Original Article

Clinical and hematological evaluation of geriatric anemia

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Abstract

Background: Anemia in the elderly is a cause of concern. It is not merely physiological due to aging and requires appropriate evaluation. Anemia has a significant negative impact on cardiac function, cognition, sleep, frequent hospitalization, mobility, morbidity, and mortality. Anemia in the elderly is attributable to many causes: nutrient deficiencies, chronic inflammatory diseases, thyroid disorders, diabetes mellitus, gastrointestinal (GI) tumors and bleeding, chemotherapy-induced anemia, and drug-induced hemolysis. **Objectives:** We aimed to evaluate the clinical and hematological profile of anemia in 100 patients aged above 60 years. **Methods and Material:** We performed a cross-sectional type of study in a tertiary care center including male and female patients aged 60 years and above and whose hemoglobin was less than 13 g/dl and less than 12 g/dl, respectively. Clinical history, complete blood picture, and peripheral smear were obtained in all patients. Serum iron profile was done in patients with micro-normocytic anemia. Vitamin B12 and folate assays were done in patients with normo-macrocytic anemia and those with pancytopenia. Bone marrow studies and endoscopies were done in cases wherever deemed appropriate. **Results:** The majority of the patients had either severe or moderate anemia. 49% of the patients had normocytic anemia. The commonest cause for anemia was nutritional deficiencies (45%) followed by anemia of chronic inflammation (40%) and unexplained anemia (8%). **Conclusions:** It is essential that anemia deserves its due attention in clinical practice in older patients and is not normal always.

Keywords: Anemia, elderly, iron deficiency, study of geriatric anemia, unexplained anemia

Introduction

Anemia in the elderly is a cause of concern. Irrespective of the etiology, anemia may result in increased frailty, poor exercise performance, diminished cognitive function, risk of developing dementia, decreased mobility, increased risk of recurrent falls, low bone density, low skeletal muscle density, and an increased rate of major depression. Most studies estimate the prevalence of anemia in the elderly between 10 and 45%. Etiology is diverse and may be multifactorial in most cases.

Anemia in the elderly is more challenging than that in the general population. This is attributable to a multitude of reasons, namely, vague presenting complaints of the patient, non-specific symptoms, poor history due to an impaired memory, absence of accompanying attendants or relatives in most cases, presence of one or many underlying comorbities, which may mask the symptoms of anemia, and a tendency to dismiss anemia in the elderly as merely physiological. Anemia is a sign and not a diagnosis per se. The presence of anemia may be a marker for a more severe underlying disease. Failure to correctly diagnose and treat anemia may be the reason for poor response to treatment for other coexisting disease conditions. Therefore, it is imperative for the primary care physicians as well as health care workers at the first point of contact of the patient to focus on identifying geriatric anemia. A prompt identification of anemia and its subsequent management is a great harbinger of successful outcomes of other associated illnesses as well. We aimed to study the clinical and hematological patterns of anemia in the elderly population aged 60 years and above to help us in better understanding of this common and foremost geriatric issue of concern.

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Materials and Methods

Objectives: The objective of the study was to study the clinical and hematological patterns of anemia in elderly patients aged 60 years and above and to ascertain the morphological types of anemia prevalent in them.

Ethics: Patients were included in the study after obtaining prior informed consent and Institute Human Ethics Committee Clearance [IHEC Project NO. 17/413].

Study design: It is a cross-sectional type of study performed in our tertiary care health center between January 2018 and December 2018. Male and female patients aged 60 years and above and whose hemoglobin was less than 13 g/dl and less than 12 g/dl, respectively, were included in the study. Patients who had received transfusion less than 3 months ago, patients who underwent a major surgery less than 3 months ago, and those on hematinics were excluded from the study.

Study methods: A detailed clinical history and physical examination were recorded. Complete blood picture including hemoglobin estimation, hematocrit, red blood cell count, white blood cell count, differential count, platelet count, red blood cell indices, red cell distribution width, serum iron, total iron-binding capacity (TIBC), serum ferritin levels, fasting serum B12 levels, serum folate level, peripheral smear examination, and reticulocyte count was evaluated. Transferrin saturation (TSAT %) was calculated based on the formula (serum iron/serum TIBC) × 100.

Additional investigations including bone marrow examination, hemoglobin electrophoresis, radiological studies, stool, urine examination, liver function tests, and renal function tests were done whenever necessary depending on the patient's profile. Upper and lower gastrointestinal (GI) endoscopies were performed depending on stool occult positivity and the clinical profile of the patient.

Statistical tools: Data collected from the patients was tabulated using Microsoft Excel. Data are reported as mean ± standard deviation or the median depending on their distribution. Frequencies are expressed as percentages. The Chi-square test was used to assess the difference in categorical variables between groups. A P value of < 0.05 will be taken as being of significance for all statistical tests. Data were analyzed with the statistical software Statistical Package for the Social Sciences (SPSS).

Results

In our study population above 60 years of age, we observed that the mean age was 71.4 years and patients in the 60–70 years age group were significantly higher (51%) compared to the other decades [Figure 1]. Fifty-five patients were males and 45 were female patients.

Fatigue was one of the presenting complaints in 71% of the patients, exertional breathlessness was noted in 22% of the patients, and palpitations were reported in 10% of the patients. With respect to the severity of anemia, we observed that the majority of the patients had either moderate or severe anemia [Figure 2]. The mean value of hemoglobin was 7.1 g/dl. 49% of the patients had normocytic anemia (mean corpuscular volume (MCV) 80–100 fl), 34% had microcytic anemia (MCV <80 fl), and the remaining 17% had macrocytic anemia (MCV >100 fl).

Eighty-three patients who had either microcytic or normocytic anemia were studied for serum iron profile as displayed in Figure 3. Twenty-four patients had serum ferritin <30 ng/ml and were therefore classified as iron deficiency anemia. Seventy-six patients who had either macrocytic or normocytic anemia and those who had pancytopenia were assessed for B12 and folate levels. Eighteen of them had B12 levels <200 pg/ml, three of them had folate levels <3 mcg/L, and two patients had both the deficiencies.

Ten patients had pancytopenia as noted in peripheral smear and 10 patients underwent bone marrow biopsy. Of them, three had features of multiple myeloma, two patients had acute leukemia, two patients had myelodysplastic syndrome, and two patients had megaloblastic anemia. Stool examination for occult blood was done in 56 patients and 8 were positive for the same. GI endoscopies (upper, lower, or both) were performed in 30 patients. Upper GI endoscopy findings are displayed in Figure 4. In colonoscopy, five patients had hemorrhoids, two of them had a rectal polyp, one patient had a colonic polyp, and one patient was diagnosed to have carcinoma of colon.

The etiology pattern is shown in Table 1. In the subset in which anemia was attributed to the chronic disease, the commonest underlying cause was chronic kidney disease (16 out of the 40 patients-40%). Some of the other causes were abdominal

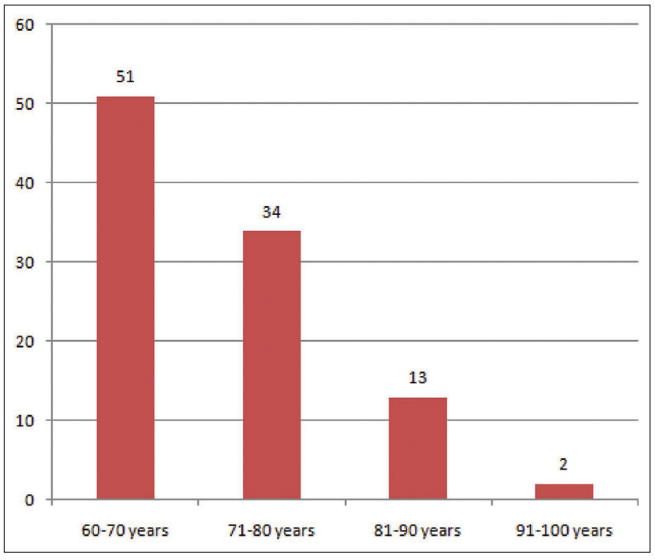

Figure 1: Bar chart showing the age-wise distribution of the 100 study participants

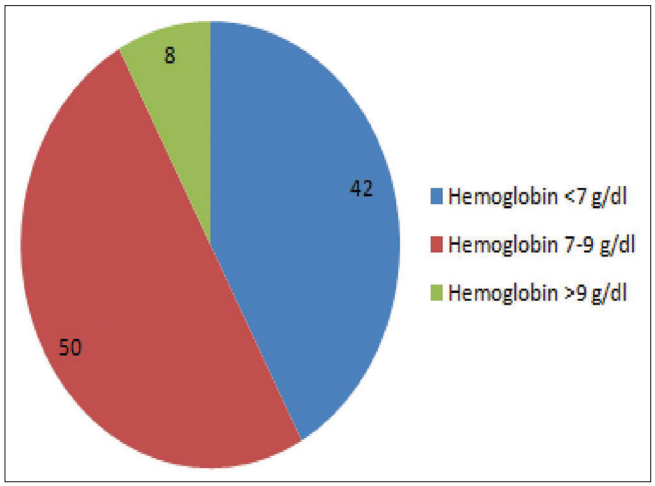

Figure 2: Pie chart showing the stratification of the study participants according to hemoglobin values and severity of anemia

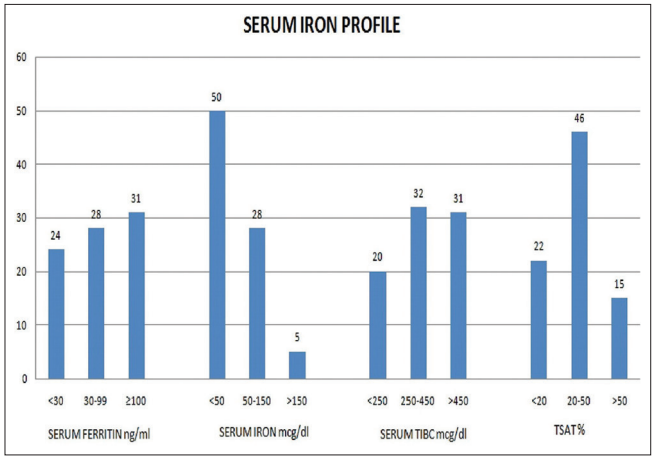

Figure 3: Consolidated bar diagram showing the serum iron indices of the selected study participants

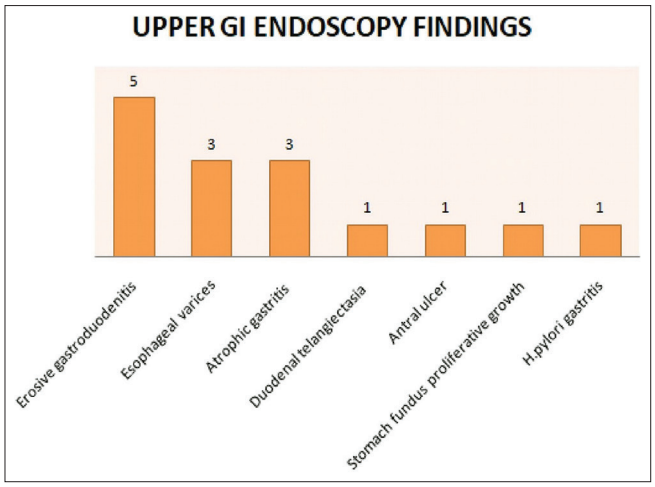

Figure 4: Bar diagram showing the upper GI scopy findings

tuberculosis and heart failure. Cancers of the gastrointestinal tract (GIT) and genital cancer contributed to iron deficiency anemia in five patients. The hematological malignancies observed were plasma cell dyscrasias and acute leukemias. Two patients had myelodysplastic syndrome. One patient had thalassemia minor diagnosed by hemoglobin electrophoresis.

Table 1: Etiological pattern of anemia in the 100 study participants

Final diagnosis	Number of patients
Nutritional causes	45
Iron deficiency anemia	24
B12 deficiency	18
Folate deficiency	3
Anemia of chronic disease	40
Hematological malignancies	7
Unexplained anemia	8

Discussion

Population aging is an observed phenomenon worldwide. This means that the current estimate of 500 million adults aged above 65 years is likely to rise to 1 billion by 2030. Therefore, it is imperative for the developing nations, which focus on increasing the average life expectancy to actively address health issues of the elderly, anemia being one among them.[1]

Anemia in the elderly is a common problem. Inflammaging was a term used by Franceschi *et al.*[2] to describe a low-grade proinflammatory state associated with aging and immunosenescence. This is attributed to the upregulation of certain proinflammatory cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)) as we age. There is growing evidence to prove that anemia in the elderly is more often pathological and may be multifactorial. Irrespective of the etiology, the presence of anemia may reflect poor health and contribute to significant morbidity and mortality.[3]

The World Health Organization (WHO) defines anemia as hemoglobin concentration <12 g/dl in women and <13 g/dl in men. Although a point of debate, this cutoff value has been used to define anemia in the elderly in most epidemiologic studies. The third National Health and Nutrition Examination Survey (NHANES-III) is one of the most extensive databases which gives the causes of anemia in elderly US adults as well as the age- and sex-specific prevalence rates of anemia.[4] According to NHANES-III, the prevalence of WHO-defined anemia among community-dwelling adults aged 65 years and older was 11.0% and 10.2% in men and women, respectively.

In our study population, the 60–70 years age group patients were higher compared to the other decades. This is quite similar to another study from Bangalore, South India where the maximum numbers of patients were in the age group of 60–69 years, and the mean age was 70.5 years.[5] A similar study from North India had a male: female ratio of 1.6:1, as compared to 1.2:1 in our study, reflecting a near similar epidemiological distribution.[6]

Data from NHANES-III show that the highest prevalence of anemia was noted in the >85 years age group (46.1%) compared to the other age groups of 65–74 and 75–84 years.[3] So also in a study of anemic elderly patients in Assam, it was noted that the patients aged above 80 years had the highest prevalence of anemia (85%).[7] A higher prevalence of anemia was noted in the female population in the same study, contrasting most other epidemiological studies probably reflecting the different epidemiological patterns of North-Eastern India. Fatigue was the commonest complaint noted at presentation in our study population similar to other studies.[5,6]

In our study population, the majority had moderate anemia and severe anemia. This is in contrast to a study by Agarwalla R, where 61% of the patients had only mild anemia and 15% of the patients had severe anemia.[8] However, in a study from Gurugram, India, it was noted the majority of anemia in the elderly was of moderate grade (53%).[9] The relatively higher prevalence of severe anemia in our study population probably reflects on their tendency of late recognition/reporting of symptoms, delaying hospital visits due to financial and physical dependence on their children, difficulty in commuting to hospital - all leading to a delayed management.

Normocytic anemia was noted in the majority of the patients in our study. Bhasin *et al.*[5] and Sharma *et al.*[6] have also reported a higher prevalence of normocytic anemia.

In our study, 24 patients had iron deficiency anemia, diagnosed based on serum ferritin levels <30 ng/ml. Conventional laboratory values follow the lower reference cutoff for ferritin as 15 ng/ml. However, notable studies and observations throw light on the fact that the sensitivity and specificity improve by raising the diagnostic value to 30 ng/ml, which we have followed in our study as well.[10,11] These patients had no other evidence of ongoing infection and therefore ferritin was a reliable marker for iron deficiency anemia.

In our study, 22 patients had a TSAT of less than 20%. TSAT reflects the iron stores of the body and therefore is a potential tool to diagnose iron deficiency or overload states. Its calculation is based on serum iron as well as the iron-binding capacity. The normal range of TSAT is 20–45%. In the early stages of iron deficiency, ferritin characteristically tends to reduce first which later reflects on the serum iron, TIBC, and TSAT subsequently. This physiological delay in TSAT decline, therefore, confers the superiority of serum ferritin in making it a valuable and sensitive indicator for iron deficiency.[12] TSAT has diurnal variation and may be influenced by infection, inflammation, malignancy, or coexistent liver diseases thereby making it a less reliable indicator.

A diagnosis of iron deficiency is made based on the interpretation of these multiple iron indicators on the background of a strong clinical acumen. The WHO's guide to program managers of iron deficiency anemia states that an ideal combination of hemoglobin, serum transferrin receptors, and serum ferritin or bone-marrow iron would reflect functional impairment, tissue avidity for iron, and iron storage, respectively.[13] We could not collect data with respect to transferrin receptor assays as they were not routinely done in our center. However, it is not always possible to use all the indicators when availability and financial constraints are significant. Serum ferritin still retains its status as being the best indicator to define iron deficiency anemia in the absence of infection.

Twenty-one patients had either vitamin B12 or folate deficiencies or both. However, it is possible that more patients had these nutrient deficiencies because serum assays of B12 and folate do not necessarily reflect tissue availability or deficiency. It is studied that serum methylmalonic acid (MMA) and homocysteine levels were elevated more than three times the normal levels in B12 deficient patients and are more sensitive markers.[14] These tests are widely available in recent years but continue to remain expensive. In a study from Finland, the prevalence of vitamin B12 deficiency was 2.7% when estimated based on serum B12 levels and macrocytosis. However, the total prevalence subsequently rose to 12% when holotranscobalamin levels, plasma total homocysteine, and erythrocyte folate levels were measured.[15] The global prevalence of B12 deficiency anemia in the elderly is around 5–40% depending on the criteria involved.[16,17]

In our study, we performed bone marrow studies in 10 patients who had pancytopenia and 7 hematological malignancies were diagnosed. In a study by Bisht *et al.*,[7] pancytopenic patients were diagnosed to have megaloblastic anemia, multiple myeloma, or aplastic anemia.

Thirty patients underwent endoscopies of the GIT in our study and an etiology was picked up in 24 patients (80%). It is essential to proceed with endoscopic studies even when the reluctance is high in the elderly for an invasive procedure. In the absence of an alternative cause for anemia, GI evaluation should be planned for all elderly patients with iron deficiency anemia. In the elderly, iron deficiency is usually the result of chronic blood loss either due to gastritis (non-steroidal anti-inflammatory drugs (NSAID) induced), ulcers, cancers of the colon, andiodysplasia, or colonic diverticulum.[18] An upper GI source is usually found in 20–40% of patients; 15–30% have blood loss from the colon; whereas 1–15% of the patients may have bleeding from both the upper and lower GIT.[19] Though it is convenient to perform and convince the patient for an upper endoscopy, bidirectional endoscopies are more productive in establishing the etiology and should be routinely considered.[20]

In our study population, the commonest cause for anemia was nutritional deficiencies (45%). In the NHANES-III study too anemia due to nutrient deficiencies was commonest.[3] In a study by Chernetsky *et al.*,[21] the most common etiology for anemia in the elderly was that due to chronic disease (65%). Sharma *et al.*[6] in Chandigarh estimated the prevalence of anemia in the elderly as 24.8% due to iron deficiencies, anemia of chronic disease (22.9%), and that due to chronic kidney disease as 12.4%.

The commonest cause for anemia of chronic disease in our study was chronic kidney disease (40%). This is consistent with various epidemiological studies.[5,22] Anemia of chronic disease constitutes one-third of the etiology of anemia in patients >65 years of age. It is more recently referred to as anemia of chronic inflammation thereby referring to anemia in any chronic disease where the central pathophysiology is attributable to inflammation and inflammatory cytokines. In this condition, there are reduced circulating serum iron levels despite normal or increased iron stores. It may be tricky to differentiate iron deficiency anemia from that due to chronic disease. Measurement of bone marrow stainable iron, transferring receptor assays, and hepcidin may help in better differentiation.[3]

8% of the patients had unexplained anemia in our study population. However, a subsequent follow-up and re-evaluation, especially of the bone marrow studies may identify a specific pathology in our patients. Unexplained anemia accounts for almost one-third of all causes of anemia in the elderly. This entity is characterized by normocytic hypoproliferative anemia, which remains unexplained by nutritional deficiencies or by chronic inflammation.[23] In a study of 732 geriatric patients in a Belgian hospital, 24% of the patients were anemic and 17% of the patients among them did not have an identifiable attributable cause for anemia.[24]

Clonal cytopenia of undetermined significance is the term used to refer to anemia in which somatic mutations are found in the leukocytes; however, diagnostic criteria for myelodysplastic syndrome or other hematological disorders are not met with.[4] NHANES-III had noted that 17% of patients of those initially with unexplained anemia met at least any one criterion for myelodysplastic syndrome.[1] Few others may be B12 deficient if tested by MMA assays. Other causes would include thalassemia minor, hereditary spherocytosis, autoimmune hemolytic anemia, multiple myeloma, and hypothyroidism.[3] Few studies have shown that IL-6 levels will increase with aging and may correlate with anemia in the elderly.[24] However, in a study by Waalen *et al.*[25] in a large cohort of elderly patients with unexplained anemia, it was found that testosterone levels were low in men rather than IL-6 and hepcidin levels - when compared to matched controls.

Treatment of anemia in the elderly largely depends on the underlying cause. Diet enrichment and alcohol abstinence are central to nutritional deficiencies. Oral supplements continue to play a major role and are the simple first step in replacement. In a recent community-based cross-sectional study of 958 subjects, 92.1% of the elderly population were anemic and it was observed that in patients with moderate to severe anemia, 29% consumed low iron and 31.3% subjects had inadequate vitamin C consumption.[26] In situations where there is decreased oral intake or ineffective absorption, intravenous iron preparations may be used. A trial of intravenous iron therapy has been shown to be beneficial both in treating identified iron-deficient patients as well in those with stainable marrow iron.[27] Erythropoietin stimulating agents have been traditionally used in chronic kidney disease patients. However, they also have a successful role in anemic patients undergoing elective surgery, chemotherapy-induced anemia as well as congestive heart failure patients with coexistent anemia.[28,29] Newer agents like hepcidin inhibitors and hypoxia-inducible factors inhibitors are being studied increasingly for their scope in stimulating erythropoiesis.[4,30]

Blood transfusion in the elderly has to be a cautiously treaded path considering the risk vs benefit ratio. Increasing age and cardiovascular status of the patient are important factors to consider while deciding on transfusion practices. In general, it is a safe and wise decision to maintain hemoglobin thresholds of 7–8 g/dl in the elderly for transfusion.[31,32]

Strengths and limitations: To our knowledge, this is among the very few studies from Tamil Nadu, which discuss the prevalence, pattern, and etiology of anemia in the elderly. However, ours is a hospital-based study and may not be truly reflective of the population. Drug history, specifically that of NSAIDs, and alcohol consumption history have not been analyzed in our study and if available may add to the discussion further. The dietary habits and financial status of the patients may help in better understanding of the factors contributing to the nutritional deficiencies. Future research can solve these limitations. Addressing such dietary deficiencies by encouraging better and focused diet counseling to the patient as well as their caretakers will go a long way in preventing geriatric anemia. So also, it is equally important to encourage the patients to report early even minor complaints to their primary physicians to pave way for on-time management.

Conclusion

In the elderly, it is indeed necessary to identify anemia, stratify the type and its severity, search for the underlying cause, and address the identified etiology subsequently. It is important to persuade and evaluate GIT by bidirectional scopies in elderly patients with iron deficiency anemia. Despite optimal work up, some proportion of the patients may not have an attributable cause to anemia in the initial presentation and may have unexplained anemia. Wherever a reversible cause for anemia is identified and corrected, it is rewarding to note that we can significantly contribute to the overall improvement in the quality of life in the elderly and their activities of daily living are enhanced. While aging is physiological and inevitable, staying healthy while aging is a basic right and necessity for many. As physicians, it is our duty to bestow this privilege on the elderly by focusing on the vital issue of geriatric anemia. A focused approach is always the forerunner for better patient outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and

due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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