

## Whether the Type of Anemia Can Infer Whether Patients with Chronic Heart Failure Have Iron Deficiency and Guide Intravenous Iron Supplementation

Zhiqin Peng<sup>1, a</sup>, Deguang Yang<sup>2, b, \*</sup>

<sup>1</sup>Department of Cardiovascular Medicine, The First Affiliated Hospital of Jinan University, Guangzhou 510000, China

<sup>2</sup>Department of Cardiovascular Medicine, The First Affiliated Hospital of Jinan University, Guangzhou 510000, China

<sup>a</sup>wacjj10000@163.com, <sup>b</sup>yangguang98198@163.com

### Abstract

**Background:** A large proportion of patients with anemia with heart failure can improve patient outcomes with intravenous iron supplementation. Here, we assessed the specific type of anemia and the proportion of iron deficiency in patients with chronic heart failure and anemia, and assessed whether further iron index tests are needed to determine whether the patient is iron deficiency to guide the use of intravenous iron therapy in patients with chronic heart failure and anemia. **Methods and Results:** In this paper, 1279 patients with chronic heart failure and anemia (including 747 males and 532 females) hospitalized in our hospital from 2015 to 2020 were enrolled in this paper, and the proportion of patients with small cell, normal cell and large cell anemia was calculated by ordinary pie chart. **Results:** There were 267 cases (20%) of small cell anemia, 1009 cases (75%) of normal cell anemia, and 63 cases of large cell anemia (5%). Among them, we can see that there are 1276 cases of small cell anemia and normal cell anemia, accounting for 95%. Further, we obtained serum ferritin indices for female patients in 127 patients (including 53 patients with small cell anemia, 70 patients with normal cell anemia, and 4 patients with large cell anemia), and the serum ferritin <300ug/ml was used as the demarcation criterion for whether chronic heart failure combined with various anemia types was iron deficiency. **Results:** A total of 42 patients with small cell anemia and iron deficiency were involved, accounting for 79%; There were 59 patients with normal cell anemia and iron deficiency, accounting for 84%; There were 3 cases of large cell anemia and iron deficiency, accounting for 75%. **Conclusion:** Patients with chronic heart failure and anemia are mainly small cell and normal cell anemia, and most of these patients have iron deficiency. Therefore, for patients with chronic heart failure and anemia, according to the type of anemia of the patient, it can be initially recommended that if the blood routine suggests small cell and normal cytomeemia, it is necessary to improve the relevant indicators of iron deficiency, clarify whether there is real iron deficiency, and give intravenous iron supplementation therapy accordingly to improve the prognosis of patients.

### Keywords

Chronic heart failure combined with anemia; Types of anemia; Intravenous iron therapy.

## 1. INTRODUCTION

Heart failure is a group of syndromes in which various structural or functional diseases of the heart lead to ventricular filling and/or ejection function impaired, cardiac output can not meet the metabolic needs of the body's tissues, systemic circulation and/or pulmonary circulation congestion, and insufficient attention to organs and tissues as clinical manifestations. It affects approximately 1% to 2% of the adult population worldwide and can lead to shorter life spans.

Anemia is a common complication in patients with heart failure and is independently associated with poor heart function, poor quality of life, and higher hospitalization and mortality rates (1-3) in patients with chronic heart failure. The cause of anemia is not clear for the time being, and may be related to erythropoietin deficiency, chronic malnutrition, absolute or relative iron deficiency, etc. At present, the inclination towards iron deficiency is more likely.

Iron is an important part of oxidative metabolism, and a considerable part of the oxidative metabolism process requires the participation of iron. At the same time, it is also involved in the metabolism of hemoglobin (oxygen transport) and myoglobin (oxygen storage), and is also an essential component of cytochrome and ferrosulfurin in the electron transport chain (oxidative phosphorylation) in the tricarboxylic acid cycle (4.5.6.7.8). Once the body has iron deficiency, it will impair the body's oxygen carrying capacity and tissue oxidation capacity, resulting in a decrease in the maximum exercise capacity (9.10.11.12).

There are many reasons for iron deficiency in patients with chronic heart failure, including absolute (systemic iron reduction, including insufficient food intake, intestinal absorption, excessive excretion, the role of hepcidin in the intestinal iron absorption process is weakened, etc.) and functional (normal or increased iron content throughout the body, the deficient part of the iron available to the body tissues, including chronic inflammatory stimulation during heart failure leading to increased hepcidin release, increasing iron accumulation in cells, inhibiting the release of iron from storage, leading to iron utilization disorders, etc.). There is reason to believe that intravenous iron supplementation for patients who are truly iron deficient has a significant effect. At present, relevant experiments have proved that in patients with heart failure and iron deficiency, intravenous iron supplementation can improve the clinical symptoms, functional ability and quality of life of patients, and increase the walking test distance of 6 minutes (13-15). And in patients with anemia, the benefits are more pronounced (15). However, it is not clinically routine to detect iron indicators. For patients with chronic heart failure, when the blood routine shows that the patient has anemia, it is often easy to be ignored, and it is impossible to routinely assess whether the heart failure patient is really iron deficient, let alone intravenous iron supplementation to improve the long-term prognosis of the patient. In normal humans, iron deficiency patients tend to present with hypochromic microcytic anemia, so is the same outcome in patients with chronic heart failure? We hope to observe whether patients with chronic heart failure with iron deficiency are as same as microcytic anemia as patients with iron deficiency in normal people by the type of anemia in patients with chronic heart failure; The proportion of patients with iron deficiency in various types of anemia is used to assess whether iron indicators need to be further improved, and then intravenous iron supplementation therapy is guided to improve the symptoms and clinical prognosis of patients with heart failure.

## 2. METHODS AND RESULTS

In this paper, 1279 patients with chronic heart failure and anemia were hospitalized in our hospital from 2015 to 2020 (including 747 males and 532 females). Average age: 73.47±13.04 years; Average hemoglobin level: 97.92±14.83 g/L; NYHA Cardiac Function Classification I-IV; Oral medications include one or more drugs such as ACEI, ARB,  $\beta$  receptor blockers, CCBs, statins, diuretics, etc. Calculate the specific number of patients of each type, using an excel table

to draw an ordinary pie chart to calculate the proportion of these patients, the results are shown in Figure 1a: there are 267 cases (20%) of small cell anemia, 1009 cases of normal cell anemia (75%), and 63 cases of large cell anemia (5%). It can be seen that there are 1276 cases of small cell anemia and normal cell anemia in patients with chronic heart failure and anemia, accounting for 95%.

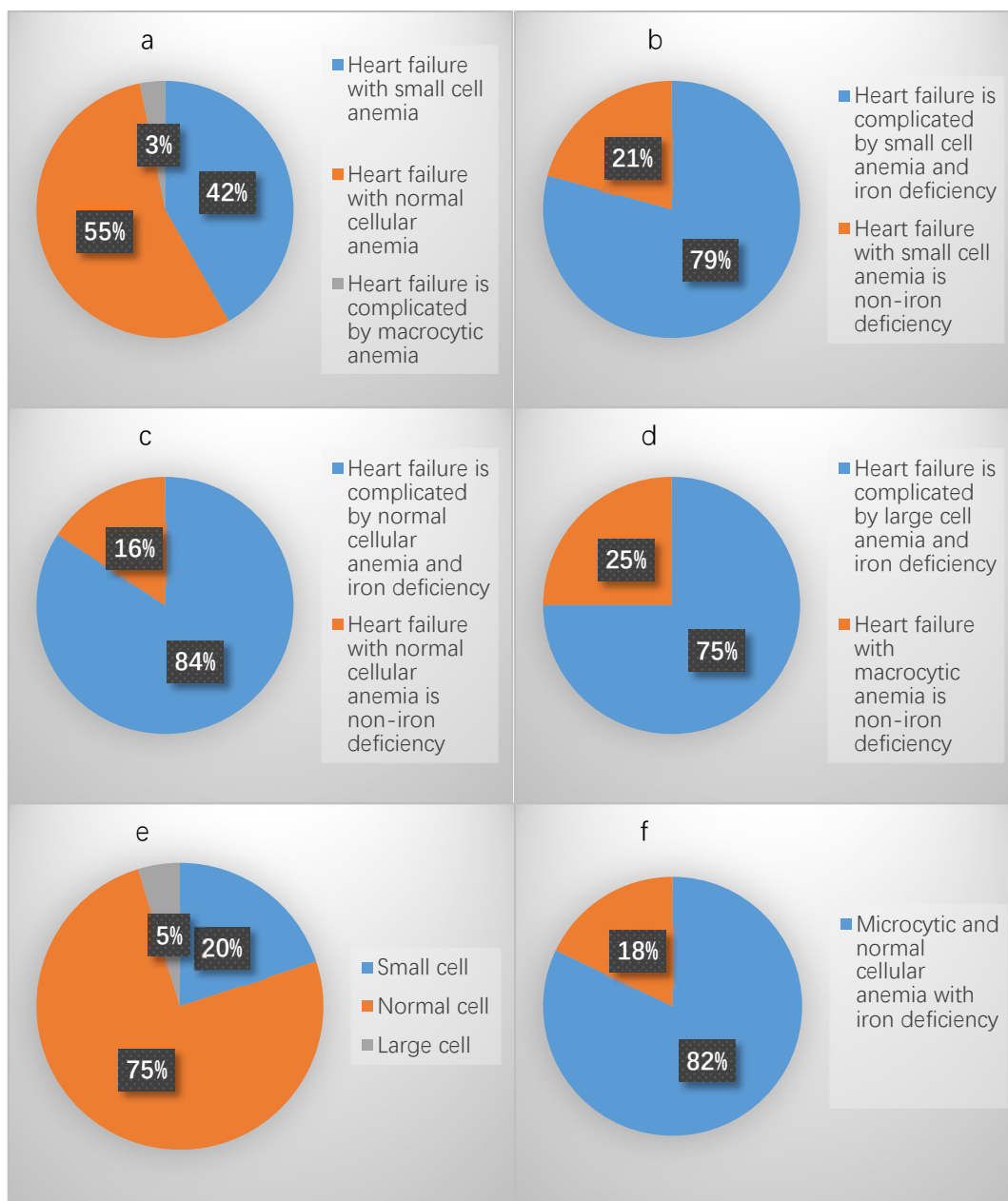


Figure 1.

Of these patients, further, we obtained serum ferritin indices in female patients (53 (42%) in patients with small cell anemia, 70 cases (55%) with normal cell anemia, and 4 cases (3%) in large cell anemia (3%) as shown in Figure 1b). < 300ug/ml as the demarcation criterion for whether patients with heart failure are iron deficiency. Results: There were 42 patients with small cell anemia and iron deficiency, accounting for 79% of patients with small cell anemia (Figure 1c); There were 59 patients with normal cell anemia with iron deficiency, accounting for 84% of patients with normal cell anemia (as shown in Figure 1d); There were 3 cases of large anemia and iron deficiency, accounting for 75% of patients with large anemia (Figure 1f).

Among them, there were 101 cases of small and normal cell anemia with iron deficiency, accounting for 82% of the total number of people in both (as shown in Figure 1e), accounting for 80% of the total number of people. Therefore, we can conclude that patients with chronic heart failure and anemia are mainly small cell and normal cell anemia, and most patients have iron deficiency. This gives us an idea: for patients with chronic heart failure, if the blood routine suggests that the patient is small cell anemia or normal cell anemia, it is necessary to further improve the iron index test, assess whether there is a real sense of iron deficiency, to guide whether further intravenous iron supplementation therapy is needed, and improve the clinical symptoms and prognosis of patients with chronic heart failure.

### 3. DISCUSSION

This paper calculates the proportion of 1279 cases of chronic heart failure with anemia during hospitalization in our hospital from 2015 to 2020 (WHO defines anemia as Hb < 13.0 g/dL in adult <men and 12.0 g/dL (16)) in adult women and the proportion of iron deficiency in each anemia type. It can be seen that about 95% of these patients are small cell and normal cell anemia. (Among them, small cell anemia accounts for 20%, normal cell anemia accounts for 75%). Among these patients, 127 cases had recorded ferritin values. Among them, the presence of iron deficiency in patients defined by ferritin <300ug/ml shows that patients with small cell and normal cell anemia combined with iron deficiency account for 82% of small cell and normal cell anemia (small cell anemia combined with iron deficiency accounts for 79% of patients with small cell anemia, and normal cell anemia combined with iron deficiency accounts for 84% of patients with normal cell anemia). This means that most of the 127 patients included in the iron index have real iron deficiency, and for these patients, intravenous iron supplementation will greatly improve the clinical prognosis and symptoms of patients. Our clinical retrospective study can guide us to encounter common patients with chronic heart failure complicated by small cells or normal cellular anemia in clinical work, further improve the patient's iron index, assess whether the patient has iron deficiency, guide further intravenous iron supplementation, improve the patient's prognosis, and provide certain guiding significance.

Of the 1279 patients we included, only 127 patients had ferritin markers checked, and the sample size was insufficient and more sample size was still needed. And only female patients were included. It cannot be ruled out whether gender causes iron deficiency and the impact of its extent. Nevertheless, this result has some clinical significance and guides treatment options for patients with heart failure and anemia. In future studies, we intend to include more data on iron indicators in patients with heart failure and anaemia.

In patients with chronic heart failure and anemia, we found that a small proportion of patients had macrocytic anemia (5%), and in 4 patients with ferritin indicators, 3 patients (75%) had iron deficiency, but this part of patients was not described. The reasons are as follows: First, the proportion of macrocytic anemia is small, accounting for only 5% of patients with chronic heart failure and anemia; Secondly, macrocytic anemia is generally associated with folic acid and B12 metabolism disorders, although chronic heart failure patients have long-term chronic inflammation, which can lead to gastrointestinal decline and affect the absorption of folic acid and B12, but whether iron supplementation has improved it has yet to be proved by further experimental evidence. Although there are fewer patients with macrocytic anemia (4 cases), the proportion of macrocytic anemia combined with iron deficiency is relatively high, and intravenous iron supplementation therapy may have a certain effect on improving the clinical prognosis in some patients.

### REFERENCES

- [1] O'Meara E, Murphy C, McMurray JJ. Anemia and heart failure. *Curr Heart Fail Rep* 2004;1:176-82.

- [2] Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004;110:149-54.
- [3] Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005;11:91-8.
- [4] Fairbanks V, Beutler E. Iron deficiency. In: Beutler E, editor. *Williams Hematology*. 6th edition. New York, NY: McGraw-Hill, 2001:295–304, 447– 440.
- [5] Dallman PR. Iron deficiency: does it matter? *J Intern Med* 1989;226:367–72.
- [6] Scrimshaw NS. Functional consequences of iron deficiency in human populations. *J Nutr Sci Vitaminol (Tokyo)* 1984;30:47– 63.
- [7] Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011–23.
- [8] Dunn LL, Rahmanto YS, Richardson DR. Iron uptake and metabolism in the new millennium. *Trends Cell Biol* 2007;17:93–100.
- [9] Davies KJ, Maguire JJ, Brooks GA, Dallman PR, Packer L. Muscle mitochondrial bioenergetics, oxygen supply, and work capacity during dietary iron deficiency and repletion. *Am J Physiol* 1982;242:E418–27.
- [10] Maguire JJ, Davies KJ, Dallman PR, Packer L. Effects of dietary iron deficiency of iron-sulfur proteins and bioenergetic functions of skeletal muscle mitochondria. *Biochim Biophys Acta* 1982;679:210 – 20.
- [11] Ohira Y, Edgerton VR, Gardner GW, Senewiratne B, Barnard RJ, Simpson DR. Work capacity, heart rate and blood lactate responses to iron treatment. *Br J Haematol* 1979;41:365–72.
- [12] Davies CT, Chukweumeke AC, Van Haaren JP. Iron-deficiency anaemia: its effect on maximum aerobic power and responses to exercise in African males aged 17– 40 years. *Clin Sci* 1973;44:5
- [13] Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009 Dec 17;361(25):2436-48. doi: 10.1056/NEJMoa0908355. Epub 2009 Nov 17. PMID: 19920054.
- [14] Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozd J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA; AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020 Dec 12;396(10266):1895-1904. doi: 10.1016/S0140-6736(20)32339-4. Epub 2020 Nov 13. Erratum in: *Lancet*. 2021 Nov 27;398(10315):1964. PMID: 33197395.
- [15] Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol*. 2008 Jan 15;51(2):103-12. doi: 10.1016/j.jacc.2007.09.036. PMID: 18191732.