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Relative hypochromia and mortality in acute heart failure

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ABSTRACT

Background: Relative hypochromia of erythrocytes defined as a reduced mean corpuscular hemoglobin concentration (MCHC) is a surrogate of iron deficiency. We aimed to evaluate the prevalence and prognostic impact of relative hypochromia in acute heart failure (AHF).

Methods: We prospectively characterized 1574 patients presenting with an adjudicated diagnosis of AHF to the emergency department. Relative hypochromia was defined as a MCHC ≤330 g/l and determined at presentation. The presence of AHF was adjudicated by two independent cardiologists. All-cause mortality and AHF-rehospitalization were the primary prognostic end-points.

Results: Overall, 455 (29%) AHF patients had relative hypochromia. Patients with relative hypochromia had higher hemodynamic cardiac stress as quantified by NT-proBNP concentrations ($p < 0.001$), more extensive cardiomyocyte injury as quantified by high-sensitive cardiac troponin T (hs-cTnT) concentrations ($p < 0.001$), and lower estimated glomerular filtration rate (eGFR; $p < 0.001$) as compared to AHF patients without hypochromia. Cumulative incidences for all-cause mortality and AHF-rehospitalization at 720-days were 50% and 55% in patients with relative hypochromia as compared to 33% and 39% in patients without hypochromia, respectively (both $p < 0.0001$). The association between relative hypochromia and increased mortality (HR 1.7, 95% CI 1.4–2-0) persisted after adjusting for anemia (HR 1.5, 95% CI 1.3–1.8), and after adjusting for hemodynamic cardiac stress (HR 1.46, 95% CI 1.21–1.76) and eGFR (HR 1.5, 95% CI 1.3–1.8, $p < 0.001$).

Conclusions: Relative hypochromia is common and a strong and independent predictor of increased mortality in AHF. Given the direct link to diagnostic (endoscopy) and therapeutic interventions to treat functional iron deficiency, relative hypochromia deserves increased attention as an inexpensive and universally available biomarker.

1. Introduction

Acute heart failure (AHF) is a worldwide public health challenge with still high mortality rates reaching 30–40% within 1 year. In addition, AHF is the most common cause of hospitalization in patients older than 60 years [1–4] and further increasing in prevalence [5]. Unfortunately, AHF has only recently been identified as likely the most important unmet need in cardiology and received increasing attention [1–9].

AHF is a heterogeneous syndrome with several important comorbidities and triggers, including anemia, iron deficiency, and infection [10]. Early and accurate detection of these comorbidities and triggers is of major clinical relevance as it allows causal and timely treatment [1–4,6]. In contrast to chronic heart failure (HF), prevalence and optimal diagnostic criteria for iron deficiency are incompletely understood in AHF. As systemic infection is the trigger of AHF in about one-third of patients, diagnostic criteria such as the acute phase reactant ferritin are imperfect for AHF [1–4]. Accordingly, relative hypochromia of erythrocytes, the well-established alternative diagnostic window for functional

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iron deficiency deserves attention, since it is less affected by the common triggers of AHF [11–13]. The mean corpuscular hemoglobin concentration (MCHC) is the relative amount of hemoglobin content in erythrocytes and reflects expanse of iron incorporated into circulating erythrocytes [13,14]. Reduced MCHC is a reliable surrogate of functional iron deficiency, even in the absence of anemia [12].

The aim of this study was to evaluate the prevalence and prognostic impact of functional iron deficiency as detected by relative hypochromia of erythrocytes among unselected patients presenting with AHF to the emergency department (ED).

2. Material and methods

2.1. Patient population and study design

Basics in Acute Shortness of Breath EvaLuation (BASEL V) was a prospective international multicenter diagnostic study aiming to advance the characterization and the early management of AHF patients (ClinicalTrials.gov registry, Number NCT01831115). To allow the characterization of AHF patients already at ED presentation irrespective of the time of the correct diagnosis by the treating physician, we prospectively enrolled unselected adult patients presenting with acute dyspnea to the ED of two Swiss university hospitals (Basel and Zürich). While enrolment was independent of renal function, patients with terminal kidney failure undergoing chronic hemodialysis and trauma patients were excluded. The study and analysis were carried out according to the guidelines of the Declaration of Helsinki and approved by the local ethics committee [15]. Written informed consent was obtained from all participants.

2.2. Clinical evaluation

All patients presenting with acute dyspnea to the ED underwent clinical assessment by two physicians (a resident and a board-certified specialist) according to the local clinical standard including detailed clinical history, physical examination, ECG, pulse oximetry, blood tests usually including B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) and serum creatinine, and chest x-ray. Echocardiography, pulmonary function, and additional imaging tests including computed tomography were performed as clinically indicated. Additionally, a physician researcher recorded symptoms and signs in a standardized manner, but did not interfere with patient management. Furthermore, to allow for comparison of the MCHC prognostic accuracy with the one of an approved clinical score - the Multiple Estimation of risked based on the Emergency department Spanish Score In patients with AHF (MEESSI AHF) including all original variables except for Barthel-Index score at admission was calculated [8,16].

2.3. Final adjudication of AHF

Two independent cardiologists reviewed all medical records pertaining to the patient and classified the diagnosis as dyspnea due to AHF or dyspnea due to non-cardiac causes. Patients with non-cardiac causes were excluded from the present analyses. Patients with dyspnea due to arrhythmias and/or acute coronary syndrome who did not have other features of AHF were considered suffering "cardiac dyspnea", but not AHF and excluded from the analysis, as well [1]. Both cardiologists had access to all available medical records pertaining to the patient from the time of ED presentation to the results of the 360- and 720-day follow-up. All clinical data including chest x-ray, medical history, BNP or NT-proBNP levels, echocardiography, left ventriculography (performed at the time of cardiac catheterization), pulmonary function test, CT scan, right heart catheterization, hospital course, response to therapy, autopsy data for deceased patients and information about clinical events or readmissions during the 360-and 720 day follow up period. The NT-proBNP level was considered as a quantitative marker of hemodynamic cardiac stress and AHF [1,17,18].

2.4. End points and long-term follow up

All-cause mortality and its combination with AHF-rehospitalizations within 720 days were the co-primary prognostic endpoints while cardiovascular mortality and its combination with cardiovascular rehospitalizations as well as the composite of all-cause mortality and all-cause rehospitalizations were investigated as secondary prognostic endpoints. Patients and their primary care physicians were contacted at 360 and 720 days to assess recurrent symptoms, recurrent hospitalizations, and major adverse cardiac events including death. In case of recurrent hospitalizations, the respective discharge letters were obtained and reviewed. In patients with uncertainty regarding vital status, the administrative database in Switzerland was interrogated.

2.5. Measurement of laboratory values

Anemia was defined as a hemoglobin <12 g/dl for woman and <13 g/dl for men [19]. Indices of anemia included hemoglobin (determined after lysis of the erythrocytes by the cyanhemoglobin), hematocrit and MCHC (mean corpuscular hemoglobin concentration) and were determined with the Advia 2120 (Siemens Healthineers, Zürich, Schweiz). Relative hypochromia was defined as a MCHC ≤330 g/l [20]. NT-proBNP concentrations were determined with the Elecsys NT-proBNP assay (Roche Diagnostics, Basel, Switzerland) and high-sensitive cardiac troponin T (hs-cTnT) was measured by Elecsys Troponin hs assay (Roche Diagnostics, Basel, Switzerland). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21].

2.6. Statistical analysis

Statistical analyses were performed by using SPSS/PC software package (version 23.0) and R statistical Software ("cmprsk", "timeROC", "predictABLE") version 3.5.1 (Vienna, Austria). Normality was assessed by Shapiro-Wilk W test and visual inspection of the shape of the variables' distribution. Continuous variables were summarized as medians with interquartile intervals (IQI). Categorical variables were summarized as proportions and frequencies. Continuous variables were compared using the Wilcoxon-Mann-Whitney *U* test and categorical variables using Pearson's chi-square test. The Kaplan-Meier survival plots were calculated from baseline to day 720 for the predefined endpoints and log-rank test was used to assess differences between groups. To evaluate the association of different covariates (age, sex, BMI, eGFR, hemoglobin at admission, NT-proBNP, left ventricular ejection fraction and hypochromia) with these endpoints, a multivariable Cox proportional hazard regression model was built. Hazard ratios are presented with 95% confidence intervals (CIs). Each variable used in the multivariable models was assessed for multicollinearity using the variance inflation factor (VIF). Furthermore, the interaction *p*-values between MCHC or relative Hypochromia and common AHF phenotypes as well as AHF precipitating factors were calculated in multivariable models by using a cox proportional hazard analysis. Competing risk analysis was performed by using the Gray method. The optimal cut-off for MCHC predicting 720 days all-cause mortality was calculated using Youden's index. For the comparison of the MEESSI AHF risk score alone and its combination with MCHC, their prognostic accuracies were quantified by using the area under the time dependent receiver operating characteristic curves and compared as described previously [22]. In addition, reclassification tables for net reclassification improvement were utilized to assess the incremental yield of the additional use of MCHC to predict all-cause mortality at 720 days. All *p*-values are from two-sided tests and a *p*-value <0.05 was considered statistically significant.

3. Results

From May 2001 to November 2015, 3116 patients presenting to the ED with acute dyspnea were enrolled. Of these, 1574 patients were adjudicated to have AHF and had complete MCHC data (Supplementary Fig. S1). Clinical characteristics of the study population are presented in Table 1. Median age was 79 years, 43% of AHF patients were female. Coronary artery disease (CAD) was known to be present in 54%, and median left ventricular ejection fraction was 45%.

3.1. Relative hypochromia

Relative hypochromia was present in 455 AHF patients (29%). AHF patients with hypochromia had higher hemodynamic cardiac stress as quantified by NT-proBNP plasma concentrations ($p < 0.001$) and more extensive cardiomyocyte injury as quantified by hs-cTnT plasma concentrations ($p < 0.001$), as well as lower eGFR ($p < 0.001$) as compared to AHF patients with normal or increased MCHC.

3.2. Characteristics according to the presence of anemia

Among the AHF patients, 712 patients (45%) were anemic and 861 patients (55%) were non-anemic (Supplementary Table S1A—B). Among anemic AHF patients, the baseline characteristics were similar between patients with and without hypochromia (Supplementary Table S1A). In contrast, among non-anemic AHF patients, multiple differences were present: patients with hypochromia had more often pre-existing CAD, higher hemodynamic cardiac stress as quantified by NT-proBNP plasma concentrations ($p = 0.001$) as well as lower eGFR ($p = 0.002$) (Supplementary Table S1B).

3.3. Mortality according to hypochromia status

During the follow-up of 720 days 592 of all patients (38%) died. In-hospital mortality in patients with or without relative hypochromia reached 2% and 3%, respectively ($p = 0.407$). Fig. 1A–C illustrates the effect of relative hypochromia on 720-day cumulative all-cause mortality. Patients with relative hypochromia had significantly higher all-cause mortality overall (Fig. 1A; HR 1.7, 95% CI 1.4–2.0; $p < 0.0001$), as well

Table 1
Baseline characteristics of all patients with acute heart failure (AHF) according to the presence of relative hypochromia ($n = 1574$).

Variables	All AHF patients ($n = 1574$)	Hypochromia ($n = 455$)	No hypochromia ($n = 1119$)	p-Value
Demographics				
Age (years)	79 (70–85)	79 (71–85)	79 (70–85)	0.936
Sex (male/female, %)	57/43	55/45	58/42	0.176
Weight (kg)	74 (64–86)	73 (62–85)	75 (64–86)	0.307
BMI (kg/m^2)	26 (23−30)	26 (23–30)	26 (23–30)	0.757
Medical history				
Coronary artery disease (%)	54	62	51	**<0.001**
Hypertension (%)	79	78	79	0.723
Peripheral artery disease (%)	18	20	17	0.296
Stroke (%)	18	17	18	0.921
Dyslipidemia (%)	54	58	53	0.111
Diabetes (%)	30	35	28	**0.006**
Current or ex-smoker (%)	63	65	62	0.387
Chronic kidney disease (%)	46	56	42	**<0.001**
Previous AHF (%)	51	58	48	**0.001**
Atrial fibrillation (%)	45	48	43	0.129
COPD (%)	26	32	23	**<0.001**
Active malignancies (%)	6	6	6	0.802
AHF precipitating conditions				
Worsening heart failure	64	62	65	0.277
Infection	21	18	22	0.103
Cardiogenic shock	1	1	1	0.446
Laboratory data				
Hemoglobin (g/l)	127 (113–141)	116 (101−131)	131 (118–143)	**<0.001**
Hematocrit (%)	38 (34–41)	36 (31–41)	38 (34–41)	**<0.001**
MCHC (g/l)	338 (329–346)	323 (317–327)	342 (337–350)	**<0.001**
MCH (pg)	31 (29–32)	29 (27–31)	31 (30−32)	**<0.001**
Creatinine (μmol/l)	107 (81–149)	119 (88–166)	103 (79–140)	**<0.001**
Urea (mmol/l)	10 (7–14)	12 (8–17)	9 (6–19)	**<0.001**
eGFR (ml/min/1.73 m^2)	51 (34–72)	44 (29–63)	54 (37–74)	**<0.001**
Albumin (g/l)	35 (32–38)	34 (31–37)	35 (32–38)	**0.001**
CRP (mg/l)	11 (5–31)	13 (5–31)	10 (4–31)	**0.039**
Sodium (mmol/l)	139 (136–141)	139 (137–142)	139 (136–141)	**<0.001**
Potassium (mmol/l)	4.2 (3.8–4.5)	4.3 (3.9–4.7)	4.1 (3.8–4.5)	**<0.001**
Clinical parameters				
sBP (mm Hg)	137 (120–156)	133 (117–150)	139 (120–158)	**0.001**
dBP (mm Hg)	80 (67–93)	77 (64–90)	80 (68–95)	**0.002**
HR (beats/min)	88 (73–107)	89 (72–108)	88 (73–106)	0.750
LV ejection fraction (%)	45 (30–56)	44 (28–55)	45 (30–57)	0.188
Cardiac biomarker				
NT-proBNP (ng/l)	5019 (2271–9764)	6082 (3230–12,113)	4574 (2022–9120)	**<0.001**
hs-TnT (ng/l)	37 (22–67)	42 (27–75)	35 (20–63)	**<0.001**
Medication at admission				
ACE inhibitors (%)	45	45	45	0.948
ARBs (%)	27	27	26	0.744
CCB (%)	22	19	23	0.081
Beta blockers (%)	59	59	59	0.967
Diuretics (%)	60	76	67	**0.017**
Aldosterone-receptor antagonists (%)	14	14	14	0.977
ASS (%)	45	43	47	**0.009**
VKA (%)	45	43	47	0.320

Abbreviations: ASS: acetylsalicylic acid; ARBs: Angiotensin II Receptor Blockers; BMI: Body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate calculated according to CKD-EPI; CCB: Calcium Channel Blocker; COPD: chronic obstructive pulmonary disease, BNP: B-type brain natriuretic peptide; CRP: C-reactive protein, dBP: diastolic blood pressure; HR: heart rate; LV: left ventricular; MCHC: mean corpuscular hemoglobin concentration; MCH: mean corpuscular hemoglobin, NT-proBNP: N-terminal pro-B-type natriuretic peptide; sBP: systolic blood pressure; hs-TnT: Troponin T high sensitive. VKA: vitamin K antagonists.
p-Values with statistical significance were highlighted in bold.

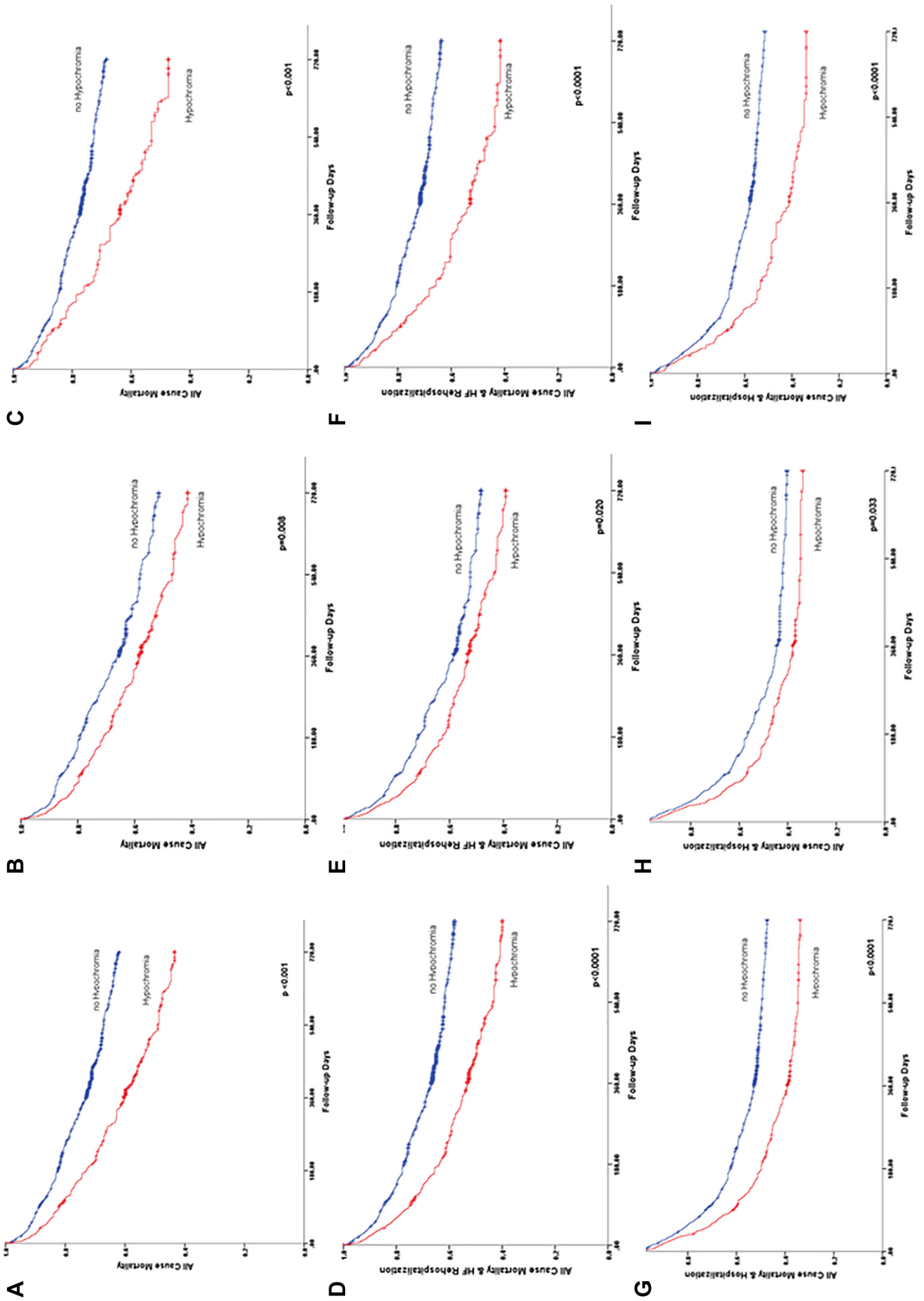
as in the subgroups of those with (Fig. 1B) and without (Fig. 1C) anemia. AHF patients with hypochromia compared to non-hypochromia patients showed a significantly increased risk of death due to cardiovascular causes at 720 days (HR 1.7, 95% CI 1.4–2.2; $p < 0.0001$). Accordingly, patient groups with anemia and hypochromia showed an HR of 1.3 (95% CI 1.1–1.7; $p = 0.008$) for all-cause mortality as compared to patients presenting with anemia, but without hypochromia. Of note, in patients with hypochromia and no signs of anemia, the HR increased in patients with hypochromia as compared to the patients without hypochromia to 1.8 (95% CI: 1.4–2.4, $p < 0.0001$).

3.4. Combined endpoint: all-cause mortality or AHF rehospitalization

Fig. 1D–F demonstrates the effect of relative hypochromia on the combined endpoint of 720 days' cumulative risk for all-cause mortality or rehospitalization due to AHF. Patients presented with hypochromia had a significantly increased risk for the combined endpoint of all-cause mortality or rehospitalization due to AHF with a HR of 1.7 (95% CI 1.4–1.9; $p < 0.0001$; Fig. 1D). Again, similar findings emerged in the subgroups with (Fig. 1E) and without (Fig. 1F) anemia. Furthermore, in patients with or without hypochromia and AHF rehospitalization a competing risk analysis was performed, considering all-cause mortality as a competing risk. Patients with relative hypochromia had a significantly increased risk of AHF rehospitalization with a HR of 1.26 (95% CI 1.00–1.59, $p = 0.047$).

3.5. Combined endpoint: all-cause mortality or all-cause rehospitalization

Fig. 1G–I demonstrates the increased risk for all-cause mortality or all-cause rehospitalization in patients with relative hypochromia


A
All Cause Mortality
no Hypochromia
Hypochromia
p <0.001
Follow-up Days
B
All Cause Mortality
no Hypochromia
Hypochromia
p=0.008
Follow-up Days
C
All Cause Mortality
no Hypochromia
Hypochromia
p<0.001
Follow-up Days
D
All Cause Mortality & HF Rehospitalization
no Hypochromia
Hypochromia
p<0.0001
Follow-up Days
E
All Cause Mortality & HF Rehospitalization
no Hypochromia
Hypochromia
p=0.020
Follow-up Days
F
All Cause Mortality & HF Rehospitalization
no Hypochromia
Hypochromia
p<0.0001
Follow-up Days
G
All Cause Mortality & Hospitalization
no Hypochromia
Hypochromia
p<0.0001
Follow-up Days
H
All Cause Mortality & Hospitalization
no Hypochromia
Hypochromia
p=0.033
Follow-up Days
I
All Cause Mortality & Hospitalization
no Hypochromia
Hypochromia
p<0.0001
Follow-up Days

(Fig. 1G), irrespective of the presence (Fig. 1H) or absence (Fig. 1I) of anemia.

3.6. Multivariable Cox proportional hazards models

The variables used in the Cox proportional hazard regression models showed VIFs 1.1–1.5 indicating no multicollinearity. After adjusting for age, sex, BMI, eGFR, hemoglobin at admission, NT-proBNP and **LV ejection fraction**, relative hypochromia remained an independent predictor of all-cause mortality, all-cause mortality or AHF rehospitalizations, all-cause mortality or all-cause rehospitalizations (Table 2, Supplementary Tables S2, and S4). These results could be confirmed for the endpoints of cardiovascular mortality and its combination with cardiovascular rehospitalizations.

3.7. Combination of MCHC with MEESSI AHF risk score

MEESSI AHF risk score was calculated for 1145 patients (73%) during 720 days follow-up. The combination of MCHC with MEESSI AHF risk score did not provide a relevant prognostic improvement for predicting all-cause mortality as quantified by the area under the time dependent receiver operating characteristic curves (Supplementary Fig. S3). The net reclassification improvement of MCHC was modest and reached 0.321 (95% CI 0.242–0.400, $p < 0.001$). Integrated discriminatory improvement was calculated at 0.011 ($p < 0.001$; Table S8).

4. Discussion

In this large prospective multicenter diagnostic study of patients with an adjudicated final diagnosis of AHF, we analyzed the prevalence and the prognostic implications of relative hypochromia, a well-established diagnostic window for functional iron deficiency also reliable in AHF. We report four major findings:

First, 29% of AHF patients had relative hypochromia at ED presentation. Second, AHF patients with relative hypochromia had substantially higher all-cause mortality, as well as higher rates for death or AHF rehospitalization and death or all-cause rehospitalization. Third, these associations were seen consistently irrespective of the presence or absence of anemia. Fourth, relative hypochromia remained an independent predictor of mortality and of the combined endpoints in multivariable analyses.

These findings extend and corroborate pilot studies on relative hypochromia [12]. MCHC reflects the amount of hemoglobin incorporated into the erythrocytes and serves as a reliable indicator of iron load in erythrocytes with a specificity up to 96% for detecting iron deficiency [23]. Multiple physiologic functions such as oxygen transport, -storage (myoglobin) or oxidative metabolism are associated with the availability of iron. In 197 ambulatory patients with chronic systolic and symptomatic heart failure, who underwent comprehensive echocardiographic evaluation, Simbaqueba and colleagues showed that relative hypochromia was associated with higher natriuretic peptide levels ($r = -0.40$, $p < 0.0001$) and lower eGFR ($r = 0.45$, $p < 0.0001$) and that hypochromia correlated modestly with indices of left and right ventricular diastolic dysfunction (all $p < 0.05$), but were not related to left ventricular ejection fraction ($r = 0.17$, $p = 0.079$). After 5 years of follow-up, lower MCHC levels were associated with higher risk of death and hospitalization due to heart failure [20].

Table 2
Multivariable Cox proportional hazards model for all-cause mortality, cardiovascular death, combined endpoint of all-cause mortality or AHF-related hospitalizations and all-cause mortality or all-cause hospitalizations.

	Hazard ratio	95% CI	*p*-Value
All-cause mortality			
Age (years)	1.033	1.019–1.048	<**0.001**
Sex	0.700	0.554–0.884	**0.003**
BMI	0.956	0.933–0.980	<**0.001**
eGFR (ml/min/1.73 m^2)	0.987	0.982–0.993	<**0.001**
Hemoglobin at admission (g/l)	1.000	0.994–1.006	0.991
Hypochromia (yes/no)	1.509	1.191–1.910	**0.001**
lg NT-proBNP (ng/l)	2.099	1.507–2.925	<**0.001**
LV ejection fraction (%)	1.003	0.995–1.011	0.505
Cardiovascular mortality			
Age (years)	1.029	1.011–1.047	**0.001**
Sex	0.778	0.580–1.043	0.093
BMI	0.955	0.925–0.986	**0.005**
eGFR (ml/min/1.73 m^2)	0.983	0.976–0.991	<**0.001**
Hemoglobin at admission (g/l)	1.000	0.993–1.008	0.959
Hypochromia (yes/no)	1.553	1.159–2.081	**0.003**
lg NT-proBNP (ng/l)	2.002	1.311–3.057	**0.001**
LV ejection fraction (%)	0.993	0.982–1.003	0.156
All-cause mortality or AHF rehospitalization			
Age (years)	1.017	1.005–1.029	**0.006**
Sex	0.794	0.642–0.982	**0.033**
BMI	0.975	0.954–0.996	**0.022**
eGFR (ml/min/1.73 m^2)	0.990	0.984–0.995	<**0.001**
Hemoglobin at admission (g/l)	1.002	0.996–1.007	0.586
lg MCHC (g/l)	0.000016	0.00000005–0.005	<**0.001**
lg NT-proBNP (ng/l)	1.903	1.412–2.563	<**0.001**
LV ejection fraction (%)	1.001	0.993–1.008	0.840
All-cause mortality or AHF rehospitalization			
Age (years)	1.017	1.005–1.029	**0.006**
Sex	0.811	0.656–1.003	0.053
BMI	0.976	0.955–0.997	**0.025**
eGFR (ml/min/1.73 m^2)	0.990	0.985–0.995	<**0.001**
Hemoglobin at admission (g/l)	1.001	0.955–1.006	0.791
Hypochromia (yes/no)	1.484	1.195–1.843	**0.001**
lg NT-proBNP (ng/l)	1.915	1.421–2.581	<**0.001**
LV ejection fraction (%)	1.000	0.993–1.008	0.953
All-cause mortality or all-cause rehospitalization			
Age (years)	1.007	0.997–1.018	0.162
Sex (male)	0.856	0.709–1.034	0.107
BMI	0.973	0.955–0.992	**0.005**
eGFR (ml/min/1.73 m^2)	0.993	0.989–0.998	**0.004**
Hemoglobin at admission (g/l)	0.998	0.994–1.003	0.475
Hypochromia (yes/no)	1.360	1.118–1.656	**0.002**
lg NT-proBNP (ng/l)	1.393	1.082–1.800	**0.010**
LV ejection fraction (%)	0.999	0.993–1.006	0.819

Abbreviations: AHF: acute heart failure, BMI: Body mass index; NT-proBNP: N-terminal pro-B-type natriuretic peptide, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate calculated according to CKD-EPI, LV = left ventricle.

The pathophysiology of relative hypochromia include intestinal blood loss, resistance to erythropoietin [12], and dilution effects induced by changes in osmotic pressures in the presence of congestion; it may affect the relative concentration of hemoglobin within the erythrocytes. These effects indicate that hypochromia is more pronounced in advanced diastolic dysfunction and with increased BNP-levels, the latter in line with our current results.

Fig. 1. Cumulative all-cause mortality (A–C), all-cause mortality or acute heart failure (AHF) rehospitalization (D–F) and all-cause mortality or all-cause rehospitalization (G–I) according to relative hypochromia in patients with acute heart failure (AHF). Cumulative 720-day all-cause mortality in patients stratified according to hypochromia (MCHC ≤ 330 g/l) vs. non-hypochromia in the overall AHF cohort (A), in anemic AHF patients according to hypochromia (B), and in non-anemic AHF patients according to hypochromia (C). Cumulative 720-day all-cause mortality or AHF rehospitalization in patients stratified according to hypochromia (MCHC ≤ 330 g/l) vs. non-hypochromia in the overall AHF cohort (D), in anemic AHF patients according to hypochromia (E), and in non-anemic AHF patients according to hypochromia (F). Cumulative 720-day all-cause mortality or all-cause rehospitalization in patients stratified according to hypochromia (MCHC ≤ 330 g/l) vs. non-hypochromia in the overall AHF cohort (G), in anemic AHF patients according to hypochromia (H), and in non-anemic AHF patients according to hypochromia (I).

Iron deficiency has been investigated in patients with heart failure [24,25], since these patients have a high suspicion to develop iron deficiency due to gradual depletion of iron stores caused by low iron intake, gastrointestinal blood loos or iron malabsorption [26]. Even in patients with normal hemoglobin levels, patients with iron deficiency showed decreased functional capacity, impaired left ventricular ejection fraction, leading to a diminished outcome. In addition to the absolute iron deficiency, functional iron deficiency defined by an activation of pro-inflammatory cytokines, diverts iron from the circulation into the reticuloendothelial system and plays an important pathogenic role leading to decreased iron availability for targeted organs [27]. Prior results suggest that non-anemic iron deficient patients had an increased risk for deaths as compared to anemic iron-repleted patients [12]. Our current results underline that a defined cut-off for iron deficiency may underestimate patients with relative impairment of iron metabolism, leading to the argument that these patients may benefit from iron supplementation to improve AHF and outcome in this specific patient cohort.

The monitoring of the iron indices in patients with AHF is cost summing; therefore using MCHC as a surrogate marker of iron deficiency, especially in high-risk patients with impaired outcome, could be easily implemented in daily clinical routine.

4.1. Study limitations

Some limitations should be considered when interpreting these findings. First, this study used a surrogate of iron deficiency because routine blood analyses in the ED do not include parameters of iron indices in all patients to evaluate the presence of underlying iron deficiency; nevertheless prior studies have shown a strong correlation between parameters of iron deficiency and MCHC-levels [19]. Therefore, the evaluation of MCHC levels is an indirect measurement of the degree of relative hypochromia in the erythrocytes rather than a measurement of circulating substrates of iron. Second, we cannot comment on relative hypochromia in patients with terminal renal failure on chronic dialysis, as these patients were not enrolled. Third, we cannot comment on the frequency of the underlying causes of relative hypochromia, as patients did not receive a prospective standardized work-up for relative hypochromia.

4.2. Conclusions

In conclusion, relative hypochromia is a strong and independent predictor of increased mortality in AHF. Given the direct link to diagnostic (endoscopy) and therapeutic interventions to treat functional iron deficiency, relative hypochromia deserves increased attention as an inexpensive and universally available biomarker.

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Disclosures

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the letter, and decided to publish. All authors have read and approved the letter. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the letter. The letter and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible websites or e-print servers. Dr. Twerenbold has received research support from the Swiss National Science Foundation (P300PB_167803) and speaker honoraria/consulting honoraria from Roche, Abbott, Siemens, Singulex, and Brahms. Dr. Boeddinghaus has received research grants from the University of Basel and the Department of Internal Medicine and speaker honoraria from Siemens. Dr. Nestelberger has received speaker honoraria from Beckman Coulter. Dr. Walter reports a research grant from the Swiss Academy of Medical Sciences and the Bangerter-Rhyner Foundation (YTCR 23/17). Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, Amgen, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, the University of Basel, and the University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, Sanofi, and Singulex. The other authors report no conflicts.

Appendix A. Supplementary data

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