

# Diagnosis, treatment, and work impact of iron deficiency anemia in a Portuguese urban community

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## Abstract

**Introduction:** Little is known about iron deficiency anemia (IDA)'s treatment in Portugal. We aim to estimate the proportion of anemia, IDA, and iron deficiency without anemia; characterize the diagnostic procedures and prescription patterns; assess anemia's impact over work absenteeism, in a Local Health Unit.

**Material and methods:** Cross-sectional study that evaluated complete blood counts, iron-containing prescriptions, comorbidities, economic failure, and disability certificates issued in 2015 at the Local Health Unit.

**Results:** We evaluated 62,794 complete blood count. The proportion of anemia was 16.5%, higher in patients with economic failure, pregnant women, and patients with congestive heart failure. Of the patients with anemia 87.8% had not serum iron and/or ferritin dosing, and of those with serum iron/ferritin levels tested 50.6% had IDA. IDA was higher in pregnant women, women aged  $\geq 15$  years and in patients with congestive heart failure. Approximately 56.2% of patients with IDA did not receive iron-containing medication, and in 38% of the cases the prescribed dose was subtherapeutic. Of the total iron prescriptions 44.1% were association therapies. Anemia accounted for 5.2% of the disability certificates issued in 2015 (1749 workdays lost).

**Discussion:** Most patients with anemia are not being adequately evaluated and a major proportion does not undergo treatment or has subtherapeutic doses of iron. These results may explain the anemia's impact on work capacity.

**Conclusion:** This is one of the largest studies on anemia in Portugal. An effort to adapt to the established recommendations is urged, to minimize the consequences of this disease.

**Keywords:** absenteeism, anemia, iron compounds/therapeutic use, iron deficiency

## Introduction

The diagnosis of anemia in men is based on a hemoglobin of  $<13$  g/dL; in women, it is  $<12$  g/dL.<sup>1</sup> Iron-deficiency anemia (IDA) is a diminished red blood cell production due to low iron stores in the body.<sup>1,2</sup> Iron deficiency (ID) is not the only cause of anemia, but it usually is its most common cause, accounting for approximately half the anemia cases worldwide.<sup>1,2</sup> In fact, the prevalence of anemia, defined by low hemoglobin or hematocrit, is commonly used to assess the severity of ID in a population.<sup>3</sup>

ID is the most common nutritional disorder and varies from iron depletion without anemia to IDA.<sup>4,5</sup> Worldwide, the prevalence of IDA is 15% to 20% and varies greatly according to host factors: age, sex, physiological, pathological, environmental, and socioeconomic conditions.<sup>1,6</sup> In the developed countries more than 500 million people are iron deficient.<sup>7-9</sup>

Anemia is associated with increased morbidity and mortality,<sup>1</sup> and IDA may be the first presenting feature of an occult gastrointestinal malignancy.<sup>10-12</sup>

Anemia may exacerbate chronic diseases namely heart failure, and is associated with an increased risk of hospitalization in older adults.<sup>13,14</sup> IDA during pregnancy has been associated with increased risk of preterm delivery, low birth weight, and maternal perinatal and young child mortality.<sup>13,15</sup> From 1990 to 2010 IDA has only changed from 14th to 15th cause of global disability adjusted life years.<sup>16</sup>

A Portuguese survey conducted in 2015 in the adult population, showed a prevalence of anemia of 19.9%, and a prevalence of IDA of 5.8%.<sup>17</sup> This survey revealed the surprising statistic that 84% of the individuals were not aware of being anemic and were not receiving any treatment. Despite that the impact of such finding on work absenteeism was not assessed, as much as 30% impairment of physical work capacity and performance is reported in iron-deficient men and women.<sup>1</sup> Even without anemia, mild to moderate ID has adverse functional consequences.<sup>18</sup> Mild ID without anemia could explain chronic

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fatigue and impaired cognitive performance.<sup>1</sup> Iron supplementation improves progressive fatigue resistance.<sup>19,20</sup>

Although prevalence of ID is already known, the extent to which ID is effectively treated in the general population and the compliance with the national guidelines are not so well documented.<sup>21</sup>

This study aims to estimate the prevalence of anemia, IDA and ID without anemia among patients of Matosinhos Local Health Unit medical services (MLHU); to characterize the diagnostic procedures and prescription patterns regarding compliance with national guidelines, and to assess anemia impact over work absenteeism.

## Methodology

### Study design

We conducted a cross-sectional study in MLHU which is a mixed unit composed by all public healthcare services (namely 1 hospital and 14 primary care centers) of Matosinhos, a county located at the north of Portugal with 172,366 patients. Between January 1st and December 31st of 2015 we accessed all blood counts analyzed in the MLHU Clinical Pathology Laboratory. We used the World Health Organization (WHO) criteria for diagnosing anemia.<sup>1</sup> To characterize the diagnostic procedures according to the Portuguese Directorate-General of Health Guidelines, we evaluate the proportion of anemic patients with blood iron or ferritin levels accessed. The cut-off for ID was set for a serum iron <50 µg/dL or a serum ferritin <30 ng/mL.<sup>5</sup>

The study included all outpatient drugs used for the treatment of iron-deficiency anemia in MLHU (Table 1).

The list of these medications was obtained by consultation of the drug database, Informed of the National Institute of Pharmacy and Medicine, with the filter Therapeutic Classification "4.1.1. iron compounds."<sup>22</sup>

As the Portuguese General Directorate of Health recommends a daily dose of 100 to 200 mg of elemental iron for treatment of ID, we set a prescribed daily dose (PDD) to 100 mg of elemental iron for all medications included in this study.<sup>5</sup>

The pregnant women and the patients with congestive heart failure (CHF) were identified from the electronic clinical database using the International Classification of Primary Care, Second Edition codes K77 and W78.<sup>23</sup> The patients with economic failure were identified using the National Information System of the Primary Health Care. This administrative economic status is

granted to patients who integrate a household whose average monthly income, divided the number of people who are responsible for the direction of the household (taxpayers in terms of tax return), is ≤€628.83 (1.5 times the Social Support Index).<sup>24</sup>

### Statistical analysis

The association of anemia with sex, pregnancy, age, economic failure, and CHF was analyzed with the calculation of odds ratio using logistic regression models. The analysis was performed in STATA 11.0 (StataCorporation, College Station, TX).

The study protocol was approved by the MLHU Ethics Committee.

## Results

We evaluated 62,794 complete blood counts (CBC), ranging 36.4% of the 172,366 MLHU patients. The proportion of anemia found was 16.5% (n=10,387), higher in patients with economic failure (18.7%), pregnant women (21.0%), and patients with CHF (47.4%) (Fig. 1; Table 2).

The hemoglobin levels were less than 10 mg/dL in 18.4% (n=1915) of the anemic patients.

Of the 10,387 patients with analytically proven anemia, 87.8% (n=9121) had no serum iron and/or ferritin quantified during the study period.

Of the 1266 patients with anemia and serum iron/ferritin levels tested, 50.6% (n=640) had IDA.

Of the 2291 patients with normal hemoglobin value and an iron/ferritin assay, 307 (13.4%) had ID.

The proportion of patients with IDA was particularly high in pregnant women (62.5%), women aged 15 years or older (55.8%), and patients with CHF (47.2%) (Table 3).

In the logistic regression analysis, the risk of anemia was significantly higher in women [adjusted odds ratio (OR) 1.56, 95% confidence interval (CI) 1.20–2.04] (Table 4).

The risk of ID was higher in women (adjusted OR 2.66, 95% CI 2.41–2.94), pregnant women (adjusted OR 7.03, 95% CI 6.0–8.22), patients with <12 years of age (adjusted OR 1.56, 95% CI 1.28–1.91), patients with economic deficiency (adjusted OR 1.15, 95% CI 1.06–1.24), and patients with CHF (adjusted OR 3.25, 95% CI 2.74–3.86).

**Table 1**  
Defined daily dose of drugs with iron compounds and or associations of iron compounds with folic acid available in Portugal

Drug	Medicine	Pharmaceutical presentation	Dosage	Type of packaging	Elemental iron content	DDD* (mg)
Ferrous gluconate	Hemototal	Oral solution	300 mg/10 mL	Ampoule - 20 units - 10 mL	35 mg	200
Ferrous sulfate	Ferro-gradumet	Extended release tablets	329.7 mg	Blister - 20 or 60 units	105 mg	200
	Ferro-Tardyferon	Extended release tablets	256.3 mg	Blister - 20 or 60 units	80 mg	200
Ferrous sulfate + aolic acid	Ferro-Tardyferon Fol	Extended release tablets	247.25 + 0.35 mg	Blister - 20 or 60 units	80 mg	200
	Ferrograd Fólico	Extended release tablets	325 + 0.35 mg	Blister - 20 or 60 units	105 mg	200
Anhydrous iron + folic acid	Folifer	Coated tablet	1 + 90 mg	Blister - 20 or 60 units	90 mg	200
Iron protein succinylate	Fervit	Oral solution	800 mg/15 mL	Vial - 20 units - 15 mL	40 mg	80
	Fetrival	Oral solution	800 mg/15 mL	Vial - 20 units - 15 mL	40 mg	80
	Legofer	Oral solution	800 mg/15 mL	Ampoule - 20 units - 15 mL	40 mg	80
Iron hydroxide polymaltose complex	Ferrum Hausmann	Chewable tablet	357 mg	Blister - 20 or 60 units	100 mg	90
	Ferrum Hausmann	Oral solution	178.6 mg/mL	Vial - 1 units - 30 mL	50 mg/mL	90
	Maltofer	Oral solution	357 mg/5 mL	Ampoule - 20 units - 5 mL	100 mg	90
Iron hydroxide polymaltose complex + folic acid	Ferrum Fol Hausmann	Chewable tablet	0.35 + 357 mg	Blister - 20 ou 60 units	100 mg	90

DDD = defined daily dose.

## Anexo I

**COMISSÃO DE ÉTICA PARA A SAÚDE**  
**CENTRO HOSPITALAR SÃO JOÃO, EPE**  
**FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO**  
**PARECER**

**Título da Investigação:** “Consumo de Antidepressivos e Ansiolíticos em Trabalhadores Universitários”

**Investigador:** Pedro Manuel Pinhal Neves Salazar Norton

**Orientador:** N.A.

**Serviço onde se realizará a Investigação:** Faculdade de Medicina da Universidade do Porto

**Elo de ligação:** N.A.

**Promotor:** N.A.

**Objetivos do estudo:**  
 O estudo tem por objetivos determinar a prevalência do consumo de antidepressores e ansiolíticos, sedativos e hipnóticos numa população de trabalhadores universitários, e os seus principais determinantes.

**Pertinência e Conceção do estudo:**  
 Em 2013, o Estudo Epidemiológico Nacional de Saúde Mental determinou que mais de 19% da população portuguesa sofre pelo menos um episódio de depressão ao longo da vida. A ansiedade é a comorbilidade mais comum nos indivíduos que sofrem de depressão. Assim, os antidepressores constituem um dos grupos terapêuticos com maior peso no consumo do SNS em ambulatório.  
 Sendo a saúde ocupacional uma atividade obrigatória para todas as entidades empregadoras, os profissionais que integram este tipo de serviços estão em posição privilegiada para delinear e aplicarem programas de promoção de saúde, que começam precisamente na determinação da dimensão de determinado problema.  
 O trabalho em apreciação será um estudo retrospectivo, observacional transversal.  
 A amostra será constituída pelos trabalhadores universitários que realizaram consulta de Saúde Ocupacional entre 2013 e 2014.  
 Os dados serão recolhidos pelo respetivo médico do trabalho, pela consulta do processo clínico, e introduzidos pelo mesmo numa base de dados anonimizada.  
 Variáveis a colher: terapêutica farmacológica antidepressiva e ansiolítica, sedativa e hipnótica, idade, género, estado civil, categoria profissional, unidade orgânica e habilitações literárias.

**Benefício/Risco:** Dada a natureza retrospectiva do estudo não existem quaisquer riscos ou incómodos para os doentes. Contudo, o investigador espera poder vir a elaborar estratégias preventivas e de controlo, bem como de diagnóstico precoce.

**Respeito pela liberdade e autonomia do sujeito:** Dada a natureza retrospectiva do estudo, não se aplica a necessidade da obtenção do consentimento informado.

**Confidencialidade dos dados:** As bases de dados utilizadas serão confidenciais e apenas os investigadores terão acesso aos dados.

**Financiamento:** N.A.

**Indemnização por danos:** N.A.

**Figure 1.** Schematic representation of results. CBC = complete blood count, ID = iron deficiency.

During the study period iron-containing medication was prescribed to 43.8% (n=280) of patients with analytically proven IDA and to 9.1% (n=28) of patients with ID without anemia. A total of 314,358 PDDs of oral iron were prescribed to MLHU patients, excluding pregnant women during the year 2015. The distribution of PPDs was 55.9% for monotherapy and

44.1% for therapeutic associations containing oral iron (Table 5).

With respect to monotherapy, the PDD distribution by active substance was 33.4% for iron-polymaltose hydroxide complex, 20.2% for iron sulfate, 2.1% for iron protein succinylate, and 0.1% for iron gluconate. The treatment was carried out with a daily dose of

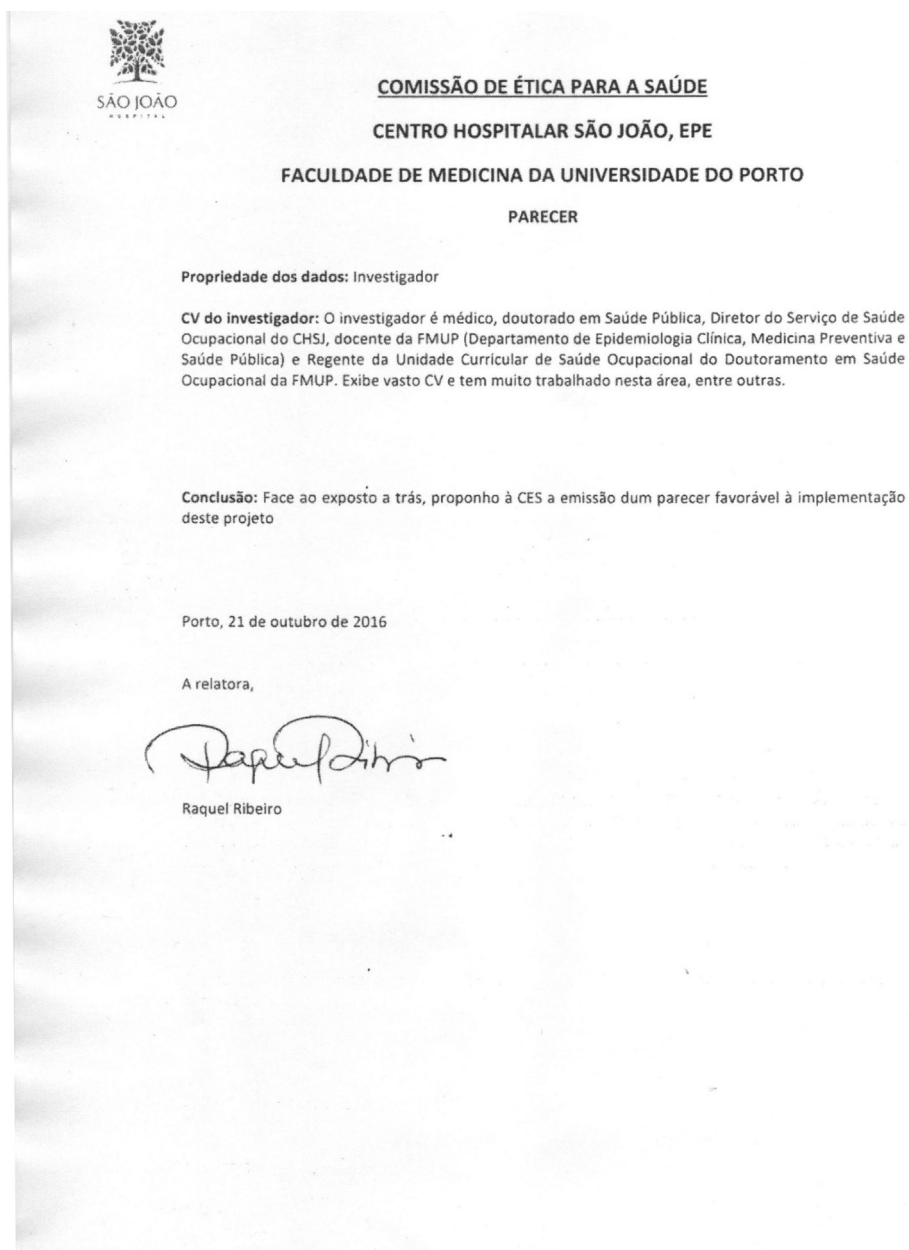


Figure 1. (Continued)

elemental iron of <100 mg in 38% of cases (regardless of whether it was prescribed as monotherapy or fixed combination).

In 2015, of the patients who performed at least 1 CBC at MLHU, 1278 had a Disability Certificate for Work as a result of natural disease. Of these, absence to work was specifically motivated by anemia diagnosis in 67 (5.2%), corresponding to a total of 1749 workdays lost (4.79 years), with a median of 12 days of absence for each Disability Certificate for Work issued. The median number of workdays lost was similar (n=12) in patients with anemia who were and were not medicated, but was lower in patients with IDA (n=10) either medicated (n=11) or unmedicated (n=4).

## Discussion

This is one of the largest anemia studies conducted in Portugal, evaluating 62,794 blood counts, covering 36.4% of the 172,366

patients enrolled in the MLHU. The proportion of anemia found was 16.5%, a figure higher than that estimated by the WHO for Portugal (15%),<sup>24</sup> but lower than what was found in another Portuguese study (19.9%), which only evaluated patients aged 18 years or more.<sup>17</sup>

It should be noted that the results reflect the proportion of patients with anemia who underwent a blood count during the study period, rather than the prevalence of anemia in the municipality of Matosinhos. However, the MLHU is an institution that integrates primary and secondary healthcares, internalizing some complementary means of diagnosis, so most of the CBC and biochemistry with iron kinetics prescribed in this local health unit are analyzed at the MLHU Clinical Pathology Laboratory. As such, this study has analyzed not only hospital but also primary health care prescriptions.

The General Directorate of Health recommends ID screening, regardless the clinical condition, for pregnant women, infants,

**CES**  
COMISSÃO DE ÉTICA PARA A SAÚDE

**7. SEGURO**

a. Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?

SIM  (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO

NÃO APLICÁVEL

**8. TERMO DE RESPONSABILIDADE**

Eu, Pedro Manuel Pinhal Neves Salazar Norton  
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 03 / Outubro / 2016

[Signature]  
O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 14 / Outubro / 2016

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

[Signature]

Prof. Doutor Filipe Almeida  
Presidente da Comissão de Ética

VI

Figure 1. (Continued).

and preschool children (6–12 months old) with poor social-economic conditions, institutionalized elderly, at hospital admission, and at preoperative period.<sup>25</sup> The Centers for Disease Control and Prevention recommends periodic screening among high-risk populations of infants and preschool children, pregnant women, and nonpregnant women of childbearing age, every 5 to 10 years starting in adolescence.<sup>15</sup>

The most common method of screening ID involves determining the prevalence of anemia by measuring blood hemoglobin or hematocrit levels.<sup>1</sup> Hematocrit measurement is

an acceptable and recommended method for anemia determination, but has no advantage compared to hemoglobin measurement.<sup>1</sup> A major limitation of hemoglobin or hematocrit measurements is that levels change only when they are very low at the outset, and when ID is already severe.<sup>26</sup> In resource-adequate situations, the usual practice involves the use of further, specific, and more sensitive tests for individual assessment such as serum iron or serum ferritin,<sup>27</sup> although the biological variability of serum iron limits its utility for daily practice.<sup>28,29</sup>

**Table 2**  
Proportion of Matosinhos Local Health Unit patients with anemia

	Patients with anemia		
	Sample	N	%
Men ( $\geq 15$ yr)	24,150	3402	13.2
Women ( $\geq 15$ yr)*	35,529	6775	18.8
<15 yr	3115	216	6.9
Pregnant	998	210	21.0
Congestive heart failure	1516	718	47.4
Economic failure	25,003	4668	18.7
Total	62,794	10387	16.5

\* Except pregnant women.

Of the 10,387 patients with analytically proven anemia, the majority (87.8%) had no serum iron and/or ferritin quantified during the study period, which may reflect an insufficient diagnostic investigation of the anemia cases found in all subgroups analyzed.

As expected, the proportion of patients with IDA was particularly high in pregnant women and patients with CHF. It is also noted that, in addition to the increased IDA risk in CHF, these patients were 3.25 times more likely to have ID (OR 3.25; 95% CI 2.74–3.86). As such, it is fundamental to systematically determine serum iron or ferritin in addition to the CBC in this patient subset.

According to the Clinical Guideline of the General Directorate of Health's regarding the treatment of ID in the adult, oral iron is the first-line option as its administration is simple, physiological, economical, and safe.<sup>5</sup> There are multiple formulations on the market, and a daily dose of 100 to 200 mg of elemental iron is recommended. Nevertheless, in this study 56.2% of patients with IDA did not receive iron-containing medication, and in 38% of cases the prescribed dose was subtherapeutic (<100 mg/day). The absence or subtherapy may be associated with the perpetuation of the disease and the symptoms. In the specific case of CHF, 47.2% of the patients had concomitant IDA. According to the Guidelines of the European Society of Cardiology,<sup>30</sup> the diagnosis and treatment of IDA in CHF is particularly important since its nontreatment is associated with a worse prognosis. Iron supplementation should always be considered for the improvement of CHF symptoms, exercise capacity and quality of life when ferritin <100  $\mu\text{g/L}$  or when ferritin 100 to 299  $\mu\text{g/L}$  and transferrin saturation <20%. However, we found that iron medication was prescribed to only 42.9% of these patients.

Provided that the dosage allows reaching the recommended daily dose, all the iron active principles are valid options. Nevertheless, the treatment should be adapted to the patient

**Table 3**  
Proportion of Matosinhos Local Health Unit patients with iron-deficiency anemia

	Patients with iron-deficiency anemia		
	Sample	n	%
Men ( $\geq 15$ yr)	335	126	37.6
Women ( $\geq 15$ yr)*	873	487	55.8
<15 yr	50	22	44.0
Pregnant	8	5	62.5
Congestive heart failure	89	42	47.2
Economic failure	542	274	42.8
Total	1266	640	50.6

\* Except pregnant women.

**Table 4**  
Odds ratio of anemia and iron deficiency using logistic regression model

	Anemia adjusted OR (95% CI)	Iron deficiency adjusted OR (95% CI)
Age		
<12 yr	0.39 (0.20–0.78)	1.56 (1.28–1.91)
$\geq 55$ yr	0.36 (0.28–0.47)	1.04 (0.95–1.13)
Sex (F)	1.56 (1.20–2.04)	2.66 (2.41–2.94)
Pregnancy	0.78 (0.18–3.31)	7.03 (6.00–8.22)
Congestive heart failure	1.33 (0.85–2.08)	3.25 (2.74–3.86)
Economic failure	1.02 (0.81–1.29)	1.15 (1.06–1.24)

CI = confidence interval, F = female, OR = odds ratio.

tolerability. Of the formulations available in Portugal, there are only 2 active substances that allow to reach the dose of elemental iron recommended in only one daily intake (iron hydroxide polymaltose complex and ferrous sulfate), which may increase adherence and therapeutic maintenance. However, ferrous sulfate is only available in sustained release forms and therefore its use should not be considered as the first line.<sup>31</sup> Nonetheless, 20.2% of the packages prescribed in MLHU during the study period are sustained release formulations.

In IDA treatment, the association of iron with folic acid is not advisable since the patient's response may not be easily interpreted.<sup>32</sup> Despite this recommendation, 44.1% of the total iron prescriptions corresponded to association therapies, excluding prescriptions for pregnant women. This therapeutic strategy does not improve the treatment effectiveness and may even increase the frequency of adverse effects.<sup>32</sup> Moreover, from the economic point of view, the therapeutic associations adds a considerable cost to the patient and to the National Health Service because they have a higher retail price than that of monotherapy.

Therefore, an effort is required to adapt to the national and international recommendations, encouraging the training and continuous evaluation of the indicators evidenced in this study to minimize the consequences of this pathology. In addition, it is estimated that 10% to 20% of patients discontinue oral iron therapy due to side effects.<sup>33</sup> Intolerance to oral iron will certainly be one of the explanations for the low proportion of patients treated in this study. In this case, the alternative is intravenous injection iron therapy, which is of exclusive hospital use in Portugal.

Therefore, patients must first be referred to the hospital outpatient consultation and then referred to the Day Hospital for treatment. It may take several months from the request of the Primary Care physician to the effective treatment in the Day

**Table 5**  
Iron-containing medication prescribed (except pregnant women)

	PDD	%
Iron monotherapy	175,602	55.9
Iron-polymaltose hydroxide complex	104,845	33.4
Iron sulfate	63,598	20.2
Iron protein succinylate	6984	2.2
Ferrous gluconate	175	0.1
Iron associations with folic acid	138,756	44.1
Iron sulfate + folic acid	30,254	9.6
Iron-polymaltose hydroxide complex+ folic acid	56,500	18.0
Iron oxide+ folic acid	52,002	16.5
Total	314,358	100.0

PDD = prescribed daily dose.

Hospital, with the risk of clinical worsening of the patient. The establishment of protocols for referral of patients directly to hospital care, namely to the Day Hospital for treatment with intravenous iron in cases of intolerance or inefficacy of oral iron, would be an important way to increase the proportion of patients treated. Suspected infection may also explain some cases of undertreatment with iron, particularly in the hospital setting. However those cases are not significant for the conclusions of this study.

The differential diagnosis with anemia of inflammation is challenging. The soluble transferrin receptor could be useful, although the cost of its evaluation makes difficult the large-scale implementation. We also think that diet recommendations are often and erroneously used instead of iron supplements to treat low-grade anemia. This can contribute to the undertreatment. Bioavailability, especially of nonheme iron in anemic patients is low. It is difficult to achieve the intake of recommended daily dose (at least 100 mg) with diet alone.

Finally, it was evaluated the emission of Disability Certificates for Work by the patients with diagnosis of anemia in the study period. Anemia accounted for 5.2% of the disability certificates issued, demonstrating an important impact in the active population. The main reason was fatigue, which affected the absenteeism. The median number of workdays lost was similar in patients with anemia who were and were not medicated, but was lower in patients with IDA (either medicated or unmedicated). This probably reflects a greater severity of the disease rather than a better control of the hemoglobin value in the medicated group.

## Conclusion

The proportion of anemia was similar to that described by WHO for developed countries. The risk of IDA was particularly high in pregnant women, women younger than 15 years of age, and patients with CHF. Most patients with anemia were not being evaluated for iron kinetics. A large proportion of patients did not undergo any treatment or were undergoing subtherapeutic doses of oral iron. These results may explain the strong impact that anemia had on work capacity, accounting for 5.2% of all Work Disability Certificates issued in 2015 at MLHU.

## Acknowledgments

None.

## Conflicts of interest

The authors declare no conflicts of interest.

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