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ORIGINAL ARTICLE

Prevalence and determinants of iron deficiency in cardiac amyloidosis

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Abstract

Aims Iron deficiency (ID) is common in patient with chronic heart failure (HF) and has been widely studied. In contrast, data concerning ID in cardiac amyloidosis (CA) are limited. Amyloidosis is a severe and fatal systemic disease, characterized by an accumulation of amyloid fibrils in various tissues/organs, including nerves, kidneys, gastrointestinal tract, and heart. Amyloid deposits in the heart eventually cause HF. The main subtypes of CA are light chain (AL), hereditary transthyretin (ATTRv), and wild-type transthyretin (ATTRwt). We performed this study to determine the prevalence, clinical outcome (all-cause mortality), and determinants of ID among the three main subtypes of CA.

Methods and results Iron deficiency status were analysed in 816 CA patients enrolled at the French Referral Centre for Cardiac Amyloidosis: 271 (33%) had AL, 164 (20%) ATTRv, and 381 (47%) ATTRwt. ID affected 49% of CA patients, 45% with AL, 58% with ATTRv, and 48% with ATTRwt. We identified ATTR status (ATTRv P = 0.003, ATTRwt P = 0.037), diabetes (P = 0.003), aspirin treatment (P = 0.009), haemoglobin levels (P = 0.006), and altered global longitudinal strain (P = 0.02) as independent ID determinants. There is no difference in all-cause mortality considering ID status.

Conclusions Iron deficiency is common in patients with CA, irrespective of the subtype. Patients seem more likely to have ID if diagnosed with ATTR, if diabetic, and/or treated with aspirin. In CA, the benefit of intravenous iron therapy, for ID, on morbidity and mortality needs further study.

Keywords Amyloidosis; Iron deficiency; Heart failure

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Introduction

Worldwide, iron deficiency (ID) is a very common nutritional disorder, even in industrialized nations where it often occurs with cardiovascular disease.[1] ID also frequently occurs with chronic diseases, like chronic heart failure[2] and chronic kidney disease.[3] There are two types of ID: functional ID when serum ferritin levels are between 100 and 299 μg/L and transferrin saturation is below 20%, and absolute ID when serum ferritin levels drop below 100 μg/L.[4,5] In patients with functional ID, iron is inadequately distributed for proper tissue function: often from chronic inflammation with iron retention (sequestration), by macrophages and hepatocytes, that is frequently associated with decreased iron absorption.[6] Absolute ID can result from chronic blood loss and inadequate iron intake, or develops from functional ID.[6]

Moreover, absolute ID is associated with specific diseases. In heart failure (HF) gastrointestinal iron malabsorption, decreased duodenal iron transfer from gut oedema, and macrophage iron sequestration from inflammation (with high circulating levels of pro-inflammatory mediators) leads to ID.[7] Approximately 50–62% of HF patients have ID.[2,8,9] ID occurs irrespective of the left ventricular ejection fraction (LVEF). Indeed, a single-centre, prospective study reported that 53% of HF patients had ID: among these 50% had HF with reduced (HFrEF), 61% had HF with mildly reduced (HFmrEF), and 64% had HF with preserved ejection fractions (HFpEF).[9] Overall, ID prevalence tends to increases as diastolic function deteriorates.[10] Moreover, ID in HF is a strong, independent predictor of mortality[2] and is associated with reduced exercise capacity, and diminished quality of life.[8–10] Recent studies have reported that iron therapy with carboxymaltose ferric improves quality of life and exercise capacity in HFrEF patients and reduces heart failure re-hospitalization in patients with acute heart failure (LVEF $<$50%).[4,11–14] The impact of iron therapy on HFpEF patients with ID is being evaluated in the FAIR HFpEF study (NCT03074591).

Recently, several studies have shown that cardiac amyloidosis (CA) is an underestimated cause of HF.[15–17] A study in elderly patients found that wild-type TTR amyloidosis (ATTRwt) represented 13% of HFpEF hospitalizations.[16] Amyloidosis is a severe, progressive systemic disease characterized by deposits of misfolded, insoluble, toxic proteins (amyloid fibrils) in the extracellular matrix of various organs, including the heart.[18] Numerous proteins are implicated in CA, among these immunoglobulin light chains (ALs) and transthyretin (TTR) are the most frequent. The three main types of CA are AL, wild-type TTR amyloidosis (ATTRwt), and hereditary TTR amyloidosis (ATTRv).[19] ATTRv results from a genetic variant of the *TTR* gene, which produces unstable amyloidogenic TTR.[20–22] In CA, the thickening and increased stiffness of the cardiac walls from amyloid deposits leads to HF, conduction disorders, atrial arrhythmias, and eventually cardiovascular death.

In CA patients besides HF because of oedema in organs, amyloid fibrils also infiltrate the extracellular matrix of the gastrointestinal tract, vessels, and the nervous system.[23,24] Nervous system infiltration causes gastroparesis and dysphagia that leads to malnutrition. Vascular vessels infiltration may lead to bleeding and ID. Gastrointestinal amyloid infiltration may aggravate the HF malabsorption and amplify ID associated with HF. We hypothesized that pathophysiological mechanisms observed in CA and associated with HF lead to ID. Thus, amyloid infiltration severity may correlate to ID severity. To our knowledge, ID prevalence and determinants have not yet been assessed in patients with CA.

The aim of our study was to evaluate ID prevalence and its association with clinical, biological, and imaging characteristics in CA patients with AL, ATTRv, and ATTRwt.

Methods

Study population

This retrospective cohort study was conducted in the French Referral Centre for Cardiac Amyloidosis at the Henri Mondor Teaching Hospital (Creteil) from August 2010 to March 2020. All consecutive patients with confirmed CA (with either AL, ATTRv, or ATTRwt amyloidosis) and baseline iron status were prospectively included. Patients had a comprehensive medical evaluation at arrival with clinical and laboratory assessments, including complete blood count, bilirubin, albumin, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T, and serum ID tests, electrocardiography, echocardiography, and ^{99m}Tc-hydroxy-methyl-diphosphonate (HMDP) scintigraphy.

Definition of cardiac amyloidosis and its type

Cardiac amyloidosis was suspected when the interventricular septum thickness (IVST) was $>$12 mm, measured by echocardiography, in the absence of other known cause of cardiac hypertrophy. AL amyloidosis was diagnosed by an excess of serum and/or urinary free-light chains (FLCs) and AL deposits assessed by immunohistochemistry or immunofluorescence, with a specific anti-FLC antibody, on an extra-cardiac or endomyocardial biopsy. CA severity was assessed using cardiac biomarkers: NT-proBNP and troponin T.[25] ATTR amyloidosis was diagnosis using the method previously described.[26] Genetic sequencing of patients with ATTR amyloidosis was performed to differentiate ATTRwt and ATTRv subtypes.

Biological tests and assessment of iron deficiency status and anaemia

Iron deficiency was diagnosed using the baseline serum levels of ferritin and transferrin. ID was diagnosed when patients had serum ferritin $<$100 μg/L (absolute ID), or serum ferritin between 100 and 299 μg/L with transferrin saturation $<$20% (functional ID).[27,28] Anaemia was defined as haemoglobin levels $<$13 g/dL for men and $<$12 g/dL for women, as recommended by the World Health Organization (World Health Organization/United Nations University/UNICEF. Iron Deficiency Anaemia, Assessment, Prevention and Control: A Guide for Programme Managers. Geneva: WHO; 2001).

Clinical follow-up

Patient follow-up visits were performed according to standard of care. Patients usually consulted every 6–9 months. During these visit, standard clinical evaluations were performed.

Ethical considerations

All patients provided oral consent to be included in the Amyloidosis Network registry. The study was approved by the local ethics committee and data were recorded electronically in accordance with the French CNIL (*Commission National de l'Informatique et des Libertés*; N°1846564 v0).

Statistical analysis

Continuous variables were expressed as median with interquartile range (IQR) and dichotomous data as numbers with percentages. Frequencies for quantitative variables were compared using the χ^2 test with Pearson's correction. Continuous data were compared using the Mann–Whitney test for two groups and the Kruskal–Wallis test for more than two groups. Follow-up data were obtained from medical files, or if required, by contacting the patients' families. The study assessed all-cause mortality in patients with or without ID.

The statistical analyses were performed using the SPSS software (version 19.0 for Windows 2010 SPSS Inc.). A *P* value below 0.05 was considered as statistically significant.

Logistical regression was used to assess the association between ID and baseline characteristics.

Table 1 Baseline characteristics of patients according to amyloidosis status

N (%)	All 816 (100)	AL 271 (33)	ATTRv 164 (20)	ATTRwt 381 (47)	*P*
Clinical characteristics					
Age at inclusion, years	76 (67; 82)	67 (59; 75)	72 (66; 78)	81 (76; 85)	<0.001
Gender, women *n* (%)	210 (26)	103 (38)	55 (34)	52 (14)	<0.001
BMI, kg/m^2	25 (22; 27)	23 (21; 26)	24 (22; 27)	25 (23; 28)	<0.001
CV risk factors					
Diabetes, *n* (%)	151 (19)	45 (17)	32 (20)	74 (19)	0.615
Hypertension, *n* (%)	438 (54)	107 (40)	91 (56)	240 (63)	<0.001
Dyslipidaemia, *n* (%)	259 (32)	73 (27)	42 (26)	144 (38)	0.068
CV characteristics					
NYHA Class III–IV vs. I–II, *n* (%)	342 (42)	130 (48)	69 (42)	143 (38)	0.003
Heart rate, beats/min	76 (68; 86)	82 (73; 94)	75 (66; 84)	74 (67; 81)	<0.001
Systolic blood pressure, mmHg	122 (108; 137)	112 (101; 127)	121 (108; 133)	129 (115; 143)	<0.001
Atrial fibrillation, *n* (%)	213 (26)	30 (11)	32 (20)	151 (40)	<0.001
Ischaemic heart disease, *n* (%)	150 (18)	38 (14)	12 (7)	100 (26)	<0.001
Echocardiography characteristics					
LVEF, %	51 (42; 60)	55 (45; 62)	49 (36; 59)	50 (41; 58)	<0.001
IVST, mm	17 (15; 19)	15 (14; 17)	18 (15; 20)	18 (15; 20)	<0.001
GL Strain, %	−10 (−8; −13)	−10 (−8; −14)	−10 (−8; −13)	−10 (−8; −13)	0.452
Blood parameters					
NT-proBNP, ng/mL	3550 (1740; 6735)	5074 (2257; 10982)	2525 (1065; 5368)	3247 (1734; 5802)	<0.001
Troponin T HS, ng/mL	71 (45; 106)	83 (53; 136)	67 (40; 96)	66 (43; 95)	<0.001
eGFR, mL/min/1.73 m^2	50 (37; 67)	55 (38; 75)	54 (38; 68)	48 (37; 60)	0.002
Haemoglobin, g/dL	13.1 (11.8; 14.1)	12.7 (10.9; 13.8)	12.9 (11.8; 13.7)	13.4 (12.2; 14.4)	<0.001
Mean corpuscular volume, fL	92 (87; 95)	91 (87; 95)	90 (85; 94)	92 (88; 96)	<0.001
Ferritin, μg/L	204 (109; 328)	225 (118; 360)	139 (72; 283)	210 (124; 314)	<0.001
Transferrin saturation, %	18 (13; 24)	18 (12; 24)	17 (13; 25)	18 (13; 24)	0.560
Iron deficiency treatment[a]					
Oral iron during follow-up, *n* (%)	30 (8)	4 (3)	7 (8)	19 (10)	0.069
I.V. iron during follow-up, *n* (%)	191 (48)	57 (47)	44 (47)	90 (50)	0.883
Anticoagulant and antiplatelet treatment					
Aspirin, *n* (%)	213 (26)	75 (28)	34 (21)	104 (27)	0.220
Clopidogrel, *n* (%)	46 (6)	12 (4)	6 (4)	28 (7)	0.135
Oral anticoagulants, *n* (%)	434 (53)	111 (41)	74 (45)	249 (65)	<0.001
Heart failure treatment					
ACE inhibitor, *n* (%)	216 (26)	42 (16)	54 (33)	120 (31)	<0.001
ARB, *n* (%)	121 (15)	25 (9)	29 (18)	67 (18)	0.007
Digoxin, *n* (%)	14 (2)	2 (1)	1 (1)	11 (3)	0.055
Selective beta-blocker, *n* (%)	221 (27)	63 (23)	48 (29)	110 (29)	0.223
Non-selective beta-blocker, n (%)	16 (2)	5 (2)	1 (1)	10 (3)	0.297
Calcium antagonist, *n* (%)	222 (27)	62 (23)	45 (27)	115 (30)	0.123
Amiodarone, *n* (%)	159 (19)	38 (14)	31 (19)	90 (24)	0.010
Loop diuretic, *n* (%)	595 (73)	197 (73)	107 (65)	291 (76)	0.030
Thiazide diuretic, *n* (%)	278 (34)	69 (25)	61 (37)	148 (39)	0.001
Vasodilator, *n* (%)	25 (3)	8 (3)	5 (3)	12 (3)	0.991

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; GL, global longitudinal; I.V., intravenous; IVST, interventricular septum thickness; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
Values are median (interquartile range).
[a]*N* = 400.

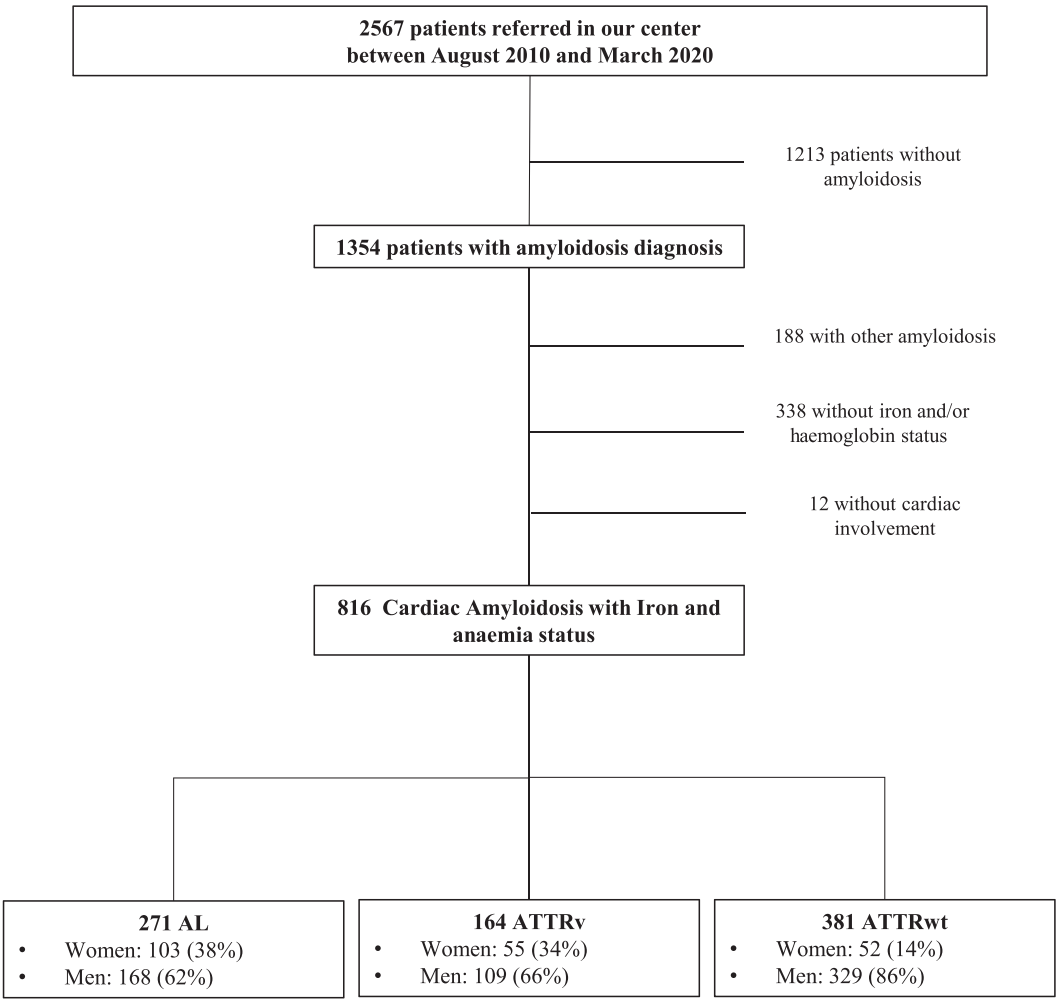
The Kruskal–Wallis test was used to analyse the association between malabsorption and ferritin levels in the CA population. Ferritin levels were compared with albumin tertiles. Similarly, in AL patients, where hepatic dysfunction is frequent and can affect ferritin production, we compared ferritin levels to bilirubin tertiles (T1–T2 vs. T3).

Results

Patient characteristics

From August 2010 to March 2020, of the 2567 patients that presented at the French Referral Centre with suspected CA, 816 patients had CA with iron status and were enrolled in the study: 271 (33%) with AL, 164 (20%) with ATTRv, and 381 (47%) with ATTRwt (*Table 1* and *Figure 1*). The median age in the overall population was 76 years (IQR: 67–82): 67 years (IQR: 59–75) for patients with AL, 72 years (IQR: 66–78) with ATTRv, and 81 years (IQR: 76–85) with ATTRwt. Women represented 38% of AL, 34% of ATTRv, and 14% of ATTRwt patients. The baseline characteristics of the overall population and according to subtypes of CA are shown in *Table 1*. Overall, patient age, cardiovascular risk factors, clinical laboratory, and echocardiography variables differed significantly between CA subtypes (*Table 1*). Median age, hypertension, and ischaemic heart disease were significantly higher in ATTRwt patients ($P < 0.001$). While New York Heart Association (NYHA) status ($P = 0.003$), NT-proBNP and high-sensitivity troponin T levels ($P < 0.001$) were significantly higher in AL patients. ATTRwt patients had more atrial fibrillations ($P < 0.001$) and received significantly more oral anticoagulant ($P < 0.001$) than AL and ATTRv patients.

Figure 1 Flowchart.



Prevalence of iron deficiency among cardiac amyloidosis patients

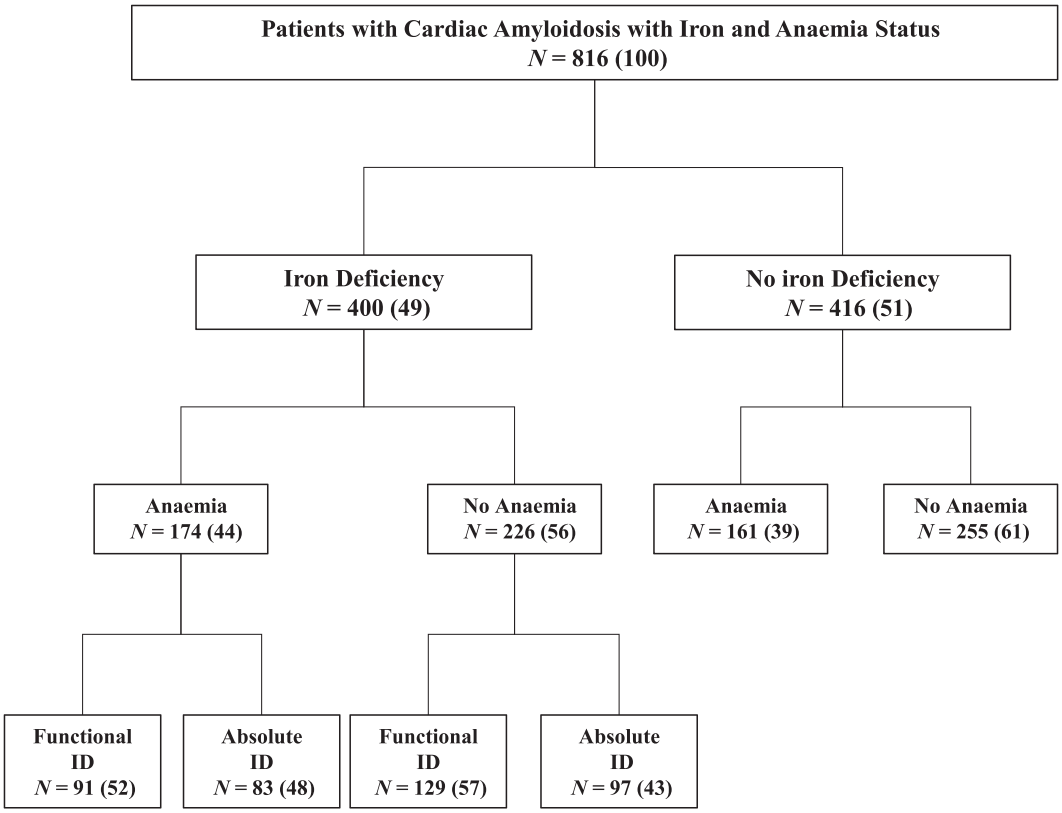
Iron deficiency was diagnosed in 400 CA patients (49%): 123 (45%) with AL, 95 (58%) with ATTRv, and 182 (48%) with ATTRwt (*Table 2*, *Figures 2* and *3A*). The baseline characteristics of the overall population and according to the presence or not of ID are shown in *Table 2*. The median ferritin levels in patients with ID were 113 μg/L compared with 326 μg/L in those without ID. Similarly, the median transferrin saturation levels were 14% in ID patients and 23% in those without ID.

Table 2 Baseline characteristics of patient according to iron status

	All CA		
ID status	ID	No ID	
N (%)	400 (49)	416 (51)	*P* value
Clinical characteristics			
Age at inclusion, years	76 (68; 83)	76 (67; 82)	0.212
Gender, women *n* (%)	125 (31)	85 (20)	<0.001
BMI, kg/m^2	25 (22; 27)	24 (22; 27)	0.285
CV risk factors			
Diabetes, *n* (%)	94 (24)	57 (14)	<0.001
Hypertension, *n* (%)	219 (55)	219 (53)	0.297
Dyslipidaemia, *n* (%)	137 (34)	122 (29)	0.336
CV characteristics			
NYHA Class III–IV vs I–II, *n* (%)	179 (48)	163 (43)	0.204
Heart rate, beats/min	75 (68; 85)	77 (68; 87)	0.171
Systolic blood pressure, mmHg	122 (108; 137)	121 (107; 139)	0.803
Atrial fibrillation, *n* (%)	106 (29)	107 (28)	0.812
Ischaemic heart disease, *n* (%)	84 (21)	66 (16)	0.085
Amyloidosis status			0.032
AL, *n* (%)	123 (45)	148 (55)	
ATTRv, *n* (%)	95 (56)	69 (44)	
ATTRwt, *n* (%)	182 (48)	199 (52)	
Echocardiography characteristics			
LVEF, %	50 (40; 59)	52 (43; 60)	0.069
LVEF class:			0.129
LVEF <40%, *n* (%)	86 (23)	67 (17)	
LVEF 40–50%, *n* (%)	108 (29)	112 (29)	
LVEF ≥50%, *n* (%)	183 (48)	210 (54)	
IVST, mm	17 (15; 20)	17 (15; 19)	0.828
GL strain, %	−10 (−7; −12)	−11 (−8; −13)	0.022
Biology variables			
NT-proBNP, ng/mL	3493 (1810; 6659)	3655 (1688; 6736)	0.988
Troponin T HS, ng/mL	72 (45; 106)	68 (45; 105)	0.519
eGFR, mL/min/1.73 m^2	50 (38; 67)	51 (37; 67)	0.996
Haemoglobin, g/dL	12.9 (11.5; 13.9)	13.3 (12.0; 14.3)	0.002
Mean corpuscular volume, μm^3	90 (85; 94)	93 (89; 97)	<0.001
Anaemia, *n* (%)	174 (44)	161 (39)	0.164
Ferritin, μg/L[a]	113 (63; 194)	326 (211; 520)	<0.001
Transferrin saturation, %[a]	14 (10; 17)	23 (20; 28)	<0.001
Anticoagulant and or antiplatelet treatments			
Aspirin, *n* (%)	122 (31)	91 (22)	0.004
Clopidogrel, *n* (%)	26 (7)	20 (5)	0.286
Oral anticoagulants, *n* (%)	209 (53)	225 (55)	0.655
Treatment of CHF			
ACE inhibitor, *n* (%)	101 (26)	115 (28)	0.465
ARB, *n* (%)	68 (17)	53 (13)	0.081
Digoxin, *n* (%)	8 (2)	6 (2)	0.649
Selective beta-blocker, *n* (%)	117 (30)	104 (25)	0.157
Non-selective beta-blocker, *n* (%)	7 (2)	9 (2)	0.678
Calcium antagonist, *n* (%)	114 (29)	108 (26)	0.388
Amiodarone, *n* (%)	75 (19)	84 (20)	0.629
Loop diuretic, *n* (%)	304 (77)	291 (71)	0.036
Thiazide diuretic, *n* (%)	140 (35)	138 (34)	0.544
Vasodilator, *n* (%)	11 (3)	14 (3)	0.620

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; GL, global longitudinal; ID, iron deficiency; I.V., intravenous; IVST, interventricular septum thickness; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
Values are median (interquartile range).
P: ID vs no ID in each category: All, AL, ATTRv, ATTRwt.
[a]By definition.

Figure 2 Prevalence of iron deficiency (ID) with or without anaemia.



Interestingly, median ferritin levels were significantly lower in ATTRv patients (139 μg/L) compared with those with AL (225 μg/L) and ATTRwt (210 μg/L) (*Table 1*).

Iron deficiency was functional in 67 patients with AL (55%), 40 with ATTRv (42%), and 113 with ATTRwt (62%) (*Figure 3 (B)*). It is noteworthy that ID was predominantly absolute in ATTRv patients (58%) (*Figure 3B*). The prevalence of anaemia was similar in patients with and without ID. Indeed, 174 patients (44%) with ID had anaemia vs. 161 (39%) without ID (P = 0.164) (*Table 2*).

Relationship between iron deficiency and clinical and biological imaging characteristics

In the overall population, there were no differences between patients with and without ID in terms of NYHA III–IV (48% vs. 43%; P = 0.2), NT-proBNP levels (3493 pg/mL vs. 3655 pg/mL; P = 0.988), nor high-sensitivity troponin T (72 ng/mL vs. 68 ng/mL; P = 0.519) (*Table 2*, *Figure 4A–C*). In terms of echocardiography characteristics, LVEF (50% in ID patients vs. 52% in non-ID patients; P = 0.069) and median IVST (17 mm in both groups; P = 0.828) were similar. In contrast, the left ventricular global longitudinal strain (GLS) was increased in patients with ID compared with those without ID (−10% vs. −11%; P = 0.022) (*Table 2*).

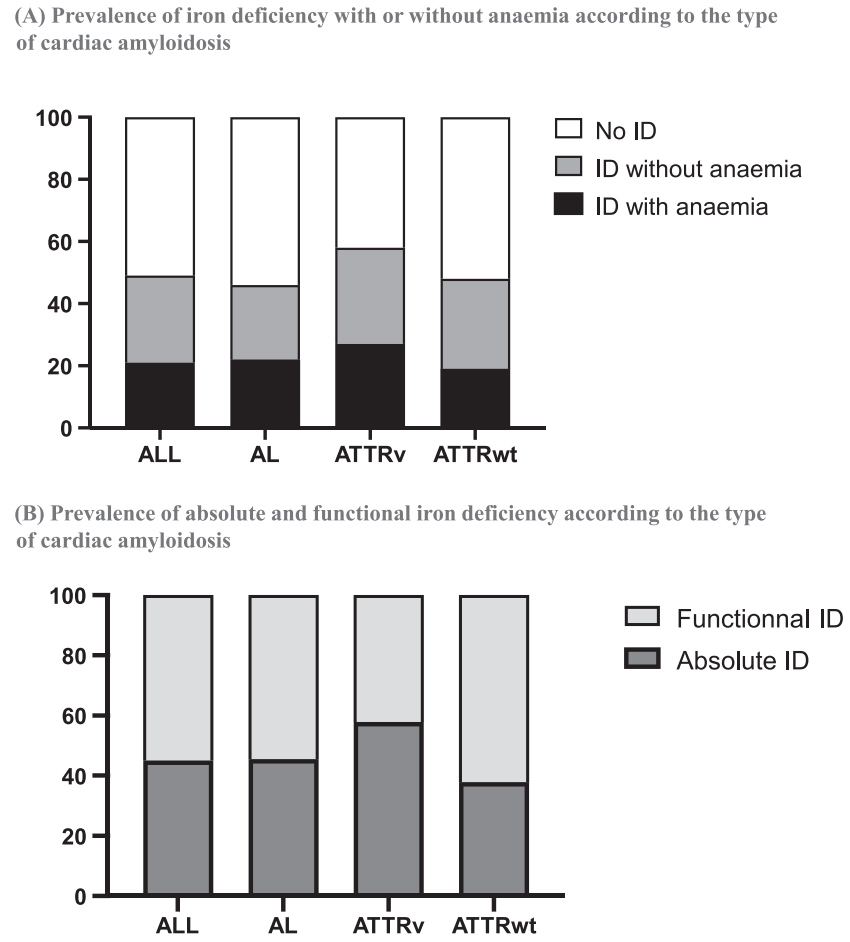
In ATTRwt subtype, ID patients presented more dyspnoea, with 46% classified NYHA III-IV compared with 34% of non-ID patients (P = 0.023) (*Table 3*). There were no other differences in the subtypes concerning symptoms, cardiac biomarkers, or echocardiography attributes.

In the overall population, the C-reactive protein (CRP) levels were significantly higher in patients with functional ID, 4.3 ng/mL, compared with 2.8 ng/mL in those with absolute ID (P = 0.001) (*supporting information*, *Table S1*).

Determinants of iron deficiency in cardiac amyloidosis

In multivariate analysis, by logistic regression (*Table 4*, *Figure 5*), the following variables were found to be significantly associated with ID: female sex, amyloidosis subtype (ATTRv/ATTRwt vs. AL), diabetes status, aspirin treatment, haemoglobin levels, and altered GLS.

Figure 3 Prevalence of iron deficiency (ID) among amyloid population. (A) Prevalence of iron deficiency with or without anaemia according to the type of cardiac amyloidosis. (B) Prevalence of absolute and functional iron deficiency according to the type of cardiac amyloidosis.



Impact on outcome

During a mean follow-up 17 months, a total of 299 deaths occurred (*Figure S1*) illustrates the freedom from all-cause mortality depending on the presence or not of ID. The difference in mortality was not significant different in CA patients with or without ID (log rank = 0.785).

Discussion

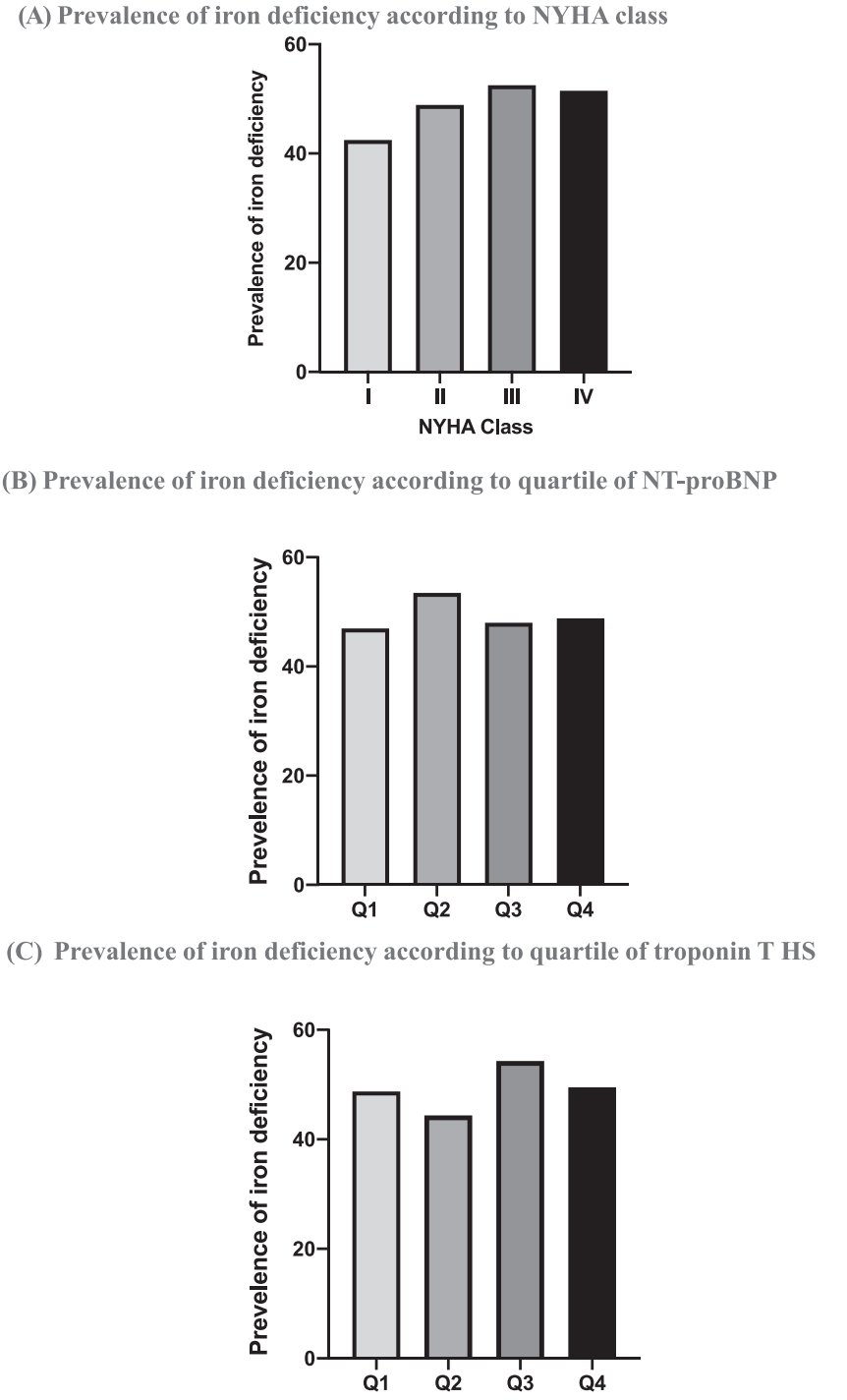
We found a high prevalence of ID in the CA patients (49%), which is comparable with that found in HF patients (50–62%).[2,8,9] ID was more frequent in ATTRv amyloidosis patients compared with those with ATTRwt and AL. The prevalence of ID was significantly associated with diabetes, aspirin treatment, altered GLS, and lower haemoglobin levels.

High prevalence of iron deficiency in cardiac amyloidosis

Iron deficiency incidence in CA is similar to that observed in HF patients and is not specific to a CA subtype. Thus, ID cannot be used for diagnosis. Multiple assessments, including electrocardiography, transthoracic echocardiogram, magnetic resonance imagery, and biological assessments (clonal expressions), should be used to diagnose CA. It is crucial that CA be diagnosis rapidly so that appropriate treatment, specific to the amyloidosis subtype, can be implemented. CA is a severe and debilitating disease with limited treatments to improve prognosis and symptoms.

In HF, several mechanisms cause inflammation and malabsorption of iron that results in ID.[6] Functional ID results from chronic inflammation with iron sequestration by macrophages.[6] Elevated levels of interleukin-6 are associated with inflammatory iron sequestration in HF and increased iron metabolism.[29] HF is also associated with structural and

Figure 4 (A) Prevalence of iron deficiency according to New York Heart Association (NYHA) class. (B) Prevalence of iron deficiency according to quartile of N-terminal pro-B-type natriuretic peptide (NT-proBNP). (C) Prevalence of iron deficiency according to quartile of troponin T HS.



functional changes in the gut that result in peritoneal oedema and malabsorption, causing absolute ID.[30] We analysed albumin levels classified by tertiles according to ID status. Patients with ID had significantly decreased albumin levels, affirming the malabsorption hypothesis (*Figure S2*, T1 vs. T2 vs. T3, $P = 0.022$).

In our study, we observed a more pronounced systemic inflammation (higher levels of CRP) in CA patients with functional ID than those with absolute ID. Thus, in patients with absolute ID, we suspect that other mechanisms specific to amyloidosis, such as gastrointestinal bleeding, might be involved.[23] Recently, a study confirmed, by duodenal biopsy,

Table 3 Baseline characteristics of patient according to iron status by amyloidosis status

Type of amyloidosis	AL			ATTRv			ATTRwt		
ID status	ID	No ID		ID	No ID		ID	No ID	
N (%)	123 (45)	148 (55)	*P*	95 (58)	69 (42)	*P*	182 (48)	199 (52)	*P*
Clinical characteristics									
Age at inclusion, years	68 (55; 75)	67 (60; 74)	0.845	74 (68; 79)	71 (63; 78)	0.131	82 (76; 86)	81 (76; 84)	0.124
Gender, women *n* (%)	61 (49)	42 (28)	<0.001	33 (35)	22 (32)	0.702	31 (17)	21 (11)	0.066
BMI, kg/m^2	24 (22; 27)	23 (21; 27)	0.248	25 (22; 27)	24 (21; 27)	0.879	25 (22; 28)	25 (23; 28)	0.979
CV risk factors									
Diabetes, *n* (%)	22 (18)	23 (16)	0.605	24 (25)	8 (12)	0.029	48 (26)	26 (13)	0.001
Hypertension, *n* (%)	43 (35)	64 (43)	0.165	59 (62)	32 (46)	0.045	117 (64)	123 (62)	0.617
Dyslipidaemia, *n* (%)	31 (25)	42 (28)	0.590	24 (25)	18 (26)	0.948	82 (45)	62 (31)	0.029
CV characteristics									
NYHA Class III–IV vs. I–II, *n* (%)	60 (53)	70 (56)	0.650	41 (45)	28 (44)	0.988	78 (46)	65 (34)	0.023
Heart rate, beats/min	81 (71; 94)	82 (74; 93)	0.543	75 (67; 82)	74 (65; 84)	0.700	73 (67; 80)	75 (66; 81)	0.361
Systolic blood pressure, mmHg	112 (101; 128)	111 (100; 126)	0.639	126 (108; 139)	115 (107; 130)	0.078	128 (114; 140)	130 (116; 145)	0.093
Atrial fibrillation, *n* (%)	12 (11)	18 (13)	0.584	21 (23)	11 (19)	0.551	73 (44)	78 (42)	0.704
Ischaemic heart disease, *n* (%)	20 (17)	18 (12)	0.176	9 (10)	3 (4)	0.141	55 (30)	45 (23)	0.173
Echocardiography characteristics									
LVEF, %	53 (44; 62)	55 (46; 62)	0.420	48 (35; 59)	50 (37; 58)	0.549	50 (40; 58)	51 (42; 58)	0.189
IVST, mm	15 (14; 17)	15 (13; 17)	0.254	17 (15; 21)	18 (16; 20)	0.700	17 (15; 20)	18 (16; 20)	0.213
GL strain, %	10 (8; 13)	11 (9; 14)	0.320	10 (8; 12)	10 (8; 14)	0.150	10 (7; 12)	10 (8; 13)	0.116
Biology variables									
NT-proBNP, ng/mL	4960 (2036; 10 541)	5 227 (2394; 13 099)	0.634	2553 (1253; 5404)	2150 (799; 5440)	0.296	3310 (1929; 6368)	3233 (1556; 5605)	0.388
Troponin T HS, ng/mL	83 (46; 123)	84 (56; 151)	0.358	65 (41; 99)	67 (30; 95)	0.536	70 (46; 98)	62 (41; 93)	0.050
eGFR, mL/min/1.73 m^2	58 (41; 77)	52 (35; 72)	0.162	51 (38; 65)	58 (36; 79)	0.157	47 (35; 58)	48 (37; 61)	0.500
Haemoglobin, g/dL	12.4 (10.9; 13.6)	12.8 (10.8; 13.9)	0.320	12.7 (11.5; 13.6)	13.0 (11.8; 13.9)	0.259	13.2 (11.9; 14.2)	13.6 (12.6; 14.7)	0.001
Mean corpuscular volume, μm^3	90 (85; 94)	96 (88; 97)	0.001	88 (84; 92)	92 (89; 96)	<0.001	91 (86; 94)	94 (90; 97)	<0.001
Anaemia, *n* (%)	59 (48)	76 (51)	0.579	44 (46)	26 (38)	0.278	71 (39)	59 (30)	0.054
Ferritin, μg/L[a]	118 (59; 185)	343 (252; 578)	<0.001	81 (56; 141)	308 (183; 482)	<0.001	126 (75; 208)	307 (205; 511)	<0.001
Transferrin saturation, %[a]	13 (9; 17)	22 (18:27)	<0.001	14 (10; 17)	25 (21; 31)	<0.001	14 (11; 18)	23 (20; 28)	<0.001
Anticoagulant and or antiplatelet treatments									
Aspirin, *n* (%)	37 (31)	38 (26)	0.350	27 (29)	7 (10)	0.004	58 (32)	46 (24)	0.068
Clopidogrel, *n* (%)	5 (4)	7 (5)	0.825	5 (5)	1 (1)	0.191	16 (9)	12 (6)	0.322
Oral anti-coagulants, *n* (%)	45 (38)	66 (45)	0.241	41 (44)	33 (48)	0.637	123 (68)	126 (64)	0.499
Treatment of CHF									
ACE inhibitor, *n* (%)	16 (13)	26 (18)	0.343	27 (29)	27 (39)	0.178	58 (32)	62 (32)	0.961
ARB, *n* (%)	11 (9)	14 (10)	0.935	21 (23)	8 (12)	0.071	36 (20)	31 (16)	0.313
Digoxin, *n* (%)	1 (1)	1 (1)	0.881	1 (1)	0 (0)	0.388	4 (2)	7 (4)	0.427
Selective beta-blocker, *n* (%)	28 (23)	35 (24)	0.952	29 (31)	19 (28)	0.615	60 (33)	50 (26)	0.111
Non-selective beta-blocker, *n* (%)	3 (3)	2 (1)	0.490	0 (0)	1 (1)	0.244	4 (2)	6 (3)	0.601
Calcium antagonist, *n* (%)	23 (19)	39 (26)	0.165	34 (37)	11 (16)	0.004	57 (31)	58 (30)	0.715
Amiodarone, *n* (%)	14 (12)	24 (16)	0.288	18 (19)	13 (19)	0.934	43 (24)	47 (24)	0.936
Loop diuretic, *n* (%)	91 (76)	106 (72)	0.437	42 (61)	65 (70)	0.230	148 (81)	143 (73)	0.054
Thiazide diuretic, *n* (%)	33 (28)	36 (24)	0.554	33 (36)	28 (41)	0.508	74 (41)	74 (38)	0.563
Vasodilator, *n* (%)	3 (3)	5 (3)	0.674	4 (4)	1 (1)	0.299	4 (2)	8 (4)	0.297

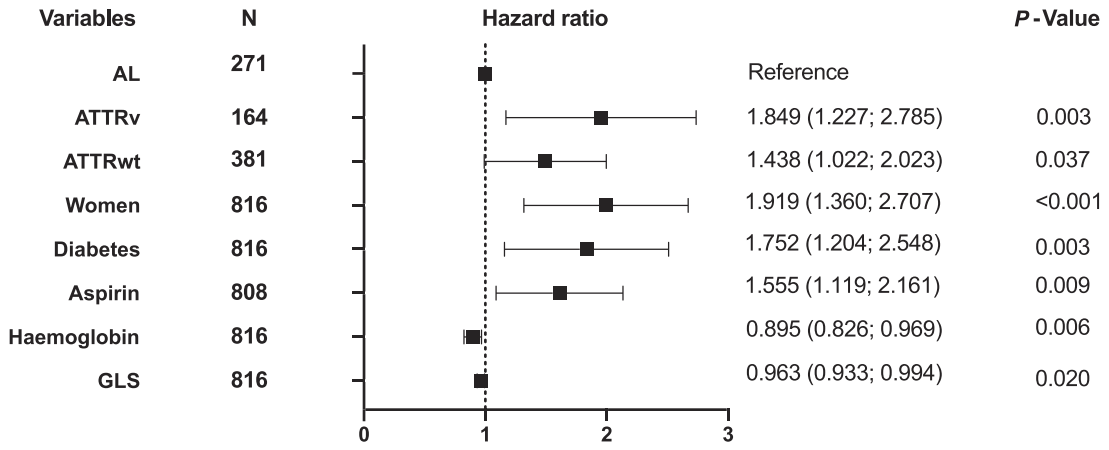
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; GL, global longitudinal; ID, iron deficiency; I.V., intravenous; IVST, interventricular septum thickness; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
P: ID vs. no ID in each category: All, AL, ATTRv, ATTRwt.
Values are median (interquartile range).
[a]By definition.

Table 4 Univariate and multivariate logistic regression of the iron deficiency determinants in cardiac amyloidosis

		Univariate			Multivariate		
Variables	*N*	Hazard ratio	CI	*P* value	Hazard ratio	CI	*P* value
Women	816	1.770	1.287; 2.434	<0.001	1.919	1.360; 2.707	<0.001
Amyloidosis type	271		AL reference			AL reference	
ATTRv	164	1.657	1.120; 2.451	0.012	1.849	1.227; 2.785	0.003
ATTRwt	381	1.100	0.805; 1.504	0.548	1.438	1.022; 2.023	0.037
Diabetes	816	1.935	1.346; 2.780	<0.001	1.752	1.204; 2.548	0.003
Aspirin	808	1.581	1.153; 2.168	0.004	1.555	1.119; 2.161	0.009
Haemoglobin	816	0.892	0.827; 0.961	0.003	0.895	0.826; 0.969	0.006
Absolute GLS	816	0.970	0.941; 1.000	0.049	0.963	0.933; 0.994	0.020

CI, confidence interval; GLS, global longitudinal strain.

Figure 5 Iron deficiency's determinants in cardiac amyloidosis.



submucosal amyloid deposits of AL and TTR fibrils in systemic amyloidosis.[24] As the duodenum is the predominant site of iron absorption, this infiltration may limit iron absorption in the intestine, leading to ID. In addition, intestinal bleeding, a major cause of ID, is associated with amyloidosis.[31] Amyloid deposits on blood vessel walls may cause erosive changes and mucosal friability leading to intestinal bleeding.[31] Aspirin treatment can accentuate this gastrointestinal frailty.[32]

The AL amyloidosis, contrary to ATTR, is often associated with hepatic amyloid infiltration.[33] This liver involvement includes hyperbilirubinemia and hepatic insufficiency.[34] In our AL CA population, we analysed bilirubin levels classified by tertiles: patients with ID had higher bilirubin levels (data not shown, T1 vs. T2 vs. T3, $P = 0.031$).

Variations of iron deficiency prevalence and severity among cardiac amyloidosis types

Iron deficiency severity was different in the CA subtypes. ID was more severe (with lower ferritin levels) in ATTRv while HF severity appears to be less severe in the same patients (with lower NT-proBNP levels). The increased severity of ID resulting from the prolonged exposure of the intestinal tract to amyloid protein in ATTRv amyloidosis due to early onset because of its genetic aetiology. This extended exposure can lead to chronic intestinal bleeding in ATTRv patients that exacerbates ID. ATTRv amyloidosis is also associated with gastroparesis, leading to malnutrition, attributed to autonomic dysfunction by nerve infiltrations.[23] In contrast, these gastrointestinal autonomic dysfunctions are poorly described in AL and ATTRwt amyloidosis.

Clinical and imaging variables associated with iron deficiency in amyloidosis

Several characteristics were significantly associated with ID, including diabetes, aspirin treatment, and GLS. Diabetes was present in 24% of patients with ID compared with 14% in those without ID ($P < 0.001$). The association between ID and diabetes has already been described.[2,9,35] Indeed, Praveen *et al*. reported that 14/89 (16%) diabetic patients had ID[35] and identified a significantly increased inflammatory response in these patients. They suggest that chronic inflammation in diabetic patients leads to macrophage iron

sequestration (functional ID) and intestinal malabsorption (absolute ID).

Aspirin treatment was identified as a determinant of ID in our CA population (HR = 1.55, P = 0.009). As previously described, chronic use of aspirin increases the risk of gastrointestinal bleeding. A randomized control trial reported a 60% increase in gastrointestinal bleeding in patients using aspirin.[32]

Altered GLS was also associated with ID (P = 0.049). Altered GLS is an established independent prognosis marker in CA and is strongly associated with cardiac amyloid burden.[36,37] Data regarding a potential link between iron status and LV function are limited. Iron participates in several enzymatic reactions implicated in cellular respiration, oxidative phosphorylation, citric acid cycle, and production of reactive oxygen species.[38,39] Indeed, mitochondrial and left ventricular dysfunction have been associated with ID in an animal model.[40] Therefore, ID could be associated with amyloid infiltration and toxicity, leading to cardiomyocyte dysfunction in CA patients.

Iron therapy for HF patients with ID is beneficial, particularly in HFrEF and HFpEF patients.[4,41–44] The benefits include fewer cardiovascular-related hospitalizations, with improved heart function, exercise capacity, and quality of life. HF patients with anaemia benefit more from intravenous iron therapy than those without anaemia. Intravenous iron therapy reduces heart failure hospitalization but not cardiovascular mortality in HFrEF patients with ID.[15] Considering the prevalence of ID in CA, the benefit of iron therapy in these patients needs to be assessed.

Study limitations

This study has several limitations. Our study was designed as an observational study and not a randomized controlled trial. HF is strongly associated with ID. Thus, in CA patients, the severity of HF may interfere with ID prevalence. Indeed, ID was associated with ATTRv patients that had less severe HF signs compared with AL or ATTRwt patients. Unfortunately, we did not collect data concerning the cardiac hepcidin–ferroportin axis shown to be essential for cardiomyocyte iron homeostasis and heart function. We spared patients from invasive cardiac biopsies that would have allowed us to assess cardiac iron concentration. In HFrEF, cardiac iron concentrations have been shown to be unrelated to biomarkers of systemic iron status or anaemia.[45] However, cardiac iron concentrations are associated with disease severity. It would have been interesting to see if this association also exists in CA.

Our retrospective study design does not allow us to further assess mortality in patients with and without ID, found to be not significantly different. A prospective study is needed to confirm our result. Finally, our study does not address the therapeutic use of iron in CA. The benefit of intravenous iron therapy in CA needs to be evaluated in a randomized, placebo-controlled trial.

Conclusions

Iron deficiency is frequent in patients with CA and more prevalent in ATTRv compared with AL and ATTRwt amyloidosis. ID was independently associated with female gender, amyloidosis type, diabetes, aspirin treatment, lower haemoglobin levels, and altered left ventricular GLS. The presence of ID does not seem to be associated with increased mortality. Prospective studies are needed to assess whether ID affects morbidity and mortality, as well as the benefit of iron in CA patients.

Conflict of interest

T.D. has received grant and/or consultant fees from Pfizer, Alnylam, Vifor, Akcea, Novartis, Resmed, Bayer, Astra-Zeneca, Sanofi-Aventis. A.J.D. has received grant and/or consultant fees from Novartis, Amicus, Sanofi-Genzyme, Boehringer Ingelheim.

Supporting information

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

Figure S1: Survival according iron status.
Figure S2: Ferritin levels according to albumin.
Table S1: CRP levels according ID status and CA subtype.

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