

Anaemia in the Elderly: A Narrative Review

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ABSTRACT

Anaemia is a common morbidity in elderly people (i.e., people who belong to the age group of 60 years or higher). Present-day knowledge is that senescence is the consequence of homeostatic interference. The processes responsible for maintaining it comprise hormones, immune-regulating mechanisms along with oxidative stress/antioxidant equilibrium. Anaemia is caused by any change in these factors. The moment anaemia comes into the picture, it hampers the supply of oxygen causing further deterioration, culminating in debility and infirmity. Anaemia in the senile citizens can lead to certain adverse health events, including functional dependence and may amplify the risks of therapeutic complications, falls, dementia and mortality. Anaemia has a high potential of producing serious impediments in elderly people when compared with younger adults. As a result of which, the Quality Of Life (QOL) of the senescent age group is adversely affected. Hence, early diagnosis of anaemia aids in preventing unforeseen medical situations later. More emphasis is being given to this aspect because of the fact that despite its fair prevalence amongst the elderly, the chances of it being missed on routine clinical examinations are higher.

Keywords: Ageing, Community-health, Geriatric-health, Nutrition

INTRODUCTION

According to the guidelines issued by World Health Organisation (WHO), anaemia in elderly people is stated as haemoglobin (Hb) concentration of <13 g/dL in men and, <12 g/dL in women [1]. Anaemia is also determined in terms of Hb concentration wherein the Red Blood Cell (RBC) numbers are lower than the normal range and therefore incomplete to fulfilling an individual's physiological requirements [2]; it affects nearly about one-third of the worldwide population [3]. Anaemia is related to significant morbidity and mortality in women and children [4, 5], poor birth outcomes [6], reduction in the productivity of work in adults [7], and impaired cognitive and behavioural development in children [8]. Pre-School Children (PSC) and Women of Reproductive Age (WRA) are particularly affected [9]. Standardising the Hb thresholds to define anaemia is crucial to ensure appropriate identification in order to bypass its unfavourable consequences. It is imperative to correlate the diverse and complex aetiology of anaemia for the development of relevant interventions that aim at addressing the context-specific causal factors of anaemia and to monitor the triumph of anaemia control programs [9]. Routinely detected via decreased Hb concentration or a subnormal haematocrit, the same is also achieved using Red Blood Cell (RBC) count, Mean Corpuscular Volume (MCV), blood reticulocyte count, blood film analysis, or Haemoglobin (Hb) electrophoresis [10]. Generally, Hb concentration is by far the primary modality devised for an individual's haematological assessment [11], along with being the commonest indicator for detecting anaemia.

The pivotal role played by Hb in delivering oxygen to the tissues justifies the most common clinical symptoms of anaemia, namely, fatigability, breathlessness, bounding pulses or palpitations, and conjunctival and palmar pallor [12]. The clinical signs [13] together with medical history of the patient are adopted to identify anaemia when haematological reports aren't present, and likewise have certain limits in their ability to detect anaemia [14]. Severe anaemia (Hb <70 g/L in children less than five-year-old, whereas Hb levels <80 g/L in other age groups as per World Health Organisation (WHO)) is highly relevant on clinical grounds, as it may lead to high-output Heart Failure (HF) and death [2]. Over decades, it has been realised that a surge in life expectancy has also increased the proportion of individuals living with age-related conditions and

complications. Also, it is well-known that anaemia in elderly people is associated with a decline in physiological status, a comparatively deranged lifestyle and a surge in morbidity and mortality. Hence, it becomes imperative that anaemia in the elder people has emerged as a public health concern of paramount importance, with the notion in which this review was conducted [15].

Burden of Anaemia

Global scenario: Nearly, a third of the people around the globe (32.9%) were observed suffering from anaemia more than a decade ago, i.e., in 2010 [3]. The age groups most vulnerable to anaemia include under five-year-olds (42% with anaemia in 2016), especially infants and children of less than 24 months of age; work Related Asthma (WRA) (39% with anaemia in 2016); and pregnant women (46% with anaemia in 2016) [16,17]. Females were mostly found to be at higher risk of anaemia than men geographically in most places [3]. Other at-risk groups involve the elderly, because the prevalence of anaemia amongst adults beyond 50 years of age progresses with advancing age [18], still the information remains limited [9]. Anaemic prevalence has shown variation in different regions. Sub-Saharan Africa, South-Asia, the Caribbean, and Oceania had the highest figures regarding the same across all age groups and both sexes in 2010 [3].

At the country level, anaemia among WRA and children below five years of age is a moderate-to-severe public health issue (20% or greater as defined by WHO) in most of WHO member states [19,20]. Progress on its decline is overall slow-paced and uneven. For all age groups and both sexes, anaemia is assumed to have plunged by roughly seven percentage points between 1990 and 2016, from 40% to 33% [3]. The WHO Global Nutrition Target 2025 on anaemia has an aim to reduce anaemia in WRA by 50% by the end of 2025 [21]. On the basis of a global prevalence of 29-38% anaemia among WRA (non pregnant and pregnant, respectively) as of 2011, a deduction of 1.8-2.4 percentage points per year would be needed to reach this goal [9].

Indian scenario: The Iron Deficiency Anaemia (IDA) is the most common micronutrient nutritional health concern in India, posing a major threat to people of all ages irrespective of gender, caste, creed, or religion. This silent crisis is abundant among WRA (15-49 years). Children (6-35 months) and people of low socio-economic status.

Anaemia affects 72.7% of children under the age of three among urban dwellers and 81.2% of children under the age of three in rural regions. During analysis of the statistics for states with level of anaemia to about 70% amongst the children, all the states other than Punjab had a prevalence of 50% of anaemia amongst pregnant women. This confirms the substantial link between anaemia levels in mothers and children. Furthermore, the overall prevalence has risen from 74.2% in 1998-99 to 79.2% today (2005-06). Nagaland had the lowest rate (44.3%). Goa came in second (49.3%), followed by Mizoram (51.7%). Bihar had the highest prevalence (87.6%), followed by Rajasthan (85.1%) and Karnataka (85.1%). Even among educated households in both urban and rural settings, moderate to severe anaemia is common. There are inter-state disparities in anaemia prevalence, which may be due to variances in nutritional intake as well as access to health care [22].

Anaemia has managed to create a profound effect generally from a health perspective, ranging from poorer academic accomplishment and analytic defacement in children to becoming one of the substantial causes of maternal mortality [23]. The National Nutritional Anaemia Prophylaxis Programme (NNAPP), with the centre of attention being alleviation of nutritional anaemia comprised of children within the age group 1 to 11 years as well as WRA group [24]. In the year 1991, it was retitled "National Nutritional Anaemia Control Programme and composed of newer goals to combat anaemia. Its failure at national level due to numerous factors have been depicted [25]. Contemplating the amount of harm anaemia can precipitate to a single person and the community with availability of a brief understanding for its management, it is not at all acceptable to have anaemia when the country still strives for sustainable development goals [24]. The [Table/Fig-1] below shows the change in the prevalence of anaemia in India from 1990 to 2019. It is imperative to note that even though the prevalence of anaemia in elderly has decreased, on an average still over 50% of elderly have anaemia across all the age groups over 60 years of age [26].

S. No.	Age group (Years)	Prevalence in 1990 (%)	Prevalence in 2019 (%)	Difference in prevalence (%)
1.	60-64	58.05	51.7	-6.35
2.	65-69	61.43	57.06	-4.37
3.	70-74	65.76	62.06	-3.70
4.	75-79	71.9	69.26	-2.64
5.	80-84	67.89	63.35	-4.54
6.	85-89	71.11	67.24	-3.87
7.	90-94	65.41	61.12	-4.29
8.	95 and above	68.05	62.68	-5.37

[Table/Fig-1]: Change in the prevalence of anaemia in India from 1990 to 2019 across ages 60 and above [26].

ANAEMIA IN ELDERLY PEOPLE

With the population gradually aging, increased attention is being paid on the occurrence of anaemia in the elderly. Generally, anaemia as well as senility has a specifically complex epidemiology due to enlarged heterogeneity within a highly variable social and biological risk factors with growing age. It is known to occur in individuals exceeding 10% in proportion aged more than 65 years of age and is potent in more than half of the people beyond 80-year-old. Albeit the anaemia is usually mild and doesn't present immediately, it is evenly linked to elevated morbid conditions and deaths, as evaluated via huge cohort experiments. Anaemia presents as a reliable indicator in estimating these unfortunate sequelae, both in healthy community dwellers, besides patients bearing serious co-morbid diseases. The methods devised for further exploring the pathogenesis of anaemia, particularly the ones declared suffering from "unexplained anaemia" have stressed the possible involvement of the inflammatory pathways, resistance to EPO and modifications

in the haematopoietic stem cells to the age-dependent plunge in the masses of red cells [27].

Aetiology

Elderly people suffering from anaemia could be attributed to a wide spectrum of aetiological factors, some of which are more specific to the senescent age group when compared to younger adults or the paediatric population. Most elderly people manifest with Anaemia of Chronic Disease (ACD), which is related to long-term ailments, inflammatory disease, malignancies, etc. IDA is a frequent observation in senile individuals, due to acute/chronic gastrointestinal bleeding, dietary Vitamin B12 deficiency or improper absorption, and renal diseases. Also, there is a strong correlation between anaemia and Vitamin-D deficiency in senescence [28].

Basic mechanism of anaemia in elderly people: There are multivariate causes for anaemia in elderly people and are usually related to multiple precipitating factors. When the functional aspects of the human body are taken into account, the disorders are categorised into inflammatory anaemia (in particular as a consequence of chronic kidney disease), clonal haematopoiesis and nutritional inadequacy. Inadequate manufacture of EPO is notable, usually detected in individuals with renal insufficiency; nonetheless, patients with normal renal physiology, and holds great concern in patients with clonal cytopenia of uncertain relevance [29]. Cases of inflammatory illnesses could have hepatic hepcidin synthesis, resulting in reduced formation of RBCs and also deduced iron absorption in the Reticuloendothelial system. Moreover, the generation of EPO as a compensatory mechanism after the onset of anaemia is minimal, therefore has a very minute effect on erythropoiesis. Another distinguishing feature is enhanced, phagocytosis of senile RBCs (eryptosis) [30].

The primary investigations to eliminate gastrointestinal bleeding and nutritional anomalies of variables that lead to anaemia are necessary in older patients with anaemia. Following this initial evaluation, it is noted that a third of cases with Chronic Kidney Disease (CKD) or inflammatory anaemia (caused by malignancy, autoimmune illness, or persistent infections) can present with a pro-inflammatory condition with impaired synthesis of EPO [30]. The increased concentration of hepcidin, which is connected to "inflammation-aging," is proportional to age. In the present condition, pro-inflammatory cytokines such as Interleukin (IL)-1, IL-6, and Tumour Necrosis Factor-alpha (TNF- α) are increased; however, a reduction in autophagy is due to increased NF- κ B signalling and Reactive Oxygen Species (ROS) may lead to an inflammatory response.

It is crucial to determine the actual pathophysiology in this circumstance, i.e., if it occurred as a result of a change in normal functioning as a result of ageing, or if it indicates the presence of an undiscovered disease. IL-6 levels are slightly raised due to changes in the composition of the body or underlying inflammatory conditions that could impede Erythropoietin (EPO) synthesis and/or hepcidin activation. Due to the difficulties in recognising IL-6, routine assessment skills are restricted [31]. Clonal leukocytes are found in older adults, and somatic mutations increase with age. This clonal haematopoiesis is associated with an increased prevalence and mortality from haematologic malignancies such as Myelodysplastic Syndrome (MDS). This syndrome is recognised as Clonal Haematopoiesis of Indeterminate Potential (CHIP) in healthy persons; Although, many individuals with Cytopenia of Unknown Significance (CCUS) acquire MDS, the diagnosis shifts to Clonal CCUS or MDS after anaemia is detected [32]. Patients with unexplained cytopenia should have a full leukocyte examination, as well as bone marrow plus flow cytometry screening to see whether cytogenetic abnormalities are present because both CHIP and CCUS patients can develop further haematologic malignancies [30,31,33]. Cases of cytopenia without molecular abnormalities or criteria for other illnesses such as MDS will be classified as having Idiopathic

Cytopenia of Unknown Significance (ICUS), whereas people having anaemia would be categorised as ICUS-A [34]. It has also been referred to as 'older age anaemia' on the basis of its strong connection with age [35]. Low EPO levels in the absence of CKD or other inflammatory reasons could result in ICUS-A, which would very well be justified by the intrinsic deficiency of EPO due to a senescent kidney or decreased testosterone and oestrogen synthesis. The probability of ICUS-A to present with sufficient EPO production still remains ambiguous. Patients with Myelodysplastic Syndromes (MDS) may also have low EPO levels, which may respond to recombinant EPO therapy [36].

Iron-Deficiency Anaemia in the Elderly

The IDA has been identified as a primary aetiological cause for impairment in both adults and children, as well as teenage females, reproductive-age women, and pregnant women. It is becoming more well-known as a clinical disease that affects patients who present to a variety of medical and surgical specialities, especially those with chronic illnesses and the elderly [37]. Poor cognitive performance and delayed motor and cognitive development in children, poor physical performance and QOL in adults, particularly WRA, and cognitive decline in the elderly have all been associated with IDA [38-40]. These symptoms may be connected to IDA's reduced oxygen flow to physiological tissues, notwithstanding their vagueness. They can also be a direct outcome of ID [41-44], most likely owing to low iron levels in muscle or brain tissue, and affect energy production, myoglobin synthesis, and brain development. Deoxyribonucleic Acid (DNA) replication and cell cycle disruption (oral lesions, hair loss, nail abnormalities), immunological response (increased susceptibility to infections), myelogenesis and neurotransmission (restless leg syndrome), and cytochrome P450 synthesis suppression are all additional ID effects (altered drug metabolism) [45].

These could also be a direct consequence of Iron Deficiency (ID), possibly because of decreased iron concentration in the muscular or cerebral tissues, and thus negatively influence energy and myoglobin production along with hampering brain development. Both the Deoxyribonucleic Acid (DNA) replication and cell cycle are affected, which can cause lesions in the buccal cavity, loss of hair, Koilonychia-nail abnormalities, increased susceptibility to infections, myelogenesis, and neurotransmission (restless leg syndrome), and cytochrome P450 production inhibition (altered drug metabolism) [43,45,46].

Chronic inflammatory conditions: The burden of IDA on people with chronic inflammatory illnesses can be significant, leading to worsening and exacerbation of symptoms. This is especially important in older individuals with numerous morbidities when even slight anaemia might increase mortality [30]. In chronic HF, IDA is a risk factor for disease development, poor QOL, and an increase in cardiovascular-related mortality [47,48]. Iron deficit without anaemia has also been linked to greater fatigue, decreased activity tolerance, decreased standards of survival, and a gradual rise in the number of hospitalisations; in comparison to those who don't have ID or receive iron replenishment [46,49-55]. Animal studies support this, demonstrating that ID within cardiac musculature, regardless of internal iron concentrations, is linked to lowered contraction of the heart, expansion of ventricles and HF, as a result of a decrease in iron-sulphur cluster formation and mitochondrial electron transport as a response to stress [37,56].

Effects of Anaemia in Elderly People with Chronic Kidney Disease (CKD)

In the frail elderly with CKD, anaemia has been associated with decreased QOL, higher hospitalisation risk, longer hospital stays, functional decline, increased cardiovascular and cerebrovascular disease burden and increased death. Less is known about the anaemia-related consequences, particularly in elderly CKD patients [57,58].

Anaemia of Inflammation and Heparin

Anaemia of Inflammation (AI) or ACD can be interchanged to point toward a condition usually noted in a wide spectrum of diseases, comprising of malignancies, infections, etc., [59]. It is known that Rheumatoid Arthritis (RA) is a consequence of systemic inflammatory disorders. Reduced iron entrance into growing RBCs despite normal or enhanced iron levels in the bone marrow are the hallmarks of the condition. It is distinguished biochemically by lower levels of serum iron, optimal or sub-optimal Total Iron Binding Capacity (TIBC), and altered ferritin values. Albeit, during an acute inflammatory response, a level of more than 200 mg/dL rules out IDA. The revelation, segregation and characterisation of hepcidin as the major component driving the iron-deficient haematopoiesis with appropriate iron reserves has revolutionised our understanding of the mechanism of this anaemia [27,60-62].

Hepcidin is an anti-bacterial peptide generated by the liver which plays an important role in iron metabolism. Targeting the primary iron transporter lowers intestinal iron absorption and macrophage iron release and ferroportin for destruction. Hepcidin-overexpressing transgenic mice die of severe anaemia, while hepcidin-null mice expire due to iron overload. Furthermore, the pro-inflammatory cytokine Interleukin-6 (IL-6) substantially produces hepcidin, and it is assumed that the relationship between inflammation and anaemia is mediated by IL-6-induced hepcidin elevation and subsequent alterations in iron availability for developing erythrocytes [27,63,64].

Anaemia and Cognitive Decline in Old Age

The growth in the population of elderly people, especially the very elderly (age group of 80 and above), is speeding worldwide, and have a higher possibility of dementia and associated cognitive impairment. If Hb levels are found to be related to either incident or prevalent dementia or cognitive decline, there may be a chance of intervention to fend off or postpone the onset of dementia; crucial for potential sufferers, carers as well as in economic terms [65].

Association between Anaemia and Frailty

Frailty is defined as a medical condition in which people are more susceptible to stress and are more prone to acquire unfavourable outcomes such as physical dependence and death, as well as excessive healthcare expenses. The operationalisation of frailty differs depending on the criteria used. Some concentrate on physical aspects like weight loss and poor grip strength, whilst others integrate social, psychological, and physical issues. Fried LP et al., Cardiovascular Health Study criteria, which consist of five elements: unintended weight loss, weariness, weakness, slow walking speed, and low physical activity, are the most generally used definitions of frailty [67]. Frailty is common among the aged, with an estimated frequency of 8-16% in community-dwelling seniors [66-74].

Correlation between Anaemia and Heart Failure (HF)

The HF is a medical condition in which the heart is unable to efficiently execute circulation duties owing to anatomical or functional issues. With an estimated worldwide prevalence of more than 37.7 million individuals, it remains a serious global health problem [74]. The number of HF patients globally is anticipated to climb by 25% by 2030 due to an epidemic of coronary artery disease, diabetes mellitus, and other lifestyle problems [75]. Anaemia affects one-third of HF patients, and ID affects almost half of ID [73]. In HF patients, anaemia and ID are both linked to poor clinical outcomes [72].

Causal factors: Anaemia in HF is complex. Almost half of all HF patients have ID; either they have depleted iron stores (low ferritin less than 100 ug/dL) and low transferrin saturation (equal to or less than 20%) or they have functional ID in the form of normal iron stores (ferritin 100-300 ug/dL) and low transferrin saturation (equal to or less than 20%) [76,77]. Nutrient shortage can arise as a result of either lower consumption or decreased iron absorption in the

stomach. Other nutrient deficiencies, such as folic acid and vitamin B12, are less clearly described as contributory factors [72].

Anaemia in the Elderly with Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS)

Chronic diseases such as cardiovascular disease and Chronic Obstructive Pulmonary Disease (COPD) are long-term illnesses and malignancies that emerge earlier in HIV patients, indicating that HIV may be a model for rapid ageing. Despite the presence of several early treatment techniques, modification in this paradigm remains a matter of debate. The effect of anaemia on the effects of HIV is comparable to that seen in the elderly. Anaemia is an effective predictor of HIV survival, even after the advancement of combination Antiretroviral Therapy (cART); this was formerly explored in the Veterans Administration Cohort Research (VACS), the natural course of HIV in elderly veterans was the topic of extensive cohort research. Justice AC et al., established a "Veterans Aging Cohort Study (VACS) index" based on this group to predict the prognosis of HIV-related disease, emphasising the role of age, CD4 counts, viral load, anaemia, and inflammatory markers in survival [78]. Recombinant human erythropoietin (rhEPO) is used as a medication that is used as a first-line treatment for the cases of ACD, cancer chemotherapy, AIDS and lower-risk MDS [79].

EXPLORING ANAEMIA

In approximately, a third of older anaemic patients, no cause can be found. When investigated, they do not have any nutrient deficiency, renal dysfunction or very high systemic inflammatory cytokines. Even hepcidin levels are only elevated minimally. EPO levels are in the normal range. Unexplained anaemia of ageing is related to a higher number of falls, hospitalisation, development of frailty and mortality [80].

Anaemia in the elderly is generally discovered after they have been scheduled for elective surgical operations. Anaemia is a well-known complication in surgical patients, and it has been associated with a higher rate of perioperative death [81]. When anaemia is discovered during pre-admission testing prior to elective surgery, it should be treated as a severe and treatable medical concern rather than simply an aberrant laboratory value [82]. The presence of unexpected anaemia in patients scheduled for elective surgery who have experienced considerable blood loss may be regarded as a reason to postpone surgery until the anaemia has been assessed and handled. In conventionally taught approaches to evaluate a patient with anaemia, the MCV has typically been utilised as a first indication [83], followed by a biochemical examination. In measuring macrocytosis, the MCV has been shown to be more informative than the Red cell Distribution Width (RDW) for diagnosing macrocytosis [84]. MCV is less effective for microcytic anaemias, especially in individuals with comorbidities and an ID [85]. Despite the absence of the conventional laboratory results of transferrin saturation <16% and ferritin <30 ng/mL, 22% of older people can be classified as having iron-deficient anaemia based on their response to ORAL iron treatment [86]. Inflammatory anaemia is a common diagnosis. Despite low transferrin saturation, which indicates impaired iron delivery to red cell precursors, the MCV is normal in 70% of people with anaemia or inflammation [87]. Standard markers such as MCV, transferrin saturation, and ferritin are difficult to interpret in ordinary practice due to the overlap of these two common causes of anaemia (ID and inflammation) [88].

MANAGING ANAEMIA

The evaluation results dictate how anaemia is managed. While folate insufficiency is becoming less of an issue as a result of folate addition in wheat, some conditions require special care, such as poor diet combined with drunkenness or folate supplementation failure in a

dialysis patient. Conversely, although Vitamin B12 insufficiency is uncommon, if the constellation of symptoms and indications is consistent with Vitamin B12 deficiency, a diagnostic trial of Vitamin B12 treatment may be necessary. Additional methylmalonic acid and homocysteine testing may be helpful, although they might be inconclusive [89]. To rule out extreme ID, a diagnostic or therapeutic trial including intravenous (i.v.) iron treatment may be necessary, as previously noted [90-92]. Because the patient's anaemia has already been proved to be responsive to iron therapy in some of these cases, even the "gold standard" diagnostic bone marrow aspirate revealing the presence of some stainable iron may disguise a storage iron shortfall [90, 93].

Finally, Erythropoiesis Stimulating Agents (ESAs) medicine may be used to address one of the several causes of anaemia in the elderly. ESAs can be used to treat anaemia in patients with end-stage kidney disease [94], anaemia in patients with inflammation/chronic disease who are scheduled for elective surgery [90], and moderate to severe anaemia in patients with MDS [95], where repeated blood transfusions may be the only available option [85]. ESAs were initially tested and authorised in patients with end-stage CKD who were on dialysis [96], and then in those who did not need dialysis [97]. ESAs were approved in patients undergoing elective surgery [98] and cancer patients with chemotherapy-induced anaemia based on prospective randomised trials that demonstrated reduced allogeneic blood transfusion [99].

CONCLUSION(S)

Anaemia in the elderly is thought to be a risk factor for a variety of morbidities and an increase in mortality. The elderly who has anaemia have a lower QOL than those who do not. Anaemia is not solely the result of ageing and is frequently attributed to suspected pathologies that are more common in the elderly. With the world's geriatric population on the rise, anaemia in the elderly can no longer be dismissed as just another sign of ageing. While there has been a decrease in the prevalence of anaemia as an impairment in the elderly over a 29-year period, it is still a concern that anaemia remains prevalent in more than half of all age groups over 60 in India. It is critical to understand how anaemia in the elderly affects not only direct health outcomes but also the prognosis of diseases such as Human Immuno-deficiency Virus(HIV)/Acquired Immuno-deficiency Syndrome (AIDS) and patients with HF when present as a co-morbidity. Given the magnitude of the burden and a range of effects ranging from minor infirmity to cognitive impairment, it is critical to include the elderly as one of the key populations at risk of anaemia. There are numerous existing programmes in India aimed at preventing anaemia. However, the elderly are frequently overlooked as target beneficiaries. As a first step toward addressing this problem, including the elderly in existing programmes aimed at reducing the burden of anaemia should be considered.

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