



Original Article

Extremely Old Patients Hospitalized in Internal Medicine: What about Their Anemia?

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Competing interests: The authors declare no conflict of Interest.

Abstract. In western countries, about half of the hospitalized patients are anemic. Generally, these patients are old, often with multiple diseases, and anemia worsens the prognosis, finally increasing the risk of death. We describe a monocentric observational study that evaluates 249 consecutive adult patients (160 women and 89 men) with anemia admitted in the internal medicine department over five months. They represent 71.5% of all patients admitted in the study period. Demographic, historical, and clinical data, laboratory tests, duration of hospitalization, readmission at 30 days, and death were recorded. Patients were stratified by age (75-84=old, >85 years=oldest-old), anemia severity, and etiology of anemia.

Anemia was found in 67.5% of old and in 77.2% of oldest-old patients. In 37% of old and 32% of oldest-old patients, anemia was mild, in 43% old and 59% of oldest-old moderate and in 20% old and 9% of oldest-old severe in agreement with WHO criteria. Moderate anemia was significantly more common in the oldest-old ($p=0.01$).

The causes of anemia were iron deficiency in 10.6% of patients, other deficiencies in 2.8%, chronic diseases in 38.2%, hematologic neoplasms in 6.1%, multifactorial in 24.1%, and undetermined in 19.9%. The oldest-old have a higher frequency of multifactorial anemia ($p=0.04$), while hematologic neoplasms were more common in old patients ($p=0.03$). Most patients with undetermined anemia had mild/moderate forms. An anti-anemic treatment, mainly blood transfusion, was adopted in 100% of oldest-old patients and in 60% of old ($p= 0.04$). Anemia (and/or its treatment) was reported in the discharge letter in 19% of old and in 28.2% of oldest-old patients.

From a general point of view, physicians seem to disregard anemia in the context of more important pathologic conditions. In oldest-old patients, multifactorial anemia seems to be considered only "one more cause of disability." When borderline anemia occurs, even if it can represent a relevant adverse condition in frailty, it is poorly considered.

Keywords: Anemia; Outcome of hospitalization; Physicians.

Citation: Randi M.L., Bertozzi I., Santarossa C., Lucente F., Biagetti G., Fabris F. Extremely old patients hospitalized in internal medicine: what about their anemia? *Mediterr J Hematol Infect Dis* 2021, 13(1): e2021038, DOI: <http://dx.doi.org/10.4084/MJHID.2021.038>

Published: May 1, 2021

Received: February 11, 2021

Accepted: April 16, 2021

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Introduction. Anemia is a very common feature all over the world. The world health organization (WHO) developed diagnostic criteria for anemia in 1968,¹ based on large populations but did not include people over 65

years. However, the prevalence of reduced hemoglobin levels (Hb) in elderly patients is very high, being 40% of hospitalized and 47% of institutionalized patients.² The more common causes of anemia in old patients are

nutritional deficiency (iron and vitamins), occult hemorrhages, gastrointestinal blood loss, use of antithrombotic drugs, ineffective erythropoiesis³ and anemia related to chronic diseases (CDA), comprehending chronic kidney disease (CKD).^{4,5} Moreover, multifactorial anemia is extremely frequent, meaning that it has to be related to more than one pathologic condition.

It is a general knowledge that old patients are the largest part of patients hospitalized in internal medicine department, and these patients frequently suffer from cardiovascular disease and not only severe but also mild anemia are associated with an adverse outcome in patients with heart failure,⁶ acute coronary syndrome (ACS),⁷ stroke,⁸ etc., all common pathologies in olds.

At present, we know that reduced physical performance,⁹ reduced muscle strength leading to a higher incidence of falling,² more frequent hospitalizations,¹⁰ and to an increased risk of death^{10,11,12,13} are typical complications of old patients with low hemoglobin levels. The paucity of data describing extremely older people with anemia suggests that more information regarding anemia's relevance in this setting is needed.

Recently, we have observed¹⁴ that scarce attention is given to anemia in internal medicine units, at least when a low level of hemoglobin is not directly related to a hematologic disease or to significant bleeding: anemia does not receive an appropriate etiopathological diagnosis, it is not treated if mild or moderate, and it is often ignored in the discharging letter.

In the present observational study, the characteristics of a large monocentric cohort of very old adults hospitalized in an internal medicine department of a third-level hospital are reported.

Material and Methods. Within January and May 2018, we collected the data of all consecutive adult patients admitted in our internal medicine department of a hub hospital with the aim to evaluate the prevalence of anemia and its characteristics in this setting. The patients' data were collected in an ad hoc performed anonymous database, and the study was approved by the Ethical Committee of Padua Hospital, and the criteria of Helsinki were adopted.

The patients were divided into two groups: old patients (75-84 years of age) and oldest-old (≥ 85 years):¹⁵ anemia severity, cause of hemoglobin reduction, and the clinical outcome were considered.

In all the patients, Barthel index to evaluate activities of daily living (an index ≥ 75 was considered a good functional status) and the National Early Warning Score (NEWS 1)¹⁶ to evaluate the severity of the disease (the higher the score, the greater the severity) were collected.

Length of recovery, sudden readmission, and death were also registered. In June 2019, we checked the online

registry offices to know how many of the patients enrolled in the study were still alive.

Authors evaluated laboratory tests and underlying medical treatment: peripheral blood count to identify the anemia cause: comprehensive of reticulocytes, serum iron (Fe), ferritin, transferrin saturation (TIBC), soluble transferrin receptor (sTfR), serum cobalamin (B12), and serum folic acid (fol), serum erythropoietin (EPO) when available. Iron deficiency anemia (IDA) was diagnosed in the presence of ferritin < 45 ug/L and/or TIBC $< 16\%$ and C-reactive protein (CRP) < 5 mg/L, here considered as a good confirmation marker of the absence of an inflammatory condition; other deficiency anemias with vitamin B₁₂ < 206 ng/L, and/or folic acid < 1.8 ug/L together or not with ferritin < 100 mg/L. The diagnosis of CDA required the following conditions: CRP > 5 mg/L, ferritin > 100 ug/L and TIBC $< 20\%$, sTfR < 1.76 mg/L. Chronic kidney disease (CKD) was considered the cause of anemia when the estimated GFR was < 30 ml/kg. All patients in the CDA group, thereby defined from a clinical point of view as it is usual in Internal Medicine, have a functional iron deficiency. Multifactorial anemia was ascribed to patients with more than one of the previous medical conditions.

Anemia severity was defined in agreement with WHO criteria: indeed mild anemia is with Hb > 110 g/L (and < 120 in females or 130 in males), moderate with Hb $80-109$ g/L and severe Hb < 80 g/L.

Statistical analysis. The Fisher's exact test or the X² test were used to compare categorical variables among the different patient groups. The difference of distribution of continuous variables was analyzed using the Mann-Whitney U- test. Kaplan-Mayer method was used to evaluate survival. All statistical calculations were performed using SPSS Statistics

Results. During the observation period, we accepted in our department 249 patients (120 male and 129 females) older than 75 years of age. At admission, reduced hemoglobin levels were found in 178 patients (71.5%): 100 of them (56.2%) were old and 78 (43.8%) oldest-old (**Table 1**). No significant difference was observed in the two groups out of the more frequent occurrence of anemia in old compared to oldest-old males.

Comparing all patients together, those with anemia had shorter overall survival ($p=0.001$), as anemic old patients compared to those with normal hemoglobin levels (**Figure 1**). However, the rate of deaths in old and oldest-old anemic patients is not different.

The median hemoglobin levels were not different in the two age groups, and a similar prevalence of mild and severe anemia but not of moderate anemia ($p=0.01$) was observed (**Table 2**). The most common cause of anemia was a chronic disease (38%), with no difference between old and oldest-old. In this group, 4 patients had ferritin

Table 1. Main relevant data of anemic patients.

	TOTAL (249)	Old (148)	Oldest-old (101)	p
N° of patients with anemia	178 (71.48%)	100 (67.5%)	78 (77.22%)	NS
Males	89 (50%)	61 (61%)	28 (35.9%)	0.01
NEWS ≥ 5 at hospital admission	39 (22%)	20 (20%)	19 (24.3%)	NS
Barthel index ≥ 75 (available in 202 patients)	6 (33%)	3 (3%)	3 (3.8%)	NS
Median recovery duration (days)	10 (1-47)	10 (3-47)	9 (2-43)	NS
Patients with recovery duration >10 days	81 (45.5%)	50 (50%)	31 (39.7%)	NS
New recovery within 30 days	40 (22.4%)	19 (19%)	21 (26.9%)	NS
Deceased during recovery	20 (11.2%)	8 (5.4%)	12 (15.4%)	NS
Deceased within 1 year	38 (17%)	20 (20%)	18 (23%)	NS

Table 2. Severity and causes of anemia.

	TOTAL	old	Oldest old	p
Patients with anemia n°	178	100 (56.2%)	78 (43.8%)	
Hemoglobin level g/L (Mean \pm ST)	100.2 \pm 12	99 \pm 19	101 \pm 14	NS
Severity of anemia				
Mild	62 (33.3%)	37 (37%)	25 (32%)	NS
Moderate	89 (50%)	43 (43%)	46 (59%)	0.01
Severe	27 (15%)	20 (20%)	7 (9%)	NS
Chronic diseases	68 (38%)	38 (38%)	30 (38.5%)	NS
Multifactorial	43 (24%)	18 (18%)	25 (32%)	0.04
Undetermined	32 (18%)	19 (19%)	13 (16.6%)	NS
Iron deficiency	19 (10.6%)	13 (13%)	6 (7.7%)	NS
Hematologic neoplasms *	11 (6.2%)	10 (10%)	1 (1.2%)	0.03
Other deficiencies	5 (2.8%)	2 (2%)	3 (3.8%)	NS

* within hematologic causes of anemia 3 patients had acute myeloid leukemia, 2 myeloma, 1 monoclonal gammopathy of unknown cause, 1 acute lymphoblastic leukemia 2 myelodysplastic syndrome and 1 marginal advanced lymphoma. The oldest-old patient had a myelodysplastic syndrome.

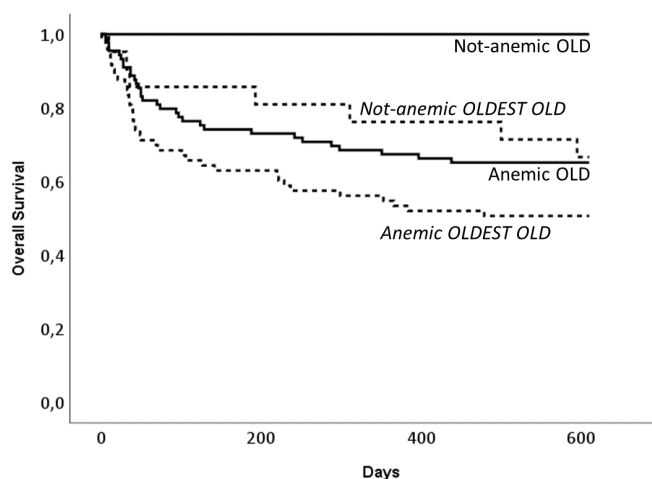


Figure 1. Overall survival after hospital admission was significantly worst in anemic than in not- anemic patients ($p=0.001$). A significant reduction of survival was found comparing old with and without anemia ($p<0.001$), but not comparing anemic oldest old with non-anemic age matched even if a trend can be appreciated.

> 100, TIBC < 20%, and sTRF > 1.76 and all had CKD. Multifactorial anemia was significantly prevalent in

oldest-old ($p=0.045$) and hematologic neoplasms in old patients ($p=0.03$).

Taking together all the patients, the undetermined etiology of anemia was significantly less common in severe than in moderate ($p=0.02$) or mild ($p=0.039$) forms (**Figure 2**).

When we stratified our patients on the basis of anemia severity, the prevalence of different causes of anemia were similar in the two groups of patients, excepting for multifactorial anemia ($p=0.03$) that was more frequent in moderate oldest-old patients compared to old (**Figure 3**),

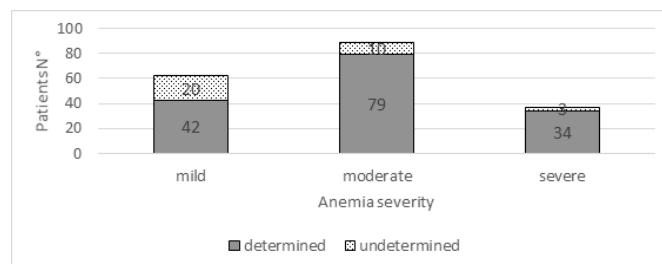


Figure 2. The prevalence of undetermined anemia is progressively reduced from mild to severe cases.

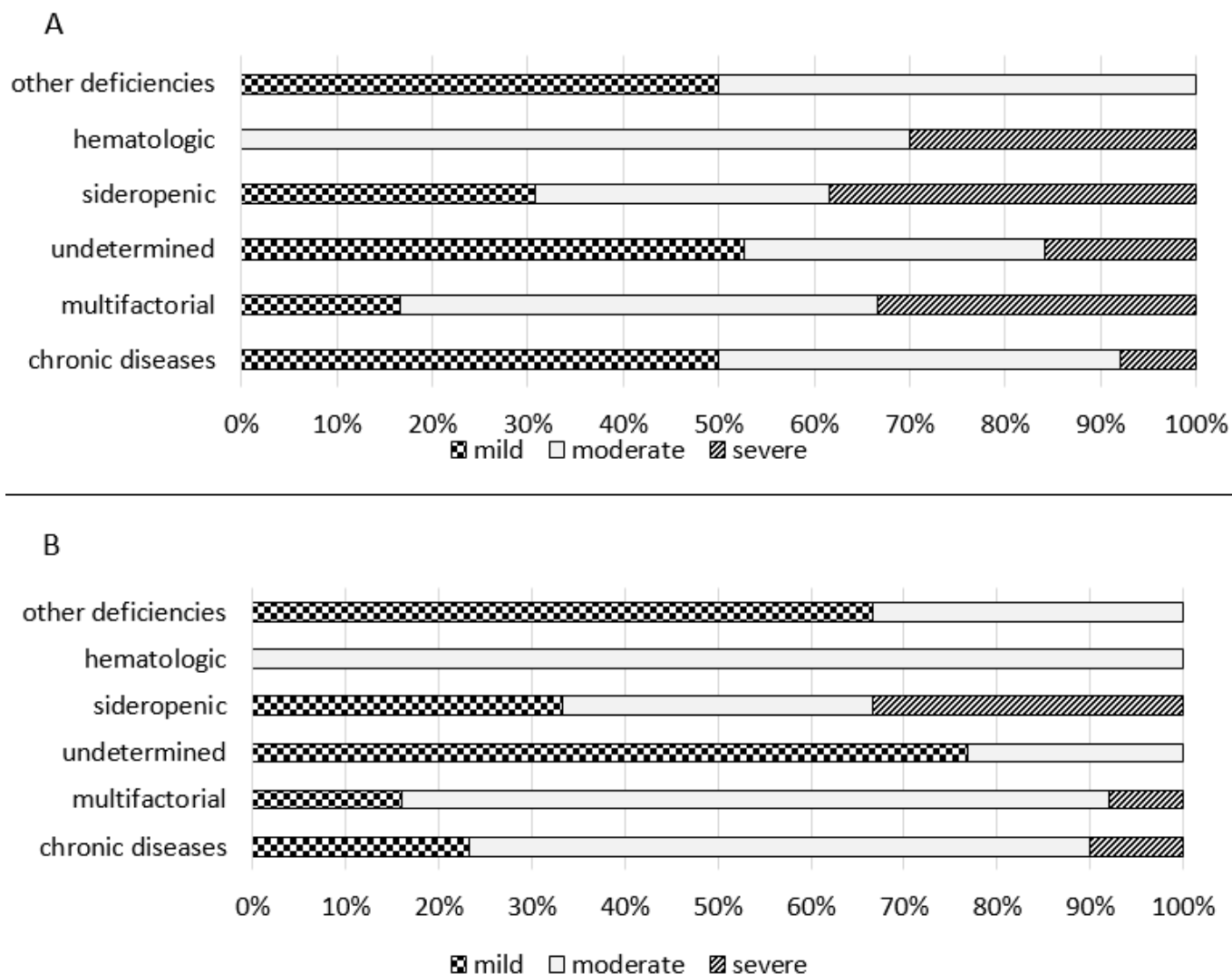


Figure 3. Different causes of anemia stratified on the basis of its severity. Figure 2A: old, Figure 2B: oldest-old IDA= iron deficiency anemia, FIDA= functional iron deficiency anemia.

ferritin level of our patients did not differ comparing old and oldest-old patients. An average serum ferritin level 17.4% had clearly reduced ferritin (< 45 ug/L) and (45-250 ug/L) was found in 18.5% of patients, while 32% had ferritin higher than 250 ug/L.

Only thirty-five old (39.3%) and 22 oldest-old (36%) patients received treatment for anemia, in 10 cases combined (erythropoietin in 3, iron mainly i.v. in 30, vitamin B12 and folic acid in 14, blood transfusion in 22), with no difference among the old and oldest-old group.

The most common cause of admission in our cohort of patients was heart failure (30%): comparing the 28 old and the 27 oldest-old patients with heart failure, one vs. 1 had IDA, 2 vs. 1 had vitamin deficit, 8 vs. 6 had a chronic disease, 4 vs. 12 had multifactorial anemia, 6 vs. 0 a hematologic disease while in 7 vs. 8 patients had undefined anemia. We failed to observed different severity or different causes of anemia in this setting

Anemia was described in the discharging letter of 19 old (21.3%) and in 14 (22.9%) oldest-old.

Discussion. In the Internal Medicine departments, most patients are over 65 years of age, and most of them are frail, frequently suffering from multi-pathologies. Prevalence of anemia in the elderly is a public health problem:³ about 15 million elderly in the European Union may be anemic,¹⁷ and analyses restricted to subjects aged >80 years found that the prevalence of anemia increased to over 25% in the community-living.¹⁸ About half of the old hospitalized patients have reduced hemoglobin levels, and a large body of studies shows the relevance of anemia in geriatrics and in patients affected by multiple medical conditions.^{11,19}

Recently, we provided further support to these data in a hospital-based study¹⁴ as our observations are in line with the percentage of anemia in geriatric patients as reported in other hospital-based studies,¹⁸ confirming the high prevalence of anemia in patients hospitalized in our Internal Medicine department and its impact on the duration of hospital stay, on the number of readmissions and, ultimately on mortality.^{10,19,20,21} However, physicians perceive anemia as a minor problem in multi-

pathologic patients, even if frailty, decreased physical performance, reduced muscular strength with increased risk of falls, cognitive decline, and dementia, and increased mortality occur in elder with low hemoglobin levels.³

In the present study, we evaluated a large cohort of \geq 75-year-old patients during and after hospitalization in an internal medicine unit. Overall, our findings are in agreement with the results of previous studies investigating anemia in the elderly hospitalized population.^{10,20,21}

In our cohort, we did not find a different prevalence of anemia comparing patients before or after 85 years of age²² in contrast with the data of Tettamanti et al.¹⁰ that reported a prevalence of anemic patients that seems to increase dependently to age. While most patients in the old group were males, after 85 years, we found more females with anemia:²¹ the longer expected survival may explain this datum in women. While anemic patients had a worse development than non-anemic patients,¹⁸ no differences were observed in the NEWS and Barthel indexes, recovery duration, new sudden recovery, and prevalence of deaths in the two age groups we previously observed. The overall survival of anemic patients was significantly shorter than non-anemic; in old but not in oldest-old patients, the survival after hospital discharge is significantly reduced in the presence of anemia.

Chronic diseases resulted in the most common causes of anemia in our patients,²³ with the same prevalence in the two cohorts. Hyper-inflammatory state is typical of CKD, cancers, and chronic infections and is the most frequent cause of anemia in our cohort, in agreement with other reports.²¹ Chronic inflammatory diseases are often present in advanced age, and the high prevalence of viral and often multi-resistant infections, mainly in institutionalized patients, is well known.²⁴ Within nutritional deficiency anemias, lack of iron is the most frequent cause, while folate and/or vitamin B12 deficiency occurs rarely. However, unfortunately, homocysteine and methylmalonic acid evaluation were not available in our cohort: they could offer a more precise diagnostic tool, but they are not routinely performed.²⁵ Nevertheless, the rarity in particular of folic acid defect can be a surprising result considering that the use of wine, even if not a clear abuse, is very common in our Veneto Region. Isolated iron deficiency was not common in both cohorts, considering that hemorrhages often occult and related to antithrombotic agents are

frequent in the elderly.^{26,27}

Some hematological diseases were the cause of anemia in old and multifactorial anemia was frequent in oldest-old: interestingly, a chronic disease is present in these latter cases.²⁸ Mild or moderate anemia resulted of undetermined origin in elderly hospitalized patients.¹⁴ It may be that, in patients with a lot of clinical problems, mild anemia does not seem a priority, and the doctors are not focused on clarifying its cause.¹³ Even if the number of patients is very small, curiously, about 50% of old and 80% of oldest-old had undetermined mild anemia: we think that most physicians do not give attention to borderline hemoglobin levels as much as the patient is old.

Only 15% of our patients had severe anemia, in most cases due to hematologic diseases or to iron deficiency or multifactorial associated to iron deficiency. Most of them received an anti-anemic treatment, usually a blood transfusion.

Considering that blood transfusions are risk factors for mortality in heart failure and many of our patients had symptoms of heart insufficiency or had a serious risk to develop them, the use of blood transfusion is particularly inappropriate. Probably the use of novel i.v. compound may be better managed in this setting of patients.²⁹

In contrast, few cases with mild or moderate anemia, who represent about half of all the anemic patients, received a treatment to improve hemoglobin. Considering that most patients in internal medicine departments are admitted for cardiovascular pathologies, this is a remarkable problem.

In fact, for example, not only evident anemia but the sole iron deficiency act as a negative prognostic factor in heart failure³⁰ and this stress the need to pay attention to slightly reduced hemoglobin levels in advanced age.

Conclusions. The monocentric and the consecutive collection of patients' data are the strength of this paper describing the real-life approach to anemia in internal medicine of a third level hospital department; the limit is the deficit of some precise data for the etiologic cause of anemia.

From a general point of view, physicians seem to disregard anemia in the context of more critical pathologic conditions. The older the patients, the more doctors reduce their attention to anemia, mainly when it is borderline, and this behavior can represent a relevant adverse condition in frailty.

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