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ORIGINAL PAPER

Long-term effects of iron deficiency in patients with heart failure with or without anemia: the RAID-HF follow-up study

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Abstract

Introduction Iron deficiency (ID) has been recognized as a relevant comorbidity in heart failure with reduced ejection fraction (HFrEF); however, study data have shown that diagnostic and therapeutic efforts on ID are primarily performed in patients with anemia.

Methods The RAID-HF registry investigated consecutive patients with ID and HFrEF in 11 heart centers in Germany and Switzerland. The present analysis focuses on 1-year follow-up data in patients with versus without anemia.

Results In 505 patients with HFrEF and ID and 418 patients with HFrEF without ID 1-year follow-up was performed. Patients with ID had a higher long-term mortality compared to those without ID (19.5% vs. 13.7%, $p=0.02$) and reported a lower quality of life. Only a minority of patients with ID (9.3%) received iron supplementation during long-term course, just 4.7% intravenously. Anemia was associated with an elevated mortality whereas ID versus no ID did not predict mortality in anemic patients (log-rank $p=0.78$). However, in patients without anemia ID versus no ID predicted mortality (log-rank $p=0.002$). In the adjusted analysis a significant interaction remained, with ID being a significant predictor of 1-year mortality in patients without anemia (HR 2.15, 95% CI 1.12–3.78), but not in anemic patients (HR 0.99, 95% CI 0.65–1.49).

Conclusions RAID-HF demonstrates the impact of ID on long-term mortality and quality of life in patients with HFrEF and reveals an underuse of iron supplementation in current clinical practice. Particularly in patients without anemia the diagnosis of ID is of clinical relevance to identify patients at higher mortality risk.

Keywords Iron deficiency · Heart failure with reduced ejection fraction · Anemia · Iron supplementation

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Introduction

An increasing number of studies reported that iron deficiency (ID) in patients with heart failure with reduced ejection fraction (HFrEF) is associated with impaired outcomes including death, heart transplantation as well as heart failure symptoms [1–4]. Intravenous iron supplementation in patients with ID and HFrEF has been shown to improve the functional status of HFrEF patients in different studies [5–8]. In the randomized FAIR-HF and CONFIRM-HF trials intravenous ferric carboxymaltose improved symptoms and exercise capacity [6, 7]; a recent meta-analysis of four randomized trials suggests that recurrent cardiovascular hospitalization rates are reduced by iron therapy in patients with ID and HFrEF [9].

International guidelines, therefore, recommend assessment of iron status in all patients with HFrEF and iron

supplementation by ferric carboxymaltose in symptomatic patients with HFrEF and ID to alleviate symptoms [10–12]. However, in a previous analysis of the RAID-HF registry our study group demonstrated a low rate of diagnostic and therapeutic efforts on ID in HFrEF in clinical practice [13]. The presence of anemia was an important factor driving assessment of iron status and treatment of ID in patients with HFrEF.

The purpose of the RAID-HF follow-up study was to analyse the long-term effects of ID in HFrEF with a focus on the anemia status. The study further aimed to investigate the current use of iron supplementation in a "real-world" setting of patients with HFrEF and ID with and without anemia.

Methods

The RAID-HF follow-up study

RAID-HF was an international multicenter study with the purpose to assess management and prognosis of patients with HFrEF and ID in contemporary clinical practice [13]. The participating centres were requested to enrol their consecutive patients with chronic systolic HF who agreed to participate. Inclusion criteria of the study were: age ≥ 18 years, left ventricular ejection fraction ≤ 40% and chronic heart failure known since at least 3 months. The only exclusion criterion was missing written informed consent. The electronic case report form (eCRF) collected baseline information on demographics, presentation, medical history, clinical evaluation and diagnostics, pharmacological treatment and non-pharmacological interventions, quality of life and adverse events. Specific information on diagnosis and therapy of ID was obtained (laboratory measurements as ferritin, transferrin saturation, serum iron and documentation of iron treatment). In the present analysis 1-year follow-up results of the RAID-HF study are presented. Follow-up information was obtained by telephone calls and information requested from general practitioners and hospitals. Follow-up information was performed by a well-trained and supervised study team (centrally performed by the Stiftung Institut für Herzinfarktforschung Ludwigshafen, Germany).

As the participation in the registry protocol did not require or recommend or discourage any treatments just for the sake of inclusion that were beyond the ones delivered in routine care for the patients, the study could be regarded as prospective but strictly observational. Positive votes were obtained from the ethical review boards of the Landesärztekammer Rheinland-Pfalz, Germany and of the participating centers.

The participating centers were cardiology departments of hospitals that offered specialized care for HF-patients with inpatient and outpatient facilities. In the time period from December 2010 through October 2015, 7 centers in Germany and 4 centers in Switzerland participated in the RAID-HF study.

Definitions

ID was defined as ferritin < 100 ng/ml or 100–299 ng/ml if transferrin saturation was < 20%. Anemia was defined according to the definition of the World Health Organization (WHO): hemoglobin < 12 g/dl in women and < 13 g/dl in men [14].

Glomerular filtration rate (GFR) was defined according to the abbreviated Modification of Diet in Renal Disease study (MDRD) formula by Levey et al. [15]. Chronic kidney failure by judgement of the treating physician was defined as a durable reduction of GFR (< 60 ml/min/1.73 m^2) or hemodialysis.

To assess quality of life the EuroQoL questionnaire (EQ-5D) with visual analogue scale using the German value set was used [16]. The EQ-5D is a standardized and widely used instrument for measuring quality of life. The visual analogue scale records the patient's self-rated health status on a graduated (0–100) scale, with higher scores for higher quality of life; the endpoints are labelled "best imaginable" and "worst imaginable".

Statistical analysis

The patient population was described by absolute numbers and percentages. The distributions of continuous variables were characterised by medians and interquartile ranges or by mean values and standard deviations. Different groups were compared in an unifactorial analysis by Pearson's Chi-square test or Mann–Whitney test. The results of logistic regression models were described as odds ratios, 95% confidence intervals and p values of the Wald test.

One-year mortality was assessed using methods of survival analysis (Kaplan–Meier estimator, log-rank test) including events which occurred up to 366 days after discharge from the index hospitalisation. The follow-up duration was defined as the time from index discharge to the date of the follow-up contact, i.e. when information on the patient's status was obtained. Information on the 1-year status of surviving patients was restricted to follow-up contacts performed between 300 and 450 days after discharge.

The predictors of mortality were analyzed by a multivariable Cox regression model. In addition to ID and anemia, age (linear), female gender, NYHA class III or IV on admission, and left ventricular ejection fraction ≤ 30% were entered as clinically important risk factors. Further variables significantly associated with the presence of anemia were included in a forward selection with an entry level of $p < 0.1$: valvular origin of cardiomyopathy (versus other

cardiomyopathy), diabetes, creatinine > 1.2 mg/dl, chronic liver disease, peripheral arterial disease, chronic obstructive pulmonary disease, malignancy, prior stroke, and admission due to worsening heart failure. For all included variables, a test for interaction with ID was done.

In all comparisons two-tailed tests were applied and p values ≤ 0.05 were considered statistically significant without adjustment for multiple testing. The statistical analyses have been performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Study population

949 patients with HFrEF and known iron status were included in the study. 84.1% were initially treated in-hospital, 15.9% were recruited on an outpatient basis.

Follow-up information regarding vital status and serious events was obtained from 923 of 926 (99.7%) patients discharged alive or with initial outpatient treatment. At telephone contact additional information on quality of life (482 patients) and medication (509 patients) was documented.

The median follow-up duration was 383 days (interquartile range 367–425).

Clinical characteristics and laboratory findings at begin of study

ID was present in 516 patients (54.4%). Patients with ID were more often female (30.6 vs. 18.9%, $p < 0.001$) and had a higher rate of admission due to worsening heart failure (54.8% vs. 43.4, $p < 0.001$) compared to patients without ID (Table 1). Ferritin < 100 ng/ml was diagnosed in 61.0% of patients, ferritin 100–299 ng/ml and transferrin saturation < 20% in 39%. Among patients with ID, 48.1% had anemia compared to 37.4% of patients without ID ($p < 0.001$).

Table 1 Patients with HFrEF and ID versus no ID; comparison of clinical characteristics and laboratory findings at begin of study

Variable	Iron deficiency		p
	Yes (n = 516)	No (n = 433)	
Clinical characteristics			
Age (years)	70.1 ± 12.1	68.9 ± 12.4	0.09
Female (%)	30.6	18.9	< 0.001
Admission due to worsening heart failure (%)	54.8	43.4	< 0.001
New York Heart Association class III/IV, (%)	73.6	66.8	0.022
New York Heart Association class I (%)	6.4	9.7	0.06
Ejection fraction ≤ 30% (%)	65.3	64.4	0.78
History of atrial fibrillation (%)	40.5	40.6	0.96
Ischemic cardiomyopathy (%)	57.4	53.1	0.19
Valvular cardiomyopathy (%)	7.9	4.6	0.037
Chronic kidney failure (%)	40.5	40.6	0.96
Hemodialysis (%)	1.2	3.0	0.044
Diabetes (%)	37.6	35.1	0.43
Chronic obstructive pulmonary disease (%)	16.7	16.4	0.91
Malignancy (%)	11.0	10.9	0.92
Laboratory measurements			
Ferritin (ng/ml)	85.4 (53.0; 142.0)	296.0 (178.2; 459.0)	< 0.001
Iron (µg/dl)	52.5 (38.5; 67.6)	84.9 (63.1; 106.1)	< 0.001
Transferrin saturation (%)	14.0 (10.2; 17.7)	24.6 (20.2; 31.0)	< 0.001
Ferritin < 100 ng/ml (%)	61.0	0	< 0.001
Ferritin 100–299 ng/ml and transferrin saturation < 20% (%)	39.0	0	< 0.001
Hemoglobin (g/dl)	12.7 (11.3; 14.1)	13.4 (12.1; 14.6)	< 0.001
Anemia, %	48.1	37.4	< 0.001
Creatinine (mg/dl)	1.2 (1.0; 1.7)	1.3 (1.0; 1.7)	0.30
Glomerular filtration rate ≤ 60 ml/min/1.73 m^2 (%)	54.7	52.9	0.59

Data are percentages, means ± standard deviations or medians (interquartile ranges)

Adverse events, quality of life and medication during 1-year follow-up

During 1-year follow-up patients with ID had a significantly higher mortality (19.5% compared to 13.7%) than patients without ID ($p=0.018$) (Table 2).

The rate of resuscitations, ICD shocks or heart transplantations as well as the rate of rehospitalisations was not significantly different between the groups.

Self-reported quality of life was significantly worse in patients with ID compared to those without ID (EQ-5D visual analogue scale, $p=0.02$). An improvement in quality of life during 12 months was reported in a lower proportion of patients with ID compared to patients without ID (36.7 versus 47.2%, $p=0.018$).

Regarding medication a higher proportion of patients with ID was treated with diuretics (85.5 versus 75.5% in those without ID, $p=0.004$), while the opposite was the case for beta blockers (86.0% in patients with ID versus 92.5% in those without ID, p 0.018). Only 9.3% of the patients with ID received iron supplementation therapy, and only 4.7% of the patients received intravenous therapy, mostly (83%) ferric carboxymaltose.

Patients with and without anemia

Patients with anemia had lower survival than patients without anemia. Among patients with anemia, survival did not differ significantly between patients with ID versus without ID (log-rank $p=0.78$, Fig. 1a). However, in patients without anemia the role of ID was stronger (unadjusted p for interaction $=0.011$) and a significant difference between patients with ID versus without ID was observed, with a better survival in patients without ID (log-rank $p=0.002$, Fig. 1b).

Multivariable analysis of 1-year mortality

In a multivariable analysis adjusting for known prognostic parameters the significant interaction between ID and anemia was sustained (p for interaction $=0.027$). ID was a significant predictor of 1-year mortality in patients without anemia (HR 2.15, 95% CI 1.23–3.78), but not in anemic patients (HR 0.99, 95% CI 0.65–1.49). The strongest other predictors of mortality in this analysis were creatinine >1.2 mg/dl (HR 2.06, 95% CI 1.41–2.99) and older age (HR 1.33 per 10-year increase, 95% CI 1.12–1.58). Further predictors identified by forward selection were chronic obstructive pulmonary disease, malignancy and valvular origin of heart disease (Fig. 2).

Discussion

The RAID-HF follow-up study revealed the following major findings.

The presence of ID in patients with HFrEF was associated with impaired long-term survival as well as quality of life. Although randomized studies have shown beneficial

Table 2 One-year follow-up results of patients with HFrEF and ID versus no ID

Variable	Iron deficiency		p
	Yes ($n=505$)	No ($n=418$)	
Adverse events			
One-year mortality (%) (Kaplan–Meier)	19.5	13.7	0.018
Resuscitation or ICD shock (%)	4.1	4.6	0.75
Heart transplantation (%)	0.6	0.7	0.97
Rehospitalisations (%)	47.6	51.2	0.38
≥3 Rehospitalisations (%)	13.3	12.7	0.83
QoL[a]			
EQ-5D visual analogue scale [0–100]	60 [50;75]	70 [50;80]	0.021
QoL better than 12 months before (%)	36.7	47.2	0.018
QoL worse than 12 months before (%)	20.6	14.9	0.10
Medication[b]			
ACE inhibitors/ARB (%)	84.0	87.0	0.34
Beta blockers (%)	86.0	92.5	0.018
Mineralocorticoid receptor blockers (%)	53.9	61.7	0.08
Diuretics (%)	85.5	75.5	0.004
Iron medication, total (%)	9.3	2.8	0.002
Iron medication, intravenous (%)	4.7	2.0	0.09

[a]Follow-up information in 242 surviving patients (ID) and 240 patients (no ID), respectively

[b]Follow-up information in 256 surviving patients (ID) and 253 patients (no ID), respectively

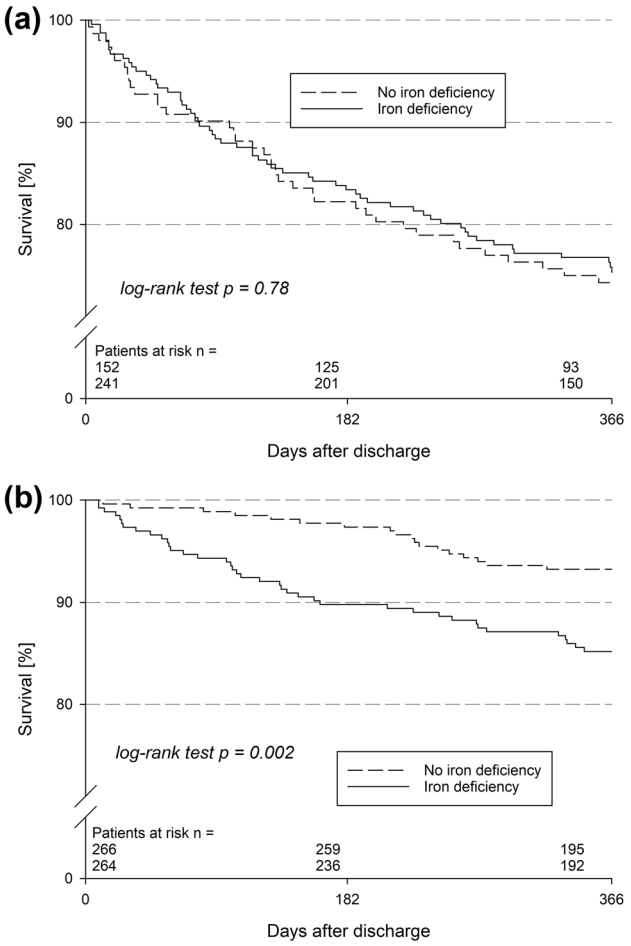

Fig. 1 Survival curves of patients with and without anemia, stratified for ID versus no ID. **a** Patients with anemia; **b** patients without anemia. Patients with anemia had a worse long-term survival than patients without anemia. The survival curves in patients without anemia showed a significant difference between patients with ID versus without ID (log-rank $p=0.002$), while there was no difference between ID versus no ID in patients with anemia (log-rank $p=0.78$)

effects of intravenous iron supplementation in patients with HFrEF and ID, only a minority of patients (9%) received iron therapy in this "real-world" cohort of HFrEF-patients.

Previous investigations reported that in clinical practice diagnostic and therapeutic efforts on ID in patients with HFrEF are primarily performed in patients with anemia. However, this study shows that particularly in HFrEF patients without anemia diagnosis of ID is crucial to identify patients at higher risk of death.

Relevance and long-term prognosis of patients with HFrEF and ID

The burden of HFrEF in the actual clinical practice is often underestimated and outcomes after hospitalizations of patients with HFrEF are still serious [12, 17, 18]. The contribution of comorbidities to mortality in patients with HFrEF is controversial [12, 19].

An increasing number of studies focuses on ID and anemia in patients with HFrEF. Pathophysiology of ID in HFrEF is complex and new studies on hepcidin [20], soluble transferrin receptors (sTFRs) [20] or iron-regulatory proteins (IRPs) [21] suggest that our understanding of this comorbidity in patients with HFrEF will be further modified in the next years.

ID is present in approximately 50% of patients with HFrEF, depending on patient selection [1, 2, 13, 22]. In Germany, a rate of 42.5% previously unknown ID was observed in HF outpatients in the recently published PrEP registry; anemia was found in 18.9% of patients (previously known in only 4.8%) [22]. Given the clinical relevance and treatability, the authors concluded that ID should be considered more in ambulatory healthcare settings [22].

The RAID-HF follow-up study focused on long-term course of patients with HFrEF and ID, most of them hospitalized at time of study inclusion. It has been reported in

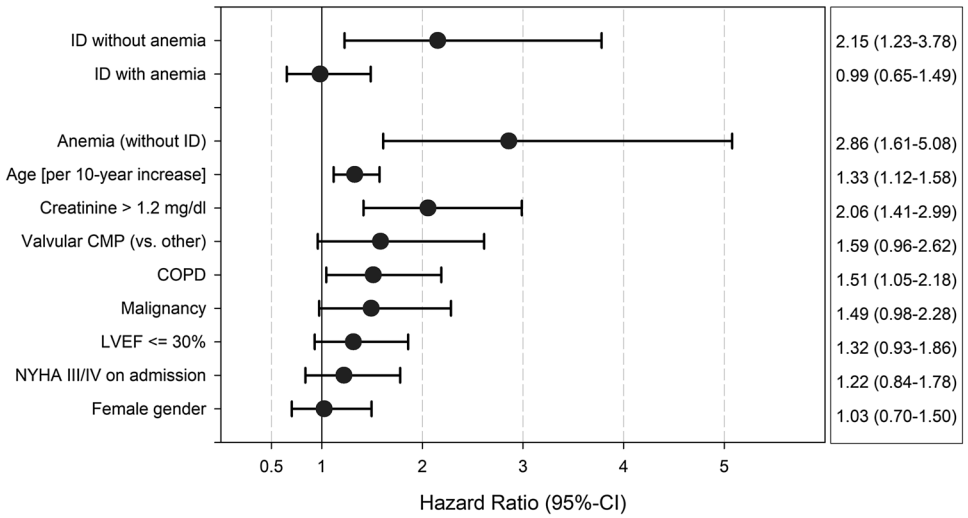

Fig. 2 Multivariable analysis on predictors of 1-year mortality. After multivariable analysis a significant interaction between ID and anemia was found (p for interaction = 0.027). ID without anemia was a significant predictor of 1-year mortality, but not ID with anemia. Anemia was a strong predictor of 1-year mortality, the strongest other predictors of mortality in this analysis were creatinine and age. *CMP* cardiomyopathy, *COPD* chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction

previous studies that ID in patients with HFrEF was associated with an impaired prognosis, reduced exercise capacity as well as quality of life [1–4, 20, 23]. This could be confirmed in the RAID-HF follow-up study: patients with ID had a significantly impaired clinical course compared to patients without ID, with a higher long-term mortality and a reduced quality of life after 1 year. No significant difference was observed regarding rehospitalisations, this might be explained by a too small event number in surviving patients with HFrEF.

Use of iron supplementation therapy

Several studies have shown favorable effects of intravenous iron supplementation on the functional status of patients with HFrEF and ID, in particular the randomized FAIR-HF und CONFIRM-HF trials [5–8, 24]. In these trials intravenous ferric carboxymaltose was associated with an improvement of symptoms, functional capacity, quality of life and rehospitalisations due to worsening HF in iron-deficient patients with HFrEF [6, 7]. In a recent meta-analysis Anker et al. showed that patients on intravenous ferric carboxymaltose compared to those taking placebo had lower rates of recurrent cardiovascular rehospitalisations and cardiovascular mortality (RR 0.59, 95% CI 0.40–0.88, $p = 0.009$) [9]. Furthermore, health economic studies demonstrated that iron supplementation with intravenous ferric carboxymaltose in iron-deficient patients with HF was cost-effective [25, 26]. Regarding oral iron supplementation there are no data supporting the use of oral iron in patients with HFrEF; in the recently published IRONOUT trial high-dose oral iron did not improve exercise capacity among participants with HFrEF and ID [27], in the IRON-HF trial intravenous iron supplementation was superior to oral therapy with respect to exercise capacity [8].

Despite these data only 9.3% of the iron-deficient patients with HFrEF received any iron therapy in the RAID-HF follow-up study and just 4.7% received intravenous therapy. These data indicate that intravenous iron supplementation plays a minor role in the actual clinical management of patients with HFrEF. Education of physicians as well as publication of further studies should be increased to improve the awareness to diagnose and treat ID in HFrEF.

Anemia and ID

Anemia has been shown to be a strong predictor for diagnostic and therapeutic efforts on ID in patients with HFrEF in clinical practice [13]. In RAID-HF anemia was an independent predictor of iron status assessment by physicians (odds ratio 1.46, 95% confidence interval 1.11–1.92) [13].

We, therefore, performed an interaction analysis on anemic and non-anemic patients in the RAID-HF follow-up study showing that the presence of ID versus no ID predicted mortality in patients without anemia, but not in patients with anemia.

One explanation could be that anemia was a dominant and heterogenous mortality risk factor and a large part of these patients died during short-term course, independent of less malignant co-diagnoses, such as ID. However, in patients without anemia, a longer-living, less sick patient cohort, the moderate prognostic effect of ID became relevant over time. If there are further pathophysiologic factors of anemia that modify the prognostic impact of ID cannot be completely elucidated by our registry and should be addressed in future studies.

The relation of anemia and ID regarding long-term prognosis has recently been investigated by Tkaczyszyn et al. [28]. The authors reported that a trend towards higher mortality in patients with ID (vs. no ID) was observed after adjustment for HF prognosticators and MCH or MCHC, but not hemoglobin, and concluded that the detrimental impact of ID on long-term prognosis is partially independent of red cell indices [28]. Jankowska et al. reported that the effect of ID on prognosis was independent of the anemia status of the patient [1].

In the RAID-HF follow-up study anemia was a strong predictor of long-term mortality. This has been observed in different previous trials on patients with HFrEF [29–31]. However, specific effective treatment options for anemia are lacking and studies on treatment of anemia with erythropoiesis-stimulating agents have been disappointing [12, 32].

In contrast, different trials reported beneficial effects of intravenous iron supplementation in patients with HFrEF and ID, and the FAIR-HF and CONFIRM-HF studies proved that the effects of iron therapy were independent of anemia [6, 7].

Consequently screening for ID in patients with HFrEF should be performed irrespective of the presence of anemia; to identify patients with impaired prognosis and to identify patients that are eligible for intravenous iron supplementation therapy.

Study limitations

RAID-HF is an observational study and despite adjustment for confounding factors in multivariable analyses selection effects cannot be completely excluded. However, the study design as a multicenter observation in a large contemporary patient cohort is also a strength of the study to reflect "real-world" data on HFrEF and ID.

At the telephone follow-up contacts some additional status informations were limited by missing data, while the information regarding vital status and serious events during follow-up could be obtained very completely (99.7%).

Conclusions

The international RAID-HF follow-up study demonstrates a detrimental impact of ID on long-term mortality and quality of life in patients with HFrEF. Despite proven effects of intravenous iron supplementation in patients with ID and HFrEF, only a minority of patients received iron therapy in clinical practice. This study increases evidence that more awareness on iron status in patients with HFrEF is needed in contemporary clinical practice.

RAID-HF also investigates the interaction of anemia and ID with respect to long-term mortality in a "real-world" setting. ID was a mortality predictor in patients without anemia, but not in patients with anemia. One explanation could be that anemia is a very dominant and heterogenous risk factor that nivellates the effects of ID.

In conclusion the data emphasize that the diagnosis of ID is of high clinical relevance, particularly in patients without anemia, to identify patients at higher mortality risk that are eligible for iron supplementation therapy.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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