Iron deficiency in patients with cancer: a prospective cross-sectional study

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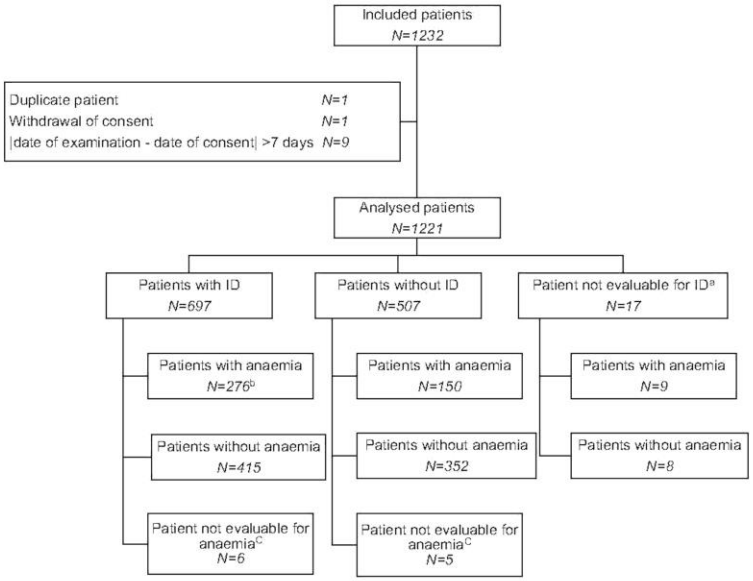

Iron deficiency in cancer patients: a prospective cross-sectional study

Running head: Iron deficiency in cancer patients

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Abstract

Background

Despite the deleterious consequences of iron deficiency (ID) in patients with cancer, under-diagnosis is frequent. The CARENFER study aimed to assess the prevalence of ID using both serum ferritin concentration and transferrin coefficient saturation (TSAT) index, as well as iron deficiency anaemia in cancer patients.

Methods

This prospective cross-sectional study was conducted in 15 oncology units in France in 2019. All patients present in the medical unit during the 2-week study period, regardless of the type of tumour (solid or haematological) and treatment, were eligible. Serum ferritin concentration, TSAT index and haemoglobin (Hb) level were determined. ID and iron deficiency-associated anaemia were defined according to ESMO 2018 Guidelines: ID was defined either as ferritin <100µg/L (absolute ID) or as ferritin ≥100µg/L and TSAT <20% (functional ID).

Results

A total of 1221 patients with different types of solid malignant tumours were analysed: median age 64 years; 89.4% under treatment for their cancer, mainly by chemotherapy (75.4%). Overall, ID was found in 57.9% (55.1-60.6) of patients. Among them, functional ID accounted for 64% of cases. Iron deficiency anaemia was reported in 21.8% (19.6-24.2) of all cancer patients. ID was highly prevalent in untreated (75/130, 57.4%) and non-anaemic (419/775, 54.1%) patients.

Conclusion

This study highlights the high prevalence of ID in cancer patients, whether or not associated with anaemia or treatment. These results emphasise the need to a better detection and management of ID in cancer, thereby optimising overall patient care.

Keywords

Anaemia; iron-deficiency; Cancer; Epidemiology; Prevalence; Adults.

Key Messages Box

1. What was already known?
    - ID is frequently undetected and untreated in cancer patients.
2. What are the new findings?
    - ID is highly prevalent (≥50%), whether patients are anaemic and treated for their cancer or not.
    - Using both TSAT and serum ferritin improves ID diagnosis.
3. What is their significance?
    - Early detection and management of ID in all cancer patients is warranted.

INTRODUCTION

Iron deficiency (ID) with or without anaemia is highly prevalent in patients with cancer,[1] with studies reporting prevalence estimates as high as 63% in patients with pancreatic cancer.[2] Solid tumours, in particular pancreatic, gastrointestinal and lung cancers, being at an advanced stage of disease and undergoing chemotherapy are associated with a higher risk of ID.[3]

Before the onset of anaemia, ID causes fatigue, weakness, impaired physical and cognitive functions, all contributing to a reduced quality of life.[4][5][6] Anaemia is often the final consequence of ID. It is an additional risk factor for mortality in cancer patients [7] and it has also been shown to compromise response to cancer treatment.[8][9][10]

In patients with chronic condition such as cancer, ID is mainly the consequence of impaired erythropoietic activity and disturbed iron homeostasis due to the release of inflammatory cytokines.[11][12] In such a case, ID is categorized as functional ID where iron stores are filled but iron cannot be efficiently mobilised from stores to the erythroblast. To a lesser extent, ID is due to an insufficient iron intake or chronic blood loss, leading to a decrease in iron stores (absolute ID). Therefore, ID diagnosis in cancer patients cannot be based on ferritin level only. It must rely on the combined use of both circulating ferritin level and iron-saturation of transferrin (TSAT) index that is an indicator of biologically available iron.[13][14][15] Therefore, the French National Authority for Health (Haute Autorité de Santé, France) recommends that diagnosis of ID in patients with chronic inflammatory diseases such as cancer must systematically be based on both biomarkers.[16] These recommendations are in line with the latest guidelines from the European Society of Medical Oncology (ESMO) for the management of ID and anaemia in patients with cancer.[17]

However, despite the high prevalence and potential deleterious consequences of ID and anaemia in patients with cancer, under-diagnosis is frequent. Concomitant existence of ID and anaemia and type of ID (functional *vs.* absolute) using both biomarkers are rarely determined.[18] A recent study based on French healthcare databases including more than

100,000 patients undergoing iron replacement therapy from 2006 to 2015 showed that ID was highly under-detected, including in patients with cancer.[19] Under-detection and potential misclassification of patients with cancer regarding ID, iron deficiency-associated anaemia and type of ID hindered their appropriate management based on the ESMO guidelines.[17]

In this large, prospective study, we aimed to assess the prevalence of ID, anaemia and iron deficiency-associated anaemia based on ESMO recommendations in patients with cancer.

MATERIALS AND METHODS

Study sites and population

The CARENFER study was conducted in France between May 2019 and July 2019. It is a cross-sectional, prospective study carried out in 15 wards for the management of patients with cancer, which were selected based on a voluntary basis at a national level. Based on the conservative assumption that the prevalence of iron deficiency is 50%,[20] we calculated that 1,200 patients had to be recruited to estimate the prevalence of ID with a precision between 2.5% and 3%.

All patients present in the medical unit during the study period, whether in-patient or out-patient, regardless of the type of tumour (solid or haematological) and treatment, were eligible. Few inclusion criteria were considered in order to limit selection bias: 18 years old or more, registration with a Social Security system, and signed written informed consent. Patients under guardianship or curatorship as well as patients hospitalized without consent were not included.

Study procedures

For all included patients, a standardised questionnaire was conducted. The following information was recorded: patient's demographic and clinical data (age, sex, weight and height), date of cancer diagnosis, ongoing treatment (yes/no, and type of treatment), iron replacement therapy before inclusion in the study (yes/no, oral *vs* intravenous iron and dose administered), and ongoing treatment for anaemia such as red blood cell (RBC), transfusion or

erythropoietin (EPO). A 4 mL venous EDTA blood sample (for Hb level determination) and a 4 mL total blood sample (for serum iron and ferritin concentrations determination) were collected at inclusion. For patients who had a recent (i.e., within 7 days before their inclusion in the present study) determination of Hb level and iron stores, no additional biochemical assessment was performed at inclusion.

Finally, a data quality control was performed throughout the study to ensure that individual data collection was complete and consistent with the patient's medical record and hospital registers.

Definitions

In 2018, ESMO released updated clinical practice guidelines on the management of anaemia and iron deficiency in patients with cancer.[17] In this study, ID, anaemia and iron deficiency-associated anaemia definitions were based on those guidelines: ID was defined as either serum ferritin <100µg/L (absolute ID) or the combination of serum ferritin ≥100µg/L and TSAT <20% (functional ID); anaemia (all causes) was defined as an Hb ≤11g/dL. The definition for iron deficiency-associated anaemia was also based on ESMO guidelines for the management of anaemia: between 10 and 11g/dL it was defined as TSAT< 20% or ferritin <100 µg/L; and between 8 and 10g/dL, it was defined as ferritin <100µg/L or the combination of ferritin ≥100µg/L and TSAT<20%. ESMO recommends that patients with Hb <8g/dL should be transfused, as their anaemia cannot be corrected by iron and/or EPO therapy. It was therefore decided not to include these patients in the definition of iron deficiency-associated anaemia. However, these patients were classified as anaemic (i.e., with Hb≤11g/dL).

Statistics

First, patients' demographic and clinical characteristics were described. Second, the prevalence of ID, anaemia and iron deficiency-associated anaemia was calculated. The proportion of ferritin level <100µg/L, TSAT index <20%, ID, and iron deficiency-associated anaemia was computed according to both the existence of anaemia and ongoing treatment for their cancer.

Continuous variables with a Gaussian distribution are presented as mean ± standard deviation (STD). For variables distributed in a non-Gaussian manner, the data are shown as medians with interquartile ranges (IQR). Normality was checked by the Shapiro–Wilk statistic. Categorical data were expressed as percentages. The prevalence of events was estimated with Agresti-Coull 95% confidence interval.[21] Missing data were not taken into account in the analysis. All statistics were performed using SAS Version 9.4.

Ethics

The protocol complied with recommendations of the Declaration of Helsinki, and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations. The protocol also complied with the French laws and regulations. Ethical approval was granted by an Ethical Committee (Comité de Protection des Personnes) designated randomly by the French Ministry of Health. All subjects provided written informed consent. ClinicalTrials.gov Identifier: NCT03924271.

RESULTS

Study population and laboratory investigations

A total of 1,232 patients were included in 15 centres (12 oncology units and 3 onco-geriatric units). Among them, 11 were excluded from the analysis because of consent withdrawal (n=1), duplicate inclusion (n=1) or a too long delay between patient's study acceptance and examination (Figure 1). For 17 (1.3%) patients, TSAT index and/or ferritin level was not available and ID could not be determined.

Patient's characteristics at inclusion are presented in Table 1. Males represented 44.6% of the study population. Patients' median age was 64 years. Pre-menopausal women (i.e. ≤ 50 years old) represented 19.2% of the female population. Cancer was diagnosed for less than 1 year in 28.5% of patients, and more than 5 years in 18.4%. Almost 90% of patients were currently being treated for their cancer. The two main ongoing therapies were chemotherapy for 75.4%

of patients, and targeted therapy for 17.8% of them. Ongoing iron replacement therapy was recorded in 5.8% of patients. Recent or current RBC transfusion and EPO administration was recorded in 9.9% and 2.0% of patients, respectively.

Table 1. Baseline Characteristics of the patients.

Characteristics	**Study population** ***(N = 1221)***	
Gender		
Male, n (%)	545	(44.6)
Female, n (%)	676	(55.4)
Age (years), median (IQR)	64.0	(55.0;71.0)
BMI (kg/m²), median (IQR)	24.4	(21.6;27.8)
BMI categories, n (%)		
Underweight: <18.5 kg/m²	86	(7.1)
Normal weight: [18.5-250[kg/m²	579	(47.7)
Overweight: [25.0-30.0[kg/m²	353	(29.1)
Obesity: ≥30.0 kg/m²	195	(16.1)
Time from cancer diagnosis, n (%)		
<1 year	348	(28.5)
[1-2[years	347	(28.4)
[2-5[years	301	(24.7)
[5-10[years	140	(11.5)
≥10 years	84	(6.9)
Currently treated for cancer n (%)	1091	(89.4)
If yes[a],		
Neo-adjuvant treatment	143	(13.4)
Adjuvant treatment	300	(28.1)
Metastatic treatment	626	(58.6)
Treatment regimen[b]		
Chemotherapy	823	(75.4)
Targeted therapy	194	(17.8)
Immunotherapy	112	(10.3)
Hormone therapy	37	(3.4)
Chemoradiation	33	(3.0)
Radiation	10	(0.9)
Oral iron[a], n (%)	20	(1.6)
Intravenous iron[a], n (%)	49	(4.2)
Red blood cell transfusion[a], n (%)	120	(9.9)
Erythropoietin administration[a], n (%)	24	(2.0)

[a] *Ongoing treatment at inclusion;* [b] *Several possible treatments.*
Missing data: 8 for BMI and Erythropoietin, 1 for time from cancer diagnosis, 22 for type of treatment, 3 for treatment regimen, 6 for oral iron, 46 for IV iron, 4 for red blood cell transfusion.
BMI: body mass index; IQR: interquartile range.

For 12.1% (148/1221) of the patients, the determination of both Hb level and iron stores was performed in doctors' practices prior to inclusion, for 87.9% it was performed in hospital at the time of inclusion. The proportion of patients with a ferritin level <100µg/L was 20.5% and those with a TSAT index <20% was 50.6% (Table 2). Iron deficiency based on both ferritin level and TSAT index could be investigated in 98.6% of patients (1204/1221, 17 missing evaluations).

Table 2. Patients' biological characteristics.

Characteristics	**Study population** ***(N = 1221)***	
Laboratory analysis[a]		
Serum iron (mg/L), median (IQR)	0.6	(0.4;0.8)
Haemoglobin level (g/dL), mean±STD	11.7	±1.9
Haemoglobin level categories, n (%)		
<8g/dL	25	(2.1)
[8-10] g/dL	220	(18.2)
]10-11] g/dL	179	(15.7)
>11g/dL	775	(64.0)
Serum ferritin level (µg/L), median (IQR)	258.0	(118.5;538.0)
Serum ferritin level categories, n (%)		
<100µg/L	247	(20.5)
≥100µg/L	957	(79.5)
TSAT (%), median (IQR)	19.0	(14.0 ;27.0)
TSAT categories, n (%)		
<20%	609	(50.6)
≥20%	594	(49.4)

[a] *Laboratory analysis with available data (around 5% of missing data).*
Missing data: 18 for serum iron and TSAT, 11 for haemoglobin level, and 17 for serum ferritin level.
TSAT: iron-saturation of transferrin; IQR: interquartile range.

Prevalence of ID, anaemia and iron deficiency-associated anaemia

ID prevalence was reported in 57.9% (55.1-60.6) of patients (Table 3). Functional ID represented 64% of all ID cases. Women were more likely to suffer from ID than male (64.6% vs. 49.5%, respectively). ID was more prevalent in pre-menopausal (76.0% [67.9-82.6]) *vs.* post-menopausal women (61.9% [57.7-65.9]). More than one third (36.0%) of patients were anaemic, and approximately half of them had an Hb level between 10 and 11g/dL.

Table 3. Prevalence of iron deficiency, anaemia and iron deficiency-associated anaemia.

Parameter	**n/N**	**Study population *(N = 1221)***	
		%	95%CI
Iron deficiency [a]	697/1204	57.9	[55.1-60.6]
Anaemia [b]	435/1210	36.0	[33.3-38.7]
Iron deficiency-associated anaemia [c]	263/1206	21.8	[19.6-24.2]

[a] *Iron deficiency was defined as ferritin level less than 100µg/L or TSAT index less than 20%.*
[b] *Anaemia defined as an Hb level ≤ 11g/dL.*
[c] *Iron deficiency-associated anaemia was defined as: 1) Hb level between 8 and 10g/dL and ferritin < 100µg/L, 2) Hb level between 8 and 10g/dL and TSAT<20% and ferritin ≥ 100µg/L, 3) Hb level between 10 and 11g/dL and TSAT<20%, or 4) Hb level between 10 and 11g/dL and ferritin < 100µg/L.*
TSAT: iron-saturation of transferrin; Hb: haemoglobin.

The prevalence of ID was 64.8% (60.1-69.2) in anaemic patients. Of note, 54.1% of non-anaemic patients also presented an ID (50.6-57.6) (Table 4).

Table 4. Iron parameters and iron deficiency indicators (ID and iron deficiency-associated anaemia) according to the presence/absence of anaemia.

Parameter	**Anaemia[a] *(N = 435)***		**Absence of anaemia[a] *(N = 775)***	
	%	95%CI	%	95%CI
Iron deficiency[b]	64.8	[60.1-69.2]	54.1	[50.6-57.6]
Iron deficiency-associated anaemia[c]	61.7	[57.0-66.2]	-	-
Ferritin level < 100µg/L	11.9	[9.2-15.4]	25.3	[22.3-28.5]
TSAT < 20%	63.1	[58.4-67.5]	43.7	[40.2-47.2]

[a]*Anaemia defined as an Hb level ≤ 11g/dL*
[b]*Iron deficiency was defined as ferritin level less than 100µg/L or TSAT index less than 20%*
[c]*Iron deficiency anaemia was defined as: 1) Hb level between 8 and 10 g/dL and ferritin < 100µg/L, 2) Hb level between 8 and 10g/dL and TSAT<20% and ferritin ≥ 100µg/L, 3) Hb level between 10 and 11g/dL and TSAT< 20%, or 4) Hb level between 10 and 11g/dL and ferritin < 100µg/L.*
TSAT: iron-saturation of transferrin; Hb: haemoglobin.

Table 5 shows the distribution of iron parameters and the prevalence of ID according to main ongoing treatments (chemotherapy, immunotherapy and targeted therapy). The prevalence of ID appeared quite similar in all treatment categories, ranging from 54.9% to 60.7%. It is important to note that ID prevalence was similar in treated cancer patients compared with

untreated patients (58.0% *vs* 57.4%, respectively). Patients treated with chemotherapy were more likely to have a TSAT index <20%, but less likely to have a low ferritin level compared to patients receiving other treatments.

Table 5. Iron parameters and iron deficiency indicators according to ongoing antineoplastic treatment.

	Ongoing treatment												No treatment	
	Curative				Palliative		Regimen							
Parameter	**Neo-adjuvant** ***(N = 143)***		**Adjuvant** ***(N = 300)***		**Metastatic treatment[a]** ***(N = 626)***		**Chemotherapy[b]** ***(N = 823)***		**Targeted therapy[b]** ***(N = 194)***		**Immuno-therapy[b]** ***(N = 112)***		***(N = 130)***	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI	%	95%CI
Ferritin level < 100µg/L	23.2	[17.0-30.9]	21.2	[16.9-26.2]	19.1	[16.2-22.4]	18.0	[15.5-20.8]	28.4	[22.5-35.2]	25.7	[18.4-34.7]	23.1	[16.6-31.1]
TSAT < 20%	51.0	[42.9-59.1]	47.1	[41.5-52.8]	53.8	[49.8-57.7]	53.0	[49.6-56.4]	42.9	[36.1-50.0]	49.5	[40.2-58.9]	48.8	[40.4-57.4]
Iron deficiency[c]	56.6	[48.5-64.5]	54.9	[49.2-60.4]	60.7	[56.8-64.5]	58.9	[55.5-62.3]	56.0	[48.9-62.9]	60.2	[50.7-68.9]	57.4	[48.7-65.6]
Anaemia[d]	39.0	[31.3-47.3]	31.3	[26.3-36.8]	39.1	[35.3-43.0]	41.5	[38.1-44.9]	20.9	[15.7-27.3]	21.6	[14.9-30.2]	32.8	[25.3-41.4]
Iron deficiency-associated anaemia[e]	26.1	[19.5-33.9]	18.5	[14.5-23.3]	23.9	[20.7-27.4]	25.3	[22.4-28.4]	13.7	[9.5-19.3]	13.6	[8.3-21.4]	17.8	[12.1-25.4]

[a] *Exclusive categories: neo-adjuvant, adjuvant or metastatic treatment (or no treatment).*

[b] *Patients could have several treatments (chemotherapy + targeted therapy for 81 patients, chemotherapy + immunotherapy for 11 patients, targeted therapy + immunotherapy for 4 patients, and all the 3 for 1 patient).*

[c] *Iron deficiency was defined as ferritin level less than 100µg/L or TSAT index less than 20%.*

[d] *Anaemia defined as an Hb level ≤ 11g/dL.*

[e] *Iron deficiency-associated anaemia was defined as: 1) Hb level between 8 and 10g/dL and ferritin < 100µg/L, 2) Hb level between 8 and 10g/dL and TSAT<20%. and ferritin ≥ 100µg/L, 3) Hb level between 10 and 1g/dL and TSAT< 20%, or 4) Hb level between 10 and 11g/dL and ferritin < 100µg/L.*

TSAT: iron-saturation of transferrin; Hb: haemoglobin.

Overall, iron deficiency-associated anaemia based on ESMO guidelines was diagnosed in 21.8% [19.6-24.2] of patients (Table 3). In anaemic patients, anaemia was considered to be related to ID in 61.7% [57.0-66.2] (Table 4). In contrast to what was observed for ID, patients treated with chemotherapy were more likely to be anaemic compared with patients treated with targeted therapy and immunotherapy (41.5% [38.1-44.9], 20.9% [15.7-27.3] and 21.6% [14.9-30.2], respectively) (Table 5). The same trend was observed for iron deficiency-associated anaemia (25.3% [22.4-28.4], 13.7% [9.5-19.3] and 13.6% [8.3-21.4]).

DISCUSSION

In this relatively large prospective study, we show that as many as 57.9% of patients present an ID based on both serum ferritin concentration and TSAT index, as recommended by the latest 2018 ESMO guidelines.[17] Functional ID represents 64% of all ID cases. ID is highly prevalent regardless of ongoing treatment for cancer. Importantly ID was also found in patients without cancer treatment (57.4%) or anaemia (54.1%). Finally, iron deficiency-associated anaemia is diagnosed in 21.8% of the total patients (2/3 of anaemic patients). These findings add to the few available data on the prevalence of ID—where estimated prevalence ranges from 32 to 60% [2][22][23]—and iron deficiency-associated anaemia in cancer patients.[24][25]

We found a vast discrepancy in the estimate of absolute ID in this population when ID diagnosis included TSAT results or otherwise. A low TSAT index (<20%) was 2.4-times more likely to be reported in patients with cancer than a low ferritin level (<100µg/L), reflecting a functional ID rather than an absolute ID pattern. Such a high difference in the proportion of low ferritin level and the proportion of low TSAT index has already been described in case of inflammation and it is related to the intrinsic characteristics of each of the parameters.[2][20] Our results

reaffirm the need for the combined use of both biomarkers in the context of inflammatory disease,[18] as recommended by ESMO. Recently, results from a large retrospective study conducted in France among 96,000 patients receiving iron replacement therapy have shown that only one third of treatment episodes had a pre-treatment biochemical assessment of iron stores whether patients had an inflammatory disease or not.[19] Also, serum ferritin level measurement was 30-times more frequent than TSAT measurement. Despite a steady increase in the realisation of both ferritin level and TSAT measurements from 2006 to 2015, TSAT index was measured in only 2.5% of patients in 2015.

ID was highly prevalent whether patients were anaemic or not. In particular, we showed that more than half of non-anaemic patients suffered from ID. This proportion is similar than that reported in the European Cancer Anaemia Survey (ECAS), which is one of the largest studies conducted in patients with cancer. In this study, approximately 50% of iron-deficient patients were not anaemic.[5] Globally, these findings argue in favour of systematically detecting ID in cancer patients regardless of the existence of an anaemia. Timely administration of iron therapy in those patients can reduce the symptoms of ID and may also prevent the occurrence of anaemia.

In the present study, iron-deficiency anaemia was reported in 21.8% of patients and it was attributed to functional ID in most cases. Anaemia mediated by inflammatory cytokine release —leading to functional ID— is the most common mechanism for cancer-related anaemia.[26] Interestingly, we found that anaemia was not considered to be associated with ID based on ESMO guidelines in almost 4 patients out of ten. This finding probably reflects the multifactorial nature of cancer-related anaemia, including other mechanisms than ID such as chemotherapy-induced anaemia.[8] As reported in the ECAS study, we showed that anaemia and iron deficiency-associated anaemia were more frequent in treated patients compared with

untreated patients.[5] However, we did not find evidence of a clear higher prevalence of ID in patients undergoing chemotherapy. Whether or not patients were being treated for their cancer, they had a high prevalence of ID.

We acknowledge some limitations to the present study. We did not collect information on the type of tumour of included patients. All these factors might have influenced the occurrence of ID and iron deficiency-associated anaemia.[2][8][27] Also, most of the patients were currently treated for their cancer at their inclusion in the study, with no information collected regarding treatment initiation and duration. Overall, it is likely that other factors than the tumour itself such as cancer treatment, nutritional deficiency and blood loss contributed to ID and iron deficiency-associated anaemia in our population. However, our aim was to document the prevalence of ID from a public health rather than pathophysiological perspective. Finally, our prevalence estimates are not based on a representative sample of cancer patients. However, they rely on a relatively large number of participants recruited from 15 centres across France, including some of the largest French cancer care centres.

Conclusion

This study highlights the high prevalence of ID, with or without anaemia, in patients with cancer. Also, ID prevalence was high whether patients were treated for their cancer or not, justifying early detection of ID in all cancer patients. Also, our study points out the importance of functional ID as a common aetiology in these patients, reaffirming the need for using both TSAT index and ferritin concentration for the diagnosis of ID in this context. Recognition of these results may lead to better management of ID and iron deficiency-associated anaemia in cancer patients, which is a critical component of cancer treatment.[17] In addition to reducing

the symptoms associated with ID, administration of iron therapy in these patients helps to correct existing anaemia,[3] thereby improving patients' quality of life.[28]

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Declaration of Interest statement

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Author contributions

Conceptualization and Funding acquisition: E. Luporsi (EL), P. Cacoub (PC); *Investigation*: A. Carnot (AC), V. Massard (VM), S. Morin (SM), B. Chauffert (BC), A. Turpin (ATu); *Supervision*: EL, AC, VM, SM, BC, ATu, PC, V. Andrieu (VA), G. Berrut (GB), G. Choukroun (GC), A. Cohen-Solal (ACS), N. Fares (NF), A. Lopez (AL), G. Nicolas (GN), K. Peoc'h (KP), A. Pesce (AP), L. Peyrin-Biroulet (LPB), A-M. Ruppert (AMR), N. Sakek (NS), H. Simon (HS), A. Tchalla (ATc), J-M. Tourani (JMT), J-N. Trochu (JNT); *Validation*: EL, AC, VM, SM, BC, ATu, PC, VA, GB, GC, ACS, NF, AL, GN, KP, AP, LPB, AMR, NS, HS, ATc, JMT, JNT; *Roles/Writing - original draft*: EL, PC; *Writing - review & editing*: EL, AC, VM, SM, BC, ATu, PC, VA, GB, GC, ACS, NF, AL, GN, KP, AP, LPB, AMR, NS, HS, ATc, JMT, JNT.

Data sharing and data accessibility

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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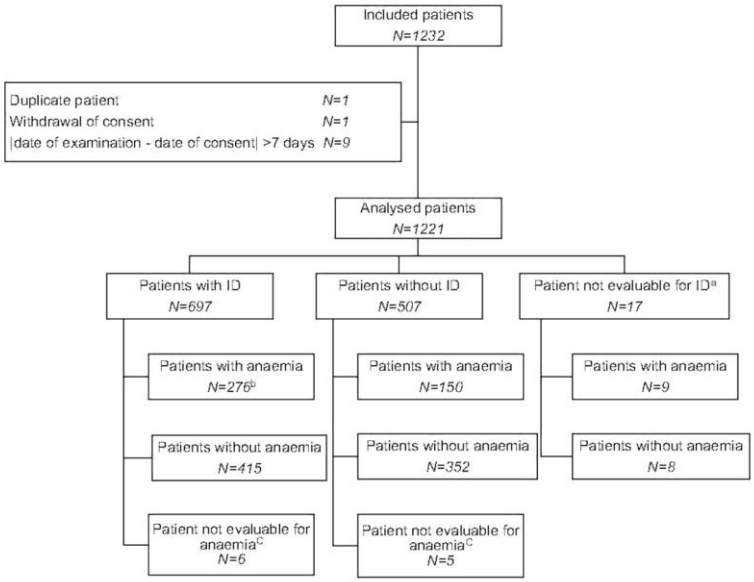
Figure 1. Flow chart, CARENFER study.

[a] Missing data for ferritin level and/or TSAT index (N=17); those patients did not contribute to ID analysis, but to anaemia analysis; [b]13 patients are not classified as having iron deficiency-associated anaemia because Hb <8g/dL; [c] Missing data for Hb level.

ID: iron deficiency; TSAT: iron-saturation of transferrin.


Included patients
N=1232
Duplicate patient N=1
Withdrawal of consent N=1
|date of examination - date of consent| >7 days N=9
Analysed patients
N=1221
Patients with ID
N=697
Patients without ID
N=507
Patient not evaluable for ID[a]
N=17
Patients with anaemia
N=276[b]
Patients without anaemia
N=415
Patient not evaluable for anaemia[c]
N=6
Patients with anaemia
N=150
Patients without anaemia
N=352
Patient not evaluable for anaemia[c]
N=5
Patients with anaemia
N=9
Patients without anaemia
N=8