Prognostic significance of anaemia in patients with heart failure with preserved and reduced ejection fraction: results from the MAGGIC individual patient data meta-analysis.

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Abstract

Objective: Anaemia is common among patients with heart failure (HF) and is an important prognostic marker. We sought to determine the prognostic importance of anaemia in a large multinational pooled dataset of prospectively enrolled HF patients, with the specific aim to determine the prognostic role of anaemia in HF with preserved and reduced ejection fraction (HF-PEF and HF-REF respectively).

Methods: Patients with haemoglobin (Hb) data from the MAGGIC dataset were used. Anaemia was defined as Hb <120 g/L in women and <130 g/L in men. HF-PEF was defined as EF≥50%; HF-REF was EF<50%. Cox proportional hazard modelling, with adjustment for clinically relevant variables, was undertaken to investigate factors associated with 3-year all-cause mortality.

Results: 13,295 patients with HF from 19 studies (9887 with HF-REF and 3408 with HF-PEF). The prevalence of anaemia was similar among those with HF-REF and HF-PEF (42.8% and 41.6% respectively). Compared to patients with normal Hb values, those with anaemia were older, were more likely to have diabetes, ischaemic aetiology, NYHA class IV symptoms, lower eGFR, and were more likely to be taking diuretic and less likely to be taking a beta-blocker. Patients with anaemia had higher all-cause mortality (adjusted hazard ratio [aHR] 1.38, 95% confidence interval 1.25-1.51), independent of EF group: aHR 1.67 (1.39-1.99) in HF-PEF and aHR 2.49 (2.13-2.90) in HF-REF.

Conclusions: Anaemia is an adverse prognostic factor in HF irrespective of EF. The prognostic importance of anaemia was greatest in patients with HF-REF.

Key words: anaemia, heart failure, prognosis, ejection fraction

Key questions

What is already known about this subject?

Anaemia is common in heart failure and is associated with adverse prognosis.

What does this study add?

Anaemia is prognostically important, irrespective of left ventricular ejection fraction. Patients with anaemia and heart failure with a reduced ejection fraction have the highest mortality; however measurement of haemoglobin can also stratify patients with heart failure with preserved ejection fraction into higher and lower risk subgroups.

How might this impact on clinical practice?

As patients with abnormal haemoglobin levels are at increased risk of adverse outcome, increased vigilance and optimisation of heart failure management becomes all the more important in these HF patients.

Introduction

Anaemia is common and important in heart failure (HF). Anaemia in HF is of multifactorial aetiology and is associated with worse symptoms and higher mortality.[1-6] Several uncertainties remain about the clinical significance of anaemia. For example, the Norwegian Heart Failure Registry found that anaemia did not predict all-cause mortality in community-dwelling patients with advanced HF.[7] A recent literature-based meta-analysis has shown that anaemia predicts all-cause mortality in patients with HF with both preserved and reduced ejection fraction (HF-PEF and HF-REF).[4] However, this meta-analysis was based on heterogeneous inclusion criteria, with inconsistent definitions of anaemia, and as the analysis did not include patient-level data, multivariable analyses were not performed. We aimed to study the characteristics and prognostic significance of anaemia in patients with HF-PEF and with HF-REF using pooled patient-level data.

Methods

The methods for study selection and data extraction for the MAGGIC individual patient data meta-analysis have been described previously.[8] In brief, we pooled individual patient data from 31 studies that prospectively collected all-cause mortality among HF patients, and did not restrict entry criteria by EF. Data from the individual studies were re-coded into a uniform format at the Central Co-ordinating Centre at the University of Auckland, New Zealand and incorporated into one database. The protocol of the meta-analysis was approved by the University of Auckland Human Subjects Ethics Committee.

This analysis was restricted to those patients for whom haemoglobin (Hb) data at baseline were available within the main MAGGIC dataset.[8] Anaemia was defined as Hb <120 g/L in women and <130 g/L in men.[9] Patients were classified into groups according to the presence or absence of anaemia and according to ejection fraction (HF-PEF or HF-REF). As in the primary analysis of the MAGGIC dataset, preserved EF was defined as EF ≥ 50% (majority assessed by echocardiography). Reduced EF was therefore defined as EF < 50%.

Cox proportional hazard models were used to investigate the association between anaemia and 3-year all-cause mortality. Models were adjusted for age, gender, ischaemic aetiology, atrial fibrillation (AF), diabetes, hypertension, and eGFR, and were stratified by study. An interaction between gender and anaemia was assessed. Imputation of missing data was not performed. Cox models were further used to model the relationship between Hb level (per 10 g/L) and 3-year mortality per EF group. A statistically significant interaction between Hb and gender within the HF-PEF group (p=0.01) led to models being stratified by gender. These models were adjusted for age only and used a referent concentration of 120-130 g/L for women and 130-140 g/L for men. SAS v9.2 was used for all analyses.

Results

Haemoglobin data were available for 13,295 patients from 19 studies. For the whole group, mean age was 68 years (SD 12 years), 36% were women, 46% had a history of hypertension, 56% ischaemic aetiology of HF, 23% AF, the majority (73%) had NYHA Class II or III symptoms of HF, and mean Hb was 126 g/L (SD 25 g/L). 9,887 patients had HF-REF of whom 4,238 (43%) had anaemia, and 3,408 patients had HF-PEF of whom 1,419 (42%) had anaemia. Irrespective of EF group (HF-REF or HF-PEF), patients with anaemia were older, more likely to have had a myocardial infarction, to have diabetes, ischaemic aetiology of HF, NYHA class IV symptoms, lower eGFR, and were more frequently prescribed a diuretic and less likely prescribed a beta-blocker, than those without anaemia (p-values < 0.05, Table 1). Patients with anaemia were also more likely to have oedema although this information was unavailable in 54% of patients.

Anaemia was associated with higher all-cause mortality among patients with HF-REF and patients with HF-PEF (Table 1, Figure 1). Among patients with HF-REF, 1,325 (31.3%) patients with anaemia died compared with 889 (15.7%) patients without anaemia; for patients with HF-PEF, 283 (19.9%) patients with anaemia died compared with 229 (11.5%) patients without anaemia. In multivariable analysis, the presence of anaemia was independently associated with higher risk of death from any cause (adjusted hazard ratio [aHR] 1.38, 95% confidence interval 1.25-1.51), as were HF-REF, age, male gender, AF, ischaemic aetiology, diabetes, and worsening renal function (Table 2). There was no interaction between anaemia and gender for

either EF group (HF-REF p=0.13, HF-PEF p=0.08) therefore these models were not stratified by gender.

The risk of death increased as Hb decreased through the anaemic range for all patients. However the risk of death among women with HF-PEF also increased as Hb increased through the non-anaemic range (Figure 2). Only 139 women with HF-PEF had Hb ≥150 g/L, and although the increase in mortality is close to reaching statistical significance (aHR = 1.67, 95% CI 0.99-2.79), this is based on only 23 deaths in that subgroup. Patient characteristics over the range of Hb values were consistent with the trends seen when classified by anaemia status (Supplementary Tables 1-4).

Discussion

The main findings of our study are firstly, HF patients with anaemia were more likely to be older, have ischaemic aetiology, and have more severe signs and symptoms. Secondly, anaemic patients were less likely to be treated with a beta-blocker and more likely to be receiving a diuretic, regardless of whether they had HF-REF or HF-PEF. Thirdly, anaemia was an independent predictor of adverse outcome for patients with HF-REF and those with HF-PEF.

As has been established in a number of prior studies, anaemia is of prognostic importance in patients with HF[4 10], particularly among those with HF-REF. The current analyses clearly now confirm the prognostic importance of anaemia among patients with HF-PEF. The worst prognosis was observed among those patients with

anaemia and HF-REF, followed by patients with HF-PEF with anaemia, who had similar prognosis to those with HF-REF without anaemia. We have previously reported from this meta-analysis that patients with HF-PEF have lower mortality than patients with HF-REF.[8] These findings suggest that one simple marker, the Hb, is able to further stratify patients with HF-PEF (and HF-REF) into higher and lower risk subgroups. The influence of anaemia on mortality was independent of other common predictors of outcome regardless of the EF group.

Previous studies involving patients with HF with iron deficiency (with or without anaemia) have shown that treatment with iron supplements results in an improvement in quality of life and functional capacity.[5 11] However, the recent Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial, which assessed the use of this erythropoietin analogue in patients with HF-REF and anaemia, showed that correction of anaemia did not improve survival.[12 13] Although large-scale clinical outcome studies of the effects of erythropoietin analogues in patients with HF-PEF and anaemia are not available, a recent phase II study reported that treatment with epoetin alfa did not improve left ventricular volumes or mass, submaximal exercise capacity or quality of life.[14] These results suggest that anaemia may be a marker of poor prognosis rather than a therapeutic target for patients with HF. Reflecting these results, the recent American College of Physicians guidelines on treatment of anaemia in patients with heart disease now recommend against the use of erythropoiesis-stimulating agents in patients with anaemia and heart failure.[15] Small scale studies of the effects of intravenous iron infusions in patients with heart failure and anaemia with low ferritin levels suggest beneficial effects on exercise tolerance and quality of life.[11] However, longer term effects on

clinical events remain uncertain. Such treatment is not approved for use in the United States at present[15], although is discussed as a potential option for appropriate patients in the 2012 ESC Heart Failure Guidelines.[16]

The causes of anaemia in chronic HF may be multifactorial and include haemodilution, iron loss or impaired utilisation, chronic renal failure, bone marrow suppression, inflammation and chronic disease.[2 17 18] Across a range of clinical trials and cohort studies, including the RED-HF trial[13] and the Study of Anaemia in Heart Failure Trial (STAMINA-HeFT)[19], community studies[20 21], and those in the current analysis, heart failure patients with anaemia were older and had worse functional capacity than those who were not anaemic. Advanced HF is a pro-inflammatory condition[18] which, together with the common comorbidities such as renal dysfunction, will contribute to increasing frailty.[20] Thus anaemia is a common co-morbidity which is prognostically important.[6 22 23]

The current data suggest the possibility of higher mortality among women with non-anaemic, higher Hb levels. The prognostic significance of higher Hb levels among women with HF-PEF may be influenced by other gender-related differences in cardiovascular disease, such as proximal arterial stiffness.[23 24] Women may be more susceptible to the deleterious effects of greater pulsatile and early arterial load on diastolic function and ventricular-arterial interaction[24], and higher Hb levels (and blood viscosity) may enhance vascular stiffness in women more than in men.[25] However women with HF-PEF and Hb > 150 g/L were not older than other women with HF-PEF, and did not have a significantly higher prevalence of hypertension, so the reasons behind the suggested increase in mortality in this group are unclear.

While a “U-shaped” relationship between Hb and mortality in patients with HF has been reported in previous studies[26 27], this finding needs further evaluation.

Our study has some limitations. The definition of anaemia is based on a single determination of the blood count, and other potentially relevant information, such as treatment for anaemia, intercurrent bleeding, fluid overload, or other variations in Hb levels were not available, or not available with sufficient data. With regards to drug therapy, we lack information on contraindications or intolerance to evidence-based drugs. Finally, we were unable to adjust the analyses for the extent and nature of unmeasured comorbidity other than the clinical variables incorporated in the multivariable model. Variables were included on the basis of clinical relevance, and each were missing <10% of data in the MAGGIC meta-analysis. A greater number of variables were included in the MAGGIC HF risk score[28] as multiple imputation was used to help account for missing data. Although different approaches were used, the associations between predictors and mortality in the current model are consistent with those found in the HF risk score.

In conclusion, this large individual patient data meta-analysis has demonstrated that the increased risk of death among patients with anaemia is observed among those with HF-PEF and HF-REF and the risk is independent of other common prognostic variables. Although correcting anaemia for all patients does not appear to improve outcomes, anaemia is a marker of increased risk which should trigger greater vigilance in follow-up and management.

Competing interests: None declared

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Table 1. Characteristics of patients with HF-REF and HF-PEF at baseline according to the presence or absence of anaemia.

	Whole group	HF-REF		HF-PEF	
		Anaemic	Not Anaemic	Anaemic	Not Anaemic
N, % (19 studies)	13295	4238 (32)	5649 (42)	1419 (11)	1989 (15)
Age, years	68 (12)	70 (12)	66 (13)**	73 (12)	69 (12)**
Women, %	36	29	31*	53	56
Medical history:					
Hypertension	46	39	42**	59	61
Myocardial infarction	39	45	41**	29	22*
Atrial fibrillation	23	23	22	26	25
Diabetes	24	25	23*	32	23**
Ischaemic aetiology	56	65	55**	50	46*
Medication					
ACE inhibitor or ARB	82	88	87	63	67*
Beta-blocker	37	32	40**	34	40**
Diuretic	81	87	78**	82	77**
Spironolactone	22	23	25	17	17
Digoxin	40	48	42**	28	29
Clinical status					
NYHA class (I/II/III/IV)	17/43/29/11	10/34/41/15	17/51/24/8**	26/38/24/12	29/43/20/8**
Heart rate, bpm	81 (20)	81 (19)	81 (20)	80 (20)	80 (22)
SBP, mmHg	133 (26)	128 (26)	131 (24)**	142 (30)	144 (27)
DBP, mmHg	78 (14)	75 (14)	79 (14)**	77 (16)	82 (15)**
Haemoglobin, g/L	126 (24)	103 (17)	143 (13)**	106 (15)	141 (13)**
eGFR, mL/min/1.73m^2	62 (25)	56 (25)	66 (24)**	56 (28)	65 (25)**
Oedema	29	35	23**	50	35**
LVEF, % (median, IQR)	39 (15)	30 (24,38)	32 (24,39)	60 (54,66)	59 (54,60)
Total deaths	2726	1325	889**	283	229**

Data are presented as mean (standard deviation) or %. eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation.

*p=0.001-0.05, ** p<0.001; from chi-squared or Student t-tests comparing anaemic vs not anaemic, within EF group.

Table 2. Multivariable Cox proportional hazard model for death from any cause.

	Adjusted hazard ratio (95% CI) All-cause death n= 11093
Anaemia	1.38 (1.25,1.51)
HF-REF	1.47 (1.32,1.65)
Age, per year	1.03 (1.02,1.03)
Male gender	1.28 (1.17,1.40)
Atrial fibrillation	1.15 (1.05,1.23)
Hypertension	0.92 (0.85,1.01)
Ischaemic aetiology	1.19 (1.09,1.30)
Diabetes	1.13 (1.03,1.24)
eGFR, per mL/min/1.73m^2	0.987 (0.985,0.989)

FIGURE LEGEND

Figure 1 Hazard of all-cause mortality according to EF group and presence or absence of anaemia. Adjusted for age, gender, ischaemic aetiology, atrial fibrillation, diabetes, history of hypertension, and eGFR.

Figure 2 Hazard of all-cause mortality for haemoglobin according to EF group and gender. Adjusted for age.

Figure 1

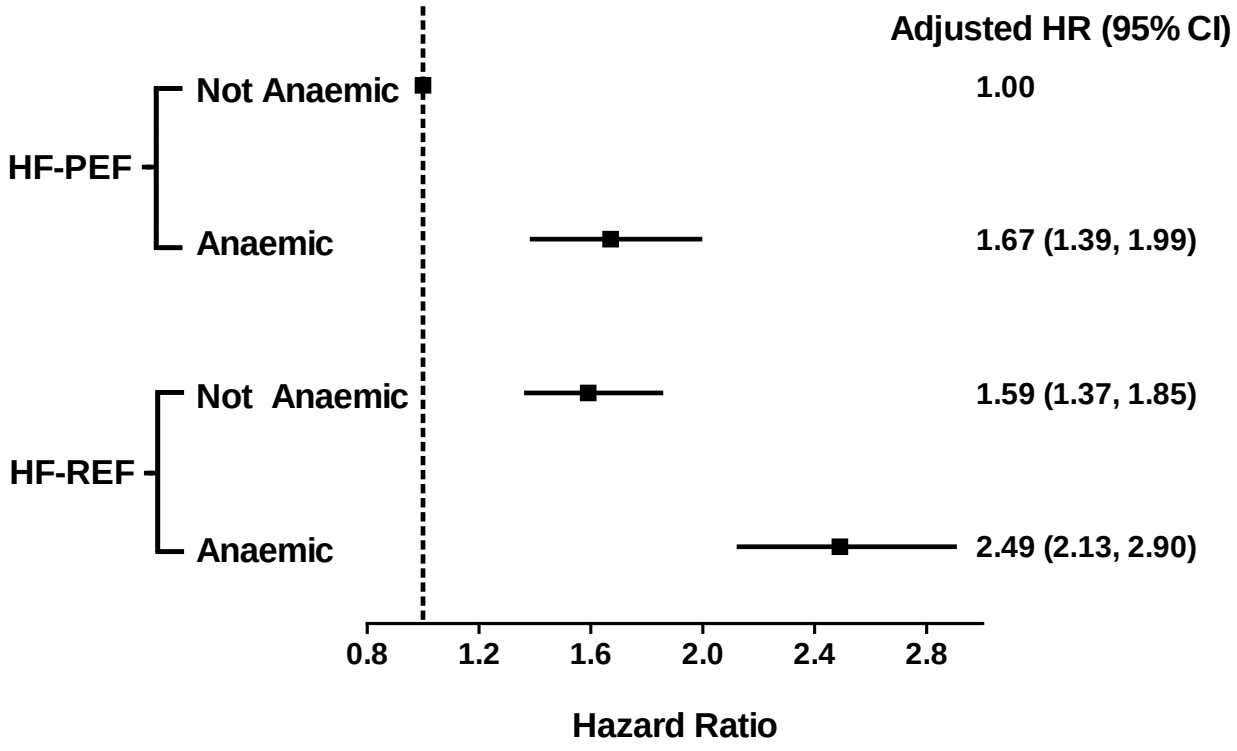
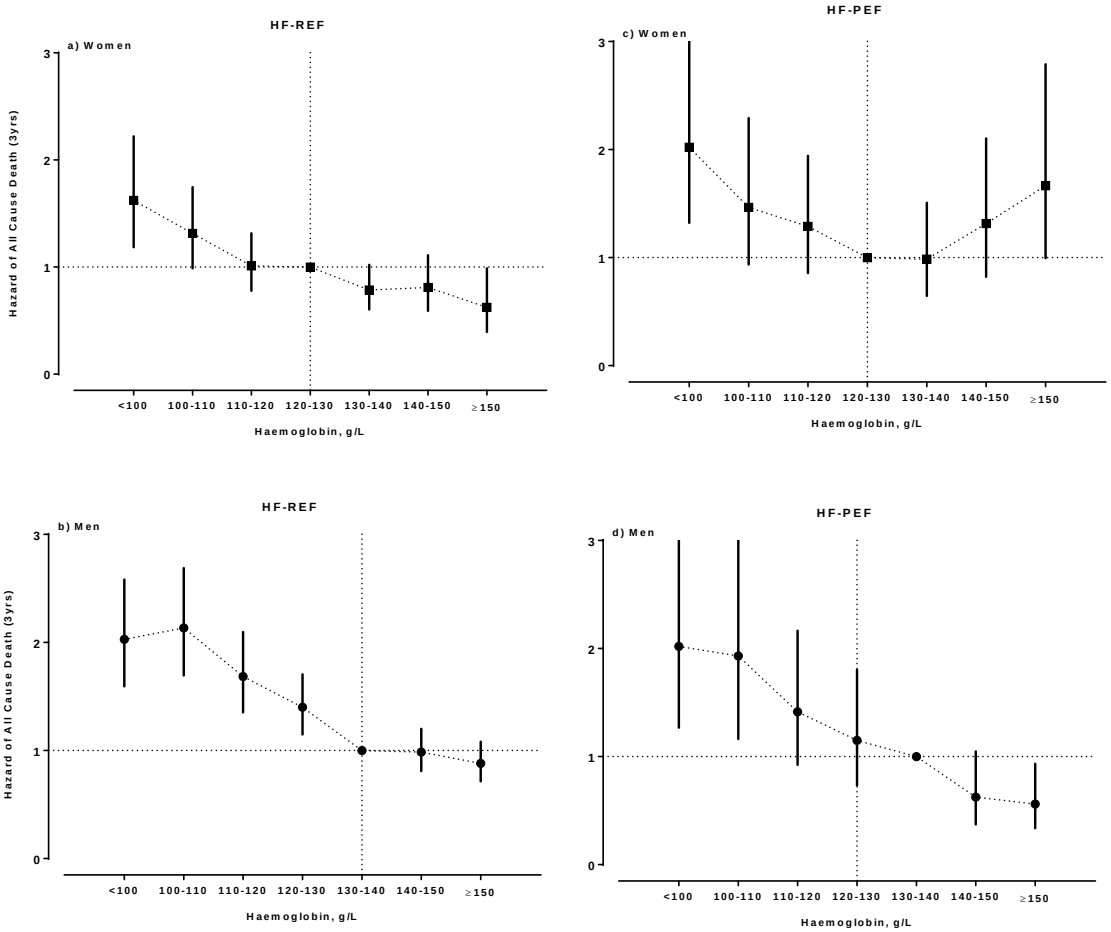

Adjusted HR (95% CI)
Not Anaemic
1.00
HF-PEF
Anaemic
1.67 (1.39, 1.99)
Not Anaemic
1.59 (1.37, 1.85)
HF-REF
Anaemic
2.49 (2.13, 2.90)
0.8
1.2
1.6
2.0
2.4
2.8
Hazard Ratio

Figure 2


HF-REF
a) Women
Hazard of All Cause Death (3yrs)
0
1
2
3
<100
100-110
110-120
120-130
130-140
140-150
≥150
Haemoglobin, g/L
HF-PEF
c) Women
0
1
2
3
<100
100-110
110-120
120-130
130-140
140-150
≥150
Haemoglobin, g/L
HF-REF
b) Men
Hazard of All Cause Death (3yrs)
0
1
2
3
<100
100-110
110-120
120-130
130-140
140-150
≥150
Haemoglobin, g/L
HF-PEF
d) Men
0
1
2
3
<100
100-110
110-120
120-130
130-140
140-150
≥150
Haemoglobin, g/L