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Anaemia as Predictor of All-Cause Mortality in Patients with Systolic Dysfunction

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ABSTRACT

Anaemia has been associated with worse outcomes in patients with chronic heart failure (HF). We aimed to characterize the clinical profile and outcome (all-cause mortality) of hospitalized patients with reduced ejection fraction (<45%) related to presence of anaemia (haemoglobin <12 g/dL for women and <13 g/dL for men according to WHO definition).

We studied 485 patients with systolic dysfunction. Information was retrospectively collected from our database IMAGE, which contains details on demographic, clinical, laboratory, instrumental and follow-up data of all consecutive patients admitted to the Coronary Unit of the Institute of Clinical Physiology, Italian National Research Council. Patients presenting anaemia on admission were older, with lower body mass index, higher white blood cell count (WBC) and creatinine levels. Other inflammatory indices were also higher in anaemic patients, as well as highly sensitive troponin T and N-terminal pro-brain natriuretic peptide. In our HF population, anaemia was a common finding affecting 24% of the patients, it was associated with inflammatory and oxidative stress indices and it represents an independent predictor of mortality.

Overview

Anaemia is a complex, multifactorial and multidimensional issue in patients with chronic heart failure (HF) associated with adverse outcomes in such patients.[1–3] Development of anaemia in HF is surely due to a complex interaction of multiple determinants, which include iron deficiency, kidney disease, inflammation and oxidative stress, and many other factors still under study.[4] In the present study, we aimed to characterize the clinical profile and outcome (all-cause mortality) of hospitalized patients with reduced ejection fraction (EF<45%) related to presence of anaemia according to WHO definition (haemoglobin, Hgb <12 g/dL for women and <13 g/dL for men).[5]

Methods

485 subjects with reduced ejection fraction (<45%) were selected to participate in the study. Information were retrospectively collected from our database IMAGE, which contains detailed information on demographic, clinical, laboratory, instrumental and follow-up data of all consecutive

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patients admitted to the Coronary Unit of the Institute of Clinical Physiology, Italian National Research Council.[6,7] Data on smoking habits, family history of ischemic heart disease, arterial hypertension (diastolic / systolic blood pressure >90/140 mmHg or use of antihypertensive medication), diabetes (twice fasting glucose > 110 mg/dl or use of antidiabetic treatment), obesity (body mass index, BMI; > 30 kg/m2), and dyslipidaemia (total cholesterol ≥ 200 mg/dL, or triglycerides ≥150 mg/dL, or current use of lipid-lowering drugs) were coded in a dichotomized fashion. Medical therapy included ACE inhibitors, beta-blockers, lipid-lowering and anti-diabetic agents, diuretics, and aspirin, nitrates, calcium-channel antagonists. An annual telephone interview with each patient or patient's family members was done to collect follow-up data. Information on deaths was gathered using medical records or death certificates provided by local health authorities.

Data Records

Table 1 below presents the data structure in file 01205_Vassalle_Anaemia_Predictor.xls (and the accompanying file with extension .ods).

Validation

In our cohort of hospitalized patients with reduced ejection fraction (<45%) we have enrolled the patients (age 67±11 years) stratified according to anaemia (Hgb <12 g/dL for women and <13 g/dL for men according to the WHO definition). HF patients with anaemia were older ($p<0.05$) and differed significantly with regard to baseline clinical and laboratory parameters compared to those without anaemia; these patients were characterized by a lower BMI ($p<0.05$), and higher white blood cell count (WBC; $p<0.001$) and creatinine levels ($p<0.001$). Anaemic patients also presented higher NTproBNP levels ($p<0.01$), as well as highly sensitive troponin T ($p\leq0.05$), in addition to a significant association between NTproBNP and hsTnT and creatinine and inflammatory parameters. Age, BMI, creatinine and WBC were evaluated as determinants for anemia via multivariate regression analysis, which identified creatinine (T-value 3, <0.01), and WBC (2.8, <0.01) as independent correlates of anaemia.

During a mean follow-up period of 29 ± 21 months, there were 52 (11 %) deaths. The Kaplan–Meier survival estimates showed a significantly worst outcome in patients with anemia ($p < 0.01$).

Table 1. Data records – description of variables included in the dataset.

Column	Variable	Variable (Coding)
A	ID of the subject	
B	Gender of the subject	male (1) or female (0)
C	Age of the subject	Years
D	Body Mass Index	weight (kg) divided by the square of the body height (m)
E	Hypertension	presence (1) or not (0)
F	Diabetes	presence (1) or not (0)
G	Smoking habit	presence (1) or not (0)
H	Dyslipidaemia	presence (1) or not (0)
I	Left ventricular ejection fraction	%
J	Creatinine	mg/dL
K	Total bilirubin	mg/dL
L	Iron	µg/dL
M	White Blood Count	$*10^3/\mu L$
N	Haemoglobin	g/dL
O	Fibrinogen	mg/dL
P	N-terminal pro-brain natriuretic peptide	ng/L
Q	Erythrocyte sedimentation rate	mm/h
R	C reactive protein	mg/dL
S	Troponin T	ng/L

At univariate analyses the following variables resulted in significant (p value ≤ 0.05) anaemia – age (25th percentile: 60 yrs), obesity, EF (<30%), creatinine levels (> 1.3 mg/dL). At multivariate adjustment in a Cox multivariate proportional hazard model anaemia (hazard ratio /HR/ 1.9, 95 % confidence interval /CI/ 1.1-3.3, $p<0.05$) together with elevated creatinine (HR 1.8, 95% CI 1-3.1, $p<0.05$) and reduced EF (HR 1.8, 95% CI 1-3.1, $p<0.05$) remained significant prognostic risk determinants for mortality.

The prevalence of iron deficiency corresponded to 24 %, and iron resulted inversely associated with creatinine levels ($n=475$, $p<0.05$). Further, we found that higher level of oxidative stress (d-ROMS) in patients with reduced EF ($n=36$, $r = 0.4$, $p < 0.05$) and levels of oxidative stress sig-

nificantly and directly correlate with NTproBNP ($r=0.5$, $p<0.01$), BNP ($r=0.4$, $p\leq0.01$) and inflammatory parameters (CRP, $r=0.6$, $p<0.01$; ESR, $r=0.6$, $p<0.01$).

Use and Potential Reuse of the Dataset

Dataset presented in this paper confirmed that anaemia, which resulted closely associated with biomarker of inflammation and renal function, is common in patients with HF (affecting one fourth of patients) and it independently predicts an increased risk of all-cause mortality.

Anaemic patients presented a lower BMI which may be correlated to the decreased functional capacity, a reduced quality of life, and an increased comorbidity burden associated with anaemia. It has been suggested that patients with cachexia may be at major risk for anaemia.[8–10] In this context, recommendations of the European guidelines for the management of HF already suggest the routine evaluation of iron status and the iron store restoration in symptomatic patients with systolic HF to improve functional status as well as quality of life.[11]

Renal impairment, anaemia and inflammation represent an intermingled triangle and the perfect storm for HF worsening.[4] We found that anaemia was closely associated with inflammatory indices and creatinine levels. In our cohort, patients with anaemia showed higher creatinine levels, and creatinine remained an independent determinant of anaemia at the multivariate analysis, adding evidence of the kidneys' major role in the relationship with anaemia in HF. According to previous data, anaemic patients also presented higher NTproBNP levels, as well as highly sensitive troponin T.[12,13]

Many factors could be involved, including the reduced clearance of these biomarkers due to renal failure, and a greater stimulation for the release of natriuretic peptides by the myocardium secondary to the plasma volume increase present with anaemia. On the other hand, main determinants for the association of anaemia with NTproBNP could be again inflammation and kidney dysfunction.[12,14,15]

Although several factors have been implicated in the multifactorial HF-associated anaemia, which include impaired erythropoietin production and resistance, iron status deficiencies, inflammation and cytokine activation, precise underlying pathophysiology remains largely unknown.[4] Nonetheless, inflammation associated with HF may be another cause of anaemia due to reduced iron utilization.[4] We found all inflammatory parameters higher in the anaemic HF group, and WBC remained an independent factor for anaemia after multivariate adjustment. This result confirmed previous data, which found higher levels of CRP, hepcidin, tumour necrosis factor-α, and interleukin-6 related to iron status in HF.[4,16]

Interestingly, eryptosis (suicidal erythrocyte death) has been recently proposed as a new and additive contributor to HF-induced anemia.[17] In particular, erythrocytes may become more sensitive to oxidative stress in HF, and increased oxidative stress in HF may accelerate eryptosis and lead to anaemia.[17] These observations may have important therapeutic implications, as eryptosis could represent a new target for future therapeutic strategies. In fact, available therapy presents adverse aspects, as intravenous iron therapy could further increase oxidative stress, and treatment with erythropoietin or erythropoietin-stimulating agents are still under discussion also for their increased thromboembolic risks.[4,18] Moreover, multiple randomized trials, including the recent RED-HF trial, evaluating anaemia treatment in HF patients did not demonstrate a clear effect on mortality or HF hospitalizations.[19,20] Thus, thymol, a natural antioxidant which inhibits eryptosis and decrease oxidative stress, might represent an innovative tool to be studied for its effectiveness in the treatment of HF-associated anaemia.[21]

One limitation of the study is that we have no information on ferritin and transferrin values, essential for further delineation of anaemia. Nonetheless, it is important to remind that ferritin concentration may be elevated in HF independent of iron status, due to its function as an acute phase reactant and therefore not useful to estimate iron deficiency in such patients.[22] Moreover, there were no data of some biomarkers for all patients. For this reason, these parameters cannot be included in the multivariate analysis. Also, this retrospective study only includes data from admission, preventing our ability to evaluate the relationship of Hgb change over time and mortality. In any case, our aim was exactly to provide evidence for the utility of a simple, inexpensive and widely available biomarker, exploitable in providing basic and yet relevant information in the clinical practice.

The dataset described herein could represent an additive source of data to integrative databases supporting studies focused on the relationship between biochemical parameters and cardiac function and available to evaluate and compare different patient populations.

Conclusion

In conclusion, in our HF population, anaemia was a common finding affecting 24% of the patients. It was associated with inflammatory and oxidative stress indices and represents an independent predictor of mortality. Hgb is a simple routine biomarker, generally available at patient admission, which may be helpful in the routine assessment of patients with systolic chronic HF and of utility in stratifying the prognosis.

Data Files

The data described in this paper is presented in an openly accessible spreadsheet: "*01304_Vassalle_Anaemia_Predictor.xls*".

The file is available also in the Open Document Spreadsheet format.

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