Prevalence of Anemia in Patients with Heart Failure

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Abstract

Background: The prevalence of anemia and the morphology of red blood cells in patients hospitalized with heart failure (HF) are not totally known.

Objective: To check the prevalence of anemia in patients diagnosed with HF, characterize the morphology and check its association with NYHA functional class.

Methods: Cross-sectional retrospective study with 144 patients from the Brazilian Public Health System hospitalized for HF at Hospital da Cruz Vermelha, Curitiba, PR, January 2010 to July 2014. Sociodemographic data and admission blood count information were taken from the patients’ medical records. The blood count analysis included: hemoglobin levels, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and anisocytosis index (RDW). The reference values to characterize anemia followed the World Health Organization’s guidelines.

Results: Population studied with similar distribution of sex (52.8% men), mean age 67.8±13.8 years and nearly all of them (95.8%) self-reported white ethnicity. Anemia prevalence in this population was 41.0%, the majority (38.2%) corresponding to mild to moderate degrees. Functional class III (FC III) was the most prevalent one (63.2%), followed by FC IV (31.3%). The main morphological characteristic found was normocytic and hypochromic with 49.1%. Correlation of anemia with increasing age (>60 years) was found with p=0.008.

Conclusions: Prevalence of anemia in patients with HF was higher in older age groups, in FC III and IV, and the main morphological characteristic was normocytic and hypochromic.

Keywords: Anemia; Heart failure; Epidemiology; Comorbidity

Introduction

Cardiovascular diseases are the leading cause of death worldwide. Of these, heart failure (HF) is the final pathway for most cardiac diseases.

 Decompensated heart failure (DHF) is a syndrome caused by structural or functional changes in the body, causing difficulties in ejecting or accommodating blood, maintaining the physiological blood pressure levels¹. The main factors that cause decompensation are infections, renal failure, systemic arterial hypertension (SAH), abandonment of treatment and nutritional deficiencies, particularly anemia.

Anemia in patients with heart failure could be easily considered anemia of chronic, normocytic and normochromic disease, with low reticulocyte count²,³. However, the pathophysiology of anemia in HF is not well explained. Several hypotheses are postulated, even suggesting different etiologies, especially iron deficiency. The main hypotheses are: nutritional – iron deficiency, vitamin B12 and folate⁴,⁵; blood loss from the use of AAS⁶; comorbidities – hypertension, diabetes and chronic

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It should be considered that anemia worsens the prognosis in patients with HF due to reduced oxygen supply, ventricular remodeling, neurohormonal profile and proinflammatory state, combined with several comorbidities, including renal failure and cardiac cachexia. Therefore, anemia is both a mediator and a poor prognosis marker in HF.

Anemia is a common comorbidity in chronic heart failure and is associated with increased cardiovascular outcome, reduced ability to exercise due to reduced ability to carry and store oxygen, impaired quality of life and increased risk of hospitalization. Patients affected by HF usually have other associated comorbidities that expose them to a range of organ dysfunctions which, interrelated, worsen the clinical picture and make treatment more difficult. The presence of anemia would be a poor prognostic factor, regardless of ventricular dysfunction. Moreover, it is related to intolerance to physical activity, advanced clinical stage and acceleration of heart failure. Therefore, identifying the morphology of red blood cells is critical to optimize appropriate treatment for patients with this condition.

The prevalence of anemia in patients with heart failure varies depending on the type and its severity. Until then, there is no consensus on the most common morphological type of red blood cells and it is not possible to compare anemia and functional class of the New York Heart Association (NYHA). The NYHA classification is a dynamic assessment related to the clinical state of the patient at the time of medical assessment; worse FC have a worse degree of anemia.

The purpose of this study was to determine the prevalence of anemia in hospitalized patients with HF in a university hospital in Curitiba, PR, Brazil, to characterize its morphology and check its association with the NYHA functional class.

Methods

Cross-sectional study with collection of retrospective data from medical records of patients admitted with a diagnosis of heart failure in a university hospital in Curitiba, PR, from January 2010 to July 2014.

This study has been approved by the Research Ethics Committee of Universidade Positivo under no. 742883 (CAAE: 31510114.9.0000.0093), in accordance with the Declaration of Helsinki. The Research Ethics Committee did not require Informed Consent Form.

The population sample was defined as all patients hospitalized for HF in the cardiology service of Hospital Cruz Vermelha, Curitiba, PR. The selection of patients followed the flowchart shown in Figure 1.
Subsequently, demographic data were collected from electronic medical records: age, sex, education and ethnicity and clinical information: length of hospital stay, death, need for blood transfusion and/or iron supplementation.

Admission blood count was assessed and verified: hemoglobin count (HB), mean corpuscular volume (MCV), anisocytosis index (RDW) and mean corpuscular hemoglobin concentration (MCHC).

In this study, anemia was defined according to the reference values of the World Health Organization (WHO): for men, hemoglobin <13.0 g/dL and for women, <12.0 g/dL. It is further classified according to its severity:

- in men: mild (10.0 – 12.9 g/dL), moderate (8.0 – 10.9 g/dL) and severe (<8.0 g/dL)
- in women: mild (11.0 – 11.9 g/dL), moderate (8.0 – 10.9 g/dL) and severe (<8.0 g/dL)

All patients included in the study met the hospitalization criteria for decompensation of HF; they were all older than 18. Patients with acute coronary syndrome, renal failure, end-stage liver failure previously been diagnosed and registered in the medical records; and patients with active bacterial infection diagnosed through antibiotics or alterations in blood count (leukocytosis >12,000 or <4,000 or rod cells >10%) were excluded from the study. Patients with comorbidities such as systemic arterial hypertension (SAH) and diabetes mellitus (DM) were not excluded.

Quantitative variables were expressed as mean and standard deviation and the categorical variables were expressed as absolute and percentage frequencies. To investigate the association between anemia and other variables (sex, FC, ICU, death and age group), the chi-square test was used, considering a 0.05 significance level.

Results

144 medical records of patients with HF were included. The average age found was 67.8±13.8 years. The median was 67, ranging from 26-97 years (Table 1).

The prevalence of anemia in this population was 40.97% (n=59), occurring in varying degrees of intensity (Table 2).
Table 3  
Population studied according to the NYHA functional class

<table>
<thead>
<tr>
<th>NYHA Functional Class</th>
<th>Frequency (n=144)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>4.9</td>
</tr>
<tr>
<td>III</td>
<td>91</td>
<td>63.2</td>
</tr>
<tr>
<td>IV</td>
<td>45</td>
<td>31.3</td>
</tr>
</tbody>
</table>

NYHA – New York Heart Association

Table 4  
Anemia intensity and NYHA functional class in the study population

<table>
<thead>
<tr>
<th>Anemia / NYHA</th>
<th>FC I (n %)</th>
<th>FC II (n %)</th>
<th>FC III (n %)</th>
<th>FC IV (n %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
<td>25 (17.3)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0.0)</td>
<td>1(&lt;1.0)</td>
<td>11 (7.6)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>No anemia</td>
<td>1 (&lt;1.0)</td>
<td>4 (2.7)</td>
<td>53 (36.8)</td>
<td>27 (18.7)</td>
</tr>
</tbody>
</table>

NYHA – New York Heart Association

Table 5  
Population studied according to the morphology of anemia, hospitalization and outcome for death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (n=59)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology (size/color)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocytic/ normochromic</td>
<td>18</td>
<td>30.5</td>
</tr>
<tr>
<td>Normocytic/ hypochromic</td>
<td>29</td>
<td>49.1</td>
</tr>
<tr>
<td>Microcytic/ hypochromic</td>
<td>7</td>
<td>11.9</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>15.3</td>
</tr>
<tr>
<td>No</td>
<td>50</td>
<td>84.7</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>No</td>
<td>54</td>
<td>91.5</td>
</tr>
</tbody>
</table>

ICU – Intensive Care Unit

The morphological pattern of anemia, the need for hospitalization at the Intensive Care Unit (ICU) and the outcome of death in 59 patients with anemia are shown in Table 5.

There were 2 deaths in the non-anemic group. Of the 5 deaths among anemic patients, 3 (60.0%) were in the NYHA FC IV and all patients presented HF as the underlying cause or mentioned in any line of the death certificate. In 3 anemic patients, it was necessary to perform blood transfusion and 2 were prescribed iron supplementation.

Several analyzes were performed to identify possible associations between variables. The frequency of the elderly (>60 years) was 84.7% among patients with HF and anemia. The frequency of the elderly in the population with HF without anemia was 60.0% with statistical significance (Table 6).
Discussion

The prevalence of anemia in hospitalized patients with HF found in this study was 40.97%. In the literature, there is a huge variation\(^{15}\). Such heterogeneity is due to the lack of consensus on the definition of anemia\(^{16-18}\) and the different exclusion criteria\(^9\) applied in the studies.

Silverberg et al.\(^9\) in a retrospective study held in Tel Aviv, Israel, found a prevalence of 55.0% of anemia among 142 patients. Sales et al.\(^10\) in a multicenter retrospective study conducted in São Paulo, Brazil in 2001 with 204 patients found a prevalence of 62.6%. This study also found that the prevalence of anemia was higher with increasing age (p=0.008), which may be explained by the high prevalence of chronic diseases such as SAH and DM, favoring the onset of anemia. Another important cause that should be highlighted are the nutritional deficiencies caused by inadequate nutrition with iron deficiency.

The difficulty presented to determine the presence of anemia meets the criteria used for this purpose. The two main criteria are: those of the World Health Organization (WHO) and those of the Center for Disease Control and Prevention - CDC\(^{20}\). The WHO criteria (men hemoglobin <13.0 g/dL and women hemoglobin <12.0 g/dL) was chosen in this study to be the most used in the literature. The CDC defines anemia for men: hemoglobin <13.5 g/dL and women: hemoglobin <12 g/dL\(^{20}\). As a direct consequence, there is inclusion of more patients when the CDC criteria are used. This divergence of the diagnostic criteria can be an explanation for the wide variation in the prevalence of anemia found in the literature.

The exclusion criteria applied in different studies also interfere directly in the prevalence of anemia. The idea of excluding, in this study, acute coronary syndrome, renal failure, end-stage liver failure and active bacterial infection aims to produce a scenario that is closer to the actual relationship between HF and anemia\(^8\). This helps limiting the causes of anemia of chronic disease.

From a pathophysiological point of view, anemia of chronic disease is mediated by inflammatory cytokines\(^22\). Therefore, the expected morphological characteristic for anemia in patients with HF would be anemia of chronic (normocytic/normochromic) disease. This morphological characteristic was the second most frequent form, with 30.5%, surpassed by normocytic/hypochromic characteristic – 49.1%. This, in turn, may be differential diagnosis of anemia of chronic disease or iron deficiency anemia; in this case, it is essential to determine the serum ferritin. Note that this protein, responsible for iron reserve, was not determined in any of the hospitalized patients. Rangel et al.\(^{21}\) point out the presence of a greater number of cases of mortality outcomes and nonfatal cardiovascular events in patients with iron deficiency and anemia (p=0.006), confirming the importance of knowing the red blood cell morphology.

The Israeli\(^{19}\) study showed 79.1% patients in FC IV and 52.6% in FC III. It is noticed that this upward distribution according to functional class would be expected and found in other studies\(^{11,19}\), which was not found in this study, where 31.3% were in FC IV and 63.2% in FC III. This may be due, among other causes, to a different population profile in the service concerned or to the subjectivity of the NYHA classification, which depends on the views and interpretation of the physician to determine it.

On the other hand, the high prevalence of FC III patients raises important questions. The first is in relation to hospitalization of patients with milder symptoms in FC III. Thinking of a public health system, this implies expenses with hospitalizations in patients that could be managed on an outpatient basis or patients seeking tertiary care as a gateway. A second reasonable question would be the existence of a parallel between FC and severity of the disease.

Most cases of anemia (38.2%) were classified as mild or moderate degree of intensity, which is similar to the 30% of mild to moderate anemia found in other studies\(^{16,23}\). Though these patients are classified as mild or moderate degree, the possibility of treatment should always be a clinical issue.

Treatment of anemia is related to improvement in the patient’s hemodynamic status. Studies indicate that a correction of 10 g/dL to 12 g/dL (correction of mild/moderate severity) is associated with the optimization of cardiac function, with improvement in left ventricular ejection fraction\(^{18-20}\). Besides this, patients present improvement in NYHA functional class, drop in the
number of hospitalizations, reduced doses of oral and intravenous diuretic (furosemide) and considerable improvement in the symptoms of fatigue. Silverberg et al. also suggest that the treatment of anemia is an alternative to avoid the cardio-renal-anemia syndrome (CRA). This association between renal failure, anemia and HF generates a vicious cycle and self-feedable. It is worth noting that there is no consensus in the literature regarding the management of cardiac patients who develop anemia, but major studies point out the relevance of this issue.

The importance of treatment of anemia is related to the mortality of patients. In this study, there was no significant association of anemia with deaths (p=0.093). A study conducted in São Paulo indicated lethality of 16.8% of anemic patients vs. 8% non-anemic patients, but that was not significant (p=0.11).

Larger studies consider the higher mortality rate for patients developing anemia to be significant. Ezekowitz et al., in a cohort study with 12,065 Canadian patients, showed higher survival of non-anemic patients on anemic patients (p<0.0001). Horwich et al., in a cohort study conducted in the United States with 1733 patients, found an increase of 16% risk of death for every 1 g/dL of hemoglobin decrease. In the multivariate analysis, the risk of death was 13% for each decrease of 1 g/dL hemoglobin (RR=1.131 and IC95=1.045-1.224). In 2006, Consuegra Sánchez et al., in Spain, also pointed anemia as an outcome with an independent association for mortality (RR=1.15, 95% CI=1.04-1.25, p=0.003). Similar results can be seen in the systematic review by Groenveld et al. Mortality parameters are also associated with sex, with a predominance of the male sex. In this study, sex showed no statistical difference (p=0.528).

The study limitations are due mainly to the fact that the data collection was retrospective, which only allowed the analysis of information from medical records. Besides, using data from a single service may not have represented the sample population in the region.

Larger multicenter studies are of great importance to define more accurately the prevalence of anemia found in patients hospitalized with HF. Furthermore, randomized clinical trials defining the actual validity of pharmacological intervention in this group turns out to be a focal point for new therapies to prevent the progression of the condition and negative outcome for the patient.

**Conclusions**

The prevalence of anemia in patients with HF was higher in older age groups, in FC III and IV, and the main morphological characteristic was normocytic and hypochromic.

**Potential Conflicts of Interest**

This study has no relevant conflicts of interest.

**Sources of Funding**

This study had no external funding sources.

**Academic Association**

This study is not associated with any graduate programs.

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