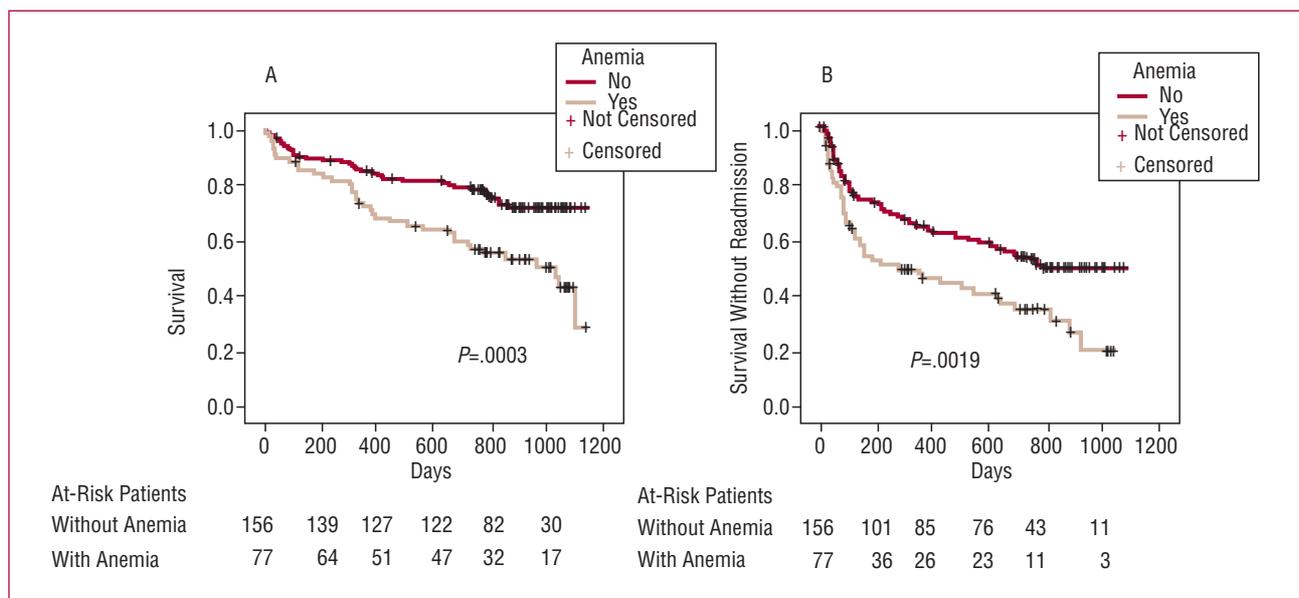


Figure 2. A: Kaplan-Meier curves for all-cause mortality in patients with and without anemia. B: Kaplan-Meier curves for repeat hospital admission in patients with and without anemia.

TABLE 2. Cox Regression. All-Cause and Cardiac Mortality

	All-Cause Mortality			Cardiac Mortality		
	HR	95% CI	P	HR	95% CI	P
Anemia	1.85	1.12-3.07	.017	1.88	1.03-3.45	.04
Hypertension	0.53	0.33-0.86	.011	0.41	0.23-0.72	.002
Diuretics >80 mg*	2.14	1.27-3.60	.04	2.08	1.11-3.91	.022
Age	1.02	0.99-1.04	.21	1.01	0.99-1.04	.37
Male sex	0.99	0.59-1.67	.97	0.80	0.43-1.50	.49
Preserved EF	0.92	0.55-1.55	.75	0.89	0.47-1.66	.71
Diabetes	1.07	0.67-1.67	.79	0.83	0.45-1.55	.56
AF	0.70	0.41-1.19	.19	0.67	0.35-1.28	.22
Creatinine	0.93	0.65-1.33	.69	1.05	0.69-1.60	.83
ACEI	1.06	0.64-1.76	.83	1.11	0.61-2.05	.73
b-blockers	0.66	0.38-1.13	.13	0.74	0.39-1.43	.37

HR: hazard ratio; CI: confidence interval; EF: ejection fraction; AF: atrial fibrillation; ACEI: angiotensin converting enzyme inhibitors.
 *Doses of loop diuretics equivalent to greater than 80 mg furosemide.

Repeat Hospitalization

A total of 117 patients were readmitted for decompensation of CHF (readmission rate, 26 per 100 patient-years). In anemic patients, the incidence of repeat admission was significantly higher (33.5 vs 21.98 per 100 patient-years, $P<.01$). Again, the Kaplan-Meier curves for event-free survival showed a significant divergence (log-rank test, 9.68; $P=.0019$; Figure 2B) and the presence of anemia was a predictor of readmission for CHF in the multivariate analysis using Cox regression (HR, 1.87; 95% CI, 1.28-2.74).

DISCUSSION

In our series of patients discharged with a diagnosis of CHF the prevalence of anemia was high (32.6%) and, in addition, a hemoglobin concentration below 12 g/dL

at discharge was predictive of long-term adverse events (all-cause and cardiac death, and readmission for CHF). It is important to note that our analysis was undertaken using hemoglobin levels at discharge, unlike most previous studies, which have used hemoglobin or hematocrit at admission. Thus, our data highlight the prognostic importance of hemoglobin levels at the time of hospital discharge in this clinical setting.

It is difficult to compare our results with those of other authors as there is a high degree of variability in the published data on the prevalence of anemia, mainly due to the lack of unified criteria for the diagnosis of anemia in patients with CHF and differences in the populations studied. The prevalence observed in our study is consistent with the results of previous case series for acute heart failure. Series that include only new cases of CHF^{8,13} obtain lower prevalences (17% and 18%) than those that include chronic cases.¹¹ Other authors have

TABLE 3. Prognostic Value of Anemia in Patients Admitted to Hospital With Acute Heart Failure

Author, Year and Reference	Number of Patients	Definition de Anemia	Length of Follow-Up	Mortality and/or Readmission
Ezekowitz et al, 2003 ⁸	12 065	ICD-9 codes	537 days	Mortality: anemia versus no anemia HR=1.34 (95% CI, 1.24-1.46)
Szachniewicz et al, 2003 ¹⁵	176	≤12 g/dL	1.5 years	Mortality: anemia versus no anemia HR=2.69 (95% CI, 1.05-6.47)
Felker et al, 2003 ^{14,*}	949	WHO (classification in 3 groups)	60 days	For each 1 g/dL reduction in hemoglobin there was an 11% increase in the risk of death and readmission.
Kosiborod et al, 2005 ^{26†}	50 405	Classification in 7 groups	1 year	Mortality: no association Repeat hospitalization: hematocrit ≤24% versus 40%-44% HR=1.21 (95% CI, 1.04-1.38)
Grigorian-Shamagian et al, 2005 ²⁷	557	WHO	1.4 years	Mortality: anemia versus no anemia HR=2.55 (95% CI, 1.49-4.36)

HR: hazard ratio; CI: confidence interval; WHO: World Health Organization.
 *Series derived from the OPTIME-CHF study.
 †Registry obtained from the Medicare & Medicaid Services' National Heart Project (USA).

obtained prevalences greater than 45% in case series including patients who were older or had advanced CHF, or in which there was a high prevalence of kidney failure.^{4,12} In Spain, data is only available from the study undertaken by Urrutia et al⁶ in outpatients, in whom the prevalence of anemia was 30%, and recently, Grigorian et al,²⁷ who obtained a prevalence of 44.5% in a series of patients admitted to hospital for CHF in whom the World Health Organization (WHO) definition of anemia was applied (hemoglobin <13 g/dL in men and <12 g/dL in women). The relatively low prevalence of anemia seen in our study may be explained by the definition of anemia used.

In our study, anemia was associated with the presence of renal failure, diabetes, female sex, and CHF with preserved systolic function. The relationship between hemoglobin levels and renal failure is a consistent finding in all studies, including our own. The levels of creatinine and urea are inversely proportional to those of hemoglobin. It is worth noting the high prevalence of diabetes mellitus in our series, a finding that is consistent with the results of other studies.^{5,8,18} An interesting finding in our study was the association between anemia and CHF with preserved systolic function. This association may be explained by the increased prevalence of CHF with preserved systolic function in women and older patients, both of which are factors associated with the presence of anemia. Most previous studies only analyzed patients with systolic dysfunction,³¹ and those studies that analyzed the relationship between ejection fraction and anemia did not find a clear association.^{6,15,26,27} Most, although not all, studies have found an association between anemia and age. In our series, the mean age of anemic patients was higher (74 years) than in patients without anemia (71 years), although this association was not maintained following correction for the other variables analyzed and is probably justified by female sex and preserved systolic function (which were predictors of anemia) being variables associated with more advanced age.

In our series of patients with acute CHF, anemia was a predictor of all-cause mortality, cardiac mortality, and repeat hospital admission. Results from studies addressing the prognostic value of anemia in patients with chronic CHF or outpatients are consistent: anemia was always found to be an independent predictor of mortality and repeat admission.^{9-12,15-20,22-25} However, this association was not maintained in all series of acute CHF (Table 3). In the series of Kalra et al¹³ and Kosiborod et al²⁷ the effect of anemia on mortality was reduced following adjustment for a number of variables; it is worth noting that the series of Kalra et al analyzed new outpatient cases of CHF. In both cases, attention was drawn to the possibility that anemia, more than a predictor of adverse events, is a marker of advanced disease. In contrast, our results are consistent with those of the in-hospital case series of acute CHF published by Ezekowitz et al⁸ and

Gregorian et al,²⁷ who analyzed all-cause mortality, and with the series of Felker et al,¹⁴ who analyzed death and repeat admission as a combined event over a follow-up period of 60 days. However, the association seen in our study between anemia and cardiac mortality in patients discharged with a diagnosis of CHF has not been reported previously.

Finally, 2 recent studies observed that anemia worsens prognosis in patients with preserved systolic function.^{18,32} The study by Brucks et al¹⁸ showed an increase in hospital admission for cardiac causes in 137 anemic patients with preserved systolic function, and Gregorian et al³² demonstrated that anemia was an independent predictor of mortality in a group of 210 patients with preserved systolic function. The results of our study are consistent with those findings and indicate that anemia also worsens survival in patients with preserved systolic function.

Limitations

The limitations of our study arise mainly from the principal source of information used (patient records for the index admission) and the small sample size, which places particular limits on analysis by subsets. Although the study involved a population of patients admitted to the cardiac unit of a tertiary hospital, the population was not as selected as in other published studies: it included patients irrespective of age, with similar sex distribution, and with a high prevalence of preserved systolic function. We also did not study the etiology of the anemia or the presence of hemodilution, nor variations in hemoglobin concentration over time; therefore, conclusions can not be drawn regarding the influence of changes in hemoglobin concentration on prognosis or whether the etiology of anemia affects its prognostic value.

CONCLUSIONS

In our series of patients discharged with a diagnosis of CHF the prevalence of anemia was high and was associated with worse long-term prognosis in terms of mortality (all-cause and cardiac) and repeat admission for decompensation. The results indicate that the concentration of hemoglobin could be considered in the assessment and treatment of patients with CHF, complementing the prognostic information provided by clinical variables and laboratory, or hemodynamic data, etc. In addition, unlike other prognostic markers that have recently been identified (inflammatory markers, natriuretic peptides, etc), blood work is simple and cheap, and is available in almost all laboratories, and therefore, represents easily obtained information for any clinician who treats patients with CHF. Anemia is a potentially reversible condition and its treatment could become another element in the treatment of patients with CHF, as is the case in patients with advanced, chronic renal

failure. Specifically designed trials are therefore needed to assess the impact of treating anemia on the prognosis of patients with CHF.

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