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Analysis of the correlation between c-reactive protein levels and ferritin in patients with chronic heart failure

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Abstract

Objective: This study was to investigate the correlation between serum CRP levels and ferritin in patients with chronic heart failure.

Methods: This study is a cross-sectional study. We investigated 210 patients with heart failure who attended the Department of Cardiovascular Medicine of the Second Affiliated Hospital of Xinjiang Medical University from December 2023 to February 2025. Comparison of iron parameters between different ultrasensitive C-reactive protein quartiles was made.

Results: The highest quartile group (Q4) of ultrasensitive C-reactive protein had significantly higher serum ferritin levels than the first (Q1) second (Q2) and third (Q3) quartile groups, Q1 [133.7 (88.4, 204.8)],Q2 [129.0 (77.1, 256.8)],Q3 [121.3 (58.7, 189.5)],Q4 [202.0 (106.3446.2)], $p < 0.05$.

Conclusion: Ferritin levels in patients with chronic heart failure are influenced by a number of factors in their condition, and the use of ferritin may overestimate the iron status of patients with chronic heart failure.

Keywords: High sensitivity C-reactive protein; Cross-sectional study; Serum ferritin.

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by dyspnea, fatigue, and fluid retention (pulmonary stasis, circulatory stasis, and peripheral edema) due to a variety of causes that result in abnormal changes in the structure and/or function of the heart, resulting in impaired ventricular systole and/or diastole(1), which affects more than 64 million people worldwide(2).

Iron deficiency (ID) is a common comorbidity in patients with heart failure, and although ID is often thought to be associated with anemia, known as iron-deficiency anemia, the two disorders do not necessarily coexist, and ID is more prevalent than anemia in chronic heart failure, with prevalence rates ranging from 50% in European(3) populations to 63% in Asia(4).

Iron deficiency has been shown associated with reduced exercise capacity, impaired quality of life(5), and an increased risk of death and rehospitalization independent of hemoglobin (HB) levels in previous studies(6), and intravenous correction of ID has been shown to improve quality of life, exercise capacity, and clinical symptoms in patients with chronic heart failure(7), as well as to reduce rehospitalization and mortality regardless of HB levels(8).

However, there is still controversy about how to accurately assess heart failure patients who may benefit from iron supplementation therapy. Currently, the diagnosis of iron deficiency in heart failure patients relies on serum ferritin(9), while opponents argue that heart failure patients are often in a state of chronic low-grade inflammation, and that ferritin levels, as an acute-phase protein, are affected by inflammation(10). The relationship between inflammation and ferritin in patients with heart failure has been poorly investigated, so the present study was undertaken to assess the relationship between inflammation and serum ferritin in patients with heart failure, using ultrasensitive C-reactive protein.

Method

Study population

This was a cross-sectional study， approved by the Medical Ethics Committee of the Second Affiliated Hospital of Xinjiang Medical University. No informed consent was required, because the data are anonymized.

The participants were selected based on following inclusion and exclusion criteria. Inclusion criteria were age 18－75 years old, Patients with clear primary cardiovascular disease (such as coronary artery disease, arrhythmia, hypertension, cardiomyopathy, valvular heart disease, etc.); cardiac ultrasound suggests that the LVEF (Left Ventricular Ejection Fraction) is ≤50% ， or LVEF >50%, laboratory tests NT-Pro BNP ≥125 ng / L, or BNP ≥35 ng / L; Complete medical records are available. Exclusion criteria were active bleeding, malignancy, haematology disorder, peptic ulcer, liver disease with SGOT/SGPT >3x normal value, History of Class III or higher surgery/severe trauma in the last 2 weeks.

210 patients with chronic heart failure who were hospitalized in the Department of Cardiology of the Second Affiliated Hospital of Xinjiang Medical University from December 31, 2023, to December 31, 2024, and were selected for the study. Patients were stratified according to the quartiles of their serum hs-CRP, with the lowest hs-CRP quartile group as Q1, the lower hs-CRP quartile group as Q2, the higher hs-CRP quartile group as Q3, and the highest hs-CRP quartile group as Q4.

Collection of general information

General data of the study subjects were collected through the admission records of the

electronic medical record system of the Second Affiliated Hospital of Xinjiang Medical University, including hospitalization number, age, gender, height, weight, body mass index (BMI) (= weight (kg)/height2 (m2)); risk factors and past medical history of the patients, including history of hypertension, diabetes mellitus, coronary atherosclerosis, atrial fibrillation, congenital heart disease, pulmonary hypertension.history of smoking, and history of alcohol consumption.

Collection of patients' clinical data

(1) Systolic and diastolic blood pressures were recorded using an electronic sphygmomanometer in patients who had been at rest for more than 30 minutes at the time of admission; pulse was used instead of heart rate in patients without atrial fibrillation and peripheral vascular disease, and ventricular rate was calculated using a twelve-lead electrocardiogram in patients with atrial fibrillation.

(2) All patients had an echocardiogram completed within 24 hours of admission, and left ventricular ejection fraction was measured using the Teichholz method.

(3) Twenty milliliters of elbow venous blood was drawn from all patients within 6 hours of admission and sent to the Laboratory Department for improvement of blood creatinine, uric acid, random blood glucose, total cholesterol (TC), total triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), hemoglobin (HB), white blood cell count, neutrophil Percentage, serum ferritin, NT-proBNP, BNP, high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin and other tests.

Statistical analysis

SPSS 26.0 (Statistical Package for the Social Sciences 26.0) was used to statistically analyze the study data. The study data were tested for normality using the Kolmogorov-Smirnov K-S test, with measures that conformed to the normal distribution expressed in the form of mean ± standard deviation ($x \pm s$), and those that did not conform to the normal distribution applied in the form of median (quartiles) [M(Q1, Q3)]. Comparisons of means between multiple groups were made using the one-way F-test. Comparisons of multiple groups were made using the Kruskal-Wallis H-test, and categorical variables should be expressed in the form of number of instances and percentage [n(%)], and comparisons of groups were made using the $\chi 2$ test and Fisher's Exact Test. $P<0.05$ was defined as statistically significant difference

Result

A total of 210 subjects were included in the present crosssectional study. The characteristics of the study population in terms of the quartiles of the hs-CRP are given in Table 1. Demographic characteristics: there were no significant differences in age, gender and BMI among the four groups of patients ($p > 0.05$). Medical history: history of coronary artery disease was

significantly different among the four groups (p = 0.018), with the highest percentage of coronary artery disease in groups Q1 and Q4 (both 98.1%). There was no significant difference between the four groups for other medical histories (e.g. hypertension, diabetes, atrial fibrillation, etc.) (p > 0.05).Clinical indicators: systolic blood pressure, diastolic blood pressure, heart rate, height, weight and left ventricular ejection fraction (LEVEF) were not significantly different between the four groups (p > 0.05)

Table 1 Characteristics among 210 participants according to quartiles of hs-CRP

Characteristics	Q1（n=52）	Q2（n=53）	Q3（n=52）	Q4（n=53）	H/F/χ2	p
Age (years)	70（58.3,78.5）	65（58,78）	73（66.2,78.0）	68（57,79.5）	1.958	0.581
Sex					4.376	0.22
Male (%)	36（69.2）	29（54.7）	28（53.8）	35（64.8）		
Female (%)	16（30.8）	24（45.3）	24（46.2）	18(33.3)		
BMI（(kg/m2）	25.58±3.17	26.2±4.66	26.0±4.36	26.5±4.8	0.485	0.693
History of hypertension (cases)	39（75）	41（77.4）	35（67.3）	34(63.0)	2.993	0.393
History of diabetes mellitus (case)	18（34.6）	25（47.2）	16（38.0）	22（40.7）	3.526	0.317
History of atrial fibrillation (case)	11（21.2）	14（26.4）	18（34.6）	7（13.0）	7.032	0.071
History of coronary heart disease (case)	51（98.1）	45（84.9）	41（78.8）	52（98.1）	10.018	0.018
History of congenital heart disease (case)	1（1.9）	1（1.9）	0（0）	1（1.9）	1.466	1.000
History of valvular disease (case)	13	8（15.1）	5（9.6）	3（5.7）	3.438	0.320
History of cardiomyopathy (case)	3（5.8）	2（3.8）	5（9.6）	7（13.0）	3.535	0.306
History of alcohol consumption (case)	9（17.3）	8（15.1）	9（17.3）	8（15.1）	4.603	0.596
History of smoking (cases)	12（23.1）	8（15.1）	14（26.9）	15（28.3）	5.037	0.539
Systolic blood pressure (mmHg)	135.8±3.17	136.6±22.0	131.54±22.7	135.6±27.3	0.481	0.696
Diastolic blood pressure (mmHg)	76.0（71.0,87.5）	76.0（68.5,88）	71.0（65.0，85.0）	78（70,89.5）	5.568	0.135
Heart rate (beats/min)	79.5（69.8,93.5）	80（72,96）	81（70,95.8）	82（73.5，103）	1.898	0.594

Height (cm)	165（160,174）	165（158,170）	166（158,170）	169（159,174）	2.586	0.460
Body weight (kg)	70（62.5,79.5）	72（60.5,81）	69.5（60.0,83.8）	70（62.5,80）	0.208	0.976
LEVEF (%)	57.5（48.7,64.8）	57（46.5,65）	55（44,62）	55（41,61.5）	4.074	0.254

P values are for test of difference across all quartiles of hs-CRP

In the comparison of laboratory tests among the four groups (Table 2), the indices with significant differences among the four groups included Na (p = 0.037), Ca (p = 0.001), Fe (p < 0.001), blood creatinine (p = 0.035), HDL (p = 0.019), WBC (p = 0.001), percentage of neutrophils (p < 0.001), serum ferritin (p = 0.001) and albumin (p < 0.001). The most significant differences were found for Fe and albumin. Indicators that were not significantly different between the four groups included NT-ProBNP (p = 0.081), K (p = 0.466), Glu (p = 0.110), uric acid (p = 0.621), ALT (p = 0.396), AST (p = 0.920), TG (p = 0.997), TC (p = 0.776), and LDL-C (p = 0.621). 0.621).

Table 2 Comparison of Laboratory Findings in Four Groups of Heart Failure Patients with Different CRPs

Characteristics	Q1	Q2	Q3	Q4	H/F/χ2	P 值
NT-ProBNP(pg/mL)	540.5（273.7,1855）	989(388.3,2467.7)	684.1(307.7,2486.3)	1001.4(516.5,5435.3)	6.743	0.081
k (mmol/L)	3.9（3.7,4.3）	3.9(3.6,4.2)	3.9(3.6,4.2)	4.0(3.7,4.4)	2.552	0.466
na(mmol/L)	141.0（139，142.2）	141(138.6,142)	140(138.7,142.1)	139(137,142)	8.483	0.037
ca(mmol/L)	2.3（,2.2,2.3）	2.2(2.1,2.3)	2.2(2.1,2.3)	2.1(2.0,2.2)	17.112	0.001
Fe(mmol/L)	14.2（11.4,18.6）	12.8(10.6,16.8)	11.7(8.3,16.7)	8.2(5.4,11.3)	36.439	0.000
Glu(mmol/L)	5.5,（5.0,7.0）	5.81(5.0,9.0)	6.1(4.9,7.5)	6.9(5.4,9.9)	6.030	0.110
Creatinine(umol/L)	75.8（69,92.9）	76(67.5,91.8)	71.8(59.1,88.5)	86.3(67.9,108.0)	8.583	0.035
Uric acid(umol/L)	321.2,（267.5,393.0）	331(282.5,437.2)	322(269,421.3)	353(283.7,442.9)	1.772	0.621
Alt（U/L）	19（15,29.8）	17(12.1,25.9)	15.6(11.6,27.0)	21.5(12.6,30)	2.970	0.396

Ast（U/L）	19.7（17.4,27.2）	19.4(14.6,26.9)	19.7(14.7,29.7)	23.1(14.2,31.65)	0.493	0.920
TG(mmol/L)	1.3,（0.89,1.62）	1.2(0.9,1.9)	1.2(0.9,1.8)	1.2 (0.9,1.6)	0.054	0.997
HDL(mmol/L)	1.1（0.9,1.3）	1.0(0.9,1.3)	1.1(0.9,1.2)	0.9(0.73,1.1)	9.990	0.019
WBC(*109/L)	6.3（5.3,7.5）	6.1(5.2,7.4)	6.8(5.4,8.2)	8.05(6.15,9.815)	15.774	0.001
HB(g/L)	139（126.,156.3）	133(122.5,149)	133.5(119,142.8)	130(108.5,142.5)	6.538	0.088
Neutrophil percentage (%)	60.0（56.2,70.2）	63.9(56.0,70.1)	65.3(59.5,73.0)	73.2(64.65,81.4)	28.622	0.000
Serum ferritin (ug/L)	133.7（88.4，204.8）	129.0（77.1，256.8）	121.3 (58.7, 189.5)	202.0（106.3446.2）	16.209	0.001
Albumin（g/L）	40.5±4.6	40.1±4.2	39.2±4.1	36.5±5.1	8.466	0.000
TC(mmol/L)	1.4±0.7	1.5±0.96	2.0±1.0	3.6±1.5	0.369	0.776
LDL-C(mmol/L)	2.2±0.9	2.2±0.7	3.6±1.4	2.2±1.1	0.591	0.621

Laboratory indices that differed between the four groups were selected: serum sodium, calcium, iron, blood creatinine, HDL, WBC, ferritin, and albumin, and were compared two by two between the groups (for significance, see Table 3.) The ferritin level in group Q4 [202.0 (106.3446.2) ug/L] was significantly higher than that in groups Q1-3 [133.7 (88.4, 204.8) ug/L, 129.0 (77.1, 256.8) ug/L 121.3 (58.7, 189.5) ug/L], the difference was statistically significant ($P < 0.05$); the percentage of neutrophils in group Q4 was significantly higher at 73.2 (64.65,81.4)% than that in groups Q1-3 [60.0 (56.2,70.2)%, 63.9 (56.0,70.1)% , 65.3(59.5,73.0)%], and the difference was statistically significant ($P < 0.05$); serum iron levels in group Q4 [8.2(5.4,11.3) mmol/L were significantly lower than those in groups Q1-3 [14.2(11.4,18.6) mmol/L , 12.8(10.6,16.8) mmol/L , 11.7(8.3, 16.7) mmol/L], the difference was statistically significant ($P < 0.05$); albumin level in group Q4 was 36.5 ± 5.1 significantly lower than that in groups Q1-2 (40.5 ± 4.6, 40.1 ± 4.2), and the difference in albumin level between groups Q3 and Q4 was not statistically significant ($P > 0.05$); the serum calcium level in group Q4 [2.1(2.0,2.2) mmol/ L] was significantly lower than that of group Q1 [2.3 (,2.2,2.3) mmol/L], and the difference was statistically significant ($p < 0.05$), the difference between the remaining groups was not statistically significant, and the difference in blood sodium level among the four groups was not statistically significant.

Table 3 Comparison of Laboratory Findings in Four Groups of Heart Failure Patients with Different CRPs

Group	Serum ferritin	Na	Ca	Fe	Creatinine	Albumin	Neutrophil percentage
Q1，Q2	1.000	1.000	0.320	1.000	1.000	0.733	1.000
Q1，Q3	1.000	1.000	0.265	0.079	0.987	0.636	1.000
Q2，Q3	1.000	1.000	1.000	0.718	1.000	1.000	1.000
Q1，Q4	0.047	0.062	0.000	0.000	0.776	0.000	0.000
Q2，Q4	0.043	0.081	0.162	0.000	0.517	0.002	0.000
Q3，Q4	0.001	0.487	0.209	0.011	0.021	0.112	0.002

Comparisons between two groups were made using the Kruskal-Wallis H-test, and the table shows significance values adjusted for multiple tests by the Bonferroni correction method.

Discussion

In the 210 patients included in this study the median hs-CRP was 6.44 mg/l, (reference value <5 mg/l) which is in line with previous studies(11), suggesting that patients with chronic heart failure tend to be in a state of chronic low-grade inflammatory response. Further analysis of the clinical data comparing different hs-CRP subgroups suggested that serum ferritin was significantly higher and serum iron levels were significantly lower in the highest hs-CRP quartile group. This result is consistent with the current view that in patients with heart failure the inflammatory state increases the secretion of ferritin, which reduces iron transfer to the blood and decreases serum iron; however, it causes the secretion of ferritin from the cells, which results in a pseudo-elevation of serum ferritin in heart failure(12), rendering serum ferritin an inappropriate tool for accurately assessing the iron status of patients with heart failure. Notably neutrophil percentages were significantly higher in the highest quartile group of hs-CRP, a phenomenon that suggests that higher serum hs-CRP in heart failure patients may be associated with infection.

In addition this study found no significant difference in ferritin levels at Q1-Q3 (hs-CRP 0-10.88mg/l), and serum ferritin levels were significantly higher than those in the Q1-Q3 group only in the highest quartile group of hs-CRP (>10.88mg/l). Whereas the range of reference values of CRP is 0-7mg/l(13), which suggests that when the CRP is normalized ferritin can still reflect the body's iron storage, whereas the use of ferritin to assess iron status in heart failure patients may be limited when hs-CRP is significantly elevated.

Currently, the management of iron deficiency in heart failure patients remains intertwined with the management of anemia. This means that non-anemic iron deficiency (NAID) is usually not screened for, that iron markers are investigated only when anemia is suspected based on a

complete blood count or hemoglobin measurement, and that even when iron markers are investigated, they are usually tested only for ferritin(14), especially when medical conditions make laboratory tests such as transferrin saturation and serum transferrin receptor difficult to perform, and that previous Clinical trials have used serum ferritin as an inclusion criterion(15–18), and it may be inadvisable to hastily abandon serum ferritin in the management of iron deficiency in patients with heart failure. The results of this study suggest that there is no significant difference in serum ferritin when serum hs-CRP is low in heart failure patients, that the use of serum ferritin to assess iron status in heart failure patients may be reasonable, and that the hs-CRP threshold available for serum ferritin may be more favorable for the management of ID in patients with heart failure in medically less developed areas.

Limitations

This study was a single-center cross-sectional study with a small sample size (n=210), and the results may not be representative of the wider population, thus limiting the general applicability of the findings and elucidating the cause-and-effect relationship between serum ultra-C-reactive protein and serum ferritin in patients with chronic heart failure.

Although hs-CRP is a commonly used marker of inflammation, its specificity is low and does not fully reflect the complexity of the inflammatory response in heart failure patients. In this study, only ultrasensitive C-reactive protein (hs-CRP) was used to assess the inflammatory state of patients with chronic heart failure, which may not fully reflect the chronic low-grade inflammatory state of patients.

Some studies have reported that the use of heart failure medications such as SGLT-2 inhibitors and ARNI (angiotensin receptor-enkephalinase inhibitors) may affect iron status in patients with chronic heart failure(19). However, this study did not investigate the medication history of patients with heart failure and therefore could not assess the effect of these medications on the iron status of patients.

Conclusion

When the CRP is normalized ferritin can still reflect the body's iron storage, whereas the use of ferritin to assess iron status in heart failure patients may be limited when hs-CRP is significantly elevated.

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