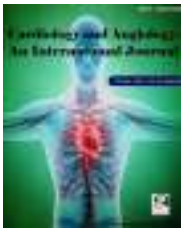

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Iron Deficiency is an Ominous Predictor of Mortality in Elderly Patients with Stable Heart Failure: a Community Based Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SG, WTMR and NIOK designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors CZ, JS and JD managed the literature searches, analyses of the study performed. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Background: Iron deficiency (ID) has been shown to be linked with poor outcomes within heart failure (HF) populations in previous clinical trials. The impact of ID has not been evaluated in stable chronic heart failure (HF) patients in the community. Our objective was to study the role of ID in stable HF patients and its impact on short term survival.
Methods: In this study we analysed 512 patients with stable HF under the care of a regional nurse-led community heart failure team. The study started in June 2007 and ended in June 2010.
Results: There were 92% of patients on loop diuretics; 83% on ACE Inhibitors, 92% on β-blockers and 48% on aldosterone antagonists. Mean age of the patients was 77.9 years, 43% were females and mean NYHA class was 2.2. Absolute Iron deficiency (ID) and anemia were defined as ferritin <100µg/L and hemoglobin (Hb)<12g/dl, respectively. Mean Hb levels were 14.1; 13.9; 14.0 and 13.7g/dL at 0, 6, 12 and 24 months. Mean serum ferritin levels in the entire study population were 212µg/L at the start, and 197µg/L

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at the end. The prevalence of ID and anemia was 21.3% and 9.4%at the start, and was 21.5% and 8.4% at the end of the study. The prevalence of ID was 63%vs. 19% in subjects with vs. without anemia [p<0.001]. Risk-adjusted hazard ratios for 24-month mortality were 1.42 (95% confidence interval: 1.09-1.98) for ID and 1.05 (95% confidence interval; 0.87-1.51) for anemic patients respectively.
Conclusions: In our study, ID was prevalent in stable HF patients in the community and was linked with poor clinical outcomes. In addition, ID was a predictor for mortality than additionally to anemia.

Keywords: Iron; heart failure; community.

1. INTRODUCTION

Heart failure (HF) is common, affecting over 20 million people worldwide [1] and up to 5.0 cases per 1000 person-years in general population studies within the UK [2]. However this figure increases sharply with age [3], which has been reported as high as 40 per 1000 person-years aged over 75 years [2].

Iron deficiency (ID) is the most common nutritional disorder in the general population [4-6] and is commonly associated with HF. This has been attributed to depletion of iron stores within the body (absolute ID) or more frequently as a result of impaired iron metabolism due to inflammatory processes associated with HF (functional ID) [7-10]. The presence of this ID may have multifaceted clinical consequences, including reduced erythropoiesis, impairment of oxidative metabolism, cellular energetics, and cellular immune mechanisms [11-16]. It is also of note that ID does not always predispose patients to microcytic anaemia [17] which was also confirmed by a report from Nanas et al. [18] that despite HF patients possessing normal serum ferritin, up to 73% still had depleted iron stores in the bone marrow. A possible explanation for this ID without clinical anaemia is the storage of the majority of the iron within the reticular endothelial system, where it is not available for eythropoietic process [19].

Recently, the importance of ID within HF patients has been emphasized. Klip et al. [20] found that ID in stable HF patients referred to secondary care outpatients was associated with a poorer prognosis with or without an anaemia, and further studies have found that correcting ID in HF patients have improved functional status and quality of life [21,22]. However these researches were performed within secondary care [22-25] despite the fact that the majority of patients received treatment for HF from general practitioners in the community, and rarely from cardiologists [26]. The purpose of this study was to evaluate the incidence rate of iron deficiency in ambulatory HF patients in the community, alongside comparing ID and anaemia as prognostic indicators for HF outcomes in primary care.

2. METHODS

2.1 Setting

The Leicestershire County & Rutland Community Health Services (LCRCHS), now part of Leicestershire Partnership Trust, are located within a fairly rural setting serving a wider population of 763,000 according to 2008record of census data. Approximately 0.9% of the population has been identified with left ventricular systolic dysfunction (LVSD). The specialist heart failure team comprises a group of five full-time equivalent advanced nurse practitioners

with clinical supervision by a community physician. The teams work closely with local General Practitioners (GP) and indeed local GPs refer patients directly to the team. The strategy of the Community Health Services of Leicestershire Partnership NHS Trust for delivering specialist care for long term conditions (LTC) is to develop models of care within other chronic diseases and to centrally locate the running and administration of the service through a single point of access- also known as the LTC Hub. Although clinicians will work along care pathways of the disease, they will coordinate care for all patients with co-morbid conditions ensuring that the right clinician with the appropriate skills, respond to the changing needs of patients. A central tenet of the service is to work in an integrated manner with all clinicians who could possibly manage the patient. HF patients are referred into the service by GP's following diagnosis for case management, secondary care physicians post-hospitalization and other internal stakeholders within the Primary Care Trust [27].

2.2 Patients

In the current study, we analysed 512patients with ambulatory HF under the care of the HF team between June 2007 and June 2010. Patient data was reviewed in an anonymised fashion through the NHS Shared Care records database operated by the primary care trust. Consequently specific patient consent forms were not required to evaluate the data. Ethic approval was not required as this was an observational study involving health services practice. The current population represents 27.2% of the total HF patients in the area under supervision. The diagnosis of HF was initially made by secondary care physician based on history, symptoms, physical signs and validated by trans-thoracic echocardiography. Peripheral venous blood samples were collected from all patients as part of their routine clinic or home appointments at 6, 12 and 24 months. The baseline characteristics of the study patients and their co-morbidities are recorded in (Tables 1, 2 and 3) respectively. In brief, the mean age of study group was 77.9±5.7 years. There were slightly more males in the study group (57%). Patients were followed up during the entire study period. Cause of death and hospitalization date was ascertained using hospital records, death certificates and hospital autopsy records. Absolute iron deficiency (ID) was defined as a serum ferritin <100µg/L and transferrin saturations (Tsat) <20%. Anemia was defined as haemoglobin (Hb) <12g/dl. Patients with ID were slightly older and sicker (left ventricular ejection fraction (LVEF) 30% vs LVEF 38%) and had a higher incidence of hypertension and atrial fibrillation than those without ID. There were no statistical differences in usage of pharmacological treatments between the two groups.

2.3 Statistical Analysis

Data are expressed as means±SD when normally distributed. Inter-group differences were analysed and performed using SAS. Statistical methods included the Student t test and the Pearson $\chi 2$ test where appropriate for categorical data, proportions and means. Logistic regression was used to determine factors associated with HF diagnosis. Variables entered into the model based on clinical relevance and published predictors of HF diagnosis. The final adjusted model included the following co-variates: age, sex, year and presence of LVEF, angina, previous myocardial infarction, atrial fibrillation and hypertension. Age was treated as continous variable. All statistical tests were 2-tailed and a p value <0.001 was considered statistically significant. To obtain the distribution curve for the survival time, an estimated value of Kaplan-Meier was calculated, and differences in survival time were analysed using the log-rank test.

Table 1. Baseline characteristics of the 512 patients. All figures are mean values unless otherwise stated

Baseline features	HF patients with Fe Def(ID) (n=120)	HF patients without Fe Def (n=392)
Age	76.8(6.9)*	74.3(4.4)
Gender (M/F, %)	57/47	56/44
LVEF, % (SD)	29.6(11.7)*	37.9(4.8)
Ischemic cause, %	64.5(4.8)	68.9(10.2)
Duration of HF, years	7.2(2.3)	5.9(4.2)
NYHA status (SD)	2.2(1.2)	2.3(1.4)
Heart rate	71.4(12.8)	73.4(11.8)
Blood pressure (mmHg)	125/76	129/81
eGFR	57.4(12.9)	60.2(13.5)
BMI	23.8(5.3)	24.6(3.9)
Hb (g/dL)	13.1±0.7	13.6±1.5
Serum ferritin (g/L)	182±14.9	301±25.5
Tsat (%)	12.6±1.7	26.9±4.1

Table 2. Co-morbidity in patients with heart failure, comparing those with and without Fe def for June 2007 to Nov 2009 n(%)

Condition (N, %)	HF patients with ID (N=120)	HF patients without Fe Def (N=392)
Cardiovascular risk factors		
Diabetes	37(35)	136(35)
Hypertension	43(41)*	180(46)
Dyslipidemias	24(22)	102(26)
Smoking history	57(53)	215(55)
Cardiovascular disease		
Previous MI	47(44)	192(49)
Angina	49(46)	198(53)
Previous Stroke	20(18)	75(19)
Atrial fibrillation	36(34)*	145(37)

Table 3. Pharmacological treatments of patients with heart failure, comparing those with and without Fe Def between June 2007 to Nov 2009 n(%)

Treatment N (%)	HF patients with ID (n=120)	HF patients without Fe Def(n=392)
Cardiovascular treatment		
Beta-blocker	109 (90)	347(91)
ACE-inhibitor	87(83)	301(80)
Angiotensin receptor blocker	20(16)	47(12)
Spironolactone	67(54)	189(48)
Loop diuretic	91(86)	301(77)
Calcium channel blocker	35(31)	106(27)
Amiodarone	25 (23)	63 (16)
Aspirin	60(50)	251(64)
Warfarin	15(12)	79(20)

3. RESULTS

Mean follow-up was 24.2±4.9 months. The prevalence of ID within the overall study patients was 21.3% (n=102). Mean Hb level was 14.1±0.7g/dl at the start of the study and remained at similar levels throughout the study. (Table 1) shows the baseline study demographics including the Tsat and ferritin levels for both groups. As expected, the baseline Hb were similar in the groups (13.1g/dl vs. 13.6g/dl); however the iron status was statistically lower the in the ID group.

(Table 4) highlights the Hb levels and iron status of the ID patients and the anemic patients in the study over the time line of the study. Mean Hb levels for the entire study population at 6, 12 and 2 months were 13.9±0.3; 14.0±0.6 and 13.7±0.2g/dl respectively. Mean serum ferritin levels in the entire study population were 212±14.9µg/L at the start and 197±13.8µg/L at the end. The prevalence of ID and anemia was 21.3% and 9.4% at the start of the study, and 21.5% and 8.4% at the end of the study. The prevalence of ID was 63% vs 19% in subjects with vs. without anemia [p<0.001].

Sixty two deaths were recorded (12.1%). Two year survival rates were 78% in non-ID HF patients and 68% in the ID group (p<0.001) (Fig. 1). On uni-variate analysis, only baseline ferritin predicted the likelihood of survival. After adjustment for demographic data, clinical characteristics and medical treatment, the relation remained significant. In the fully adjusted multivariable analysis, ID was associated with mortality at 24 month follow-up [hazard ratio:1.42 (95% confidence interval: 1.09 -1.98], but anemia was not [1.05 (95% confidence interval: 0.87-1.51] in overall patients with HF (Fig. 1).

Figure 1
Kaplan-Meier survival curve in patients with heart failure, comparing those with and without Fe Def for June 2007 to Nov 2009.

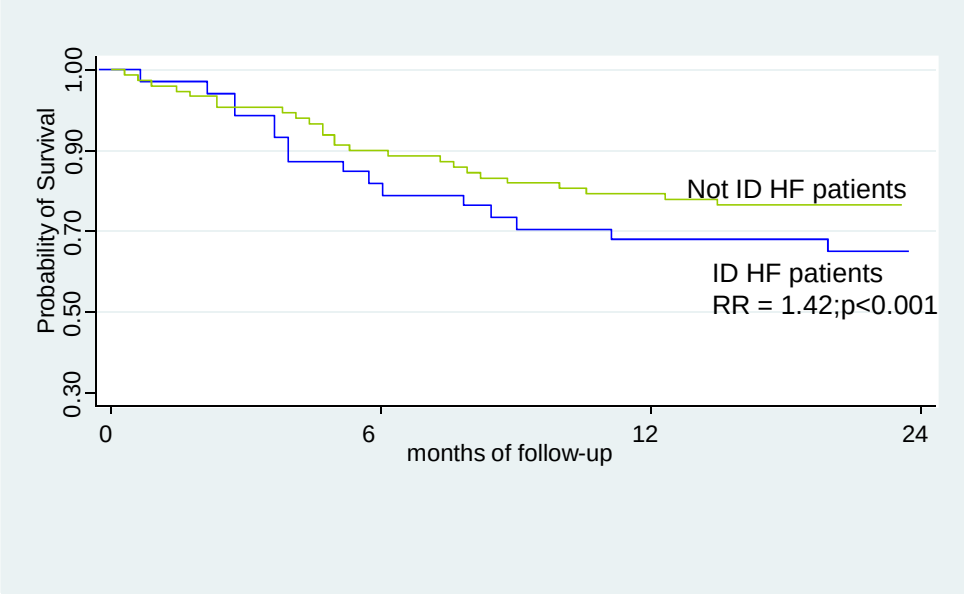

Table 4. Basic heamatinics in patients with heart failure, comparing those with ID and with anemia for June 2007 to Nov 2009 n(%)

Time/ patients	6 months		12 months		24 months	
	Hb (g/dl)	Ferritin (µg/L)	Hb (g/dl)	Ferritin (µg/L)	Hb (g/dl)	Ferritin (µg/L)
HF patients with ID (n=102)	13.9±0.3	151±34	14.0±0.6	161±26	13.7±0.2	132±17
Anemic patients (n=54)	11.9±0.5	251±84	10.7±0.8	301±38	10.6±0.5	288±97

4. DISCUSSION

There were two major findings arising from our study. Firstly, ID was common, affecting nearly 25% of the population with systolic HF. Second, we showed that ID independent of the other risk factors, including the presence of anemia, was related to poorer outcomes in HF patients. As we know, data on the effect of ID on HF were rare. ID was traditionally considered in the context of anemia in the general population and those with HF [23-25]. The prevalence of ID has been established only in HF patients with concomitant anemia years ago. Ezekowitz et al. [28] reported that anemia was present in 17% of incident hospital discharges for HF. ID was the reported cause of anaemia in 21%. Opasich et al. [21] showed that among 148 patients with HF and a low Hb level, most of them had anemia of chronic disease, and in this group nearly all demonstrated defective iron supply for erythropoiesis and/or blunted endogenous erythropoietin production. Klip et al. [20] recently reported that the prevalence was close to 50% in their cohort of mixed HF patients. They also found anemia in nearly 30% of their cohort. As their cohort represented both left ventricular systolic dysfunction and preserved LVEF, it is difficult to accurately draw conclusions from their study. Our study had the advantage of being a population that is as close to the reality of patients in the community and this was reflected in the mean age of our population.

Nanas et al. [18] investigated anaemic patients with advanced HF admitted to the hospital (NYHA class IV, mean LVEF—22%) and found using bone marrow biopsies that 73% presented with ID. In HF, there is an activation of pro-inflammatory cytokines that block intestinal absorption of iron and divert iron from the circulation into the reticulo-endothelial system, causing reticulo-endothelial block [22]. Hepcidin, a small hepatic peptide, secreted in response to pro-inflammatory cytokines, seems to play a key role in the control of these processes [29-30]. Decreased intestinal iron absorption together with its accumulation within the reticulo-endothelial stores reduces iron availability to its target tissues and organs [30]. Thus, functional ID may occur despite adequate iron stores in the body, in contrast to absolute ID, when the body iron stores are significantly depleted. In the present study, we applied a definition of ID taking account of both absolute (serum ferritin, <100mg/L) and functional ID (serum ferritin≥100mg/L and ≤300mg/L if Tsat<20%). Similar definitions had been already applied in past intervention trials, which showed that repletion of ID resulted in improvement in exercise capacity and quality of life in HF patients [22,25]. Using this definition, we demonstrated that the prevalence of ID in the whole cohort of HF patients was 21±3%, with a significant difference irrespective of Hb levels. The high prevalence of ID (approx. 20%) in non-anaemic patients was a new and important finding. Additionally, we

identified the following variables associated with ID including female sex, advanced NYHA class, and baseline high plasma BNP (sicker patients). Anemia has been established as a strong risk factor of increased mortality in patients with cardiovascular disease, including HF [31,32]. It was controversial regarding the role of ID in patients with HF and without anemia. Our report suggests that ID independent of anemia was associated with higher mortality at 2-year follow-up in patients with HF. Moreover, the inclusion of ID as an additional prognosticator to multivariable Cox regression models in patients with systolic HF resulted in a significant increase in the x2 values of these models. It was demonstrated that ID had the significant and independent input to the survival models in patients with HF. In contrast, the inclusion of anemia did not change significantly the x2 values. Taking this into consideration, the results of our study suggest that in the assessment of patients with systolic HF, laboratory biomarkers reflecting ID may be useful in routine practice to stratify the risk of subsequent outcome.

5. CONCLUSION

In conclusion, this study has provided evidence that ID prevalent in patients with stable HF and is linked with poorer outcomes. GP's should be encouraged to monitor iron stores as part of their clinical management of patients with HF in the community.

CONSENT

Informed patient consent was acquired for all patients where data analysis was performed.

ETHICAL APPROVAL

Not applicable as this was research based upon health services evaluation purposes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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