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Prevalence and prognostic impact of anemia and iron deficiency in patients hospitalized in an internal medicine ward: The PRO-IRON study

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Abstract

Objectives: To assess prevalence, predictive factors, and prognostic impact on in-hospital mortality of anemia, iron deficiency anemia (IDA), iron deficiency with or without anemia (ID), and iron deficiency without anemia (IDWA) in patients admitted to an internal medicine ward.

Methods: This 1-year prospective study collected data on demographics, medical history, and blood tests in 771 consecutive patients on admission.

Results: Most patients were ≥65 years old (80%) and had hypertension (63%), moderate chronic kidney disease (CKD) (43%), and heart failure (41%). Prevalence of anemia, IDA, ID, and IDWA was 67%, 41%, 58%, and 18%, respectively. Anemia was independently associated with age ≥65 years (OR 1.76, 95% CI 1.15-2.70), active cancer (OR 2.44, 95% CI 1.42-4.39), and moderate CKD (OR 1.65, 95% CI 1.12-2.43). ID was independently associated with female gender (OR 2.29, 95% CI 1.64-3.22), heart failure (OR 1.65, 95% CI 1.16-2.37), and moderate CKD (OR 2.95, 95% CI 2.04-4.30). Incidence of in-hospital mortality was 21% and independently associated with anemia (RR 1.82, 95% CI 1.21-2.74).

Conclusions: Anemia and iron deficiency were highly prevalent in internal medicine patients. As anemia negatively impacts on in-hospital mortality, awareness should be raised for effective diagnosis and management of these comorbidities in hospitalized patients.

KEYWORDS

anemia, internal medicine ward, iron deficiency, prevalence, prognosis, risk factors

1 | INTRODUCTION

Patients hospitalized in internal medicine wards are mostly elderly (≥65 years), have chronic diseases and multiple comorbidities leading to frequent hospitalizations and high costs to health systems. Among these comorbidities, anemia is one of the most common.[1-5] In 2002, worldwide prevalence of anemia, diagnosed according to the World Health Organization (WHO) criteria—hemoglobin <12 g/dL for females and <13 g/dL for males[6]—was estimated to be around 25% in the general adult population and 24% in people over 60 years of age.[7] Recent studies have reported that anemia is present in 6% to 22% of females and 8% to 20% of males above 65 years of age,[5,8] in 29% of females and 34% of males above 80 years of age,[9] reaching a higher prevalence of 41% to 66% in hospitalized elderly patients.[1,3,5,10-12]

Anemia has multiple etiologies, such as nutritional deficiencies (ie, iron, folate, and vitamin B_{12}), acute or chronic blood loss, chronic diseases, and even other unknown causes.[2,5] However, the most common cause for anemia is iron deficiency, accounting for more than half of the cases in the general population worldwide[4,13] and about one-third, or below, of the cases in the elderly population.[2,5,9] Iron deficiency can occur in two main forms: absolute or functional. While absolute iron deficiency arises from the depletion of total body iron stores, functional iron deficiency occurs when the supply of iron to the bone marrow is inadequate, despite normal or increased total body iron stores.[4]

Regardless of its cause, anemia and iron deficiency can contribute to patients' poorer quality of life and unfavorable outcomes in several conditions, such as heart failure, chronic kidney disease, and cancer.[14,15] In addition, comorbid anemia in elderly patients was found to be associated with an increased risk for hospitalization and mortality.[1,3,14,16] Moreover, iron deficiency, with or without anemia, has been shown to negatively affect cognitive performance and work capacity[2,4,5] and was acknowledged by the WHO as a top 20 risk factor related to the global burden of disease in 2015.[17]

Despite the potential negative prognostic impact of both anemia and iron deficiency, these comorbidities are frequently underdiagnosed and undertreated in hospitalized patients, as in the general population.[8,9] Internal medicine wards are not an exception.[2,5] On the other hand, although red blood cell transfusion is frequently performed to correct anemia in current clinical practice, this procedure is also one of the top 5 overused therapies,[18-20] carrying inherent risks and associated adverse outcomes for the patients.[20-23] Hence, a comprehensive profiling of anemia and iron deficiencies in internal medicine wards may drive a more proactive and appropriate management of these conditions in this clinical setting. However, as far as we know, data on the prevalence and risk factors for anemia and iron deficiency in hospitalized patients in internal medicine wards are scarce. Therefore, our aim in this prospective observational study was to assess the prevalence and predictive factors for anemia, iron deficiency anemia, iron deficiency with or without anemia, and iron deficiency without anemia in patients admitted to an internal medicine ward, as well as to evaluate their prognostic impact for in-hospital mortality in this acute setting.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

This observational prospective study was conducted at Hospital de São Francisco Xavier—Centro Hospitalar de Lisboa Ocidental (CHLO) in Lisbon, Portugal. All consecutive patients who were admitted to the Internal Medicine III Ward between October 2013 and October 2014 were prospectively included. Inclusion criteria were adult patients aged 18 years or over, and no exclusion criteria were applied. Per patient, only the first hospitalization within the study period was analyzed. Collected data on patients included demographics (ie, age and gender), clinical characteristics (ie, main diagnosis on discharge and most common comorbidities), and laboratory blood tests that were performed on ward admission.

The hospital ethical committee approved the study, and participants provided their signed, informed consent before study inclusion. The study conformed to the Declaration of Helsinki.

2.2 | Laboratory tests

According to a predetermined clinical practice protocol, all patients were assessed for red blood cell count (hemoglobin concentration, hematocrit, and mean corpuscular volume [MCV]), serum iron, ferritin, transferrin and transferrin saturation percentage, vitamin B_{12}, folic acid, glycemia, urea, and creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[24] eGFR <60 mL/min/1.73 m^2 was considered as moderate renal failure and eGFR <30 mL/min/1.73 m^2 as severe renal failure.

2.3 | Definition of anemia and iron deficiency status

The presence of anemia was defined according to the WHO criteria[6]: hemoglobin levels under 12 g/dL for females and 13 g/dL for males.

Iron deficiency was defined by two main categories, functional or absolute, according to cutoffs recommended by guidelines of different scientific societies,[25-27] as presented below:

Functional iron deficiency: (i) for active cancer patients, levels of transferrin saturation <50% and ferritin between 30 and 800 ng/mL; (ii) for chronic kidney disease patients, levels of transferrin saturation ≤30% and ferritin ≤500 ng/mL; or (iii) for heart failure and the remaining patients, levels of transferrin saturation ≤20% and ferritin between 100 and 300 ng/mL;

Absolute iron deficiency: (i) for active cancer patients, levels of transferrin saturation <20% and ferritin <30 ng/mL; or (ii) for heart failure, chronic kidney disease, and the remaining patients, levels of ferritin <100 ng/mL.

Vitamin B_{12} and folic acid deficiencies were defined by the reference ranges of the local laboratory: <176 pg/mL for serum vitamin B_{12} and <6.25 nmol/L for serum folic acid. Combined deficiency was defined by the combination of two or more of the following criteria: vitamin B_{12} deficiency, folic acid deficiency, iron deficiency.

Patients were analyzed according to the following categories:

1. Non-anemic and non-iron, non-vitamin B_{12}, non-folic acid-deficient (NAND), that is, all patients without anemia and functional or absolute iron, vitamin B_{12}, and folic acid deficiencies;
2. Anemia, that is, all patients with anemia regardless of their iron, vitamin B_{12}, and/or folic acid deficiency status;
3. Iron deficiency anemia (IDA), that is, all patients with anemia, and functional or absolute iron deficiency;
4. Iron deficiency with or without anemia (ID), that is, all patients with functional or absolute iron deficiency regardless of their anemia status, comprising both patients with iron deficiency with anemia (ie, the IDA group) or with iron deficiency without anemia; and

TABLE 1 Baseline demographic, clinical, and laboratory blood test characteristics of the study population

Characteristics	Total N = 771 (100%)	NAND N = 110 (14%)	Anemia n = 519 (67%)	IDA n = 316 (41%)	ID n = 451 (58%)	IDWA n = 135 (18%)
Age, mean (SD), y	75.5 (14.2)	69.42 (16.05)	77.1 (13.0)*,#	77.9 (13.5)†,#	76.7 (14.2)‡,#	74.0 (15.5)#
≥65 y, n (%)	620 (80.4)	68 (61.8)	440 (84.8)*,#	277 (87.7)†,#	383 (84.9)‡,#	106 (78.5)#
≥80 y, n (%)	323 (41.9)	27 (24.5)	240 (46.2)*,#	148 (46.8)†,#	201 (44.6)‡,#	53 (39.3)#
Female gender, n (%)	458 (59.4)	51 (46.4)	303 (58.4)#	203 (64.2)†,#	303 (67.2)‡,#	100 (74.1)§,#
No of comorbidities, n (%)						
<3	403 (52.2)	81 (73.6)	251 (48.4)	137 (43.4)	203 (45.0)	66 (48.9)
3-5	348 (45.1)	29 (26.4)	248 (47.8)	164 (51.9)	232 (51.4)	68 (50.4)
>5	21 (2.7)	0 (0.0)	20 (3.9)*,#	15 (4.7)†,#	16 (3.5)‡,#	1 (0.7)#
Diabetes, n (%)	220 (28.5)	26 (23.6)	159 (30.6)	93 (29.4)	126 (27.9)	33 (24.4)
Heart failure, n (%)	319 (41.4)	30 (27.3)	225 (43.4)#	161 (50.9)†,#	223 (49.4)‡,#	62 (45.9)#
Coronary artery disease, n (%)	130 (16.9)	19 (17.3)	86 (16.6)	60 (19.0)	84 (18.6)	24 (17.8)
Atrial fibrillation, n (%)	198 (25.7)	23 (20.9)	131 (25.2)	87 (27.5)	129 (28.6)	42 (31.1)#
Hypertension, n (%)	486 (63.0)	63 (57.3)	328 (63.2)	212 (67.1)	302 (67.0)	90 (66.7)
Stroke, n (%)	113 (14.7)	11 (10.0)	82 (15.8)	48 (15.2)	67 (14.9)	19 (14.1)
Pulmonary embolism, n (%)	8 (1.2)	0 (0.0)	6 (1.3)	3 (1.1)	5 (1.3)	2 (1.8)
COPD, n (%)	90 (11.7)	12 (10.9)	62 (11.9)	46 (14.6)	62 (13.7)	16 (11.9)
Active cancer, n (%)	117 (15.2)	13 (11.8)	93 (17.9)*	41 (13.0)	52 (11.5)‡	11 (8.1)
Thyroid disease, n (%)	79 (11.4)	8 (8.1)	53 (11.3)	32 (11.6)	50 (12.7)	18 (15.1)
CKD moderate, n (%)	326 (43.4)	14 (13.5)	257 (50.8)*,#	180 (57.1)†,#	234 (52.0)‡,#	54 (40.0)#
CKD severe, n (%)	82 (10.9)	0 (0.0)	77 (15.2)*,#	53 (16.8)†,#	58 (12.9)‡,#	5 (3.7)§
Functional iron deficiency, n (%)	205 (29.5)	-	155 (33.1)*	155 (49.1)	205 (45.5)	50 (37.0)
Absolute iron deficiency, n (%)	246 (34.5)	-	161 (33.3)	161 (50.9)	246 (54.5)	85 (63.0)
Combined deficiency, n (%)	59 (8.3)	-	46 (9.6)	46 (14.8)†	59 (13.3)‡	13 (9.7)
Vitamin B_{12} deficiency, n (%)	53 (7.4)	-	42 (8.6)	33 (10.5)†	42 (9.4)‡	9 (6.7)
Folic acid deficiency, n (%)	38 (5.3)	-	28 (5.8)	15 (4.8)	20 (4.5)	5 (3.7)
MCV, n (%)						
<80 fL	39 (5.1)	2 (1.8)	33 (6.4)	8 (2.5)	12 (2.7)	4 (3.0)
80-99 fL	668 (86.6)	106 (96.4)	433 (83.4)	271 (85.8)	394 (87.4)	123 (91.1)
≥100 fL	64 (8.3)	2 (1.8)	53 (10.2)*,#	37 (11.7)†	45 (10.0)‡,#	8 (5.9)
Hemoglobin, mean (SD), g/dL	11.3 (2.0)	13.8 (1.1)	10.2 (1.4)*,#	10.3 (1.4)†,#	11.2 (1.9)‡,#	13.3 (1.0)
Hemoglobin, median (min-max), g/dL	11.3 (6.2-17.2)	13.6 (12.0-17.1)	10.4 (6.2-12.9)*,#	10.5 (6.2-12.9)†#	11.3 (6.2-17.2)‡,#	13.2 (12-17.2)
Serum iron	55.26 (39.70)	82.75 (38.58)	46.63 (34.28)*,#	40.66 (22.66)†,#	48.58 (34.10)‡,#	67.57 (47.13)§,#
TSAT, mean (SD), %	20.8 (15.2)	30.56 (15.16)	18.9 (14.9)*,#	15.7 (11.0)†,#	17.4 (12.3)‡,#	21.1 (14.1)#
TSAT <20%, n (%)	95 (42.4)	14 (17.7)	318 (67.7)*,#	237 (77.2)†,#	315 (71.3)‡,#	78 (57.8)#
TSAT <30%, n (%)	151 (67.4)	41 (51.9)	400 (85.1)*,#	285 (92.8)†,#	389 (88.0)‡,#	104 (77.0)#
Ferritin, mean (SD), ng/mL	316.1 (823.8)	505.36 (938.82)	339.8 (905.8)#	125.3 (102.4)†#	118.9 (98.2)‡#	103.9 (86.1)§#

(Continues)

TABLE 1 (Continued)

Characteristics	Total N = 771 (100%)	NAND N = 110 (14%)	Anemia n = 519 (67%)	IDA n = 316 (41%)	ID n = 451 (58%)	IDWA n = 135 (18%)
Ferritin, n (%) (ng/mL)						
<15	27 (3.8)	-	20 (4.1)	20 (6.3)‡	27 (6.0)‡	7 (5.2)§
<30	66 (9.3)	-	44 (9.1)	43 (13.6)‡	65 (14.4)‡	22 (16.3)§
<50	131 (18.4)	-	89 (18.5)	85 (26.9)‡	126 (27.9)‡	41 (30.4)§
<100	89 (38.7)	2 (2.3)	174 (36.1)#	163 (51.6)#	250 (55.4)‡,#	87 (64.4)§,#
>800	48 (6.7)	10 (11.4)	37 (7.7)#	-	-	-
eGFR, n (%) (mL/min)						
<30	82 (10.9)	0 (0)	77 (15.2)	53 (16.8)	58 (12.9)	5 (3.7)
30-59	244 (32.4)	14 (13.5)	180 (35.6)	127 (40.3)	176 (39.1)	49 (36.3)
60-89	210 (27.9)	35 (33.7)	126 (24.9)	72 (22.9)	118 (26.2)	46 (34.1)
≥90	216 (28.7)	55 (52.9)	123 (24.3)*,#	63 (20.0)#	98 (21.8)‡,#	35 (25.9)§,#

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ID, iron deficiency; IDA, iron deficiency anemia; IDWA, iron deficiency without anemia; MCV, mean corpuscular volume; NAND, non-anemic and non-iron, non-vitamin B_{12}, non-folic acid-deficient; SD, standard deviation; TSAT, transferrin saturation.
*P-value < .05 vs patients without anemia.
†P-value < .05 vs patients without IDA.
‡P-value < .05 vs patients without ID.
§P-value < .05 vs patients without IDWA.
#P-value < .05 vs NAND patients, when applicable.

5. Iron deficiency without anemia (IDWA), that is, all patients with functional or absolute iron deficiency and without anemia.

2.4 | Study outcomes

The study outcomes were the prevalence of, and predictive factors for anemia, IDA, ID, IDWA in patients admitted to an internal medicine ward, as well as their prognosis impact on in-hospital mortality, that is, death from any cause in hospitalized patients following the first day of admission to the internal medicine ward.

2.5 | Statistical methods

Continuous variables were summarized by mean and standard deviation and compared using Student's *t* test or analysis of variance (ANOVA) as applicable. Categorical variables were expressed as number and percentage of cases in each group and compared using the chi-square test for independence with Yates continuity correction.

Variables that were significantly associated with the presence of the conditions under study and considered of clinical importance were included in a multivariable analysis. For prognostic factors of each condition under study, a logistic regression model was used and both crude and adjusted estimates of odds ratio (OR) and 95% confidence interval (CI) were reported. For mortality risk factors, Poisson regression with robust variance estimation was used to compute crude and adjusted estimates of relative risk (RR) and 95% CI.[28,29] Variable selection was performed using an automated, variable selection procedure based on the Akaike Information Criteria (AIC).[30] The model that presented the lowest AIC was chosen, regardless of the significance of the variables selected. All statistical analyses were conducted using the completers set (ie, patients that had available data for all the variables), as no imputation for missing data was used. The statistical significance was concluded at the 5% level.

All analyses were conducted using the R statistical software (version 3.2.5).

3 | RESULTS

3.1 | Baseline characteristics

During the study period of 1 year, 771 patients were consecutively hospitalized in the internal medicine ward. Baseline characteristics of the patients stratified by anemia and iron deficiency status are shown in Table 1. Most patients were old (≥65 years; 80.4%) or very old (≥80 years; 41.9%), and female (59.4%), and the most prevalent comorbidities were hypertension (63.0%), moderate chronic kidney disease (CKD) (43.4%), and heart failure (41.4%).

3.2 | Prevalence of anemia, iron deficiency anemia, iron deficiency, and iron deficiency without anemia

On admission to the internal medicine ward, anemia was diagnosed in 67% of patients, 41% had IDA, 58% had ID, and 18% had IDWA, whereas 14% of patients had neither anemia nor iron, vitamin B_{12}, or folic acid deficiencies (ie, NAND group; Table 1).

Firstly, patients with anemia were significantly older (≥65 years) and had a higher number and prevalence of studied comorbidities than patients without anemia (Table 1). In addition, compared to the NAND group, patients with anemia were significantly older, predominantly female, and showed a higher number of comorbidities. Namely, these patients presented significantly higher prevalence of heart failure, moderate or severe CKD than the NAND group (Table 1). It is apparent from Table 1 that patients with anemia presented a higher number of comorbidities, compared to patients without anemia and NAND patients.

Secondly, patients with IDA also were significantly older, mainly female, and showed a higher number of comorbidities—significantly higher prevalence of heart failure, and moderate or severe CKD—compared to patients without IDA and to NAND patients (Table 1). Nevertheless, what stands out in the table is that patients with IDA presented similar characteristics to the group of patients with anemia. Closer inspection of the table shows that IDA patients were more frequently diagnosed with vitamin B_{12} deficiency or combined hematinic deficiencies, compared to patients without IDA (Table 1).

Thirdly, patients with ID were significantly older, mainly females, and had a higher number of comorbidities than patients without ID and NAND patients. Furthermore, patients with ID presented a significantly higher prevalence of heart failure, moderate or severe CKD, compared to patients without ID and to NAND group. Patients with ID were also more frequently diagnosed with vitamin B_{12} or combined deficiencies, and presented a significantly higher prevalence of active cancer compared to patients without ID (Table 1). Finally, data regarding the IDWA group are also shown in Table 1.

3.3 | Predictive factors of anemia, iron deficiency anemia, iron deficiency, and iron deficiency without anemia

The results from the multivariable logistic regression analysis of the independent factors associated with anemia, IDA, ID, and IDWA are shown in Table 2. This analysis demonstrated that anemia was associated with age ≥65 years, active cancer, and moderate and severe CKD. Moreover, IDA was associated with age ≥65 years, moderate and severe chronic kidney disease, and combined hematinic deficiencies. On the other hand, female patients, patients with heart failure, and patients with moderate CKD presented an increased risk of ID. In contrast, patients with active cancer showed a decreased risk of ID. Finally, the multivariable model analysis also showed that the female gender was associated with increased risk of IDWA, whereas severe CKD was associated with decreased risk of IDWA.

3.4 | Clinical outcome

Incidence of in-hospital mortality is shown in Figure 1 and Table 3. Rates of in-hospital mortality were 21.3% of the total clinical sample and 6.1% in NAND patients. Compared to these patients, incidence of in-hospital mortality was significantly higher in patients with anemia (26.2%), IDA (17.7%), ID (16.2%), and higher in patients with IDWA (12.6%), although not significantly (Figure 1). From the total sample of patients who died, the prevalence of anemia, IDA, ID, and IDWA was 82.9%, 40.3%, 54.1%, and 10.6% respectively (Table 3).

Multivariable Poisson regression analysis demonstrated that anemia on admission was independently associated with all-cause in-hospital mortality (Table 3). On the other hand, ID was independently associated with decreased risk of in-hospital mortality. Moreover, there was no significant association between IDA or IDWA and in-hospital mortality. Further analysis showed a significant increase in in-hospital mortality risk in patients older than 65 years, patients with active cancer, and patients with macrocytosis (Table 3).

Figure 2 shows a conditional density plot of ferritin levels per in-hospital mortality outcome. The proportion of patients who died showed strikingly different variations throughout ferritin levels, showing peaks of mortality above 800 ng/mL.

4 | DISCUSSION

Anemia and iron deficiency are among the most common health problems affecting populations worldwide. However, they are frequently underdiagnosed or undertreated in the general population and among hospitalized patients, despite the available resources for diagnosis and management, if awareness is raised.[31] In addition, these conditions have also been associated with increased morbidity and mortality. In this study, we assessed the prevalence and risk factors for anemia and iron deficiency, as well as their prognostic impact on in-hospital mortality in patients hospitalized in an internal medicine ward.

Our findings confirm that anemia, IDA, ID, and IDWA are highly prevalent in the acute phase of disease of this unselected population of hospitalized patients. Indeed, prevalence of anemia (ie, 67%) was higher than that which was recently reported in the Portuguese general population (ie, 20%),[8] old population (ie, ≥65 years, 21%),[8] and very old population (ie, ≥80 years, 31%).[5,9] Moreover, prevalence of IDA (ie, 41%) and ID (ie, 58%) in our study population was also higher than that which was presented in the Portuguese general population for ferritin levels <30 ng/mL (10.9% for IDA and 31.9% for ID, respectively).[8] On the one hand, these results are supported by studies in other countries, which also reported a high prevalence of anemia (33%-62%) [1,3,10-12] and IDA (48%) [3,10-12] in hospitalized elderly patients in internal medicine wards or other settings, despite the difficulty of directly comparing results, due to differences in populations' characteristics and anemia and iron deficiency definitions, namely the ferritin cutoff levels. On the other hand, we had insufficient data regarding the prevalence of ID or IDWA in hospitalized patients to compare with that which was reported in our study. Nevertheless, our findings support that anemia and iron deficiency, the main cause of anemia, have very high prevalence in internal medicine wards in acute hospital settings.

To our knowledge, this study is the first to analyze factors that may predict anemia, IDA, ID, or IDWA in patients with acute diseases hospitalized in an internal medicine ward. Surprisingly, although ID

TABLE 2 Multivariable regression analysis of the factors associated with anemia, iron deficiency anemia, iron deficiency, and iron deficiency without anemia

	Crude OR [95% CI]	Adjusted OR[a] [95% CI]
Anemia		
Age ≥65 y	2.23 [1.55-3.21]	1.76 [1.15-2.70]
Age ≥80 y	1.75 [1.28-2.41]	-
Active cancer	2.07 [1.31-3.41]	2.44 [1.42-4.39]
CKD moderate	2.65 [1.91-3.69]	1.65 [1.12-2.43]
CKD severe	8.65 [3.81-24.9]	4.75 [1.98-14.1]
Iron deficiency	1.40 [1.01-1.95]	-
Functional iron deficiency	1.74 [1.21-2.54]	1.37 [0.93-2.05]
Vitamin B_{12} deficiency	1.91 [1.00-3.96]	1.67 [0.83-3.58]
MCV <80 fL	2.49 [1.33-5.11]	2.89 [1.43-6.34]
MCV ≥100 fL	2.78 [1.24-7.46]	1.98 [0.82-5.52]
Iron deficiency anemia (IDA)		
Age ≥65 y	2.34 [1.57-3.53]	1.62 [1.03-2.58]
Age ≥80 y	1.52 [1.13-2.06]	-
Female	1.43 [1.06-1.94]	1.36 [0.98-1.91]
Heart failure	1.88 [1.39-2.53]	1.35 [0.96-1.89]
CKD moderate	3.01 [2.21-4.10]	2.22 [1.53-3.22]
CKD severe	3.29 [1.99-5.59]	1.78 [1.00-3.23]
Combined deficiency	4.97 [2.71-9.76]	4.72 [2.22-10.99]
MCV <80 fL	2.55 [1.46-4.56]	3.02 [1.63-5.78]
Iron deficiency (ID)		
Age ≥65 y	1.97 [1.34-2.90]	-
Age ≥80 y	1.47 [1.07-2.03]	-
Female	2.43 [1.77-3.36]	2.29 [1.64-3.22]
Heart failure	2.15 [1.55-2.99]	1.65 [1.16-2.37]
Atrial fibrillation	1.44 [1.00-2.08]	-
Hypertension	1.39 [1.01-1.92]	-
CKD moderate	3.00 [2.14-4.23]	2.95 [2.04-4.30]
CKD severe	1.83 [1.07-3.27]	-
Active cancer	0.53 [0.34-0.81]	0.55 [0.35-0.88]
Anemia	1.40 [1.01-1.95]	-
Vitamin B_{12} deficiency	3.03 [1.48-7.07]	-
MCV ≥100 fL	0.27 [0.13-0.56]	0.24 [0.11-0.52]
Iron deficiency without anemia (IDWA)		
Female	2.21 [1.47-3.39]	2.31 [1.53-3.55]
CKD severe	0.26 [0.09-0.59]	0.25 [0.08-0.56]

CI, confidence interval; CKD, chronic kidney disease; MCV, mean corpuscular volume; OR, odds ratio.
Only significant variables are shown ($P < .05$).
[a]Calculated using Poisson regression with robust variance estimation.

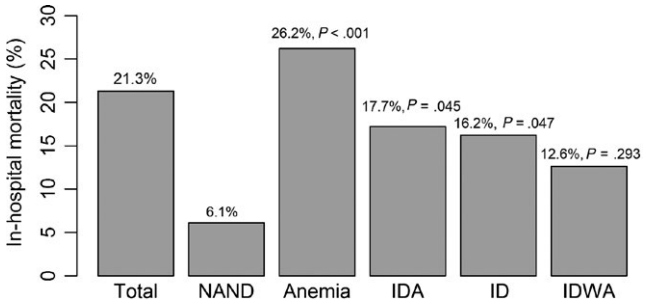

FIGURE 1 Bar plot showing the incidence of all-cause in-hospital mortality across the study population. The proportion of patients who died in-hospital was compared between non-anemic and non-iron, non-vitamin B12, non-folic acid-deficient patients (NAND) and patients with anemia, iron deficiency anemia (IDA), iron deficiency (ID), or iron deficiency without anemia (IDWA). Significant differences at *P*-value <.05

and functional iron deficiency were individual predictors for anemia in univariable analysis, none of them achieved statistical significance in the multivariable model, and strikingly, ID was not even selected for the final model. Although iron deficiency is commonly reported as an underlying cause for anemia, this finding suggests that, in hospitalized patients, iron deficiency is as prevalent in patients with anemia as in patients without anemia. Notice that only 14% of our hospitalized patients do not have anemia or any hematinic deficiency. Moreover, prevalence of iron deficiency may be underestimated due to the high prevalence of chronic conditions with inflammatory processes in our study population, such as chronic kidney disease and active cancer, increasing ferritin levels regardless of iron stores. This constitutes a significant diagnostic limitation.[4] These aspects probably justify the inconsistent relationship between ferritin levels and in-hospital mortality shown in Figure 2. This suggests a trend toward higher mortality in patients with severe inflammatory states indicated by their high

TABLE 3 Incidence and independent predictors of all-cause in-hospital mortality

	Survived n = 607 (79%)	Died n = 164 (21%)	Crude RR [95% CI]	Adjusted RR[a] [95% CI]
Anemia	383 (63.1)	136 (82.9)	2.36 [1.62-3.44]	1.82 [1.21-2.74]
IDA	260 (44.8)	56 (40.3)	0.86 [0.64-1.17]	-
ID	378 (67.6)	73 (54.1)	0.63 [0.47-0.86]	0.69 [0.51-0.94]
IDWA	118 (20.2)	17 (10.6)	0.54 [0.34-0.86]	-
Absolute iron deficiency[b]	221 (38.6)	25 (17.7)	0.34 [0.21-0.54]	-
Functional iron deficiency[b]	157 (28.1)	48 (35.6)	1.32 [0.96-1.80]	-
NAND	154 (25.4)	10 (6.1)	0.33 [0.16-0.62]	-
Age ≥65 y	471 (77.6)	149 (90.9)	2.42 [1.47-3.99]	2.08 [1.22-3.55]
Age ≥80 y	222 (36.6)	101 (61.6)	2.24 [1.68-2.94]	-
Female	372 (61.3)	86 (52.4)	0.75 [0.57-0.99]	-
Active cancer	66 (10.9)	51 (31.1)	2.52 [1.93-3.29]	2.24 [1.64-3.07]
CKD moderate	245 (41.2)	81 (51.6)	1.39 [1.05-1.84]	-
CKD severe	55 (9.2)	27 (17.2)	1.70 [1.20-2.40]	-
MCV ≥100 fL	20 (3.3)	19 (11.6)	2.46 [1.73-3.50]	2.37 [1.62-3.49]

CI, confidence interval; CKD, chronic kidney disease; ID, iron deficiency; IDA, iron deficiency anemia; IDWA, iron deficiency without anemia; MCV, mean corpuscular volume; NAND, non-anemic and non-iron, non-vitamin B12, non-folic acid-deficient; RR, relative risk.
Only significant variables are shown ($P < .05$).
[a]Calculated using Poisson regression with robust variance estimation.
[b]Not included in multivariable analysis.

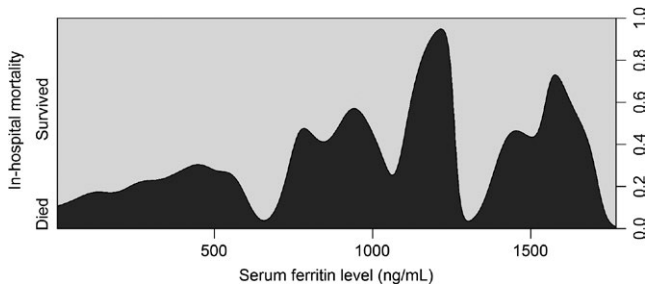

FIGURE 2 Conditional density plot of serum ferritin levels of the study population per all-cause in-hospital mortality outcome (died or survived). For each ferritin level, dark gray areas depict the probability of patient death, while light gray areas show the probability of patient survival

ferritin levels, which do not fit diagnosis of iron deficiency and may also impact prognosis. This hypothesis requires further research.

Moreover, in agreement with previous studies in the ambulatory general population of older adults (≥60 years),[32] cardiovascular risk factors were associated with a higher prevalence of anemia. Our analysis shows that severe CKD is the individual predictor with the highest impact on the prevalence of anemia. The same is true for ID, as heart failure and moderate CKD were selected as individual predictors for this condition, along with being female and having macrocytosis. Hypertension and atrial fibrillation were also significant predictors of ID in the univariable analysis, although these factors were not selected for the final model. The importance of heart failure on the prevalence of iron deficiency is well stated on the prognostic factors for IDA, as, because these populations overlap, heart failure appears as a risk factor for IDA, although not statistically significant in the multivariable model. Additionally, despite older age (≥65 years) being a strong individual predictor of anemia, and inherently for IDA, the same is not true either for ID or for IDWA. This finding may be explained by the high prevalence of IDWA in younger females (<65 years), a result supported by the strong prognostic impact of female gender on the prevalence of IDWA, probably due to prolonged non-treated ID in fertile age. CKD, either severe or moderate, is associated with the prevalence of any of the conditions. Although considered a risk factor for the development of anemia, ID, and IDA, moderate CKD emerged as a protective factor for the development of IDWA, which may be explained by the small subgroup sample size (n = 5). On the other hand, patients with moderate CKD presented very high ferritin levels more easily explained by their critical inflammatory levels, than by normal/high iron reserves, and thus not fitting our definition of iron deficiency. Finally, vitamin B_{12} deficiency was an individual predictor of anemia, IDA, and ID with statistical significance in univariable analysis. However, when included

in a multivariable analysis, it was only considered significant as a prognostic factor for IDA, suggesting that this old population with anemia frequently has multifactorial anemia, mostly due to diet deficits rather than blood loss. Therefore, all hematinic factors should be systematically screened on admission.

Anemia has been associated with an individual prognostic factor for mortality in other studies.[1,3,14,33,34] In our study, we report the association between anemia, ID, IDA, and IDWA and in-hospital mortality. As expected, anemia was considered an individual risk factor for in-hospital mortality in both univariable and multivariable analyses. When considered in multivariable analysis, the impact of anemia on in-hospital mortality was lower than when assessed in the univariable model. This may be explained by the high prevalence of active cancer and macrocytosis, which actually suggests the presence of combined anemia due to multiple deficits of hematinic factors, probably part of a global nutritional deficit, both associated with more than double the risk of in-hospital mortality.

Surprisingly, on hospital admission, ID in acute patients emerged as a protective factor of in-hospital mortality, with a risk of mortality one-third lower for ID patients in multivariable analysis. IDWA and absolute iron deficiency were also significant protective factors for in-hospital mortality in univariable analysis. This finding is not concordant with the published data, which report ID as a risk factor for long-term mortality (although no literature has been published on the prognostic value of ID to short-term in-hospital mortality). In the case of inflammatory diseases, such as active cancer and severe CKD, ferritin blood levels may be very high. Hence, patients admitted to the internal medicine ward with severe acute inflammatory conditions may present iron deficiency masked by those high ferritin blood levels that do not fit our definition of iron deficiency. In fact, active cancer is significantly less prevalent in patients with ID. Because active cancer is one of the most important predictors of in-hospital mortality in our study, this relationship may be masking the apparent protective factor of ID when considered in the general study population. Therefore, and as expected, our data confirm that ferritin blood levels are not a good diagnostic tool to assess iron deficiency in patients with acute inflammatory conditions. Soluble transferrin receptors might be better diagnostic tools in this acute scenario.[2,4] Furthermore, both ID and anemia groups present significantly higher mortality rates than the NAND population (which excludes patients with any hematinic deficiency) as shown in Figure 1—a rate of mortality almost 4 times higher for anemia and 3 times higher for the ID group. This finding supports the overall conclusion that hematinic deficiencies, especially iron deficiency, and anemia are significant prognostic factors for in-hospital mortality and that clinicians should be aware of this fact when dealing with older populations usually admitted to internal medicine wards like ours.

Some strengths and limitations may be presented for our study. Strengths of this study are the size (n = 771) and heterogeneity (varied spectrum of underlying disease or condition for admission) of the study population, being representative of a regular internal medicine hospital ward. Moreover, this was a prospective study, with anemia and iron deficiency markers and other hematinic factors collected under a protocol on admission from all patients. Although we admit that this population is probably representative of those usually admitted to internal medicine wards, we cannot ensure that those results are applicable to all internal medicine wards or other hospitalized populations.

In conclusion, our findings confirmed that anemia and iron deficiency are highly prevalent in patients admitted to internal medicine wards, that is, a predominantly elderly population with multiple comorbidities. As both conditions impacted negatively on in-hospital mortality, our results suggest that better diagnostic protocols for anemia and iron deficiency should be implemented in the acute settings of internal medicine wards to improve early risk stratification. This risk assessment should account for acute inflammatory conditions that may increase ferritin levels and thus bias diagnosis and hinder treatment of iron deficiency, which is the main cause for anemia in our population. Although further studies are needed to evaluate the impact of anemia and iron deficiency correction on the short- and long-term prognosis of patients with various comorbidities hospitalized in internal medicine wards, our study should raise awareness and serve as a call to action for effective diagnosis and management of anemia and iron deficiency in these acute settings.

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AUTHOR CONTRIBUTIONS

Cândida Fonseca, Filipa Marques, and Inês Araujo designed the study. Cândida Fonseca conducted the study. Manuel Araújo, Patrícia Moniz, Filipa Marques, Inês Araújo, Luís Costa, Joana Rodrigues, Luciana Frade, Arturo Botella, Susana Jesus, Ana Leitão, and Luís Campos collected the data. Cândida Fonseca and Filipa Marques involved in data analysis and interpretation. Cândida Fonseca and Filipa Marques drafted the manuscript. All authors revised the article critically for important intellectual content and approved the final manuscript.

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