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Perennial Parameter for Intravenous Iron Therapy in Heart Failure: Reticulocyte Crisis

ABSTRACT

Background: Managing comorbidities alongside guideline-directed medical therapy is essential in heart failure (HF) treatment. Intravenous (IV) iron therapy is recommended for HF patients with left ventricular ejection fraction (LVEF) <50% to correct iron deficiency. Traditional markers such as ferritin and transferrin saturation (TSAT) are affected by inflammation and have delayed responses, limiting their clinical utility. This study aimed to evaluate early response to IV iron therapy by monitoring reticulocyte counts, a parameter unaffected by inflammation.

Methods: Hospitalized HF patients with LVEF <50% meeting CONFIRM-HF criteria for IV iron therapy were included. Reticulocyte counts were measured at admission and 72-120 hours post treatment. Associations with hemoglobin (Hb) increase at 1 month, hospital stay duration, emergency department (ED) readmissions, and mortality were assessed.

Results: Patients with ≥1 g/dL Hb increase at 1 month had higher reticulocyte levels at admission (2.0% vs. 1.5%, $P = .04$) and 72-120 hours post treatment (2.2% vs. 1.3%, $P = .004$). A ≥9% reticulocyte increase at 72-120 hours predicted Hb rise ≥1 g/dL with 90% specificity (area under the curve: 0.79, $P = .002$). Those with higher reticulocyte increases had shorter hospital stays (7 vs. 10 days, $P = .023$) and fewer ED readmissions (24% vs. 66%, $P = .004$). Higher reticulocyte and Hb levels correlated with reduced mortality over 2 years.

Conclusion: Reticulocyte increase within 72-120 hours after IV iron therapy offers an early, inflammation-independent marker of treatment response in HF patients, outperforming ferritin and TSAT. Elevated baseline reticulocytes may indicate active bone marrow and predict therapeutic benefit.

Keywords: Ferritin, heart failure, inflammation, iron deficiency, reticulocyte crisis

ORIGINAL INVESTIGATION

INTRODUCTION

Although substantial progress has been made in reducing hospitalizations and mortality through advancements in guideline-directed medical therapy and the increased adoption of cardiac resynchronization therapy, morbidity and mortality rates among patients with heart failure (HF) continue to be substantial.[1-3] This highlights the necessity of addressing comorbid conditions associated with HF management and underscores the need for alternative therapeutic approaches.[4]

Iron deficiency (ID) as a modifiable determinant is observed in 55% of patients with chronic HF and 80% of patients with acute heart failure (AHF). Current guidelines recommend regular anemia and ID screening in all HF patients. In symptomatic patients with HF with reduced ejection fraction and HF with mildly reduced ejection fraction, intravenous (IV) iron supplementation is recommended to alleviate HF symptoms and enhance quality of life and decrease hospital admissions.[5,6] Notably, it takes 4-10 weeks for hemoglobin (Hb) levels to return to normal after oral iron replacement and 3 months to correct erythrocyte parameters. However, the reticulocyte crisis that occurs 3-7 days after oral therapy has long been used as a parameter to assess early treatment response in children with ID anemia.[7-9] Reticulocytes need at least 3-4 days to mature from their synthesis in the bone marrow to become mature red blood cells (RBCs), with half of that time spent in the peripheral blood. Consequently, reticulocyte analysis and diagnosis of the iron levels can be facilitated by using the blood sample.

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Studies testing the efficacy of IV iron therapy frequently relied on surrogate markers, which require a longer time window.[10,11] Besides, it is well recognized that inflammation also affects markers utilized in therapy indication and response, such as ferritin and transferrin saturation (TSAT).[12]

In hospitalized patients with acute decompensated HF, the reticulocyte response—unaffected by inflammation—was evaluated following IV iron therapy as an early surrogate marker of Hb response.

METHODS

Study Population

Between January 1, 2020, and December 31, 2022, 251 hospitalized patients with acute decompensated HF and a left ventricular ejection fraction (LVEF) below 50% were screened after receiving IV iron therapy for iron deficiency anemia. IV iron therapy was administered according to the 2021 guidelines recommendations, specifically to patients with an LVEF of less than 50% with serum ferritin values below 100 ng/mL, or when serum ferritin values were between 100 and 299 ng/mL with TSAT below 20%.[3,4] Iron carboxymaltose was the only IV iron preparation available during that window. The treatment protocol was adjusted according to the CONFIRM-HF study. Since all of the HF cases had Hb <12 g/dL, a loading dose of 1000 mg was administered to all patients. For subjects <70 kg with Hb <10 g/dL at presentation, an additional dose of 500 mg was given at week 6, whereas for subjects ≥70 kg with Hb <10 g/dL, 1000 mg was administered at week 6, and 500 mg was given if Hb ≥10 g/dL as per recommended.[13]

Out of 251 eligible HF patients for IV therapy, 183 were excluded due to missing baseline or follow-up laboratory data or the absence of clinical follow-up data at the center. The remaining 68 HF patients with all available iron parameters, including ferritin, TSAT, Hb levels, and reticulocyte levels at baseline and 72-120 hours after IV iron therapy, along with clinical follow-up data, were considered.

The baseline data included demographic characteristics, iron parameters, brain natriuretic peptide (BNP), electrocardiogram, LVEF measured by Simpson's in transthoracic echocardiography, and C-reactive protein (CRP) as a marker of inflammation. Among the parameters, the reticulocyte measurement was specified as the percentage of reticulocytes, a portion of the total number of RBCs in the blood sample. The typical reticulocyte count spans from 0.5% to 2.5% in adults.[14] The primary endpoint was an increase in Hb levels in the first month. Secondary endpoints included duration of hospital stay, post-discharge emergency department (ED) or outpatient visits for worsening HF during 2-year follow-up and all-cause mortality. Worsening HF was defined as ED or outpatient visits for HF accompanied by elevated BNP levels and the presence of exacerbation of HF symptoms (dyspnea, orthopnea, and signs of congestion) according to the contemporary reports.[15] The institutional electronic health records system and the national mortality database were utilized to ascertain survival status and the date of death. The follow-up period was defined as the duration between the date of the initial administration and either the date of death or the last clinical visit.

The institutional ethics committee approved this analysis and followed the rights specified in the Declaration of Helsinki (2023/05-07, February 22, 2023). The written and verbal consent was obtained from the subjects.

Statistical Analysis

The statistical analysis was performed with SPSS version 29 (SPSS Inc., Chicago, IL, USA). Histograms and the Kolmogorov–Smirnov test validated the normal distribution of continuous variables. The continuous data are shown as median (interquartile range) and means ± SDs. Where suitable, 3 tests were utilized to assess differences between groups: the chi-square, Mann–Whitney *U*, and Student's *t*-test. The efficacy of reticulocyte crisis in forecasting Hb level elevation was assessed using receiver operating characteristic curves. The area under the curve (AUC) values were calculated, and statistical significance was determined with a threshold of $P < .05$.

RESULTS

Prospectively enrolled 68 following cases who received IV iron therapy with HF were considered. The average follow-up period was 2 years. The mean age of the patients was 69.5 ± 14 years, and 39% (n = 27) were female. Regarding the baseline characteristics, 58% (n = 39) had coronary artery disease, 77% (n = 52) had hypertension, 40% (n = 27) had diabetes mellitus, and 52% (n = 35) had chronic kidney disease. The mean LVEF was 43% ± 13. The median Hb value at presentation was 10 g/dL (8.4-10.9), and at the end of the first month, the median Hb was 11 g/dL (9.8-12). At the end of the first month following IV iron therapy, 82% (n = 55) yielded increased Hb levels by more than 1 g/dL. The median reticulocyte value at presentation was 1.8% (1.3-2.4), and the reticulocyte level at 72-120 hours was 2.1% (1.4-2.7) (Table 1).

During the 2-year follow-up, 15 patients (22%) died. Subjects were classified into 2 subsets based on whether they had an Hb increase of more than 1 g/dL in the first month. Compared to patients without an increase in Hb, those with an Hb increase had substantially lower mortality during the 2-year follow-up [9 out of 55 (16%) vs. 6 out of 13 (46%), $P = .011$], and significantly fewer ED visits due to worsening HF [13 out of 55 (24%) vs. 8 out of 13 (66%), $P = .004$]. Furthermore,

HIGHLIGHTS

- Reticulocyte count may serve as an early indicator of treatment response to intravenous iron therapy in patients with heart failure (HF).
- Although recent studies have failed to demonstrate a mortality benefit of intravenous iron in HF, reticulocyte levels may be associated with long-term mortality outcomes in this population.
- As a well-known yet underutilized parameter, reticulocyte count is unaffected by inflammation and responds rapidly, making it a potentially valuable tool in monitoring iron therapy efficacy in HF patients.

Table 1. Baseline Characteristics of the Patients

Baseline Characteristic	
Age, years, ±SD	69.5 ± 14
Sex, male, n (%)	41 (61)
Coronary artery disease, n (%)	39 (58)
Hypertension, n (%)	52 (77)
Diabetes mellitus, n (%)	27 (40)
Chronic kidney disease, n (%)	35 (52)
Malignancy, n (%)	3 (4.5)
Hb at admission, g/dL	10 (8.4-10.9)
Hb at 1st month, g/dL	11 (9.8-12)
Increased Hb >1 g/dL, n (%)	55 (82)
Ferritin at admission, µg/L	73 (22-163)
Ferritin at 1st month, µg/L	240 (121-453)
Reticulocyte at admission, 10^9/L	1.8 (1.3-2.4)
Reticulocyte at 48-72 hours, 10^9/L	2.1 (1.4-2.7)
Delta Reticulocyte >9%, n (%)	48 (71)
TSAT at admission, %	8.8 (5.5-15)
TSAT at 1st month, %	16.2 (10.4-24.5)
BNP at admission, pg/mL	619 (273-1568)
BNP at 1st month, pg/mL	396 (273-547)
TTE-LVEF (%)	43 ± 13
ECG, sinus rhtym, n (%)	26 (38)
Admission to the ED with AHF, n (%)	21 (31)
GFR, mL/min/1.73 m^2	60 ± 29
CRP, mg/L	20 (11.5-47)

AHF, acute heart failure; BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ED, emergency department; GFR, glomerular filtration rate; Hb, hemoglobin; LVEF, left ventricular ejection fraction; TSAT, transferrin saturation; TTE, transthoracic echocardiography.

in patients with an Hb increase, both the initial reticulocyte level [2.0 ± 0.9 vs. 1.5 ± 0.7, *P* = .040] and the reticulocyte level at 72-120 hours [2.2 ± 0.9 vs. 1.3 ± 0.7, *P* = .004] were significantly higher.

When comparing patients with and without Hb increase, no statistically significant difference was found in ferritin levels at pretreatment [66 ng/mL (22-63) vs. 144 ng/mL (31-163), *P* = .39] and at the end of the first month [234 ng/mL (120-420) vs. 359 ng/mL (185-898), *P* = .091]. Similarly, no statistical difference was observed in TSAT levels in the first month. However, in patients with a Hb increase, the baseline TSAT level was statistically significantly lower [7.9% (5.4-15) vs. 12% (8.5-21), *P* = .038] (Table 2). No notable statistical variation was detected between CRP levels, an alternative indicator of inflammation, and reticulocyte levels. Similarly, no significant disparity in CRP levels was found between patients with and without Hb increase.

Our study checked the difference between the reticulocyte count at 72-120 hours and the basal reticulocyte count as the "delta reticulocyte." Receiver operating characteristic curve analysis revealed that a delta reticulocyte level >9% at 72-120 hours significantly predicts a 1 g/dL increase in Hb at 1 month with 90% specificity (AUC: 0.79, CI: 0.67-0.91, *P* = .002) (Figure 1). Among patients with versus without <1 g/ dL Hb increase, those with >1 g/dL Hb increase had a higher frequency of delta reticulocyte levels greater than 9% [44 (80%) vs. 4 (33%), *P* = .001].

Similarly, patients with delta reticulocyte >9% had a statistically significant shorter hospital stay [10 days (6-17) vs. 7 days (3-10), *P* = .023]. Nevertheless, no statistically meaningful association was observed between the length of hospital stay and Hb levels (*P* = .110).

Worsening HF during follow-up was significantly less common in HF patients, with a 1-gr-Hb increase during the 2-year follow-up [13 (24%) vs. 8 (66%), *P* = .004] (Table 2).

All cause mortality was lower in HF subjects with delta reticulocyte >9% or 1-gr-Hb increase during the follow-up [delta reticulocyte >9%: 8 (53%) vs. 41 (78%), *P* = .015; Hb increase >1 g/dL: 9 (15%) vs. 46 (88%), *P* = .011].

Table 2. Comparison of Patients with and Without a ≥1 g/dL Hemoglobin Increase at the End of the First Month

	Hemoglobin Increase >1 g/dL (n = 54)	Without Hemoglobin Increase >1 g/dL (n = 12)	*P*
Mortality 2 years follow-up, n (%)	9 (16)	6 (50)	**.011**
Admission to the ED with AHF-2 years follow-up, n (%)	13 (24)	8 (66)	**.004**
Hb at 1st month, g/dL	11 ± 1.6	10 ± 1.3	**.040**
Ferritin at admission, µg/L	66 (22-63)	144 (31-163)	.390
Ferritin at 1st month, µg/L	234 (120-420)	359 (185-898)	.091
Reticulocyte at admission, 10^9/L	2.0 ± 0.9	1.5 ± 0.7	**.040**
Reticulocyte at 72 hours, 10^9/L	2.2 ± 0.9	1.3 ± 0.7	**.004**
Delta reticulocyte >9%, n (%)	44 (80)	4 (33)	**.001**
TSAT at admission, %	7.9 (5.4-15)	12 (8.5-21)	.038
TSAT at 1st month, %	15.6 (10.5-27)	20.2 (11-23.8)	.420
BNP at admission, pg/mL	554 (257-1340)	959 (332-3094)	.130
BNP at 1st month, pg/mL	378 (209-524)	475 (340-3506)	.180

AHF, acute heart failure; BNP, brain natriuretic peptide; ED, emergency department; Hb, hemoglobin; TSAT, transferrin saturation. *P*-values that reached statistical significance are highlighted in bold.

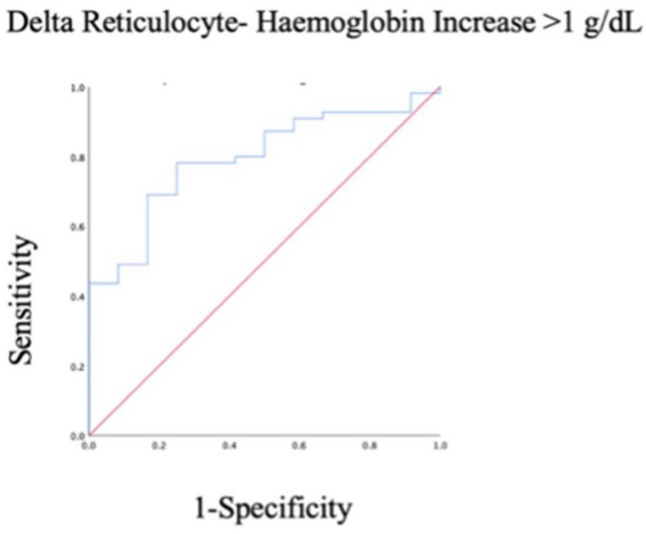

Figure 1. Receiver operating characteristic curve analysis: Delta reticulocyte-hemoglobin increase >1 g/dL. This study checked the difference between the reticulocyte count at 72-120 hours and the basal reticulocyte count, which is known as the "delta reticulocyte." Receiver operating characteristic curve analysis revealed that a delta reticulocyte level >9% at 72-120 hours significantly predicts a 1 g/dL increase in Hb at 1 month with 90% specificity (AUC: 0.79, CI: 0.67-0.91, *P* = .002).

A subgroup analysis was conducted on patients with a baseline TSAT of less than 20% (n = 59), for whom IV iron administration was indicated independently of ferritin levels. Among these patients, those who exhibited an Hb increase of >1 g/dL (n = 50) were compared to those who did not achieve this increase (n = 9), with a focus on the frequency of delta reticulocyte >9%. The group with increased Hb demonstrated a higher frequency of delta reticulocyte >9% [42 (84%) vs. 2 (22%), *P* < .001].

When comparing patients who experienced mortality (n = 15) and those who did not (n = 41) within this cohort, the group without mortality had a significantly greater occurrence of delta reticulocyte >9% [37 (82%) vs. 7 (50%), *P* = .016].

In a comparison between patients with baseline TSAT below and above 20%, no statistically significant variation was observed between the groups in terms of Hb increase (*P* = .120), reticulocyte increase (*P* = .110), mortality (*P* = .470), or hospital admissions due to AHF (*P* = .710) following IV iron therapy.

DISCUSSION

This study compared HF patients with or without a 1 g/dL Hb increase in the first month following IV iron therapy. It is well-known that Hb increase following iron therapy typically occurs between the 4th and 10th weeks.[16] When evaluating the reticulocyte levels, which is the main hypothesis of this study, the baseline reticulocyte levels were significantly frequent in cases with increased Hb (*P* = .04). It is assumed that the standard lifespan of a RBC is 120 days and that the duration of reticulocytes in peripheral blood is 1 day. From this, it can be inferred that in a person in a steady state, the reticulocytes at any given time would constitute 1/120th, or 0.8%, of all RBCs. The normal percentage ranges from 0.5% to 2%. The percentage of reticulocytes in peripheral blood indicates the RBC turnover rate if the patient is stable. The number of reticulocytes released into the blood reflects the erythropoiesis on a given day and can indicate active bone marrow.[17-19]

Based on the reticulocyte crisis observed during oral iron replacement, the control reticulocyte levels measured 72-120 hours after IV iron therapy were also statistically significantly frequent in cases with an Hb increase >1 g/dL. In the analysis of patients with a TSAT level <20%, delta reticulocyte levels were higher in patients who had an increase in Hb and in those who did not experience mortality during follow-up (*P* = .001, *P* = .016). The reticulocyte crisis may also be an appropriate parameter for assessing treatment response in patients with low TSAT. According to these results, reticulocyte levels could be an important parameter for assessing the early response to treatment (at 72-120 hours) without waiting for iron parameters at 12 weeks, which inflammation and infection may affect. The easily calculable delta reticulocyte level can also predict Hb increase with 90% specificity.

Low serum ferritin and TSAT levels in healthy individuals are reliable parameters for diagnosing ID. Still, ferritin, an acute-phase reactant, fluctuates in inflammatory conditions along with hepcidin levels. HF has long been associated with inflammation and inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1, and interleukin-6. This process complicates the diagnosis of functional ID. Therefore, in clinical studies related to HF, parameters used in the literature related to chronic kidney disease have been applied to define ID, such as ferritin levels <100 ng/mL or ferritin levels between 100 and 299 ng/mL with TSAT <20%. These criteria, first used in the FAIR-HF trial in 2008, have since become widely accepted for assessing ID in HF patients in subsequent studies.[20]

However, in a study conducted by Grote Beverborg and colleagues involving 42 HF patients undergoing coronary artery bypass surgery, these standards were evaluated against bone marrow iron staining results, which are regarded as the gold standard for diagnosing ID anemia. The study demonstrated that the FAIR-HF criteria exhibited a sensitivity of 82.4%, specificity of 72.0%, positive predictive value of 66.7%, and negative predictive value of 85.7%. Based on the FAIR-HF criteria, one-third of patients diagnosed with iron deficiency were found to have normal bone marrow iron stores.[21] Furthermore, it was shown that ferritin, as per the FAIR-HF criteria, was not associated with mortality, and evidence suggested that serum iron indices in HF could fluctuate and return to normal spontaneously without needing exogenous iron supplementation.[22,23]

These findings indicate that the currently recommended parameters may not accurately reflect ID anemia and may not be suitable for evaluating treatment responses.

Reticulocyte levels, which are less affected by these processes and directly reflect bone marrow activity, could be a more appropriate parameter.

This study's patient enrollment was based on the currently accepted FAIR-HF criteria. In this work, worsening HF events were less frequent in the group with >1 g/dL Hb increase. When comparing the results to other studies, the IRONMAN study evaluated composite outcomes of HF-related hospitalizations and cardiovascular death over an average follow-up of 2.7 years [risk ratio (RR): 0.82, 95% CI: 0.66-1.02; $P = .070$].[10] Similarly, the AFFIRM AHF study showed that hospitalizations for HF were less frequent in the group receiving IV iron therapy (RR: 0.74; 95% CI: 0.58-0.94, $P = .013$).[8] In addition, a meta-analysis by Graham et al[23], which incorporated 10 studies, revealed that IV iron therapy lowered the combined outcome of total HF hospitalizations and cardiovascular mortality (RR: 0.75, 95% CI: 0.61-0.93; $P < .01$).

In contrast to these studies, which compared IV iron treatment with usual care, the current work differentiated between patients who responded to IV iron therapy and those who did not. All-cause mortality during follow-up was also lower in the subgroup with >1 g/dL Hb increase ($P = .011$). However, in the IRONMAN and AFFIRM AHF studies, there was no statistically significant difference in cardiovascular mortality among patients who administered IV iron and those who did not.[10,11] This lack of benefit might be linked to negligence of the pathobiological response of IV iron therapy, as in the presence of a pathobiological link in the form of Hb increase, it seems there is a benefit.

It is recommended that ferritin and TSAT levels be monitored at 12, 24, and 36 weeks following the initiation of iron therapy.[24] In the CONFIRM-HF study, the treatment response was defined by increased ferritin levels to over 100 µg/L, or if ferritin levels were between 100 and 300 µg/L, a TSAT level above 20%.[13] Although different studies set varying targets, the parameters used remain consistent. However, no statistically significant differences were noted in the study's baseline and 1-month ferritin levels between patients with and without increased Hb ($P = .39$, $P = .091$). This could be attributed to ferritin acting as an acute-phase reactant. During malignancy and infection, ferritin concentrations rise to decrease the availability of unbound iron for tumor cells or pathogens, respectively, and are upregulated by pro-inflammatory cytokines. Inflammatory conditions increase ferritin levels while reducing transferrin levels, a negative acute-phase protein that carries iron. Ferritin sequesters iron and prolonged inflammation or malignancy can lead to anemia or chronic disease. Therefore, ferritin may not be a reliable marker for ongoing monitoring.[25,26]

Another parameter, TSAT levels, was lower in the group with a Hb increase ($P = .038$). However, there was no difference in TSAT values at the end of the first month ($P = .42$). This result may also be due to the influence of inflammation and infection on TSAT levels, similar to ferritin.[27,28]

Strengths and Limitations

The main strength of this work is based on an easily measurable but perennial parameter, i.e., the reticulocyte level, which, as a novel metric in this field, seems to work for

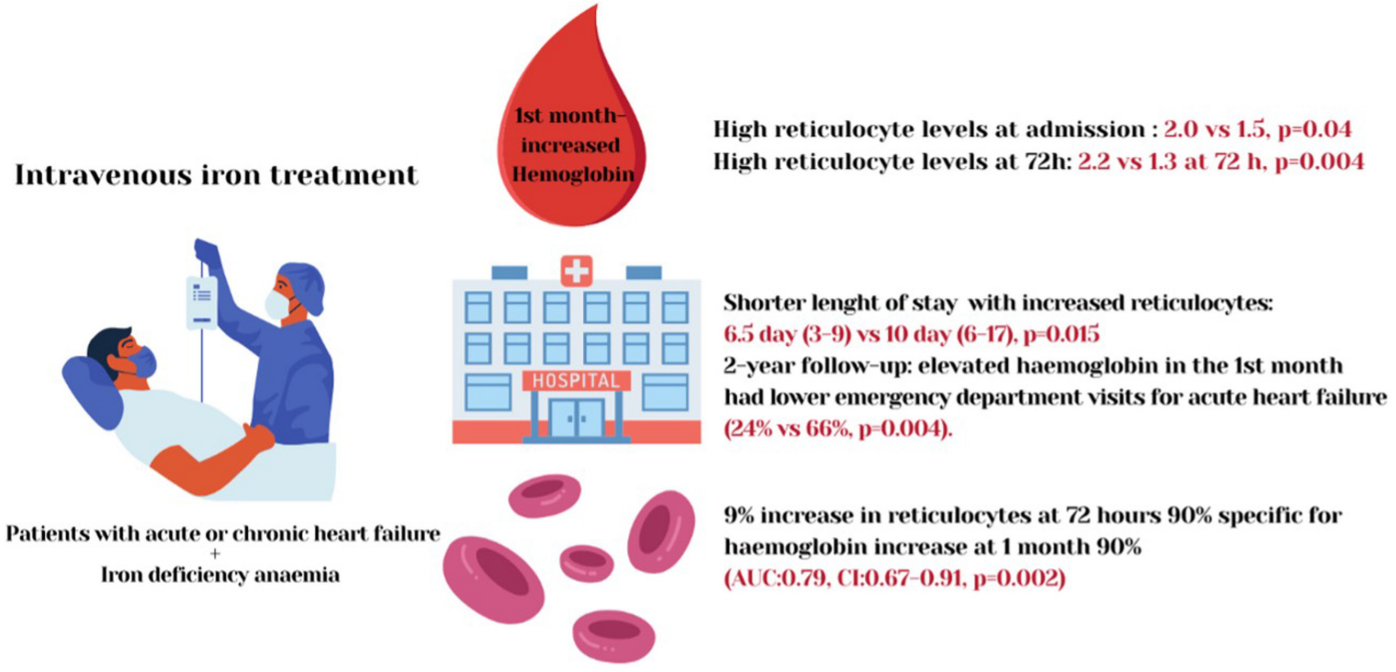

Figure 2. Central illustration. The central illustration summarizes the key findings: In patients receiving IV iron therapy for heart failure, those who exhibited increased Hb levels at 1 month had significantly higher reticulocyte levels at baseline and at 72 hours. Patients with an increase in reticulocyte levels had a shorter hospital stay. Over a 2-year follow-up period, those with increased Hb levels had significantly lower rates of heart failure-related hospitalizations. A delta reticulocyte level >9% was identified as 90% specific for predicting an increase in Hb at 1 month (AUC: 0.79, CI: 0.67-0.91, $P = .002$).

assessing the response to IV iron therapy in HF patients. This parameter, assessed at a very early stage, such as between 72 and 120 hours, remains unaltered by inflammation and predicts an increase in Hb by the end of the first month. It can be easily used in HF patients, where clinical progression is highly variable and patient monitoring is crucial.

The primary limitations of this work include the small sample size of a single-center experience and the unequal distribution of groups. Hence, only 68 patients could be included, as they were required to return for follow-up evaluations between 72 and 120 hours upon administration. While the sample size is limited for making definitive conclusions, power analysis indicated a sufficient power of 92% when comparing reticulocyte levels between patients with an Hb increase greater than 1 g/dL and those with an increase of less than 1 g/dL. Cardiovascular mortality could not be assessed to prevent the misclassification of deaths. Due to the small sample size, this study cannot establish a true causal relationship. Nevertheless, these findings may be a preliminary study showcasing the importance of reticulocyte levels in evaluating the response to IV iron therapy in HF patients. Other limitations of this study include potential laboratory errors in reticulocyte measurements, the absence of a defined cut-off value for Hb, the evaluation of increases relative to baseline, and the relatively short follow-up period. Nonetheless, this study found that a delta reticulocyte >9% was associated with 90% specificity in predicting Hb increase > 1 g/dL by the end of the first month.

CONCLUSION

This current study is among the first preliminary reports assessing reticulocyte levels and the response to IV iron therapy in HF. It is widely recognized that TSAT, ferritin, and Hb levels should be assessed before administering IV iron therapy. However, these variables are influenced by various conditions, such as inflammation and infection. They respond to treatment after 4-12 weeks. However, the reticulocyte level, which is unaffected by these factors, increases at 72-120 hours after treatment and can be used to evaluate the treatment response of patients in the early period. In addition, high reticulocyte levels on admission may indicate which patients will benefit from treatment as an indicator of active bone marrow (Figure 2).

Ethics Committee Approval: The Ethics Committee of Dokuz Eylül University approved this analysis and followed the rights specified in the Declaration of Helsinki (2023/05-07, February 22, 2023).

Informed Consent: Written consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.K., Design: Z.K., Supervision - M.B.Y., Resource - Z.K., H.U., Materials - Z.K., H.U., Data Collection and Processing - Z.K., H.U., Analysis and Interpretation - Z.K., M.B.Y., Literature Search - Z.K., H.U., Writing - Z.K., M.B.Y., Critical Reviews - Z.K., M.B.Y.

Declaration of Interests: The authors have no conflicts of interest to declare.

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