

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Geriatric Anemia

Manjit Kaur Rana and Amrit Pal Singh Rana

Abstract

Anemia is growing in importance as a public health issue and a biomedical research priority in the geriatric age group but data on the causes and prevalence is not substantial. World health organization (WHO) has defined anemia as hemoglobin concentration (Hb %) below 12 g/dL in women and below 13 g/dL in men. Although it was previously believed that decline in Hb levels might be a normal consequence of aging, later suggested that anemia does reflect underlying poor health and makes elders vulnerable to adverse outcomes. Geriatric anemia has been found to be prevalent in up to 21.1% of patients in Europe and 11.0% of men and 10.2% of women of 65 years and older in the US. There is little literature that explores the various causes of anemia and its association with socio-demographic profile with underlying diseases, hence lesser research has led anemia to go undiagnosed and untreated.

Keywords: geriatric, generalized weakness, unexplained anemia

1. Introduction

Anemia is rising in importance as a biomedical research priority and a public health issue in the old age group. World health organization (WHO) has defined anemia as hemoglobin concentration (Hb %) below 12 g/dL in women and below 13 g/dL in men [1]. Hb declines slightly with more advancing age with frequency of anemia being more pronounced in men. The geriatric anemia is related with mortality and inferior health associated quality of life [2, 3]. This is important area to be explored as there is little literature that explains the association of anemia with old age and lesser research has led anemia to go undiagnosed and untreated. In the shade of absent obvious ailment, complaints of generalized weakness left ignored [4–9]. The incidence of anemia increases comorbidities resulting in increased frequency of hospitalizations hence leading on to adverse impact on survival [10, 11]. So a better outlook is needed to define the optimal Hb levels and to diagnose out the cause of anemia in old age group [12, 13].

2. Definition of anemia and epidemiology

The definition of anemia in the elderly in the literature is controversial. The WHO criteria were established in the 1960s in a cohort lacking individuals >65 years of age [14]. According to WHO criteria anemia was defined as hemoglobin <12 g/dL in women and <13 g/dL in men and absolute iron deficiency was defined as a serum ferritin <30 ng/mL [15, 16]. The National Health and Nutrition Examination Survey

III classifies anemia into four categories as per underlying cause such as anemia from nutritional deficiency, anemia due to renal diseases, anemia of chronic disease and unexplained anemia, in the absence of other specific causes. Worldwide both the number and ratio of older adults growing and there are nearly 500 million (7%) adults, 65 years and older in the world and by 2030 will double to 1 billion (12%). It was predicted that 164 million elderly people who constitute 23.9% of geriatric population were suffering from anemia globally and death risk was elevated to 49% [3, 17]. As per a systematic review the prevalence of anemia was found to be 3–50%. Out of that 3–25% constituted from community-based studies, 31–50% from nursing homes studies and 40–72% hospital admissions [18]. The prevalence of anemia in the institutional studies was observed to be 24%, 31.4%, 46.8%, 54.5%, 66.3%, 67% and 74% in Belgium, Israel, Pakistan, Ethiopia, German, China and US A respectively [1, 19–23]. Whereas the prevalence of anemia was observed to be 7.3%, 17.7%, 19% and 38% in Turkey, rural India, Iran and urban India respectively in population-based studies [24–27].

3. Clinical features

In elderly, anemia is ignored frequently in spite of obvious evidence that due to decreased Hb levels physiologic functions may worsen in the patients [28]. It has been noticed that there are 75% chances of negligence of symptoms by the patients [29, 30]. Also no related positive finding could be recognized on general physical examinations as there are insufficient signs on physical examination that are specific for mild to moderate anemia [3, 31, 32]. However signs and symptoms vary from weakness, irritability, alopecia, xerostomia and depression especially in iron deficiency anemia (IDA). The restless leg syndrome seen in elderly is also commonly take place with iron deficiency [33–35]. Many studies searched in literature verified that anemia is an independent risk factor for rise in morbidity and mortality along with decreased quality of life in older persons [18, 28, 36–38].

4. Etiopathogenesis

Geriatric anemia to a certain extent may be due to unrevealed underlying diseases or due to reduced bone marrow functional reserve or adaptation to reduced lean body mass with diminished oxygen requirements or escaped erythropoietin secretions. There is plenty of substantiation that hematopoietic stem cells undergo some qualitative changes with age hence resulting in reduced proliferative and regenerative capacity. It has been realized that anemia at older age is rising with the possibly of changes in diagnostics and demographics. Though this also have been emphasized by authors that anemia in the elderly do has a treatable cause [18, 39, 40]. The etiopathogenesis of anemia in geriatric age group is multifaceted and varying from nutritional deficiencies to inflammatory progressions resulting in immunodeficiency. Other causes may be from bone marrow failure syndromes to chronic kidney disease. In general causes of anemia were found to be anemia of chronic disease (ACD) associated with co morbidities, deficiency anemia constituting iron deficiency, vit B 12 deficiency, folate deficiency and others and unexplained anemia. While considering the underlying diseases, anemia in elderly is also seen associated with *H. pylori* and twice prevalent in people with chronic kidney disease (CKD), with prevalence of anemia increasing with stage of CKD [22, 33, 41, 42]. Under normal circumstances, increased plasma and stored iron levels activate Hepcidin production, a hormone released by liver which in turn inhibits

dietary iron absorption. Anemia due to iron deficiencies can occur due to low iron content in diet, decreased iron uptake by intestine or excessive bleeding, and compensated by increased erythropoiesis. IDA seemed to be associated with obesity, gastritis and peptic ulcer, esophagitis, Crohn’s disease, celiac disease etc. Although, polymedication was considered independent risk factor for anemia, a 12–35% higher chance of anemia was seen in aspirin users alone. Other drugs like corticosteroids and anti-acids were also seen associated with IDA [43, 44]. Screening for under nutrition should be included in assessment of anemia in geriatric patients as low serum albumin levels are found as independent risk factors for anemia in geriatric patients [44, 45]. The association of deficient serum vitamin D levels with anemia is not considered significant as hypoalbuminemia is measured likely to be confounding factor. At the same time as considering the sociodemographic profile as a causative factor, geriatric anemia was significantly seen associated with high socioeconomic status followed by employment and chronic diseases [45, 46]. Another aspect discussed by Freedman ML and associate suggested that low values in elderly especially in men is a physiologic phenomenon or values of anemia need to be revised in this age group is not known [31, 47].

5. Types of anemia

As per National Health and Nutrition Examination Survey III anemia has been classified into four categories as per underlying cause such as anemia from nutritional deficiency, anemia due to renal diseases, anemia of chronic disease and unexplained anemia, in the absence of other specific causes.

Anemia of chronic disease (ACD) is found to be the most common cause of anemia. The prevalence of ACD varies from 33.1–77% in elderly patients (Table 1) [1, 37, 48].

The cause of ACD in hospitalized elderly patients is mostly the consequence of added chronic underlying diseases and also is an indicator of several reactive and clonal conditions.³ Many underlying diseases, like H pylori, renal impairment, congestive heart failure, myelodysplastic syndrome (MDS) is seen associated with ACD in elderly [19, 42, 51]. Although concentrations of serum ferritin, white blood counts (WBC) and C-reactive protein (CRP) levels in ACD patients remains high in ACD but high Hepcidin (H) level occurring due to inflammation facilitates development of ACD in elderly patients. Wang WJ et al. have emphasized that best threshold value for the diagnosis of ACD is 130.05 µg/L with the sensitivity of 72% and the specificity of 96% [51–53]. An analysis done by López-Sierra Metal also favored use of serum Transferrin Receptor (sTfR) to check out the state of erythropoiesis in patients with chronic disease [54].

Prevalence	Author’s name, year
35%	Joosten E et al., 1992 [1]
65.6%	Chernetsky A et al., 2002 [19]
64%	Willems JM et al., 2012 [49]
77%	Joosten E et al., 2014 [48]
46%	Gowanlock Z et al., 2016 [50]
33.1%	Michalak SS et al., 2018 [37]

Table 1.
Prevalence of anemia of chronic disease in geriatric age group.

Nutritional deficiency anemia is an important clinical problem with prevalence varying from 4% to 22.5% in older patients associated with caloric and protein restriction, iron, vitamin B12, folic deficiency [19, 37, 48, 55]. Protein and energy malnutrition cause an increase in the production of cytokine, stimulation of inflammation and anemia. Due to decreased macrophages activity and ineffective erythropoiesis, reduced red cell mass is seen. In addition, increased cytokines and hepcidin serum levels also seen associated with obesity and underweight [56]. Anemia patients with protein and energy malnutrition more frequently suffered from hypoalbuminemia [43]. Absolute IDA is well-defined as anemia with absence of total body iron. To diagnose IDA although serum ferritin is the most often used parameter, but with older age and in the presence of inflammatory diseases concentration of serum ferritin increases and loses its significance. Iron deficiency anemia (IDA) contributes approximately 13–15% of total anemia of geriatric age group, mainly associated with underlying diseases. Evidence has been supported by improvement of IDA from iron rich diet in geriatric patients [1, 37, 48, 55, 57–59]. New insights into iron homeostasis lead to new diagnostic assays such as serum baseline hepcidin levels could be a useful tool to identify ID in anemic elderly patients. Wang WJ et al. have highlighted that the best threshold in diagnosis of IDA was 93.31 µg/L with the sensitivity of 88% and the specificity of 89% [53, 54, 60, 61]. In addition serum transferrin receptor and reticulocyte hemoglobin equivalent is also an emerging investigation to diagnose the disease [54].

Anemia due to CKD fall under the category of decreased RBC production and prevalence varies from 13.2–27% of geriatric anemia [19, 49]. In a smaller number of cases, no clear-cut causes of anemia are identified and when a clear etiopathogenesis is ruled-out the anemia is defined as unexplained anemia (UA) term unexplained anemia. Although the reasons are still under-explored but common pathophysiological mechanisms seems to be associated with an age-related inflammatory process [62, 63]. These patients with unidentified causes are referred to as unexplained anemia or idiopathic cytopenia of unknown significance. The erythropoietin genesis in the kidney becomes suboptimal due to age related affects or changes. This aspect is still underestimated and unexplored while dealing with unexplained anemia. The prevalence of UA varies from 5.8% to 43.7% of the cases (**Table 2**). Many researchers have worked on UA, Price EA and fellows have observed mildly increased inflammatory markers and low erythropoietin levels in patients with this entity. Roy CN and associates have observed that testosterone treatment in case of men 65 years or older with UA and low testosterone levels significantly increased the hemoglobin levels. In testosterone trials, testosterone treatment increased Hb levels in both men who had anemia of a known cause and in men with UA [3, 37, 61, 64–66]. However, similar survival was observed in geriatric patients with UA compared with non-anemic subjects but mortality risks was increased in patients with deficiency anemia compared with non-anemic subjects [49]. The erythropoietin levels seen

Prevalence (%)	Authors name, year
36.8%	Ferrucci L et al., 2007 [64]
43.7%	Artz AS et al. 2011 [23]
35%	Willems JM et al., 2012 [49]
5.8%	Wolff F et al., 2018 [61]
28.4%	Michalak SS, et al., 2018 [37]

Table 2.
Prevalence of unexplained anemia.

inappropriately low in UA indicating that decreased erythropoietin production plays an important role in the pathogenesis of anemia of unknown etiology [50]. On further cytogenetic analysis of UA, one researcher found myelodysplastic syndrome in 4% of the total anemic patients [67]. Whereas in others, present somatic mutations were not found fit as per diagnostic criteria for MDS and condition was termed as clonal cytopenia of undetermined significance [68].

6. Microscopic patterns of anemia

Normocytic anemia being the commonest anemia followed by microcytic hypochromic and macrocytic as studied by Kim HS et al. The most common pattern of anemia in a study done by Choi CW has been found to be normocytic anemia amounting to 93.5%, and 3.5% of them being microcytic, and 3% were macrocytic anemias. Bhasin A et al. study showed that most common pattern of anemia as normocytic in 60–90 years age group [69–71].

7. Grade of anemia

WHO classified anemia as public health problem in 2008 into mild, moderate and severe category [72]. Most common grade appreciated is mild (57.1%) with mild to moderate anemia commonly affecting females. While severe and life-threatening anemia is confronted in males predominantly [73]. As greater part of the patients are mild anemia only, foremost findings are difficult to observe even pale conjunctiva usually noted when Hb level drops below 9 gm/dL [32]. So this may be the reason that patients of this grade go unnoticed. For example in a study conducted on 1,146 community-dwelling older females it was found that women with Hb levels of 12 to 13 gm/dL perform worse than women with Hb levels of 13 to 15 gm/dL on tests of walking speed, balance and ability to raise from a chair [74]. Across-sectional study including 334 elderly persons was conducted by Pathiana A and fellows in old age home. The overall prevalence of anemia was found to be 68.7%, 47.4% had mild anemia, 47.0% had moderate anemia and 5.6% had severe anemia with 45% of men with mild anemia as compared to 24.8% in women [30].

It has been suggested in the literature that a diagnostic algorithm should be followed and anemia should be classified with a therapeutic orientation. Supplements of iron, micronutrients and erythropoiesis-stimulating agents should constitute the treatment [75].

8. Conclusion

Anemia in older people is typically mild so it is likely to be overlooked. All elderly persons presenting with health issues should be evaluated for anemia first with complete list of parameters. Proportion and pattern of anemia should be confirmed so that overall outcome and quality of life in case of old age can be improved with specific treatment. Future population-based research is essential for refining for diagnostic testing to tackle out the etiology of geriatric anemia and evaluate effective therapies to reduce the disease burden on the society.

IntechOpen

Author details

Manjit Kaur Rana^{1*} and Amrit Pal Singh Rana²

1 Pathology/Lab Medicine, All India Institute of Medical Sciences,
Bathinda, Punjab, India

2 Department of General Surgery, GGS Medical College and Hospital,
Faridkot, Punjab, India

*Address all correspondence to: drmrsmanjitkaur@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Joosten E, Pelemans W, Hiele M, Noyen J, Verhaeghe R, Boogaerts MA. Prevalence and causes of anaemia in a geriatric hospitalized population. *Gerontology*. 1992;38(1-2):111-117.
- [2] Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. *Am J Med* 2004; 116 (Suppl): 3S-10S.
- [3] Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004; 104: 2263-2268.
- [4] De la Cruz-Góngora V, Manrique-Espinoza B, Villalpando S, Téllez-Rojo Solís MM, Salinas-Rodriguez A. Short-term impact of anemia on mortality: evidence from a sample of Mexican older adults. *J Aging Health* 2014; 26: 750-765.
- [5] Hong CH, Falvey C, Harris TB et al. Anemia and risk of dementia in older adults: findings from the Health ABC study. *Neurology* 2013; 81: 528-533.
- [6] Peters R, Burch L, Warner J, Beckett N, Poulter R, Bulpitt C. Haemoglobin, anaemia, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr* 2008;8:18.
- [7] Zakai NA, Katz R, Hirsch C et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. The cardiovascular health study. *Arch Intern Med* 2005;165:2214-2220.
- [8] Izaks G, Westendorp R, Knook D. The definition of anemia in older persons. *JAMA* 1999;281:3-6.
- [9] Joosten E, Lemiengre J, Nels T, Verbeke G, Milisen K. Is anaemia a risk factor for delirium in an acute geriatric population? *Gerontology*. 2006;52:382-385.
- [10] Hirani V, Naganathan V, Blyth F et al. Low hemoglobin concentrations are associated with sarcopenia, physical performance, and disability in older Australian men in cross-sectional and longitudinal analysis. *J Gerontol A Biol Sci Med Sci*. 2016;71:1667-1675.
- [11] Penninx BWJH, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci* 2006;64:74-6479.
- [12] . Alexa ID, Ilie AC, Moroşanu A, Voica A. Approaching frailty as the new geriatric syndrome *Rev Med Chir Soc Med Nat Iasi*. 2013; 117(3):680-685.
- [13] Andrès E, Serraj K, Federici L, Vogel T, Kaltenbach G. Anemia in elderly patients: new insight into an old disorder. *Geriatr Gerontol Int*. 2013 Jul;13(3):519-527.
- [14] Blanc B, Finch CA, Hallberg L, et al. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
- [15] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva, Switzerland: World Health Organization; 2011. [Accessed May 5, 2014]. Available from: <http://www.who.int/vmnis/indicators/haemoglobin.pdf>.
- [16] Ludwig H, Müldür E, Endler G, Hübl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. *Ann Oncol*. 2013;24(7):1886-1892.

- [17] United Nations Department of Economic and Social Affairs. Population Division: World Population Prospects. The 2006 Revision. New York: United Nations; 2007.
- [18] Gaskell H, Derry S, Moore R, McQuay H. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr* 2008;8:1-8.
- [19] Chernetsky A, Sofer O, Rafael C, Ben-Israel J. Prevalence and etiology of anemia in an institutionalized geriatric population. *Harefuah*. 2002 Jul;141(7):591-594, 667
- [20] Argento V, Roylance J, Skudlarska B, Dainiak N, Amoateng-Adjepong Y. Anemia prevalence in a home visit geriatric population. *J Am Med Dir Assoc*. 2008;9(6):422-426.
- [21] Tariq M, Khalid J, Sania HS, Sarfraz S, Aslam Z, Butt LQ. Morbidity profile of chronic diseases in geriatric patients. *J Pak Med Assoc*. 2018;68(6):978-981.
- [22] Chan TC, Yap DY, Shea YF, Luk JK, Chan FH, Chu LW. Prevalence of anemia in Chinese nursing home older adults: implication of age and renal impairment. *Geriatr Gerontol Int*. 2013;13(3):591-596.
- [23] Artz AS, Fergusson D, Drinka PJ et al. Mechanisms of unexplained anemia in the nursing home. *J Am Geriatr Soc* 2004; 52: 423-427
- [24] Yildirim T, Yalcin A, Atmis V, Cengiz OK, Aras S, Varlı M, Atli T. The prevalence of anemia, iron, vitamin B12, and folic acid deficiencies in community dwelling elderly in Ankara, Turkey. *Arch Gerontol Geriatr*. 2015;60(2):344-348.
- [25] Hosseini SR, Zabihi A, Ebrahimi SH, Jafarian Amiri SR, Kheirkhah F, Bijani A. The Prevalence of Anemia and its Association with Depressive Symptoms among Older Adults in North of Iran. *J Res Health Sci*. 2018;18(4):e00431.
- [26] Paul SS, Abraham VJ. How healthy is our geriatric population? a community-based cross-sectional study. *J Family Med Prim Care*. 2015;4(2):221-225.
- [27] Ramachandra SS, Kasthuri A. Anemia in the Elderly Residing in a South Indian Rural Community. *Indian Journal for the Practising Doctor*. 2008;5(4):2-7.
- [28] Penninx BW1, Guralnik JM, Onder G, Ferrucci L, Wallace RB, Pahor M. Anemia and decline in physical performance among older persons. *Am J Med*. 2003;115(2):104-10.
- [29] Bach V, Schruckmayer G, Sam I et al. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. *Clin Interv Aging*. 2014;9:1187-1196.
- [30] Pathania A, Haldar P, Kant S, Gupta SK, Pandav CS, Bachani D. Prevalence of anaemia among elderly persons residing in old age homes in national capital territory, Delhi, India. *Indian J Public Health* 2019;63:288-292.
- [31] Sanford AM, Morley JE. Anemia of Old Age. *J Nutr Health Aging*. 2019;23:602-605.
- [32] Kalantri A, Karambelkar M, Joshi R et al. Accuracy and reliability of pallor for detecting anaemia: A hospital-based diagnostic accuracy study. *PLoS One*. 2010;5(1):e8545.
- [33] Vetrano DL, Zucchelli A, Marconi E, Levi M, Pegoraro V, Cataldo N, Heiman F, Cricelli C, Lapi F. Predictors of iron-deficiency anemia in primary care older adults: a real-world European multi-country

longitudinal study. *Aging Clin Exp Res.* 2020;32(11):2211-2216.

[34] Lieske B, Röhrig G, Becker I, Schulz RJ, Polidori MC, Kassubek J. Stationärbehandelte geriatrische Patienten mit Eisenmangel-assoziiertem Restless-Legs-Syndrom: Eine retrospektive Analyse [Geriatric inpatients with iron deficiency-associated Restless Legs Syndrome. A retrospective analysis]. *MMW Fortschr Med.* 2017;159(4):12-17.

[35] Stewart, Robert MD; Hirani, Vasant MSc Relationship Between Depressive Symptoms, Anemia, and Iron Status in Older Residents From a National Survey Population, *Psychosomatic Medicine: February/March 2012*;74(2):208-213

[36] Gandhi SJ, Hagans I, Nathan K ET AL. Prevalence, Comorbidity and Investigation of Anemia in the Primary Care Office. *J Clin Med Res.* 2017;9(12):970-980.

[37] Michalak S, Rupa-Matysek J, Gil L. Comorbidities, repeated hospitalizations, and age ≥ 80 years as indicators of anemia development in the older population. *Ann Hematol.* 2018;97:1337-1347.

[38] Den Elzen WPJ, Willems JM, Westendorp RGJ, De Craen AJM, Assendelft WJJ, Gussekloo J. Effect of anaemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. *CMAJ.* 2009;181(3-4):151-157.

[39] Price EA. Aging and erythropoiesis: Current state of knowledge. *Blood Cells, Molecules, and Diseases.* 2008;41:158-165.

[40] Beerman I, Seita J, Inlay MA et al. Quiescent Hematopoietic Stem Cells Accumulate DNA Damage during Aging that Is Repaired upon Entry into Cell Cycle. *Cell Stem Cell.* 2014;15:37-50.

[41] Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One.* 2014;9(1):e84943.

[42] Hou B, Zhang M, Liu M, Dai W, Lin Y, Li Y, Gong M, Wang G. Association of active *Helicobacter pylori* infection and anemia in elderly males. *BMC Infect Dis.* 2019;19(1):228.

[43] Röhrig G, Rücker Y, Becker I, Schulz RJ, Lenzen-Großimlinghaus R, Willschrei P, Gebauer S, Modreker M, Jäger M, Wirth R. Association of anemia with functional and nutritional status in the German multicenter study "GeriAnaemie2013". *Z Gerontol Geriatr.* 2017 Aug;50(6):532-537.

[44] Frangos E, Trombetti A, Graf CE, Lachat V, Samaras N, Vischer UM, Zekry D, Rizzoli R, Herrmann FR. Malnutrition in Very Old Hospitalized Patients: A New Etiologic Factor of Anemia? *J Nutr Health Aging.* 2016;20(7):705-713.

[45] Coutard A, Garlantézec R, Estivin S, Andro M, Gentric A. Association of vitamin D deficiency and anemia in a hospitalized geriatric population: denutrition as a confounding factor. *Ann Hematol.* 2013 May;92(5):615-619.

[46] Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, Knabbe C, Berthold HK, Pilz S, Gouni-Berthold I, Gummert JF, Börgermann J, Zittermann A. Randomized supplementation of 4000 IU vitamin D3 daily vs placebo on the prevalence of anemia in advanced heart failure: the EVITA trial. *Nutr J.* 2017;16(1):49.

[47] Freedman ML, Marcus DL. Anemia and the elderly: is it physiology or pathology? *Am J Med Sci.* 1980;280:81-85.

[48] Joosten E, Lioen P. Iron deficiency anemia and anemia of chronic disease in geriatric hospitalized patients:

How frequent are comorbidities as an additional explanation for the anemia? *Geriatr Gerontol Int* 2015;15: 931-935.

[49] Willems JM, den Elzen WP, Vlasveld LT, Westendorp RG, Gussekloo J, de Craen AJ, Blauw GJ. No increased mortality risk in older persons with unexplained anaemia. *Age Ageing*. 2012;41(4):501-506.

[50] Gowanlock Z, Sriram S, Martin A, Xenocostas A, Lazo-Langner A. Erythropoietin Levels in Elderly Patients with Anemia of Unknown Etiology. *PLoS One*. 2016 Jun 16;11(6):e0157279.

[51] Solomakhina NI, Nakhodnova ES, Belenkov YN. [Anemia of chronic disease and iron deficiency anemia: Comparative characteristics of ferrokinetic parameters and their relationship with inflammation in late middle-aged and elderly patients with CHF]. *Kardiologiya*. 2018 SAug;58(Suppl 8):58-64.

[52] Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood*. 2018 Feb 1;131(5):505-514.

[53] Wang WJ, Wang H, Chen Z, Chen Y. [Diagnostic value of hepcidin in elderly patients with iron deficiency anemia and anemia of chronic disease]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2015 Feb;23(1):155-8. Chinese. doi: 10.7534/j.issn.1009-2137.2015.01.030. PMID: 25687065.

[54] López-Sierra M, Calderón S, Gómez J, Pilleux L. Prevalence of Anaemia and Evaluation of Transferrin Receptor (sTfR) in the Diagnosis of Iron Deficiency in the Hospitalized Elderly Patients: Anaemia Clinical Studies in Chile. *Anemia*. 2012;2012:646201.

[55] Sturtzel B, Elmadfa I, Hermann B, Schippinger W, Ohrenberger G. Effects of an enhanced iron dense foods offering in the daily meals served in

geriatric institutions on measures of iron deficiency anemia. *BMC Geriatr*. 2018;18(1):123.

[56] Bianchi VE. Role of nutrition on anemia in elderly. *Clin Nutr ESPEN*. 2016 Feb;11:e1-e11.

[57] Gómez M, Ble M, Cladellas M, Molina L, Comín-Colet J, Enjuanes C, Roqueta C, Soler C, Bruguera J. Effect of correction of anemia on echocardiographic and clinical parameters in patients with aortic stenosis involving a three-cuspid aortic valve and normal left ventricular ejection fraction. *Am J Cardiol*. 2015 Jul 15;116(2):270-274.

[58] Helsen T, Joosten E. IJzergebreesanemiebijouderen [Iron deficiency in the elderly]. *Tijdschr Gerontol Geriatr*. 2016 Jun;47(3):109-116.

[59] Joosten E. Iron deficiency anemia in older adults: A review. *Geriatr Gerontol Int*. 2018 Mar;18(3):373-379.

[60] Epub 2015 Apr 18. PMID: 25983280. 7Auerbach M, Spivak J. Treatment of Iron Deficiency in the Elderly: A New Paradigm. *Clin Geriatr Med*. 2019;35(3):307-317.

[61] Wolff F, De Breucker S, Pepersack T, Compté N, Mélot C, Gulbis B, Cotton F. Baseline hepcidin measurement in the differential diagnosis of anaemia for elderly patients and its correlation with the increment of transferrin saturation following an oral iron absorption test. *Clin Chem Lab Med*. 2018;57(2):250-258.

[62] Halawi R, Moukhadder H, Taher A. Anemia in the elderly: a consequence of aging? *Expert Rev Hematol*. 2017 Apr;10(4):327-335.

[63] Cappellini MD, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin

Change With Aging? *Semin Hematol.* 2015 Oct;52(4):261-269.

[64] Ferrucci L, Guralnik JM, Bandinelli S, Semba RD, Lauretani F, Corsi A, Ruggiero C, Ershler WB, Longo DL. Unexplained anaemia in older persons is characterised by low erythropoietin and low levels of pro-inflammatory markers. *Br J Haematol.* 2007;136(6):849-855.

[65] Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of Testosterone Levels With Anemia in Older Men: A Controlled Clinical Trial [published correction appears in *JAMA Intern Med.* 2019 Mar 1;179(3):457]. *JAMA Intern Med.* 2017;177(4):480-490.

[66] Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ et al. Lessons From the Testosterone Trials. *Endocr Rev.* 2018;39(3):369-386.

[67] Pang WW, Schrier SL. Anemia in the elderly. *Curr Opin Hematol.* 2012;19(3):133-140.

[68] Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood.* 2018 Feb 1;131(5):505-514.

[69] Choi CW, Lee J, Park KH et al. Prevalence and characteristics of anemia in the elderly: Cross-sectional study of three urban Korean population samples. *American Journal of Hematology.* 2004;77:26-30.

[70] Kim HS, Lee BK. Cross-sectional study on the prevalence of anemia among rural elderly in Asan. *Nutr Res Pract.* 2008;2(1):8-12.

[71] Bhasin A, Medha R. Characteristics of Anemia in Elderly: A Hospital Based Study in South India. *Indian journal of hematology & blood transfusion: an official journal of Indian Society of Hematology and Blood Transfusion.* 2011;27:26-32.

[72] Benoist BD, Erin ML, Ines E et al. Worldwide prevalence of anemia. 1993-2005: WHO global database on anemia. Spain: WHO.2008.

[73] Ershler WB, Sheng SH, McKelvey J et al. Serum Erythropoietin and Aging: A Longitudinal Analysis. 2005;53(8):1360-1365.

[74] Chaves PHM, Xue QL, Guralnik JM et al. What Constitutes Normal Hemoglobin Concentration in Community-Dwelling Disabled Older Women? 2004;52:1811-6.

[75] Gómez Ramírez S, Remacha Sevilla ÁF, Muñoz Gómez M. Anaemia in the elderly. *Med Clin (Barc).* 2017;149(11):496-503.