Journal of Pharmacy and Pharmacology 6 (2018) 481-487
doi: 10.17265/2328-2150/2018.05.006

Anemia as a Predictor of Mortality in Patients with Decompensated Heart Failure

Paulo Átila da Silva Viana[1],Vanessa Tavares Aragão[1], Esther Carneiro Vasconcelos[1], Bianca Ratts Freitas dos Santos[1], Joaquim David Carneiro Neto[2], Leandro Cordeiro Portela[2] and José Antônio de Lima Neto[2]

1. Medical-Academic League of Cardiology of Sobral, Federal University of Ceará, Sobral 62.010-560, Brazil

2. Hospital of the Heart of Sobral, Santa Casa de Misericórdia de Sobral 62.041-380, Brazil

Abstract: Objective: To correlate the presence of anemia with mortality in hospitalized patients with decompensated HF (heart failure). Methods: A total of 148 patients hospitalized for HF compensation were analyzed from April 1 to December 31, 2017 in a tertiary referral hospital for cardiovascular diseases. The diagnosis of anemia was established according to the Brazilian Ministry of Health criteria, considering a serum hemoglobin value of < 13 g/dL for men and < 12 g/dL for women. Data were collected through medical and physical attendance records. Statistical analysis was performed using the Epi Info program, version 7.0 for Windows, with Student's *t* test for unpaired variables, Chi-square test and Fischer test. The significance of $p < 0.05$ was considered. Results: Of the 148 selected patients, 63.5% were male, 60.1% were over 65 years old, 50.74% were enrolled in the first grade, and 93.2% were self-declared white. The prevalence of anemia observed in the study population was 72 (56.25%), of which 49 (68%) were male and 23 (32%) were female. The mortality rate of the anemic patients was 19.4%, a total of 14 patients, whereas the non-anemic patients rate was 7.9%. It was observed that patients with worse outcome had hemoglobin < 12mg/dL ($p = 0.045$) and Functional Class (FC IV) by the New York Heart Association (NYHA) ($p = 0.0001$) at hospital admission. Conclusions: It is noticed that anemia is a frequent finding in patients with HF and that it interferes in the clinical manifestations, with worsening of the prognosis. Anemia treatment is not yet standarized in the HF approach, but patients without anemia appear to evolve with more favorable outcomes than anemia.

Key words: HF, descompensated HF, anemia, mortality, prognosis.

1. Introduction

Heart failure (HF) is a syndrome caused by structural or functional changes in the heart, failing to provide adequate blood flow to supply the body's metabolic demands [1]. In the world, HF often represents the final stage of several comorbidities, such as systemic arterial hypertension, diabetes and coronary diseases, and is considered a serious public health problem [2, 3].

HF is a clinical condition of high mortality. According to data obtained from the Ministério da Saúde, in the year 2000, nearly 398 thousand heart failure hospitalizations were made, including 26,000 deaths. This high mortality rate is associated with conditions and morbidities associated with HF, such as: age > 65 years, functional class III and IV (New York Heart Association), severe cardiomegaly (cardiothoracic index > 0.55), ejection fraction < 30%, anemia (Hb < 11g%), creatine > 2.5mg%, atrial fibrillation, complex arrhythmias (sustained and un-sustained ventricular tachycardia), marked decrease in exercise tolerance, plasma sodium < 130 mEq/L, lack of adherence to treatment and multiple hospital admissions [4].

In Brazil, a large part of the information on HF is registered and made available by the Departamento de Informática do Sistema Único de Saúde (DATASUS), whose records indicate about 2 million patients affected, with 240 thousand new cases diagnosed per year, representing 33% of the system's expenses with diseases of the circulatory system [4]. It is believed that in 2025 Brazil will have the sixth largest population of elderly people in the world, with the potential of multiplying HF cases and the costs of treating this syndrome [5].

Corresponding author: Paulo Átila da Silva Viana, physician, research fields: cardiology and anemia.

Sometimes this syndrome is accompanied by other comorbidities, anemia being one of the most prevalent. When present, anemia is a predictor of worst outcome and increased mortality. Several studies analyzed together show that the reduction of 1 g/dL hemoglobin (Hb) increases mortality by 15.8% [6].

Anemia is a comorbidity with recognized importance in the prognosis of a series of cardiovascular diseases, including AMI. In heart failure, only recently, it has been gaining attention and proving to be a possible factor of decompensation. This association is due to the reduced supply of oxygen, ventricular remodeling, neurohormonal profile and pro-inflammatory state, caused by the anemic state.

Therefore, anemia is both a mediator and a marker of poor prognosis in HF [7]. In view of its progression and its aggravating tendency of the subject, to correlate anemia with mortality in patients with HF helps in the improvement of effective measures of treatment and stabilization of patients with known HF and makes it possible to elaborate intervention strategies for early diagnosis. Therefore, the present article aims to correlate the presence of anemia as a predictor of mortality in hospitalized patients with decompensated HF at Hospital do Coração in the city of Sobral, Ceará.

2. Materials and Methodology

2.1 Study Design

Observational and longitudinal study, which included hospitalizations for decompensation of heart failure between April 1 and December 31, 2017, was performed at the Heart Hospital inthe city of Sobral, Ceará/Brazil. The diagnosis of heart failure was defined according to the Boston criteria.

The data collection was done from anamnesis of the patient after clinical establishment, registered in a semi-structured form developed for this research. Additional information was obtained from medical records during hospitalization, such as total hospitalization time and disease outcome.

We adopted as inclusion criteria: patients of both sexes and without age limit, with hospitalization for the treatment of decompensation of heart failure independent of the ejection fraction. Exclusion criteria were defined as: being unable to provide the information requested for reasons of functional disability or refusing to participate in the study.

The variables of interest included in the study were: gender, age, age group, history of the current disease, previous pathological history, laboratory tests, hospitalization time and final clinical outcome. For this study, the diagnosis of anemia was established according to the Brazilian Ministry of Health criteria, considering a serum hemoglobin value of < 13 g/dL for men and < 12 g/dL for women.

2.2 Statistics Analysis

The information was analyzed through statistics, using the program Epi Info, version 7.1.5.2 for Windows. Data were presented as absolute number and percentile. For comparison of proportions the Chi-square test (χ^2) or Fisher's exact test was used, when the Chi-square test could not be used. The comparison of quantitative variables between two groups was analyzed by the Student *t* test for independent samples or by the Mann-Whitney test (non-parametric test), aiming to identify statistical significance among the categories of variables. Significance was assumed for p value < 0.05.

2.3 Ethics Statement

This study was approved by the Research Ethics Committee of the Universidade Estadual Vale do Acaraú-UVA, under Protocol No. 1,957,872, covering all ethical aspects according to Resolution 466, of December 12, 2012. All patients signed a consent term.

3. Results

During the established period, 148 patients hospitalized for decompensated HF were studied, of whom, 20 died during the hospital phase. The sociodemographic data are expressed in Table 1. The

mean age was 65 years, with patients from 24 to 93 years. The male gender had a higher prevalence of 94 (63.5%), with no statistically significant difference when compared to patients who died. The first degree of schooling was predominant among the patients 75 (50.7%) and the white ethnicity was significantly higher (93.2%).

The clinical-laboratory characteristics of heart failure are shown in Table 2. Comparing the groups of patients, it was observed that patients with worse outcome also had a worse Functional Class (FC IV) by the New York Heart Association (NYHA) ($p = 0.0001$) and Hemoglobin < 12 mg/dL ($p = 0.045$) at hospital admission. The Hot/Congestive hemodynamic profile and the Etiology of HF presented a prevalence of 75 (50.6%), and there was no statistical significance with the worst outcome. Atrial fibrillation was present in 37 (25%) of the patients. The Left Ventricular Ejection Fraction (LVEF) variable showed that about 54.05% had LVEF < 40%.

Analyzing the etiology of HF among non-survivors, the ischemic type has a prevalence of 70%, almost double the value of the surviving patients, suggesting that this etiology may be responsible for a higher

Table 1 Demographic data of the patients studied ($n = 148$).

Variables		$n = 148$	(%)	p
Sex				
	Male	94	63.5	Ns
	Female	54	36.5	Ns
Age group				
	Up to 50 years	21	14.2	Ns
	51 to 64 years	38	25.7	Ns
	Over 65 anos	89	60.1	Ns
Education				
	Illiterate	52	35.1	Ns
	First Degree	75	50.7	Ns
	High School	19	12.8	Ns
	Graduated	2	1.4	Ns
Ethnicity				
	White	138	93.2	Ns
	Black	10	6.8	Ns

Source: Prepared by the authors. Ns: Not significant.

Table 2 Basal characteristics of the patients ($n = 148$).

Variable	n (%)
Age	65 ± 15.6
Sex (male), n (%)	94 (63.5%)
1 to 7 years of study, n (%)	82 (55.4%)
IV functional class of NYHA	74 (50%)
Ischemic etiology	75 (50.6%)
Hot/Congest hemodinamic profile	75 (50.6%)
Hemoglobin < 12 mg/dL	52(35.13%)
Seric creatine 1,4 mg/dL	50 (33.7%)
Seric urea 40 mg/dL	99 (66.89%)
Seric sodium < 130 ou > 150 (mEq/L)	10 (6.75%)
Seric potassium 5 mEq/L	15 (10.3%)
Left ventricular ejection fraction (LVEF) < 40%	80 (54.05%)
Presence of atrial fibrillation (AF)	37 (25%)

NYHA: New York Heart Association.

mortality, something that is only proven by multivariable analysis. In addition, the clinical characteristics of the patients show a similar profile between the survivors and non-survivors in relation to the LVEF < 40%.

Analyzing the laboratory tests, 50 patients (33.7%) had serum creatine greater than 1.4 mg/dL, 99 (66.89%) had serum urea greater than 40 mg/dL, 10 (6.75%) had serum sodium less than 130 or greater than 150 mEq/L and 15 (10.3%) had serum potassium greater than 5 mEq/L.

Comparing the laboratory tests of survivors and non-survivors, 40 (31.1%), 89 (69.53%), 9 (7.03%) and 12 (9.37%) patients had serum creatinine greater than 1.4 mg/dL, serum urea greater than 40 mg/dL, serum sodium less than 130 or greater than 150 mEq/L and serum potassium greater than 5 mEq/L, respectively. Among non-survivors, 10 (50%) had serum creatine greater than 1.4 mg/dL, 10 (50%) had serum urea greater than 40 mg/dL, 1 (5%) had serum sodium lower than 130 greater than 150 mEq/L and 3 (15%) had serum potassium greater than 5 mEq/L (Table 3).

The prevalence of anemia observed in the study population was 72 (56.25%), of which 49 (68%) were male and 23 (32%) were female (Table 4). The mortality rate of the anemic patients was 19.4%, a total of 14 patients, while the non-anemic patient rate was 7.9%.

Among the male patients, mortality was much higher between anemic patients than those with satisfactory hemoglobin values, 55% versus 15%, respectively. Among women, anemia did not show significant difference, since the same values were obtained for female patients with or without anemia Table 5.

Table 3 Clinical characteristics of survivors and non-survivors.

Variables	Survivors *n* = 128	Non-survivors *n* = 20	Value of *p*
Age	65.3 ± 15.9	66.1 ± 13.8	0.11
Sex (Male), *n* (%)	80 (62.5%)	14 (70%)	0.517
1 to 7 years of study, *n* (%)	70 (54.6%)	12 (60%)	0.657
IV functional class of NYHA	57 (44.5%)	17 (85%)	< 0.001
Ischemic etiology	61 (47.6%)	14 (70%)	0.333
Hot/Congest hemodinamic profile	65 (50.7%)	10 (50%)	0.948
Hemoglobin <12mg/dL	41 (32.03%)	11 (55%)	0.045
Seric creatine >1,4 mg/dL	40 (31.1%)	10 (50%)	0.09
Seric urea 40mg/dL	89 (69.53%)	10 (50%)	0.084
Seric sodium <130 ou >150(mEq/L)	9 (7.03%)	1 (5%)	0.736
Seric potassium 5mEq/L	12 (9.37%)	3 (15%)	0.438
Left ventricular ejection fraction (LVEF) < 40%	69 (53.9%)	11 (55%)	0.567
Presence of atrial fibrillation (AF)	34 (26%)	3 (15%)	0.267

Source: Prepared by the authors.

Table 4 Anemia in the population studied according to gender (Sobral/Ceará, 2017).

Variables	*n* (%)	*p*
Male	49 (68%)	0.264
Female	23 (32%)	0.264

Source: Prepared by the authors.

Table 5 Deaths related to anemia according to gender (Sobral/Ceará, 2017).

Gender	Female		Male		Total
	Hb < 12 g/dL	Hb > 12g/dL	Hb < 13g/dL	Hb > 13g/dL	
Deaths	3 (15%)	3 (15%)	11 (55%)	3 (15%)	20

Source: Prepared by the authors.

4. Discussion

Heart failure is one of the main causes of morbidity and it affects men the most. It is known that, despite the higher prevalence found in men, HF has a greater impact on the quality of life of women [8]. In addition, although the mean age attained is 65 years, the disease prevails in patients over 65 years of age.

In the educational criteria, there is a higher prevalence in those with the first degree (50.7%) and illiterate (35.1%), which may possibly be related to a lower socioeconomic class in these groups. Cardiomyopathy due to rheumatic valve disease is still frequent in our country and socioeconomic status is an important factor in the development of rheumatic fever, also related to the quality of medical care offered to this part of the population, which may explain the previously mentioned correlation [9].

It is known that in Brazil the main cause of HF is chronic ischemic heart disease related to arterial hypertension [10] as reaffirmed by the present study in which the main comorbidity associated with HF is hypertension. HBP is a contributing factor for several other cardiovascular diseases, such as stroke, peripheral arterial disease and renal disease. The incidence of CHF is two and three times higher, respectively, among hypertensive men and women, when compared to normotensive women [11]. There is the idea that the increase in post-load in hypertension is associated with ventricular hypertrophy and HF development, but it is important to highlight the sum of HBP to CAD as the main cause of heart failure. Despite this, hypertension alone can cause HF, since it has been observed that the reduction of blood pressure levels in hypertension reduces the incidence of HF significantly [12].

Anemia (35.13%) was detected as an important risk factor, because it is related to a worse prognosis over time, which indicates the need for special attention. In addition, anemia is associated with a higher mortality regardless of sex, ejection fraction (EF), or whether the disease is chronic or decompensated, with an increase in the relative risk of death by up to 50% [13]. Despite this, the pathophysiology of the relationship between anemia and HF is not well established, which justifies the lack of standardization in its conduct, although evidences suggest repercussions of clinical and hemodynamic improvement of the patients with their presence and pre-treatment [14].

In this study, anemia was a prognostic factor of mortality. In the univariate analysis, higher mortality was observed in men with anemia than in those without anemia. Interestingly, in females, no difference in mortality was observed. This difference noticed in the sex variable needs to be investigated in future studies. However, another author has found this correlation previously. In a population study, which evaluated 204 patients hospitalized for heart failure, anemia was a predictor of events in males but not females [6]. Interestingly, this author, who used the CDC criteria for the diagnosis of anemia, found higher prevalence of anemia in men, similar to that observed in our study (63% in the general population, 58% in men and 42% in women). Therefore, just as hemoglobin levels considered anemic can fluctuate according to sex, the effect of anemia on mortality can also be different, depending on sex.

Although anemia is one of the causes for heart failure, it occurs more frequently as a consequence. The pathophysiology of anemia in patients with HF is complex and has been the subject of several studies. The mechanisms involved in its genesis are: erythropoietin production or resistance to erythropoietin, hemodilution, neurohumoral activation, pro-inflammatory state (cytokine production-IL 1, 6 and 18) and iron deficiency. Some drugs used to treat HF may also cause anemia, such as angiotensin converting enzyme inhibitors, angiotensin I receptor blockers and carvedilol, causing inhibition of erythropoietin production [15, 16]. Studies have shown that renal dysfunction, decreased body mass index, advanced age, female gender and ventricular

dysfunction are factors that are related to a higher incidence of anemia [16].

Since this study shows anemia as an independent prognostic factor, it is important to treat it, modifying its causative factors, in order to improve the outcome of patients with this condition. Despite the limited number of patients, some studies show that correcting anemia with intravenous iron or erythropoietin administration improves functional class, decreases hospitalizations, and increases LVEF [14]. There is no consensus on how to treat anemia in HF patients, but it is known that evolution is more favorable when it is treated.

5. Conclusions

The results obtained in this study show that the prevalence occurred in male patients, over 65 years of age, with complete first degree education and self-declared white ethnicity. In addition, in the correlation of variables, there was a significant predictor of mortality for patients with anemia and NYHA IV functional class at hospital admission.

Therefore, it is perceived that anemia is a frequent finding in patients with HF and that it interferes in the clinical manifestations, with worsening of the prognosis. Treatment of anemia is not yet standardized in the HF approach, but patients without anemia evolve better than anemic patients. Evidence grows that it is possible to modify evolution related to anemia, but we still need more consistent evidence. Our article shows clinical importance by proving the correlation between anemia and heart failure, making it possible to treat the aggravating agents of anemia as an attempt to improve the prognosis of patients with HF and to reduce the number of hospitalizations.

Thereby, randomized clinical trials aiming to define the real validity of pharmacological intervention in this group become a fundamental point for new studies that wish to improve the current therapy of HF, in order to avoid the progression of the clinical picture and the negative outcome for the patient.

Acknowledgments and Financing

This research did not receive any specific grants from any funding agency in the public, commercial or nonprofit sectors.

References

[1] Yanci, C. W., Jessup, M., Bozkurt, B., et al. 2013. "ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." *Circulation* 128 (16): 1810-52.

[2] Neto, J. M. R. 2004. "A dimensão do problema da insuficiência cardíaca do Brasil e do Mundo." *Rev. Socesp*. 14 (1): 1-7.

[3] McMurray, J. J., Adamopoulos, S., Anker, S. D., Auricchio, A., Bohm, M., Dickstein, K., et al. 2012. "Guía de práctica clínica de la ESC sobre diagnóstico y tratamento de la insuficiência cardíaca aguda y crónica 2012." *Ver Esp Cardiol.* 65: 938-59.

[4] De Cardiologia, S. B. 2002. "Revisão das II Diretrizes da Sociedade Brasileira de Cardiologia para o diagnóstico e tratamento da insuficiência cardíaca." *Arq Bras Cardiol.* 79 (supl 4): 1-30.

[5] Batlouni, M., Freitas, E. V. D., and Savioli, N. F. 2006. "Insuficiência cardíaca no idoso." In *Tratado de geriatria e gerontologia* (2nd ed.), edited by Freitas, E. V., Py, L., Cançado, F. A. X., Doll, J., and Gorzoni, M. L. Rio de Janeiro: Guanabara-Koogan, pp. 480-99.

[6] SALES, A. L. F., et al. 2005. "Anemia como fator prognóstico em uma população hospitalizada por insuficiência cardíaca descompensada." *Arq Bras Cardiol* 84 (3): 237-40.

[7] Cavalini, L. P. W., et al. 2016. "Prevalence of Anemia in Patients with Heart Failure." *International Journal of Cardiovascular Sciences* 29 (1): 6-12.

[8] Barbosa, R. R., Franklin, R. V., Stefenoni, A. V., Moraes, V. D., Jacques, T. M., Serpa, R. G., Calil, O. A., and Machado Barbosa, L. F. 2014. "Quality of Life Analysis among Men and Woman with Herat Failure." *Revista Brasileira de cardiologia* 27 (2): 97-103.

[9] de Cardiologia, S. B. 2002. "Revisão das III Diretrizes da Sociedade Brasileira de Cardiologia para o diagnóstico e tratamento da insuficiência cardíaca." *Arq Bras Cardiol.* 79 (supl 4): 1-30.

[10] Albuquerque, D. C., Souza, Neto., et al. 2015. I Registro Brasileiro de Insuficiência Cardíaca – Aspectos Clínicos, Qualidade Assistencial e Desfechos Hospitalares. *Arq Bras Cardiol*. 104 (6): 4424-33.

[11] Ho, K. K. L., Pinsky, J. L., Kannel, W. B., and Levy, D. 1993. "The Epidemiology of Heart Failure: The Framingham Study." *J. Am. Coll. Cardiol.* 22: 6A-13A.

[12] Pereira Barretto, A. C. 2001. "Hipertensão arterial e insuficiência cardíaca." *Rev. Bras. Hipertens* 8: 339-43.

[13] Latado, A. L., Passos, L. C. S., Braga, J. C. V., Santos, A., Guedes, R., Moura, S. S., et al. 2006. "Preditores de letalidade hospitalar em pacientes com insuficiência cardíaca avançada." *Arq Bras Cardiol*. 87 (2): 185-92.

[14] Nogueira, P. R., Rassi, S., and Corrêa, K. S. 2010. "Perfil epidemiológico, clínico e terapêutico da insuficiência cardíaca em hospital terciário." *Arq Bras Cardiol* 95 (3): 392-98.

[15] Maggioni, A. P., Opasich, C., Anand, I., Barlera, S., Carbonieri, E., Gonzini, L., et al. 2005. "Anemia in Patients with Heart Failure: Prevalence and Prognostic Role in a Controlled Trial and in Clinical Practice." *J. Card. Fail*. 11 (2): 91-8.

[16] Tang, Y. D., and Katz, S. D. 2006. "Anemia in Chronic Heart Failure: Prevalence, Etiology, Clinical Correlates, and Treatment Options." *Circulation* 113 (20): 2454-61.