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Prevalence and prognostic role of anaemia in patients with acute heart failure and preserved or depressed ventricular function

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Abstract Observations available for patients with acute heart failure (HF) show conflicting results, and the prognostic role of anaemia ascertained on hospital admission is not well defined. We investigated the database of the Italian Survey on Acute Heart Failure (IS-AHF) to analyze prevalence, factors associated with and the prognostic role of anaemia (defined as haemoglobin < 12 g/dl) in patients hospitalized for acute HF with either depressed or preserved (>40%) ejection fraction (EF). The median haemoglobin level of the 2,318 patients considered in this analysis was 13 g/dl (inter-quartile range 11.5–14.3). The prevalence of anaemia was 31%. Patients who had anaemia were older, more frequently female gender, hospitalized for a chronic destabilized HF, had higher prevalence of preserved EF, hyponatremia, elevated troponin and other comorbidities (including diabetes, peripheral artery disease, chronic renal failure) than those who did not have anaemia. During the hospital stay, they were treated with higher doses of diuretics, and more frequently required mechanical ventilation and ultrafiltration, and less frequently received ACEi/ARB, aldosterone blockers and beta-blockers at hospital discharge. In-hospital mortality

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was 12.1 and 5.3% in patients with and without anaemia, respectively ($p < 0.0001$). In the multivariable analysis, anaemia was a significant independent predictor of in-hospital mortality apart from age, low systolic blood pressure, impaired renal function, elevated troponin assay, the non use of beta-blocker and the requirement of ino-tropic drug. In conclusion, anaemia diagnosed at hospital admission for acute HF is a frequent comorbidity with meaningful implications on the clinical management and prognosis both in patients with reduced and preserved EF.

Keywords Anaemia · Congestive heart failure · Hospitalization · Left ventricular function · Outcome

Introduction

In spite of the substantial improvements in evidence-based therapy on heart failure (HF) that has occurred in the past few decades [1], hospitalizations for acute HF exhibit a relentless increase [2], and since HF prevalence increases with age [3], such a trend will presumptively proceed as result of the ageing of western societies. The management of HF in elderly people is usually compli-cated by the frequent coexistence of other clinical con-ditions [4], and among them, anaemia is increasingly recognized as a frequent comorbidity with relevant clinical implications [5, 6]. On the other hand, in patients with acute HF, conflicting data exist on the prognostic role of anaemia, which has never been clearly defined [7–9].

The aims of this study were to analyse (1) the preva-lence of anaemia in a population of patients admitted for acute HF, (2) the clinical, demographic variables correlated with anaemia, (3) whether anaemia is an independent predictor of in-hospital mortality, and (4) whether anaemia has a similar prognostic role in patients with either depressed or preserved EF.

Methods

We investigated the database of the Italian Survey on Acute Heart Failure (IS-AHF), whose protocol and results are reported elsewhere [10]. Briefly, IS-AHF is a nation-wide, prospective, observational study conducted from March 1, 2004 to May 31, 2004 that aimed to analyze the clinical aspects, the prognosis and the therapeutic approa-ches of all the consecutive patients admitted for acute HF in 206 Italian Cardiology Centres with Intensive Coronary Care Units. The enrolling Centres were well representative of the geographic distribution and level of technology of the network of the Italian hospitals.

Study population

IS-AHF was a strictly observational study designed to evaluate the current practice of management of AHF patients admitted to cardiology centres. Out of the 2,807 consecutive patients admitted with a diagnosis of acute HF in the IS-AHF database, for the purpose of the present study, we excluded the patients who reported any history of neoplasia or gastro-enteric disease (413 patients), as well as those with unavailable data on the haemoglobin level at hospital entry (76 patients). Therefore, the analyzed cohort in the present study consists of 2,318 subjects. Local Institutional Review Boards were notified of the study according to national rules.

Baseline information on demographics, medical history and prior medication were gathered at the time of hospital admission, whereas data on physical examination and selected biochemical variables, were checked out at hos-pital entry. Left ventricular ejection fraction (LVEF) was collected during hospitalization, as well as the use of pharmacological treatments and procedures (mechanical ventilation and ultrafiltration) aimed to manage respiratory failure and refractory congestion. We registered the length of stay, and the in-hospital mortality, and reported the drugs prescribed at hospital discharge.

Statistics

Categorical variables are presented as frequencies and percentages. The duration of in-hospital stay, the dose and the duration of furosemide administration are pre-sented as the median value (and inter-quartile ranges, IQR). Other continuous variables are presented as their means with standard deviations. Univariate associations between baseline characteristics, main diagnostic proce-dures, pharmacological/non-pharmacological treatments and all-cause, in-hospital mortality were tested. Cate-gorical variables were compared by the chi-square test and continuous variables by the t test or the Mann–Whitney U Test. Age, gender, presenting clinical profile, type of HF (de novo/worsening) and all the variables significantly associated at the unadjusted analysis with all-cause mortality, among which anaemia, were included in a multivariable analysis (logistic model) with the aim of identifying the independent predictors of all-cause in-hospital mortality. The linearity of the continuous vari-ables was tested by piecewise polynomials (the restricted cubic spline), and we particularly estimated the rela-tionship between in-hospital mortality and different hae-moglobin levels. Receiver Operating Characteristic (ROC) analysis was used to assess the best cut-off of haemoglobin level in order to identify patients with a poorer prognosis. For categorization, "anaemia" was

defined when values of haemoglobin level were below the prognostic cut-off value.

A multiple imputation technique was therefore used to avoid the loss of the information in those subjects with some missing variables. According to this procedure, five complete data sets were obtained using the MICE package [11] and five full data analyses were completed. Finally, the results were pooled using the method of Barnard and Rubin [12]. A p value < 0.05 was considered statistically significant. All tests were two-sided. Analyses were performed with SAS system software (SAS Institute Inc, Cary, NC, USA) and the R Development Core Team (R Foundation for Statistical Computing, Vienna, Italy).

Results

The distribution of haemoglobin level on hospital admission is shown in Fig. 1. The mean haemoglobin level in the whole cohort was 12.9 ± 2.1 g/dl (median: 13 g/dl; IQR: 11.5–14.3 g/dl). The cut-off point value of haemoglobin with the best specificity and sensitivity in predicting adverse outcome (ROC analysis) was 12 g/dl (Fig. 2). This value identified "anaemia," which was a common condition affecting 719 out of 2,318 pts (prevalence 31%). The demographic, clinical characteristics and laboratory data of the whole cohort of the 2,318 patients are reported in Table 1. The anaemic HF patients in contrast to those with higher haemoglobin levels, were significantly older, of female gender, and with significantly higher prevalence of other comorbidities like diabetes, peripheral artery disease, or chronic renal failure. In contrast to HF patients with normal haemoglobin levels, they were hospitalized, characteristically, for a "chronic" destabilized illness, with more hospital admissions for HF in the previous year, and finally, they showed a slight but significantly higher prevalence of subjects with a normal or mildly impaired LVEF. Patient with low haemoglobin level, indeed, were more
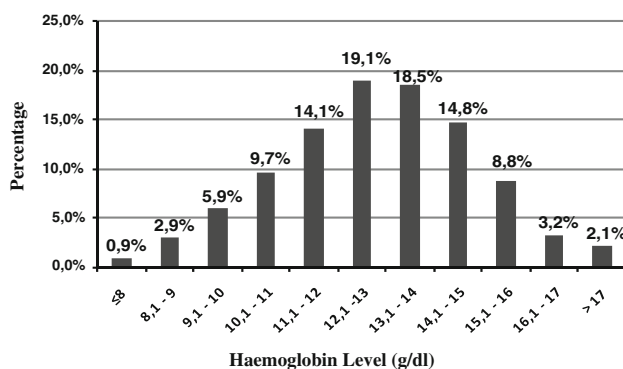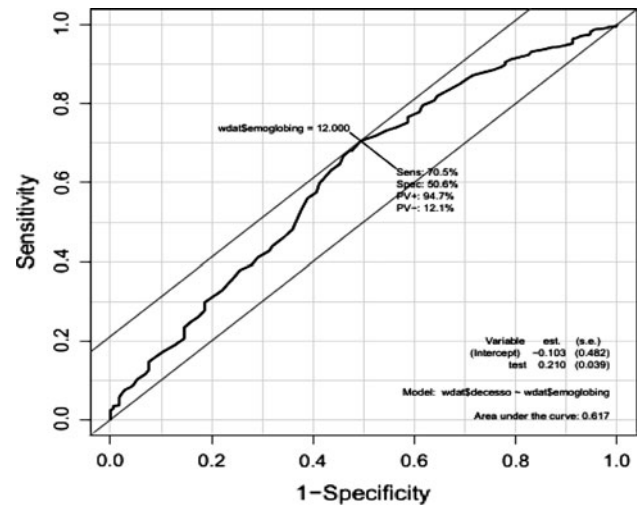
Fig. 2 ROC curve for anaemia. Area under the curve is shown. The cut-off point identifying the subgroup of patients with an adverse outcome was 12 g/dl (area under the curve 0.617)

frequently on therapy with Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB), diuretics, Anti-Aldosterone Agents (AAA), Anti-coagulant or Antiplatelets drugs.

At hospital admission, patients with low haemoglobin levels revealed some slight but significant differences from those not anaemic in clinical signs (Table 1). They showed an inferior prevalence of overweight/obese subjects (BMI > 25 kg/m^2), presented lower blood pressure values, and showed more evidence of peripheral venous congestion than those with normal haemoglobin levels. There were also some significant differences in laboratory values in anaemic patients with respect to those with normal haemoglobin level: they had a great incidence of hyponatremia and an elevated level of troponin at hospital admission; furthermore, the anaemic HF patients presented higher values of azotemia, creatininemia and lower serum bilirubin levels.

In-hospital treatment and outcome

Table 2 reports how acute HF patients with/without anaemia were managed during the in-hospital phase: anaemic patients received higher doses of loop diuretics for a longer period of time, and more frequently needed the support of inotropic drugs. Patients with anaemia, furthermore, required more frequent mechanical ventilation, and presented a twofold risk in the development of acute renal failure, or to receive ultrafiltration.

As shown in Fig. 3, there is an inverse relationship between the risk of death during hospital stay and haemoglobin level that seems "almost linear". The patient with low haemoglobin concentration presents significantly

Fig. 1 Distribution of haemoglobin level at hospital admission in the 2,318 patients enrolled in the study

Table 1 Baseline characteristic and prior medication of heart failure patients divided according with the presence of anaemia (Haemoglobin level < 12 g/dl for both sex) at hospital entry

Variable	Total (n = 2,318)	No anaemia (n = 1,599)	Anaemia (n = 719)	p
Age (years), mean ± SD	72 ± 11	72 ± 11	74 ± 11	0.0002
Age > 75 years	1,060 (45.7%)	699 (43.8%)	361 (50.2%)	0.004
Sex (female)	934 (40.3%)	580 (36.3%)	354 (49.2%)	<0.0001
Diabetes	883 (38.1%)	576 (36.0%)	307 (42.7%)	0.002
Reported renal disease	565 (24.4%)	282 (17.7%)	283 (39.4%)	<0.0001
Peripheral artery disease	646 (27.9%)	402 (25.1%)	244 (33.9%)	<0.0001
Atrial fibrillation	868 (37.5%)	601 (37.6%)	267 (37.1%)	0.84
Previous stroke	219 (9.5%)	144 (9.0%)	75 (10.4%)	0.29
Previous myocardial infarction	830 (35.8%)	533 (33.3%)	297 (41.3%)	0.0002
Smoker	353 (15.2%)	283 (17.7%)	70 (9.7%)	<0.0001
COPD	666 (28.7%)	460 (28.8%)	206 (28.7%)	0.95
Type of HF				<0.0001
"De Novo"	1,025 (44.2%)	767 (48.0%)	258 (35.9%)	
Chronic destabilized	1,293 (55.8%)	832 (52.0%)	461 (64.1%)	
Onset of symptoms (evaluated on pts with chronic destabilized HF)[a]				
<6 months	433 (35.1%)	273 (34.5%)	160 (36.1%)	0.5
>24 months	444 (36.0%)	297 (37.5%)	147 (33.2)	0.1
Hospitalization for HF in the previous year (evaluated on pts with chronic destabilized HF)	707 (54.7%)	432 (51.9%)	275 (59.7%)	0.008
Clinical presentation				0.017
NYHA III–IV	990 (42.7%)	663 (41.5%)	327 (45.5%)	
Acute pulmonary edema	1,154 (49.8%)	826 (51.7%)	328 (45.6%)	
Shock	174 (7.5%)	110 (6.9%)	64 (8.9%)	
HF etiology				0.14
Ischemic	1,059 (45.7%)	714 (44.7%)	345 (47.9%)	
Not ischemic	1,259 (54.3%)	885 (55.3%)	374 (52.0%)	
LVEF > 40%[b]	726 (34.0%)	485 (32.6%)	241 (37.0%)	0.049
Previous therapy				
ACE-i	1,264 (54.5%)	849 (53.1%)	415 (57.7%)	0.04
ARB	259 (11.2%)	171 (10.7%)	88 (12.2%)	0.27
ACE-i/ARB	1,491 (64.3%)	1,003 (62.7)	488 (67.9%)	0.017
Diuretics	1,491 (64.3%)	960 (60.0%)	531 (73.9%)	<0.0001
Beta-blockers	621 (26.8%)	413 (25.8%)	208 (28.9%)	0.12
Anti-aldosteron agents	536 (23.1%)	333 (20.8%)	203 (28.2%)	<0.0001
Anticoagulation/antiplatelet	1,418 (61.2%)	948 (59.3%)	470 (65.4%)	0.006
BMI > 25 kg/m²	1,373 (59.2%)	974 (60.9%)	399 (55.5%)	0.02
BMI < 20 kg/m²	49 (2.1%)	30 (1,9%)	19 (2,6%)	0.2
SBP (mmHg), mean ± SD	142 ± 36	145 ± 37	136 ± 35	<0.0001
DBP (mmHg), mean ± SD	83 ± 19	85 ± 19	78 ± 17	<0.0001
Peripheral congestion[c]	910 (39.3%)	584 (36.5%)	326 (45.3%)	<0.0001
Pulmonary congestion on Chest Rx[d]	1,850 (90.2%)	1,275 (90.2%)	575 (90.3%)	0.98
Hyponatremia (< 136 mEq/L)	843 (36.5%)	526 (33.0%)	317 (44.2%)	<0.0001
Creatinin level (mg/dl), mean ± SD, max value[e]	1.7 ± 1.0	1.5 ± 0.8	2.1 ± 1.3	<0.0001
Creatinin level (mg/dl), max value[e]				<0.0001
<1.5	1,240 (53.6%)	965 (60.5%)	275 (38.3%)	
1.5–2.5	779 (33.7%)	506 (31.7%)	273 (38.1%)	
>2.5	294 (12.7%)	125 (7.8%)	169 (23.6%)	

Table 1 continued

Variable	Total ($n = 2{,}318$)	No anaemia ($n = 1{,}599$)	Anaemia ($n = 719$)	p
Azotemia (mg/dl),max value[f]				<0.0001
<50	641 (29.3%)	481 (31.9%)	160 (23.4%)	
50–100	1,042 (47.5%)	757 (50.3%)	285 (41.6%)	
>100	508 (23.2%)	268 (17.8%)	240 (35.0%)	
Elevated troponine[g] (>0.1 ng/ml) at entry	726 (42.6%)	486 (40.7%)	240 (47.0%)	0.017
Bilirubin (mg/dl), max value[h]	1.21 ± 1.60	1.25 ± 1.80	1.09 ± 0.98	0.0005

SD standard deviation, *HF* heart failure, *LVEF* left ventricle ejection fraction, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a] Available for 1,234 out of 1,293 pts with chronic destabilized HF

[b] Available for 2,137 pts

[c] Presence of 2 or more of the following clinical signs: Distension of the Jugular Veins, Hepatomegaly with positive Hepato-jugular reflux, Peripheral Edema, Ascites

[d] Chest Rx available for 2,050 pts

[e] available for 2,313 pts

[f] Available for 2,191 pts

[g] Available for 1,705 pts, troponine I measured in 68% of cases, troponine T in 32%

[h] Available for 1,743 pts

**Table 2** In-hospital therapy and clinical outcomes

Variable	Total ($n = 2{,}318$)	No anaemia ($n = 1{,}599$)	Anaemia ($n = 719$)	P
Inotropic agents therapy	521 (22.5%)	323 (20.2%)	198 (27.5%)	<0.0001
Furosemide EV Max mg/die	100 [60–200]	96 [60–160]	100 [60–250]	<0.0001
No. days Furosemide EV	2 [1–4]	2 [1–4]	3 [2–4]	<0.0001
Furosemide OS Max (mg/die)	75 [50–125]	75 [50–100]	100 [50–150]	<0.0001
Length of hospitalization (days)	9 [6-13]	9 [6-13]	9 [6-14]	0.047
In hospital death (total causes)	172 (7.4%)	85 (5.3%)	87 (12.1%)	<0.0001
Acute renal failure	167 (7.2%)	91 (5.7%)	76 (10.6%)	<0.0001
Ultrafiltration	30 (1.3%)	10 (0.6%)	20 (2.8%)	<0.0001
Mechanical ventilation	120 (5.2%)	71 (4.4%)	49 (6.8%)	0.017
Pulmonary congestion on Chest Rx at H. discharge[a]	478 (31.5%)	331 (31.0%)	147 (32.5%)	0.58
Peripheral congestion at H. discharge[b]	155 (7.2%)	99 (6.5%)	56 (8.9%)	0.06
ACE-i/ARB at discharge[b]	1,815 (84.6%)	1,317 (87.0%)	498 (78.8%)	<0.0001
Beta-blocker at discharge[b]	988 (46.0%)	740 (48.9%)	248 (39.2%)	<0.0001
Antialdosteron agent at discharge[b]	1,314 (61.2%)	951 (62.8%)	363 (57.4%)	0.020

[a] On 1,520 pts discharged alive with Rx Chest at discharge available

[b] On 2,146 pts discharged alive

higher in-hospital mortality for all-causes. In these patients, the cause of death was cardiac in 92 (sudden death in 32%, pump failure in 68%), vascular in 2% and non-cardiovascular in 6% of cases. In patients without anaemia, the cause of death was cardiac in 88% (sudden death in 39%, pump failure in 61%), vascular in 5% and non-cardiovascular in 7% of cases (p = 0.6). Death for acute myocardial infarction occurred in 14 patients with anaemia (1.9%) and in 10 without anaemia (0.6%, p = ns). By considering separately the subgroups with preserved (> 40%) and reduced (≤ 40%) LVEF the in-hospital all cause mortality was higher in the latter than in the former, but the presence of anaemia significantly increases the risk of death in both groups, by roughly doubling the in-hospital mortality (Fig. 4). Also the length of hospitalization, is significantly longer in patients with anaemia. At hospital discharge, patients with anaemia less frequently received a treatment with ACEI/ARB, AAA and beta-blockers.
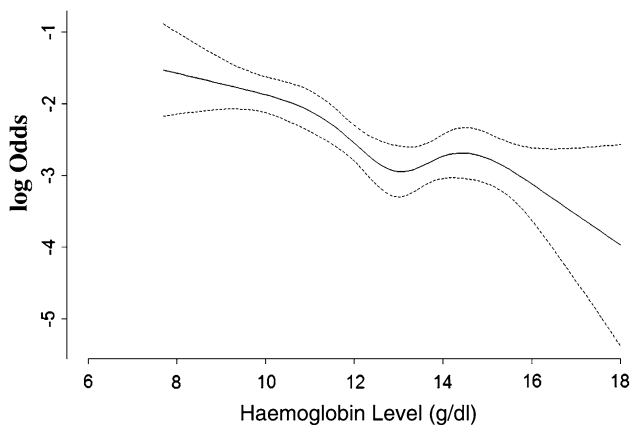
Fig. 3 Estimated relation between risk of in hospital death for the different haemoglobin levels. Log odds plot with 95% confidence intervals

Multivariable analysis

A haemoglobin level below 12 g/dl is confirmed to be a strong independent predictor of in-hospital mortality (odds ratio: 1.61, 95% confidence interval: 1.10–2.35, p = 0.013) apart from age, low systolic blood pressure, impaired renal function (expressed as high serum azotemia), evidence of myocardial damage, as suggested by elevated troponin levels, and use of inotropic drugs (Table 3).

Discussion

A low level of haemoglobin is frequently observed in patients with HF, and its prevalence depends on several variables: the severity of HF, the diagnostic criteria to define the anaemia, the selection of the patients enrolled and the setting of the study [4, 5]. Furthermore, because of

marked fluid retention, above all in destabilized HF, a "pseudo anaemia" state may occur from hemodilution and extracellular blood volume expansion [13–15]. Nevertheless in HF, a "true" anaemia may occur, with a relevant prognostic role, owing to an intense derangement of erythropoiesis as is well documented as a result mainly of a blunted production or resistance state to erythropoietin, and an impaired iron metabolism [4, 5, 16, 17]. The studies performed in the community on patients with acute heart failure [7–9, 18–20] report a prevalence ranging from 44 to 62%. In our series, we confirm the high prevalence of anaemia in patients hospitalized for acute HF (31%). Such results differ largely from those reported by randomized clinical trials and observational studies on stable and younger patients with chronic HF [4, 5, 21–23]. The higher prevalence of anaemia reported in other series [OPTI-MIZE-HF Registry (50%) [8] and Silva single-centre series (45%) [9], in which the definition of anaemia was based on the same cut-off of haemoglobin level may be the consequence of the inclusion in such studies of HF patients with gastrointestinal disease or cancer, clinical conditions with a high prevalence of anaemia, excluded in our cohort. Furthermore, our patients were Caucasian, and presented at a younger age and with less compromised renal function, relevant determinants of anaemia [18, 24, 25].

In our study, as in the OPTIMIZE Registry [8], a low haemoglobin level at hospital admission is significantly associated with a longer length of in-hospital stay, and independently predicts a greater in hospital all-cause mortality. Such observations, also reported in other large unselected cohorts of patients with acute HF [7, 8], underscore that a low haemoglobin level at hospital entry, below 12 g/dl in our case, is a powerful marker of adverse outcomes during hospital stay. The prognostic importance of a low haemoglobin level is not coloured by the HF

Fig. 4 All-cause in-hospital mortality by anaemia and EF levels (on 2,137 patients with EF measured)
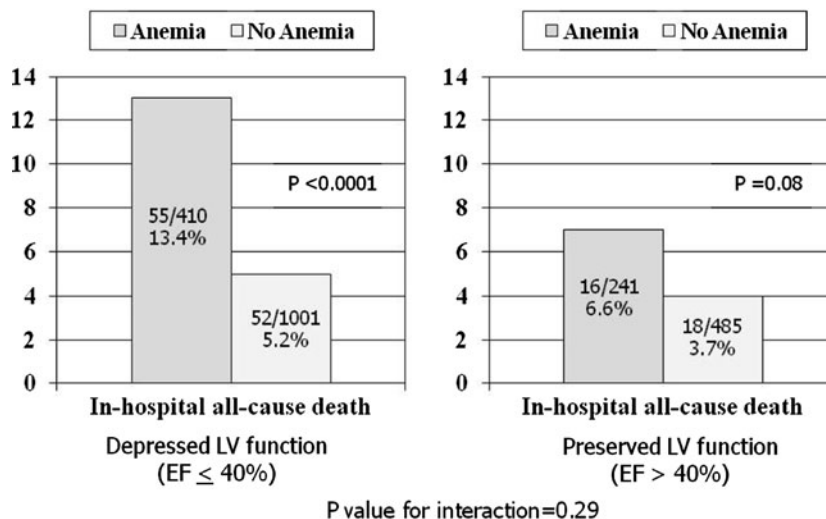
Table 3 Logistic regression analysis for multivariate estimation of variables significantly associated with in hospital mortality (all Causes)

Variable	P	OR	IC95%
Inotropes infusion	<0.0001	3.369	2.221-5.112
Troponin at hospital admission (>0.1 vs. ≤0.1 ng/ml)	0.0002	2.451	1.536-3.911
Anaemia (Hb < 12 vs. Hb ≥ 12)	0.0134	1.611	1.104-2.351
Age (continuous)	0.0004	1.037	1.017-1.058
Azotemia (continuous)	0.0010	1.008	1.003-1.012
SBP (continuous)	<0.0001	0.985	0.978-0.991
B-Blockers (before H. Admission)	0.0479	0.626	0.394-0.996

SBP systolic blood pressure

aetiology, and furthermore is not alleviated by the presence of a preserved or mildly impaired systolic function. Our findings are consistent with previous studies [8, 26–29], and have relevant clinical implications. HF with preserved systolic function, indeed, is a clinical entity not well defined with a prognosis that is still controversial [30]. Findings from a large in-hospital study [31] underline the relevance of comorbidities in defining the prognosis of HF with preserved systolic function. Our study confirms that anaemia is a relevant prognostic marker in such a subset of HF patients. In our study, the relationship between the blood haemoglobin level and the risk of in hospital death is "almost" linear. This actually may be related to several components including less comorbidities associated with depressed erythrocytes production or shorter survival, better nutrition and nutrients absorption, less hemodilution that implies less systemic circulatory load and lower neurohormonal activation. Overall, in spite of a similar acute clinical presentation, this may suggest a less severe clinical status and HF stage in non-anemic patients. However, in our population, the magnitude of patients with haemoglobin levels above 16 g/dl was very low, and this situation could influence the right side of the relationship which could be actually "U" shaped, a trend already described in other series and justified by the potential disadvantageous effect of high blood viscosity in patients with HF.

It is well known that patients with HF and a low level of haemoglobin present more frequently with significant renal dysfunction [5, 7–9, 18, 24, 25, 32, 33]. This also is the case in our cohort. Further, patients with a haemoglobin level below 12 g/dl receive more intensive diuretic therapy, and more often develop acute renal failure. Besides enhancing a marked fluid retention and consequently hemodilution, when renal dysfunction coexists with HF (the so called "cardiorenal" syndrome), the interaction between heart and kidney broadens the activity of biologic mediators (the sympathetic nervous system, the renin–angiotensin–aldosteron system, nitric oxide and reactive oxygen species, chronic inflammatory states) [34–36] with induction of positive feedback loops and the amplification of a progressive dysfunction of both systems. In such a context, anaemia is a common and essential feature of the cardio-renal syndrome [35] that may play a critical role in the maintenance or even the progression of the syndrome [35–37], and the evolution toward the failure of both cardiac and renal systems. Acute HF is a leading cause of hospital acquired renal failure [36, 38], and, in such a context, anaemia further reducing oxygen delivery to a hypo perfused kidney may facilitate the progression of a worsened renal function to overt acute renal failure [36, 39, 40].

At hospital discharge, patients with anaemia less frequently receive evidence-based therapies, such as RAAS blockers, beta-blockers, AAA recommended for the therapy of HF. Our data confirm the results reported elsewhere [8]. There may be quite a few reasons why patients with anaemia are more likely to receive less than optimal discharge care. HF patients with low haemoglobin present more frequently renal dysfunction and diabetes, and show a significantly lower systolic blood pressure at hospital entry. However, we cannot rule out that fatigue, a common symptom of anaemia, may be a potential reason for failure to prescribe drugs such as ACEi/ARB and beta-blockers.

Limitations of the study

The present study has several limitations that must be taken in account. This report is a strictly observational survey, and many unmeasured variables may have been present that might influence the results. The haemoglobin level was obtained as a single measure at hospital admission, therefore, we cannot clarify and quantify the changes in haemoglobin to verify how many patients were affected with transitory anaemia or hemodilution. For a better stratification of HF patients with anaemia, we have excluded those with a history of gastrointestinal disease and history of cancer, however we do not have any information about aetiology and specific treatments of anaemia particularly with respect to blood transfusion, iron supplements and erythropoietin receptor stimulating agents. In regards to

drug therapy, we cannot ascertain contraindications or intolerance to drugs recommended as evidence-based by guidelines. Furthermore, no comorbidity or severity index was used to adjust analyses. Our statistical approach provided for using all the variables significantly associated at the unadjusted analysis with all-cause mortality, among which anaemia, in a multivariable logistic model. Finally, it is important to underline that more than half of patients hospitalized for acute HF are managed by internal medicine wards in Italy; thus, present results do not necessarily apply to other populations with acute HF that could have been differently selected.

Conclusions

Our study underscores that anaemia is a frequent comorbidity in acute HF with relevant clinical implications, independent of the presence and degree of left ventricular systolic dysfunction, older age and lower systolic blood pressure. Prevalence of this prognostically adverse condition is high even in the community populations (such as ours), and in cohorts of patients without gastrointestinal disease or cancer, two frequent causes of non-cardiogenic anaemia that are frequent in HF patients, but were excluded in our investigation. Recent specific therapeutic approaches [41, 42] encourage to plan ad hoc studies assessing whether the pharmacological correction of anaemia can be associated with an improved outcome of patients with HF and low haemoglobin levels.

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