ORIGINAL RESEARCH ARTICLE

Prevalence of underlying gastrointestinal malignancies in iron-deficient heart failure

Pieter Martens[1,2], Lennert Minten[1], Matthias Dupont[1] and Wilfried Mullens[1,3]*

[1]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; [3]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

Abstract

Aims Anaemia and iron deficiency (ferritin level < 100 or 100–300 μg/L with transferrin saturation $< 20\%$) are prevalent in heart failure. Mechanistically, iron deficiency is linked to poor intestinal uptake, increased intestinal loss, and chronic inflammation. However, the prevalence of underlying gastrointestinal malignancies is not established in iron-deficient heart failure with or without anaemia.

Methods and results Patients followed up in a single-centre, heart failure database with baseline registration of haemoglobin and iron status were retrospectively evaluated. The proportion of patients undergoing upper and lower gastrointestinal endoscopy between inclusion and censoring was determined. Afterwards, the prevalence of biopsy that confirmed intestinal malignancies in relation to baseline iron and haemoglobin status was determined. Anaemia was defined as a haemoglobin level <12 g/dL, and iron deficiency according to the aforementioned criteria. Of the 1197 patients in the database, 699 (59%) patients underwent full endoscopic workup over a mean follow-up of 50 ± 27 months. A total of 50 intestinal malignancies were identified ($n = 42$, 84%, in iron-deficient vs. $n = 8$, 16%, non-iron-deficient patients; $P < 0.001$). The prevalence of intestinal malignancies was non-statistically different in iron-deficient patients with anaemia ($n = 12/129$, 9.3%) or without anaemia ($n = 30/287$, 10.5%; $P = 0.551$). The prevalence was much lower in patients without iron deficiency with anaemia ($n = 5/83$, 6%) or without anaemia ($n = 3/200$, 1.5%). In patients with iron deficiency but without anaemia (a group in which the role of endoscopic workup is less established), ferritin levels carried an inverse diagnostic capacity in detecting patients with an underlying malignancy (area under the curve = 0.741, $P < 0.001$). A ferritin level < 56 μg/L had the best acuity, detecting malignancies with a sensitivity of 80% and a specificity of 71%.

Conclusions Endoscopic evaluation is warranted in heart failure patients with iron-deficient anaemia given the high prevalence of underlying intestinal malignancies, as advised by gastroenterology guidelines. However, additional research is needed assessing the best approach to patients with iron deficiency without anaemia, given the high occurrence of intestinal malignancies in these patients. A lower ferritin level could potentially help stratify the need for an endoscopic workup in these patients.

Introduction

The European Society of Cardiology (ESC) guidelines for the treatment of heart failure recommend screening symptomatic heart failure patients for underlying iron deficiency.[1] Iron deficiency is common in heart failure and negatively influences exercise capacity and outcome, even in the absence of concomitant anaemia.[2–6] A multitude of processes result in iron deficiency in heart failure.[7,8] However, in general, these pathologic processes result in either a true body deficit of iron (absolute iron deficiency) or a decreased bio-availability due to reticuloendothelial system clustering (functional iron deficiency). Persisting iron deficiency might ultimately comprise the bone marrow haematopoietic capacity, leading to iron-deficient anaemia.[9] It is well established in the gastroenterology literature that patients with iron-deficient anaemia should receive a comprehensive gastrointestinal (GI) workup consisting of upper and lower endoscopy to exclude an

underlying malignancy or potentially treatable cause.[10] In contrast, the workup of iron deficiency in the absence of anaemia remains a point of discussion.[10] Additionally, criteria for iron deficiency differ between gastroenterology (ferritin level < 15–30 μg/L in the absence of inflammation) and heart failure [ferritin level < 100 or between 100 and 300 μg/L if transferrin saturation (TSAT) < 20%],[1,10] thereby complicating extrapolation of literature. Our analysis sought to determine the prevalence of underlying malignancies in heart failure patients according to the iron and anaemia status. Furthermore, in the patients with iron deficiency but without anaemia, our analysis sought out if baseline ferritin values might help steer the decision towards an endoscopic evaluation. We postulated that the risk for an underlying malignancies might be high in patients with absolute iron deficiency (reflected as a low ferritin level) even in the absence of anaemia.

Methods

Study population

The current analysis is a retrospective analysis of a database of consecutive heart failure patients included in a single tertiary care centre (Ziekenhuis Oost-Limburg, ZOL Genk) and followed up between August 2008 and January 2016. The design and results of the heart failure database have previously been published.[5] Briefly, the study cohort is the result of a pooled analysis of five different investigator-initiated prospective studies all performed at the ZOL Genk hospital, with overlapping design in terms of collection of baseline and clinical outcome data. Overlapping entry criteria included a previous heart failure hospitalization and (previously) symptomatic heart failure with reduced, mid-range, or preserved ejection fraction. In addition to baseline echocardiography, patients underwent cardiac pulmonary exercise testing and laboratory analysis at baseline. Subsequently patients were followed up prospectively to document heart failure hospitalization and all-cause mortality. The study protocols were approved by the institutional review board, and all patients provided written informed consent. The current manuscript is drafted according to the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational studies.[11]

Data collection and endpoint evaluation

For the current analysis, we performed a retrospective analysis of the aforementioned cohort to determine the proportion of patients who had undergone a GI endoscopic workup. Only endoscopic workups between the inclusion date of the study and censoring (date of death or last follow-up) were allowed to determine the relation between baseline iron and anaemia status and subsequent findings on endoscopy. Patients with a

known history of GI malignancies before the inclusion in the study were excluded. Based on the baseline laboratory analysis, it was determined if patients had anaemia and iron deficiency. Anaemia was defined according to the used criteria in major randomized controlled trials, namely, haemoglobin level < 12 g/dL irrespective of gender. Iron deficiency was defined according to established criteria in heart failure (ferritin level < 100 μg/L or ferritin level between 100 and 300 μg/L if TSAT is <20%). Patients were subsequently categorized into four categories on the basis of the presence or absence of both anaemia and iron deficiency of the baseline value at inclusion. Only patients with a full endoscopic workup consisting of upper and lower GI endoscopy were included for the current retrospective analysis. This is in order to adhere with gastroenterology guidelines, which state that in addition to an upper GI endoscopy, a lower GI endoscopy should be performed to establish the prevalence of significant lesions.[10] The endpoint for the current analysis was an endoscopically documented GI malignant tumour. Both the anatomic pathology report and the report of the subsequent multidisciplinary oncology meeting were used to assure the malignant character of the endoscopic lesion. We chose to use ferritin level to assess the risk between iron deficiency and the subsequent risk for GI malignancy, as it is the most powerful test reflecting iron deficiency (body iron content).[10]

Statistics

Continuous variables were expressed as mean ± standard deviation or median and inter-quartile range if normally or non-normally distributed. Normality was checked by the Shapiro–Wilk statistic. Categorical data were expressed as percentages and compared with the Pearson χ^2 test. Continuous variables were compared with Student's *t*-test, Mann–Whitney *U*-test, ANOVA testing, or Kruskal–Wallis test, when appropriate. Receiver operating characteristic (ROC) analysis was used to determine the relationship between the continuous predictor ferritin level and binary outcome variable presence of GI malignancy. The Youden point was identified as the value with the highest (sensitivity + specificity)/2. Statistical significance was always set at a two-tailed probability level of <0.05. All statistics were performed using SPSS Version 24 (IBM, Chicago, IL, USA).

Results

Study population and endoscopic workup

A total of 1191 patients were enrolled between August 2008 and January 2016. The overall prevalence of iron deficiency and anaemia in the cohort was 53% and 29%, respectively. Of the 1191 patients, a total of 699 (59%) patients underwent

a full endoscopic GI workup, during a mean follow-up of 50 ± 27 months. The median time between entry into the database (with lab testing) to endoscopy was 9 (inter-quartile range, 6–19) months. Therefore, the final study population constituted 699 patients. The distribution of the 699 patients with or without both anaemia and iron deficiency undergoing full endoscopic workup is reflected in *Table 1*. Patients who

had iron deficiency were more likely to have undergone an endoscopic workup during follow-up, especially if anaemia was present. *Table 2* illustrates the baseline characteristics of patients who had undergone endoscopic workup after categorization according to iron and anaemia status. Differences in baseline characteristics were present, which have been previously described for iron-deficient vs. non-iron-deficient

Table 1 Gastrointestinal workup according to presence of anaemia and iron deficiency

	ID− anaemia− (n = 399)	ID− anaemia+ (n = 150)	ID+ anaemia− (n = 465)	ID+ anaemia+ (n = 177)
No GI workup	199 (50%)	67 (45%)	178 (38%)	48 (27%)
Full GI workup	200 (50%)	83 (55%)	287 (62%)	129 (73%)

ID, iron deficiency; GI, gastrointestinal.

Table 2 Baseline characteristics of iron deficiency vs. no iron deficiency of patients undergoing GI workup

Parameter	ID− anaemia− (n = 200)	ID− Anaemia+ (n = 83)	ID+ Anaemia− (n = 287)	ID+ Anaemia+ (n = 129)	P-value
Age, years	69 ± 10	74 ± 9	70 ± 13	75 ± 8	<0.001
Sex					
Male	145 (73%)	65 (78%)	195 (68%)	91 (71%)	<0.001
Female	55 (27%)	18 (22%)	92 (32%)	38 (29%)	
Functional class					
NYHA I, %	16 (9%)	7 (9%)	19 (7%)	5 (4%)	0.004
NYHA II, %	83 (45%)	34 (44%)	89 (33%)	30 (24%)	
NYHA III, %	77 (42%)	31 (40%)	141 (53%)	76 (61%)	
NYHA IV, %	8 (4%)	5 (6.5%)	18 (7%)	13 (11%)	
Cardiomyopathy					
Non-ischaemic	86 (44%)	35 (42%)	116 (40%)	30 (24%)	0.002
Ischaemic	109 (56%)	48 (58%)	171 (60%)	97 (76%)	
Co-morbidities					
Atrial fibrillation	66 (33%)	33 (40%)	129 (45%)	67 (52%)	0.005
Diabetes	41 (21%)	24 (29%)	97 (34%)	63 (49%)	<0.001
Hypertension	117 (60%)	55 (68%)	181 (64%)	78 (61%)	0.576
COPD	47 (24%)	19 (23%)	62 (22%)	34 (26%)	0.765
Active smoker	52 (26%)	22 (30%)	65 (23%)	24 (19%)	0.575
Previous smoker	45 (23%)	24 (29%)	79 (28%)	37 (29%)	0.559
History of PCI	67 (34%)	36 (43%)	118 (41%)	59 (47%)	0.319
History CABG	25 (14%)	16 (22%)	45 (17%)	31 (28%)	0.016
Valve surgery	23 (13%)	20 (27%)	71 (27%)	29 (26%)	0.003
Heart failure type					
HFrEF	157 (79%)	68 (82%)	202 (70%)	84 (65%)	0.009
HFmrEF	31 (16%)	12 (15%)	71 (25%)	31 (25%)	0.032
HFpEF	12 (5%)	3 (3%)	14 (5%)	14 (10%)	0.083
Laboratory analysis					
Haemoglobin level, g/dL	14.1 ± 1.2	11.4 ± 1.1	13.5 ± 1.3	10.8 ± 1.4	<0.001
Ferritin level, ng/L	250 (167–415)	303 (201–439)	75 (46–109)	87 (56–138)	<0.001
TSAT %	26 (22–34)	26 (21–34)	17 (12–22)	14 (10–18)	<0.001
eGFR, mL/min	64 ± 23	56 ± 26	64 ± 24	48 ± 25	<0.001
Sodium, mmol/L	139 ± 4	138 ± 4	140 ± 4	138 ± 11	0.180
NT-pro-BNP, pg/mL	1093 (435–2467)	2412 (894–8097)	1374 (399–2815)	3342 (1290–5942)	<0.001
Heart failure therapy					
ACE-I or ARBs	157 (80%)	57 (69%)	208 (74%)	79 (65%)	0.069
Beta-blocker	162 (83%)	69 (83%)	225 (80%)	94 (77%)	0.535
MRA	111 (57%)	49 (59%)	146 (52%)	69 (57%)	0.615
Loop diuretics	86 (44%)	42 (51%)	155 (55%)	90 (74%)	<0.001
Anti-platelet therapy	111 (57%)	44 (53%)	146 (51%)	76 (59%)	0.641
Anticoagulant therapy	48 (24%)	28 (34%)	116 (42%)	50 (39%)	0.001

ACE-I: angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardio-defibrillator; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; MRA, mineralocorticoid receptor antagonist; NT-pro-BNP, NT-terminal pro-type B natriuretic peptide; NYHA, new York heart association; PCI, percutaneous coronary intervention; TR, tricuspid regurgitation.

and anaemic vs. non-anaemic patients. However, these differences in baseline characteristics are less related to the occurrence of the current study endpoint (development of a GI malignancy). *Table S1* illustrates the baseline characteristics of the patients included in the study (699 patients) with endoscopic evaluation vs. the 492 patients without endoscopic evaluation. Some differences in baseline characteristics were present but related to settings in which endoscopic evaluation is more warranted, such as a higher risk for GI blood loss (history of valve surgery, atrial fibrillation, or history of ischaemic heart disease/percutaneous coronary interventions) or factors related to a lower haemoglobin level (e.g. lower glomerular filtration rate).

## Prevalence of gastrointestinal malignancies and relationship with ferritin level

During a mean follow-up period of 50 ± 27 months, a total of 50 patients were diagnosed with a biopsy-confirmed GI malignancy. *Figure 1* illustrates the proportion of patients with an underlying malignancy according to the baseline haemoglobin and iron status. Patients with iron deficiency had the highest prevalence of underlying malignancies; however, the prevalence was not statistically different from that of patients with (n = 12, 9.3%) or without anaemia (n = 30, 10.5%; P = 0.551). Of the 50 GI malignancies encountered during follow-up, a total of 42 were found in patients with iron deficiency vs. eight in patients without iron deficiency (P < 0.001). In patients without iron deficiency, the

prevalence of underlying GI malignancies was higher in patients with concomitant anaemia (n = 5, 6%) vs. without concomitant anaemia (n = 3, 1.5%, P = 0.024). *Table 2* assesses the predictive capacity of baseline ferritin level to predict the presence of an underlying GI malignancy in patients with iron deficiency but without anaemia (a subgroup in which the importance of endoscopic evaluation is less established). Using a stringent ferritin value to define absolute iron deficiency (ferritin level < 30 μg/L) results in a high specificity (90%) for detecting an underlying malignancy. However, this was associated with a low sensitivity (13%), which was reflected in the detection rate of only three of the 30 intestinal malignancies in this patient subgroup. *Table 3* illustrates that using more lenient cut-offs for ferritin level results in a higher detection rate and higher sensitivity, however at the cost of specificity and potentially exposing a larger patient population to an endoscopic workup. *Figure 2* illustrates the result of ROC curve analysis for ferritin level in detecting an underlying intestinal malignancy (area under the curve = 0.741, P < 0.001). A ferritin level < 56 μg/L carried the highest sensitivity (80%) and specificity (71%) for detecting an underlying intestinal malignancy in a heart failure patient with iron deficiency but without anaemia.

Discussion

The current analysis addresses important and frequently encountered questions in clinical practice: what proportion of heart failure patients with iron deficiency have an underlying

Figure 1 Flow chart of results of gastrointestinal workup according to presence of anaemia or iron deficiency.
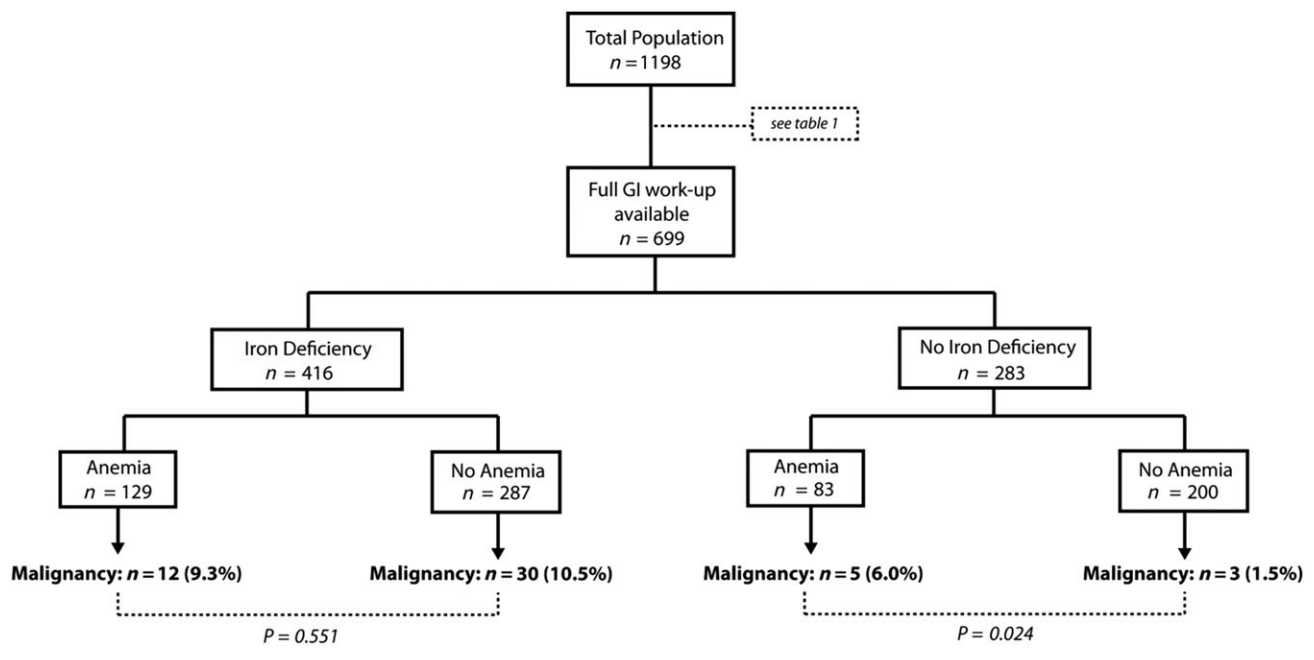
Table 3 Relationship between baseline ferritin level and risk for malignancy in iron deficiency without anaemia

Value	Number of malignancies detected	Proportion of patients needed to be exposed to a GI workup	Sensitivity (%)	Specificity (%)
Ferritin level < 30 μg/L	3/30	n = 38/287 (13.2%)	13	90
Ferritin level < 50 μg/L	20/30	n = 87/287 (30.3%)	63	75
Ferritin level < 75 μg/L	28/30	n = 148/287 (51.5%)	93	54
Ferritin level < 100 μg/L	28/30[a]	n = 204/287 (71.0%)	93	31

[a]Two patients without anaemia but with iron deficiency had a ferritin level higher than 100 μg/L (one case with 101 μg/L and another case with 231 μg/L).

Figure 2 Interaction between sensitivity and specificity of ferritin level for detecting gastrointestinal malignancy in patients with iron deficiency without anaemia.
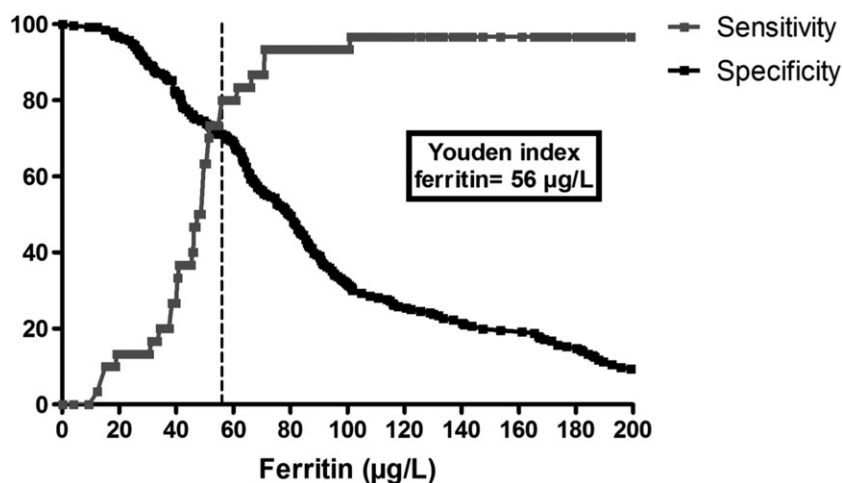
GI malignancy, and which patients really need an endoscopic workup?

It is recognized almost a decade ago that iron deficiency is present in up to half of patients with heart failure.[12] Currently, heart failure patients should be screened for iron deficiency, as three randomized controlled trials showed that alleviating iron deficiency with ferric carboxymaltose is associated with improved symptomatic status and exercise capacity.[12–14] However, it is important to emphasize that before therapy with intravenous iron is initiated, the treating physician should question himself or herself if an additional diagnostic workup is needed to determine the aetiology of iron deficiency/anaemia. Indeed, ESC guidelines for the diagnosis and treatment of heart failure recommend that patients with iron deficiency need to be screened for any potentially reversible or treatable causes.[1] However, this statement is perhaps more based on clinical reasoning than on actual data in heart failure patients themselves. Gastroenterology guidelines insist on upper and lower GI endoscopic workup in patients with iron-deficient anaemia to detect potential malignancies and in all male patients and in post-menopausal women.[10] However, in the case of iron deficiency without anaemia, gastroenterology guidelines suggest that only post-menopausal woman and men aged >50 years should be considered to undergo an endoscopic workup after discussing risks and benefits.[10] Indeed, cohort studies, in the gastroenterology literature, suggest that the prevalence of underlying malignancies is lower in patients with iron deficiency without anaemia.[15,16] However, these cohorts often included patients in their 20–40 years of age. This is important, as these patients have an intrinsically low pre-test probability for having an underlying malignancy. This is clearly not the case for most heart failure patients encountered in clinical practice, as they are older (70 ± 11 years in the current cohort) and are often exposed to carcinogenic risk factors, such as smoking. A further complicating matter that precludes blatant extrapolation from gastroenterology literature is the different cut-offs used to define iron deficiency. Gastroenterology literature often uses a ferritin level cut-off < 15–30 μg/L (in the absence of inflammation) to define a state of (absolute) iron deficiency.[10,15–18] In these patients, an underlying GI malignancy often (10–15%) contributes to the state of iron deficiency.[10] However, the heart failure syndrome itself is a pro-inflammatory disease.[19] Indeed, both haemodynamic alterations of low cardiac output and congestion result in up-regulation of pro-inflammatory

cytokines.[20,21] Inflammation itself results in a higher level of serum ferritin, thereby further complicating the question of what ferritin level constitutes absolute iron deficiency in heart failure. As a result, in heart failure literature, both a ferritin level < 30 μg/L and <100 μg/L have been used interchangeably to define absolute iron deficiency.[4,7,22–24] Therefore, perhaps the more important question is at which ferritin level should we screen an iron-deficient heart failure patient for an underlying GI malignancy, the gravest pathology to be missed resulting in absolute deficit of iron.

Firstly, our data confirm the general dogma that patients with iron-deficient anaemia should undergo thorough evaluation with upper and lower GI endoscopy. Although this concept is generally accepted in the medical community, retrospective audits indicate that under-investigation is common. Indeed, only 40–50% of patients with iron-deficient anaemia undergo an endoscopic workup.[25,26] Cardiologists should be aware of this underutilization. Importantly, ESC guidelines put a strong emphasis (Class IC level of evidence) on screening for iron deficiency.[1] Therefore, cardiologists will often diagnose the state of iron deficiency but should contemplate an appropriate diagnostic workup before therapy with intravenous ferric carboxymaltose is administered.

Secondly, our data indicate that patients with iron deficiency but without anaemia still have a significant risk of having an underlying GI malignancy. Indeed, GI malignancies can lead to chronic blood loss, inducing iron deficiency as a precursor to iron-deficient anaemia. Although cohort studies of iron-deficient patients without heart failure and without anaemia documented a lower prevalence of underlying malignancies, this finding is perhaps more driven by the age of the population being studied, with many studies assessing pre-menopausal women.[16] However, in cohorts of elderly patients (as most heart failure patients are), the prevalence of intestinal malignancies reached up to 10% in patients with iron deficiency without anaemia.[17] Our cohort exhibits a prevalence of underlying malignancies in the same degree of magnitude. Our data therefore urge cardiologists to also consider an endoscopic workup in patients with iron deficiency without anaemia. However, based on our analysis, it remains difficult to decide which heart failure patient with iron deficiency should undergo such a workup, as this was a retrospective analysis. Owing to the retrospective nature of the study, we did not have information on changes in stool pattern, GI blood loss, involuntary weight loss, or other factors that should trigger a GI workup. However, we did assess the diagnostic capacity of ferritin level to help and steer the decision process towards an endoscopic workup. A ferritin level of 56 μg/L had the highest sensitivity and specificity for detecting an underlying intestinal malignancy. However, practically, this would mean that every one in three patients with iron deficiency but without anaemia should undergo an endoscopic workup, and these numbers change drastically depending on which ferritin level is employed to trigger an endoscopic workup. Additionally, prospective research is needed to determine how ferritin levels can help guide decision making, taking into account the classic clinical red flags that normally trigger an endoscopic workup.

Limitations

Several limitations of the current study should be addressed. Firstly, this was a retrospective analysis, and therefore, the analysis is sensitive to bias by indication. Indeed, patients with iron deficiency (especially if anaemia is present) were more likely to undergo endoscopic evaluation. However, the coverage rate of endoscopy as illustrated in *Table 1* was high in our cohort, especially in comparison with the rate in the existing literature. Also, our sample size was much larger than that of previous analysis in gastroenterology literature. Furthermore, there is no reason to expect that the risk for developing a malignancy was different in the patients not undergoing an endoscopic workup. On the basis of this and the high coverage rate, we believe that the relative prevalence of GI malignancies in the four different groups is little affected if the coverage rate of endoscopy would be 100%. Secondly, we did not have any data on changes in bowel habits, GI blood loss, involuntary weight loss, or a family history of GI malignancies. Therefore, we could not determine whether the indication for the endoscopy was driven by the laboratory results (iron deficiency or iron-deficient anaemia) or symptoms suggestive of GI problem. Given the absence of data on family history of intestinal malignancies and changes in bowel status or weight, we were not able to perform binary logistic regression analysis to search for predictors of intestinal malignancies in heart failure patients (as important imputational data for such analysis were lacking). In addition, the high coverage rate of endoscopy might be the result of the Belgian national screening programme, which invites patients between 56 and 74 years of age to perform a faecal occult blood test. If this test is positive, further endoscopic workup is performed. Thirdly, we only included patients who underwent endoscopic evaluation in our hospital. Therefore, we might have missed some patients receiving an endoscopic workup in a different centre. Fourthly, we only determined the prevalence of malignancies. Our analysis did not determine the frequencies of other intestinal abnormalities that could be causally related to a state of (absolute) iron deficiency, as this is very difficult to determine retrospectively. Finally, owing to the low numbers of patients with heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), we were not able to perform a sub-analysis to see if the found cut-offs for ferritin level also apply specifically to HFmrEF and HFpEF.

Conclusions

Endoscopic evaluation is warranted in heart failure patients with iron-deficient anaemia given the high prevalence of underlying intestinal malignancies, as advised by gastroenterology guidelines. However, additional research is needed assessing the best approach to patients with iron deficiency without anaemia, given the high occurrence of intestinal malignancies in these patients. A lower ferritin level could potentially help stratify the need for an endoscopic workup in these patients.

Conflict of interest

P.M. has received consultancy fees and an unrestricted research grant from Vifor Pharma.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of patients with or without endoscopic work-up.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.

2. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJV, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010; **31**: 1872–1880.

3. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, von Haehling S, Doehner W, Banasiak W, Polonski L, Filippatos G, Anker SD, Ponikowski P. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail* 2011; **17**: 899–906.

4. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013; **165**: 575–582.

5. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 2018; **73**: 115–123.

6. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Limited contractile reserve contributes to poor peak exercise capacity in iron-deficient heart failure. *Eur J Heart Fail* 2018; **20**: 806–808.

7. Jankowska EA, von Heahling ASD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013; **34**: 816–829.

8. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016; **387**: 907–916.

9. von Heahling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. *Nat Rev Cardiol* 2015; **12**: 659–669.

10. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1309–1316.

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.

12. Anker SD, Comin-Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan B-A, Mori C, von Eisenhart, Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P. for the FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.

13. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, for the CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015; **36**: 657–668.

14. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A. EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017; **136**: 1374–1383.

15. Baicus C, Caraiola S, Rimbas M, Patrascu R, Baicus A. Ferritin above 100 mcg/L could rule out colon cancer, but not gastric or rectal cancer in patients with involuntary weight loss. *BMC Gastroenterol* 2012; **12**: 86.

16. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. *Am J Med* 2002; **113**: 276–280.

17. Joosten E, Ghesquiere B, Linthoudt H, Krekelberghs F, Dejaeger E, Boonen S, Flamaing J, Pelemans W, Hiele M, Gevers AM. Upper and lower gastrointestinal evaluation of elderly inpatients who are iron deficient. *Am J Med* 1999; **107**: 24–29.

18. Lee MH, Park E, Lee J, Kim SY, Kim SY, Lee SY, Cho YH, Yoon SY. Cutoff values of serum ferritin and TIBC saturation for the evaluation of gastrointestinal neoplasms in adult anemic patients. *Int J Hematol* 2012; **96**: 214–221.

19. Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008; **358**: 2148–2159.

20. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, Schroedl W, Karhausen T, Doehner W, Rauchhaus M, Poole-Wilson P, Volk HD, Lochs H, Anker SD. Altered intestinal function in patients with chronic heart failure. *J Am Coll Cardiol* 2007; **50**: 1561–1569.

21. Sandek A, Swidsinski A, Schroedl W, Watson A, Valentova M, Herrmann R, Scherbakov N, Cramer L, Rauchhaus M, Grosse-Herrenthey A, Krueger M, von Haehling S, Doehner W, Anker SD, Bauditz J. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms. *and cachexia J Am Coll Cardiol* 2014; **64**: 1092–1102.

22. Martens P, Verbrugge F, Nijst P, Dupont M, Tang WH, Mullens W. Impact of iron deficiency on response to and remodeling after cardiac resynchronization therapy. *Am J Cardiol* 2017; **119**: 65–70.

23. Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, 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; **51**: 103–112.

24. Parikh A, Natarajan S, Lipsitz SR, Katz SD. Iron deficiency in community-dwelling US adults with self-reported heart failure in the National Health and Nutrition Examination Survey III: prevalence and associations with anemia and inflammation. *Circ Heart Fail* 2011; **4**: 599–606.

25. Lucas CA, Logan EC, Logan RF. Audit of the investigation and outcome of iron-deficiency anaemia in one health district. *J R Coll Physicians Lond* 1996; **30**: 33–36.

26. Yates JM, Logan EC, Stewart RM. Iron deficiency anaemia in general practice: clinical outcomes over three years and factors influencing diagnostic investigations. *Postgrad Med J* 2004; **80**: 405–410.