Original Paper

Prevalence of Erythrocyte Changes in Patients with Heart Failure

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ABSTRACT. Heart failure (HF) is one of the most common causes of hospitalization in patients over the age of 65. Purpose The objective of our study was to assess the prevalence of anemia and characterize the morphology of red blood cells in patients admitted for HF decompensation. Material and Methods We have included patients with decompensated HF with left ventricular ejection fraction (LVEF). ≤45% successively hospitalized at Filantropia Clinical Hospital Craiova. Results A total of 397 patients, including 204 males (51.39%) were included. The prevalence of anemia in our group was 38.54% (153 patients). The mean age of patients with heart failure and anemia was significantly higher compared to those with normal hemoglobin (75.05±7.16 years vs. 72.27±7.91 years, p=0.00047). The majority of anemias (68.62%) were normocytic normochromic, defined as mean corpuscular hemoglobin (MCV) value between 80 to 98fl and mean corpuscular hemoglobin concentration (MCH)>27pg. 20 patients (13.07%) had microcytic hypochromic anemia (MCV<80fL and MCH<27pg), in 16 patients (10.45%) was present normocytic hypochromic anemia (MCV 80-98fl and MCH<27pg) and 12 patients (7.48%) had macrocytic anemia (MCV>98fL and MCH>27pg), respectively. Conclusions Our study suggests that the prevalence of anemia in hospitalized patients for HF decompensation is high and normocytic normochromic anemia was the most common morphological type of anemia.

KEYWORDS: anemia, decompensated heart failure, morphology of red blood cells

Introduction

Heart failure (HF) is one of the most common causes of cardiovascular mortality in the world and a frequent cause of hospitalization in patients over the age of 65 [1]. In Romania, HF affects approximately 4,7% of the general population over 35 years [2]. Despite progressions in diagnosis and treatment, HF prognosis remains reserved. In the last two decades, researchers' attention has turned to hematological changes associated with heart failure. In 1995, the European Society of Cardiology (ESC) was the first professional medical society which include anemia in the list of comorbidities associated with HF [3]. Anemia is an important comorbid condition associated with an unfavorable prognosis in patients with HF [4].

The objective of our study was to assess the prevalence of anemia and characterize the morphology of red blood cells in patients admitted for HF decompensation.

Material and Methods

In a prospective observational study, we evaluated the characteristics of red blood cells series of patients admitted for HF decompensation. The criteria for study inclusion were: a documented history of chronic HF of ≥12 months, NYHA functional class III and IV and left ventricular ejection fraction (LVEF) ≤45% as assessed by echocardiography. We excluded patients with acute coronary syndrome, any acute or chronic illness that might influence hematological profile (infection, severe renal disease requiring dialysis, severe hepatic disease, malignancy, and haematological diseases), any major surgery within the 3 months preceding the study or the administration of therapies that may alter the hematological profile of patients (blood transfusions, erythropoietin therapy, intravenous iron infusions, and also any nutritional supplements). A complete blood count was performed to all patients on inclusion in our study.

Statistical analysis. For numerical variables, mean±standard deviation were computed. Student's t test, and one-way analysis of variance (ANOVA) were performed to compare parameter levels between groups. We used Chi-square test to compare distributions for categorical variables. For all tests, we considered a statistically significant value of p<0.05.

Results

A total of 397 patients, including 204 males (51.39%) were included. Their baseline characteristics are reported in Table 1. The mean

age of the studied patients was 73.34 ± 7.75 years (range 46-91 years); 88.64% were older than 65 years. 204 patients (51.39%) were male. New York Heart Association (NYHA) heart failure class III was present in 179 (45.08%) and class IV in 218 (54.91%) patients. Ischemic etiology was present in 45% of cases. A history of hypertension (HTN) was present in 63.72% of patients, 49.62% of subjects had estimated glomerular filtration rate (eGFR) $<60ml/min/1.73m^2$ and 39.29% were diabetic.

Table 1. Baseline characteristics of the study population

Characteristics	Value
Age, years	73.34 ± 7.75
Age >65 years, n (%)	352 (88.64%)
Male gender, n (%)	204 (51.39%)
Ischemic etiology	179 (45%)
History of hypertension	253 (63.72%)
eGFR $<60ml/min/1.73m^2$	197 (49.62%)
Diabetes mellitus, n (%)	156 (39.29%)
NYHA class III/IV, n (%)	179/218 (45.08%/54,91%)

eGFR=estimated glomerular filtration rate, NYHA=New York Heart Association

Hematological data of the patients subgrouped according to gender are given in Table 2.

The average number of red blood cells was of $434.52\pm61.6x10^4/mm^3$ ($278-648x10^4/mm^3$) in the study group.

The number of red blood cells was statistically significantly higher in males than in women in the study group ($442.98\pm58.9x10^4/mm^3$ vs. $425.59\pm63.3x10^4/mm^3$, p=0.005).

**Table 2. Haematological parameters of the study population**

Parameter	All patients (n=397)	Females (n=193)	Males (n=204)	Student p-value
RBC ($x10^4/mm^3$)	434.52 ± 61.6	425.59 ± 63.3	442.98 ± 58.9	0.005
Hemoglobin, g/dl	13.02 ± 1.9	12.42 ± 1.8	13.58 ± 1.8	<0.001
Hematocrit, %	38.79 ± 5.1	37.31 ± 4.9	40.19 ± 4.9	<0.001
MCV, fl	90.35 ± 7.5	89.16 ± 8.2	91.48 ± 6.5	0.002
MCH, pg	30.23 ± 3.1	29.59 ± 3.4	30.84 ± 2.6	<0.001
MCHC, g/dl	33.52 ± 1.6	33.24 ± 1.5	33.78 ± 1.6	0.001
RDW-CV %	14.51 ± 1.97	14.73 ± 2.2	14.30 ± 1.7	0.032

Abbreviations:
RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, RDW-CV=Red Cell Distribution Width-Coefficient of Variation

The mean±standard deviation (SD) hemoglobin (Hb) concentration in the study group was $13.02\pm1.9g/dl$ (range 8.7-17.2g/dl). The mean Hb level was significantly higher in men compared to women (13.5g/dl vs. 12.42g/dl, p<0.001) in the overall study cohort and was statistically significantly higher in men over 65 compared to women of the same age (p<0.001).

The mean hematocrit (Ht) level was $38.79\pm5.11\%$ (range 26.5-51.6%) in the study group. The mean Ht was $40.19\pm4.92\%$ in men, significantly higher than that of women $37.31\pm4.89\%$ (p<0.001).
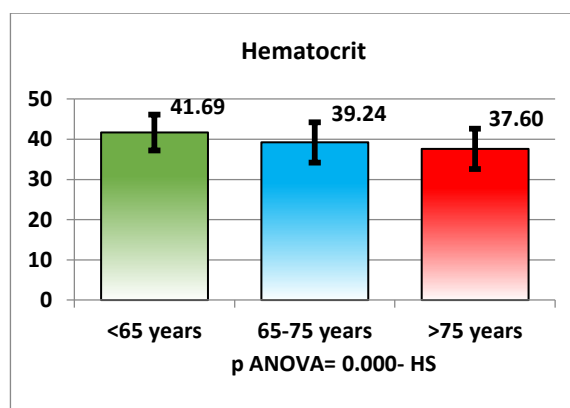
Fig.1. Comparison of Ht values (%) based on patient age

Concerning the Ht value compared by age group, we observed a gradual decrease in Ht values from 41.69±4.44% in <65 years to 37.60±5.01% in those over 75 years old (p ANOVA <0.001). Fig. 1.

We noticed that patients with Ht <35% compared to those with Ht>45% were older (75.34±7.08 years vs. 69±8.49 years, p<0.001) and mostly women (69.6% vs. 39.3% females, p<0.001).

The mean corpuscular volume (MCV) level in patients enrolled in our study was 90.35±7.45fl (ranges between 56.5-109.6fl). The mean MCV was significantly higher in men than in women (91.48±6.45fl, vs. 89.16±8.23fl, p=0.002).

Values of MCV<80 were more common in females (75%) compared to MCV values between 80-98fl which were distributed in approximately equal proportions in males and females (50.75% in males and 49.25, respectively % in women) and MCV>98fl that were more common in males (68,18%) (p χ^2=0.005).

Mean corpuscular h emoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) analysis showed that mean values of MCH and MCHC were significantly lower in women than in men (p Student <0.001 and p=0.001 respectively). 75% of patients with MCH <27pg were female compared to 45.66% in the MCH group >27pg (p χ^2=0.0002).

Depending on the MCH value, normochromic erythrocytes with MCH>27pg were more frequent than hypochromic erythrocytes with MCH<27pg (89.92% and 10.07% respectively).

In terms of erythrocyte morphology, normocytic normochromic erythrocytes, defined as MCV value between 80 to 98fl and MCH >27pg, were the most common type of erythrocytes morphology seen in both women and men (77.2% in women vs. 80.39% in men, p χ^2=0.00101).

In Table 3 we can also see that hypochromic erythrocytes were more common in females (7.77% of women had hypochromic microcytes erythrocytes, defined as MCV<80fl and MCH <27pg and 7.77% of women had hypochromic normocytes erythrocytes, with MCV between 80-98fl and MCH<27pg).

The macrocytosis (MCV>98fl) was more frequent in men (14,7%) than in women (7,25%).

Table 3. Red blood cells morphology in patients with heart failure

Red blood cells morphology	Females	Males	Total
Hypochromic microcytes	15 (7.77%)	5 (2.45%)	20 (5.04%)
Hypochromic normocytes	15 (7.77%)	5 (2.45%)	20 (5.04%)
Normochromic macrocytes	14 (7.25%)	30 (14.71%)	44 (11.08%)
Normochromic normocytes	149 (77.2%)	164 (80.39%)	313 (78.84%)

The mean value of Red Cell Distribution Width-Coefficient of Variation (RDW-CV) was 14.51±1.97% (10.8-23.9%), RDW-CV values >14.5% were recorded in 145 (36.52%) of patients. 52.38% of those with RDW-CV ≤14.5% were men compared to 49.65% of those with RDW-CV>14.5% (p=0,608>0,05).

We noticed that the mean value of RDW-CV was higher in women than in men (14.73% vs. 14.30%, p=0.032).

We analyzed the prevalence of anemia in the study group using World Health Organization (WHO) criteria (Hb<12g/dl in women and Hb<13g/dl in men) for the diagnosis of anemia [5]. The prevalence of anemia in our group was 38.54% (153 patients). Fig. 2.
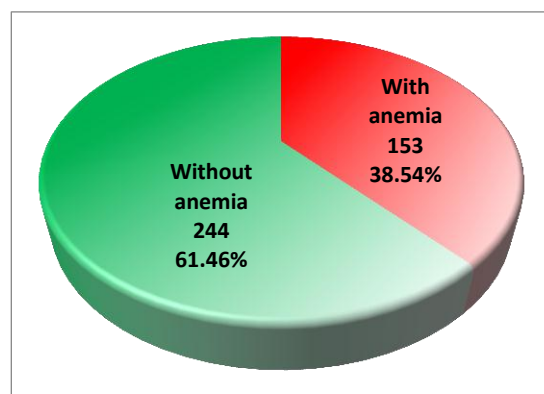
Fig. 2. Distribution of heart failure patients based on the presence or absence of anemia

The mean age of patients with heart failure and anemia was significantly higher compared to those with normal hemoglobin (75.05±7.16 years vs. 72.27±7.91 years, p=0.00047).

Analyzing the distribution of patients with heart failure in the presence of anemia and age groups, we noticed that more than half of our patients over 75 years of age had anemia, compared to those without anemia (54.25% vs. 37.70%, p=0.0011). Fig. 3.
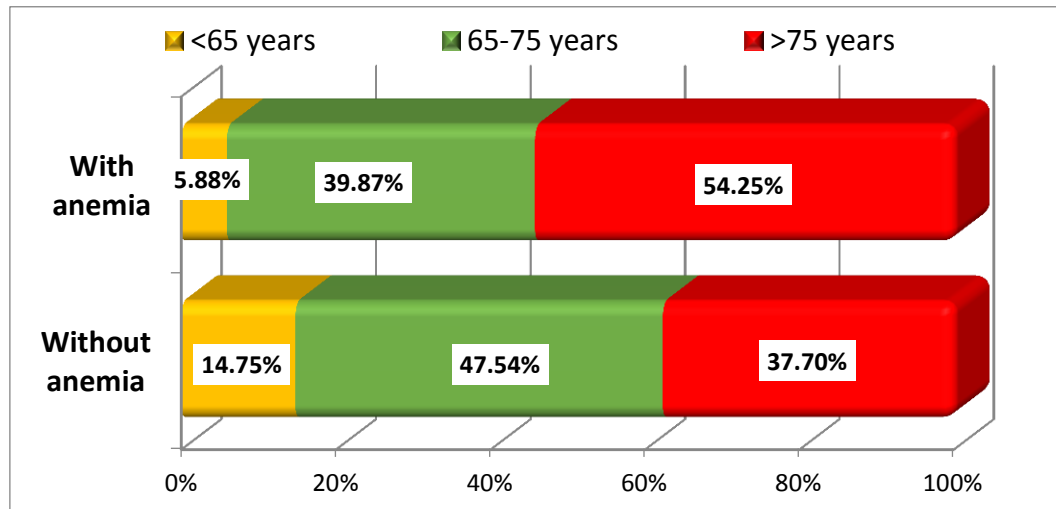
Fig. 3. Distribution of patients according to the presence of anemia and age

We also found an increasing prevalence of anemia by age groups in patients with heart failure studied respectively 20% in patients under 65 years of age, 34.46% in those with age between 65 and 75 years and 47.43% in those over 75 years of age (p=0.0011).

In the study group, anemia was more common in women, compared with men (44,04 vs. 33.33%, p=0.028). In the group of patients with anemia, the number of women was not significantly higher than that of men, 85 women (55.56%) vs. 68 males (44.44%), z test for proportions p=0.307>0.05 compared to 51.4% of women in the Dolj county. Using the Student t test, we showed that there is a significant difference between the hemoglobin values of the subjects with and without anemia, those with anemia having mean values lower than the others, 11.16±1.05 g/dl versus 14.18±1.25 g/dl (p<0.001), as expected. Fig. 4.
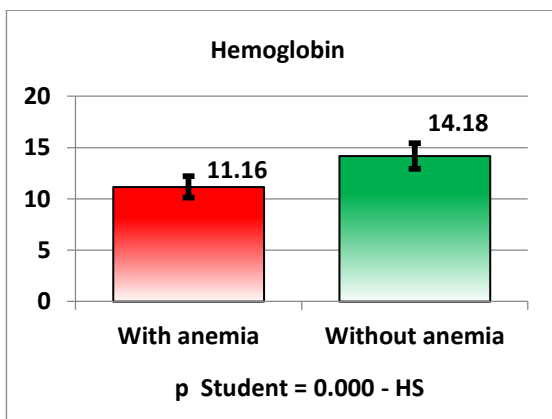

Fig.4. Hemoglobin values based on the presence and absence of anemia

The most common morphological type of anemia was normocytic normochromic anemia (anemia with MCV 80-98fl and MCH>27pg), present in 105 patients (68.62%). 20 patients (13.07%) had microcytic hypochromic anemia (anemia with MCV <80fl and MCH<27pg), in 16 patients (10.45%) normocytic hypochromic anemia was present (anemia with MCV 80-98fl and MCH<27pg) and 12 patients (7.48%) had macrocytic anemia (anemia with MCV>98fl and MCH>27pg), respectively. Fig. 5.
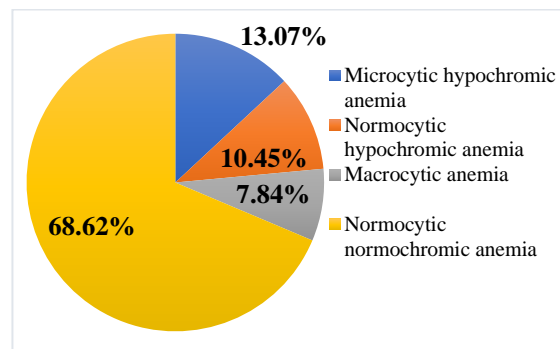

Fig. 5. Distribution of patients according to the morphological type of anemia

75% of hypochromic anemias (both microcytic and normocytic anemia) were more common in women compared to the macrocytic anemia that was most common in males (75% of macrocytic anemia) (p=0,011). Normocytic normochromic anemia was the most common type of anemia seen in both women and men (64.70% in women vs. 73.52% in men).

It is well known that RDW-CV together with MCV are useful for differentiating the etiology

of anemia [6]. As shown in Fig. 6, in 1,96% (3/153) of patients with anemia and RDW-CV≤14.5% presence of MCV<80fl suggests the presence of chronic disease anemia as opposed to 11,1% (17/153) of patients with anemia and RDW-CV>14.5% who had MCV<80fl suggesting the presence of iron deficiency. Also, MCV between 80-98fl in the presence of a RDW-CV>14.5% may suggest the presence of an incipient iron deficiency in 38,56% cases (59/153) and in the presence of a RDW-CV≤14.5% may suggest the presence of chronic disease anemia (62/153-40,52% patients).
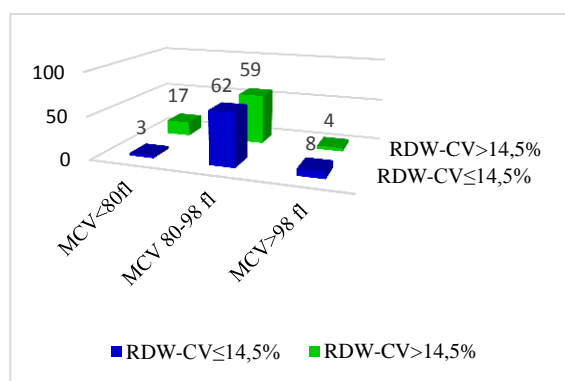
Fig. 6. Distribution of RDW-CV and MCV values in patients with anemia

Discussions

The prevalence of anemia in patients hospitalized for HF decompensation in our study was of 38.54%. Many studies have reported prevalence of anemia in patients with HF who ranged from 14.4% to 62.6% [7-13]. This variability is due to the lack of uniform criteria for the definition of anemia and of the inclusion and exclusion criteria applied in clinical trials and trials. That is why our study excluded patients with HF diagnosed for less than 1 year and the conditions and therapies that could directly influence the hematological profile of these patients to establish a scenario in which the relationship between anemia and HF is influenced by as few factors as possible.

Erythrocyte changes were common in patients with heart failure and can be influenced by a variety of factors. As we expected, the frequency distribution of erythrocyte parameters was shifted to the lower values in women than men but also in those older than younger probably due to differences in testosterone and estrogen production that vary with sex and age [14]. Other possible causes that may influence the distribution of red blood cell parameters in

HF, especially associated with anemia, are nutritional deficiencies (iron, folic acid, and vitamin B12), erythropoietin production, renal dysfunction, chronic inflammation, hematogenous bone marrow dysfunction, malnutrition, neurohormonal activation, hemodilution and some medications [15].

The increased prevalence of anemia in our study may be due to nutritional deficits, especially iron, vitamin B12 and folate. These are more common among the elderly population, probably due to inadequate nutritional intake (limitation of food intake due to severe symptoms, alteration of drug-induced taste such as angiotensin converting enzyme inhibitors, comorbid diet restrictions such as chronic kidney disease, depression, low socio-economic status). These may explain the large proportion of hypochromic (23.52%) and macrocytic (7.48%) anemic patients in our study.

We have noticed that the prevalence of anemia increases with age (p=0.0011) and can be explained by the high prevalence of comorbidities in the elderly such as HTN, diabetes mellitus, chronic kidney disease that favors anemia.

The high prevalence of normocytic normochromic anemia in the studied patients (69.28%) may be due to the fact that HF is a chronic disease characterized by the increased level of proinflammatory cytokines that mediate the occurrence of anemia and comorbidities present in these patients.

Our study suggests that chronic disease anemia could be present in 42.48% (65/153) of patients and iron deficiency anemia in 49.67% (76/153) of patients, prevalence similar to those in other studies. The prevalence of iron deficiency in HF patients ranges from 21% to 74% in literature data, with higher prevalence being reported in patients admitted for heart failure decompensation [11,17,18,19,20]. Also, the reported prevalence of anemia from chronic diseases ranges from 18.9% to 58% in HF patients [16,17,18].

Study limits

The use of MCV and RDW to define the etiology of anemia may not accurately estimate its magnitude. We did not have data on serum ferritin, transferrin saturation, total iron binding capacity, reticulocyte count, serum erythropoietin and proinflammatory cytokines, serum vitamin B12 and folic acid, and therefore we could not identify the etiology of anemia.

Conclusion

Our study suggests that the prevalence of anemia in hospitalized patients for HF decompensation is high (38.5%) and normocytic normochromic anemia was the most common morphological type of anemia (69%). A better understanding of the causes of the eritrocyte changes would represent an important step towards effective strategies for optimizing treatment.

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