Research Article / Araştırma Makalesi

A Cross Sectional Analysis of Etiology of Anemia Among Elderly Patients

Yaşlı Hastalarda Anemi Etiyolojisinin Kesitsel Analizi

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Abstract: The aim of this study is to evaluate the etiology and features of anemia in elderly patients from the perspective of hematology and to determine the rate of unexplained anemia. The medical records of elderly patients over the age of 65 who applied to the Hematology Department of Ankara Baskent University Hospital between January 2015 and January 2020 were retrospectively analyzed. According to WHO criteria, the threshold value accepted for anemia was Hb <12 g/dL for women and <13 g/dL for men. The prevalence of anemia was 18% among 3330 elderly patients. The ratio of women to men diagnosed with anemia was 1.5:1, and the mean age was 77.34±8.32. The mean Hb value was 9.79±1.75 g/dl and decreased significantly with advancing age (p<0.001). Polypharmacy was present in 68.3% of the patients. The etiological distribution of anemia was nutritional anemia in 339 (56.5%), hematologic malignancy in 127 (21.1%), anemia of chronic disease in 125 (20.8%), and unexplained anemia in 58 (9.7%) patients. 72% of the patients with indications for bone marrow biopsy had the procedure. Anemia in the elderly is a challenging issue due to comorbidity, polypharmacy, and problems in further examination. Hematological evaluation of anemia in elderly patients will reduce the rate of unexplained anemia. Patient selection for invasive procedures should be based on a risk-benefit ratio in frail elderly patients.
Keywords: Aged, Anemia, Etiology, Frail Elderly, Polypharmacy

Özet: Bu çalışmanın amacı yaşlı hastalarda aneminin etiyolojisini ve özelliklerini hematoloji bakış açısıyla değerlendirmek ve açıklanamayan anemi oranını belirlemektir. Ocak 2015-Ocak 2020 tarihleri arasında Ankara Başkent Üniversitesi Hastanesi Hematoloji Kliniğine başvuran 65 yaş üstü yaşlı hastaların tıbbi kayıtları retrospektif olarak incelendi. WHO kriterlerine göre anemi için kabul edilen eşik değer, kadınlarda Hb <12 g/dL, erkeklerde <13 g/dL idi. 3330 yaşlı hastada anemi prevalansı %18 idi. Kadınların anemi tanısı alan erkeklere oranı 1,5:1, yaş ortalaması 77,34±8,32 idi. Ortalama Hb değeri 9,79±1,75 g/dl idi ve yaş ilerledikçe anlamlı olarak azaldı (p<0,001). Hastaların %68,3'ünde polifarmasi mevcuttu. Aneminin etiyolojik dağılımı; 339 (%56,5) hastada beslenme anemisi, 127 (%21,1) hastada hematolojik malignite, 125 (%20,8) hastada kronik hastalık anemisi ve 58 (%9,7) hastada açıklanamayan anemi idi. Kemik iliği biyopsisi endikasyonu olan hastaların %72'sine prosedür uygulandı. Yaşlılarda anemi komorbidite, polifarmasi ve ileri tetkiklerdeki sorunlar nedeniyle zorlu bir konudur. Yaşlı hastalarda aneminin hematolojik olarak değerlendirilmesi açıklanamayan anemi oranını azaltacaktır. İnvaziv prosedürler için hasta seçimi, kırılgan yaşlı hastalarda bir risk-fayda oranına dayanmalıdır.
Anahtar Kelimeler: Anemi, Etiyoloji, Kırılgan Yaşlılar, Polifarmasi, Yaşlı

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1. Introduction

Anemia is a common health problem in elderly patients and is associated with decreased quality of life and increased morbidity and mortality. Although the prevalence of anaemia is highly variable according to the population studied, anaemia is observed in approximately 10% of the elderly in the community (1). Many comorbid conditions, including chronic diseases, nutritional deficiencies and inflammation may cause anemia (2). Hematological and solid organ malignancies are also important causes of anemia in the elderly population (1). After the exclusion of these causes, the diagnosis of unexplained anemia (UEA) is mentioned (3). Low serum erythropoietin (EPO) level, decreased testosterone level, occult inflammation and clonal changes in hemopoiesis have been blamed as the etiology (1, 4). In clinical practice, it is essential to determine the cause of anemia for the most appropriate treatment. However, comorbidities and multiple drug use make the diagnosis difficult in elderly patients (5, 6). In addition, it is not easy to perform an etiological evaluation with invasive procedures, including endoscopic examination and bone marrow biopsy, in elderly and frail patients. UEA has been reported with variable rates in studies. While this rate was reported between 25% and 44% in population-based studies (7, 8), rates varying according to the depth of the study are available in clinical studies. However, bone marrow biopsy was performed at a very low rate or was not performed in most studies (9–14). These differences have led to different prevalence rates of UEA in the literature. Understanding the etiology of anemia is still a challenging problem in the elderly patient population. In this study, we aimed to determine the prevalence of UEA in hematology outpatient clinics by examining the characteristics and underlying etiology of anemia in elderly patients in detail.

2. Materials and Methods

In this single center retrospective study, medical records of anemic patients over the age of 65 who were referred to the Ankara Baskent University Hematology Department between January 2015 and January 2020 were analyzed. According to WHO criteria; threshold value for anemia was accepted as Hb < 12 g/dL for women and < 13 g/dL for men. Morphologically, mean erythrocyte volume (MCV) < 80 fL was defined as microcytic, 80–100 fL normocytic, and > 100 fL macrocytic anemia (15). Patients with ferritin < 30 µg/L and/or transferrin saturation (TS) < 20% and C-reactive protein (CRP) < 3 mg/L was diagnosed with iron deficiency anemia (IDA) (16), while patients with a vitamin B12 level < 200 ng/L was diagnosed with vitamin B12 deficiency (17), and folic acid level <3.5 µg/L with folic acid deficiency (18). Anemia of chronic disease (ACD) was diagnosed with serum ferritin level > 100 µg/L and TS of < 20% in patients with chronic illness (chronic kidney disease, liver disease, congestive heart failure, chronic infection etc.) with positive acute phase reactants. In patients with advanced heart failure or chronic kidney failure undergoing dialysis; iron deficiency anemia accompanying anemia of chronic disease was diagnosed in patients with TS <20% and/or ferritin 100-500 µg/L (19). Bone marrow aspiration and biopsy (BMBX) were planned in patients without nutritional or hemolytic anemia, with unexplained cytopenia accompanying anemia, suspected hematological malignancy and/or UEA. Study approval was obtained from the Institutional Ethics Committee of Baskent University.

Statistical Analysis

Summary statistics (mean and standard deviation, median and range) were used to define continuous variables. For categorical variables, the number and percentage of participants in each category were reported. In order to compare the triple group in terms of continuous variables, ANOVA was used for the normally distributed variables, while the Kruskal Wallis test was used for the non-normally distributed variables. All statistical tests were performed at a significance level of 0.05. Statistical analyses were performed using the IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA) package program.

3. Results

In this retrospective study, the medical records of 3330 elderly patients who were referred to the hematology department between January 2015 and January 2020 were analyzed. Anemia was suspected in 968 individuals and diagnosed in 600 patients. The prevalence of anemia was 18% in patients aged 65 years and older. This rate was 18.6% for women and 17.2% for men. The ratio of anemia prevalence in women to men was 1.5:1, and the mean age was 77.34±8.32 (65-97), (77.71± 8.51 in women and 76.78±8.00 in men).

In the study population, cardiovascular disease (81.2%) was the most common comorbidity, followed by diabetes mellitus (34.7%) and chronic obstructive pulmonary disease (15.3%). Polypharmacy was present in 68.3% of the patients including anticoagulants in 24%, antiaggregants in 38.3%, proton pump inhibitors (PPI) in 36%, metformin in 19.2%, and non-steroidal anti-inflammatory drugs or steroids in 11%.

The most common complaints of the patients were fatigue (48.6%), shortness of breath (14.8%), weight loss (7.5%), and joint pain (7%). In 12.3% of the patients, the diagnosis of anemia was made during routine tests without any complaints. In symptomatic patients 14.5% of them had more than one complaint.

According to the morphological classification, normocytic anemia (66.4%) was the most common type, followed by microcytic anemia in 27.9% and macrocytic anemia in 5.7% (Table 1).

The patients were analyzed within 3 age groups; 65-75 years, 76-85 years and over 85 years old. Analysis of mean hemoglobin values between age groups showed a significant decrease with advancing age ($p<0.001$) (Table 2). There was no significant difference in MCV, leukocyte and creatinine values within age groups. Serum albumin levels were found to be significantly lower in the elderly patient groups compared to the age group of 65-75 years ($p=0.03$). The CRP level of the patients aged 76-85 years was significantly higher than that of the patients over the age of 85. There was no significant difference between the CRP levels of the other age groups ($p=0.024$) (Table 2).

Nutritional anemia was detected in 339 (56.5%) patients. Hematologic malignancy was present in 127 (21.1%) patients, and ACD in 125 (20.8%) patients. The multifactorial etiology of anemia was present in 87 (14.5%) patients, where the presence of ACD with IDA (6.3%) was the most common combination. Unexplained anemia was present in 58 (9.7%) patients (Table 3).

In 339 patients with nutritional anemia; esophagogastroduodenoscopy (EGD) was performed in 49.3% and colonoscopy in 44.8%. EGD and colonoscopy were performed together in 208 (34.6%) patients. The most common pathology detected in EGD was chronic nonatrophic gastritis (23%), followed by Hp (Helicobacter pylori) related gastritis (19%) and chronic atrophic gastritis (16%) (Fig. 1). Polyps (31%), internal hemorrhoids (31%), and colorectal tumors (17%) were the most common pathologies found during colonoscopic examination (Fig. 2).

72% of the patients with indications for BMBX had the procedure. There were 206 (34.3%) patients with an indication and 148 (24.7%) patients accepted the procedure. 50 (8.3%) of 58 patients with UEA did not accept further investigations. Although monoclonal gammopathy was detected in serum and/or urine tests in 6 (1%) of 58 patients, plasma cell dyscrasias could not be diagnosed due to the patient's unwillingness for BMBX. Despite the detailed examination of the patients, the etiology of anemia could not be diagnosed in 2 (0.3%) patients

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Table 1. Characteristics of Patients

Characteristics	
Age mean±SD (min, max)	77.34±8.32 (65, 97)
Male	76.78±8 (65, 92)
Female	77.71±8.51(65, 97)
Female:male	1.5:1
Patients' Complaints % n:600	
Weakness	48.6%
Shortness of breath	14.8%
Asymptomatic	12.3%
Weight loss	7.5%
Joint pain	7%
Anorexia	4.8%
Fatigue	3.9%
Active bleeding	2.8%
Vertigo	2.8%
Palpitation	2.5%
Others	7.1%
Multiple complaints	14.5%
Morphological classification % n:600	
Normositer anemia	66.4%
Microcytic anemia	27.9%
Macrocytic anemia	5.7%
Co-morbidities % n:600	
Cardiovasculer disorder	81.2%
Diabetes mellitus	34.7%
Chronic obstructive pulmonary disease	15.3%
Renal failure	13.3%
Gastrointestinal disorder	12.2%
Neurological disorder	12.5%
Cancer	10.2%
Rheumatic disease	7.2%
Drugs % n:600	
Anticoagulants	24.2%
Antiaggregants	38.3%
Proton pump inibitor	36%
Non-steroidal anti-inflammatory/steroid	11%
Metformin	19.2%
Multiple drug use (more than 1 drug)	93.8%
Polypharmacy (5 or more drug use)	68.3%

Table 2. Comparison of Laboratory Values by Age Groups

Age group (100%)	**1.group** 65-75 (44.7%)	**2.group** 76-85 (36.2%)	**3.group** >85 (19.2%)	**P value**	**P value between age groups**
Hb (g/dL) (Mean±std.deviation)	10.10±1.67	9.72±1.70	9.20±1.87	**<0.001**	**1-2 **** **1-3 **** **2-3 ****
MCV (fL) Median (min-max)	86,15 (53.9-126.6)	85 (57-114)	85 (56-134)	0.574	
Leukocytes (µL) Median (min-max)	6745 (90-265000)	6910 (10-224000)	6180 (1000-57100)	0.402	
Thrombocyte (µL) Median (min-max)	231500 (3000-606000)	257500 (3600-933000)	234000 (17900- 567000)	**0.020**	**1-2 **** **1-3 *** **2-3 ***

Creatinine (mg/dl) Median (min-max)	0.96 (0.52- 8.75)	1.07 (0.12 -10)	1.08 (0.58- 5.02)	0.329	
Albumin (g/dl) Median (min-max)	4 (2- 5)	3.9 (2.2- 4.9)	3.8 (2.4- 4.7)	**0.030**	**1-2 ** 1-3 ** 2-3 ***
CRP (mg/l) Median (min-max)	6.84 (0.3- 417)	10.9 (0.3-256)	4.48 (0.4-167)	**0.024**	**1-2 * 1-3 * 2-3 ****

*** p value<0.05 * p value>0.05*

Table 3. Etiological Classification of Anemia

	Patient number(n:600) Percentage(%100)
Total Nutritional Deficiency Number	339 (56.5%)
Total Iron Deficiency	284
Total Folate Deficiency	57
Total Vitamin B12 Deficiency	31
Multiple Nutritional Deficiency #	33
Total Hematological Malignancy	127 (21.1%)
Myelodysplastic Syndrome	40
Multiple Miyeloma	28
Nonhodgkin Lymphoma	26
Acute Leukemia	10
Chronic Lymphoblastic Leukemia	9
Monoclonal Gammopathy of Undetermined Significance	9
Chronic Myeloproliferative Disease	5
Total Anemia of Chronic Disease(ACD)	125 (20.8%)
Chronic Kidney Disease	28
Solid organ malignancy	21
Chronic obstructive pulmonary disease	19
Congestive Heart Failure	17
Chronic liver disease	10
Rheumatological disease	10
Other *	20
Total Bone Marrow Failure**	21 (3.5%)
Total Hemolytic anemia	17 (2.9%)
Unexplained Anemia	58 (9.7%)
Unexplored,	56
Underexplored anemia	2
More than one cause #	87(14.5%)

**Other: Complicated Diabetes Mellitus, Inflammatory Bowel Diseases, Chronic Infections*
***Bone Marrow Failure: Hypoplastic anemia, aplastic anemia, hypothyroidism,acute hyperinflammation-associated anemia and drug-associated anemia*
 # The ratios given above are the total ratios of the causes seen in the etiology, more than one etiological cause is given as a separate ratio, and it is subtracted from the total ratio to avoid double addition.

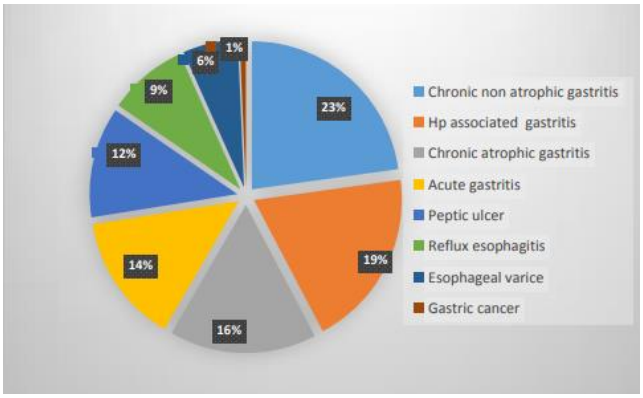

Figure 1. Esophagogastroduodenoscopy Results in Patients with Nutritional Anemia

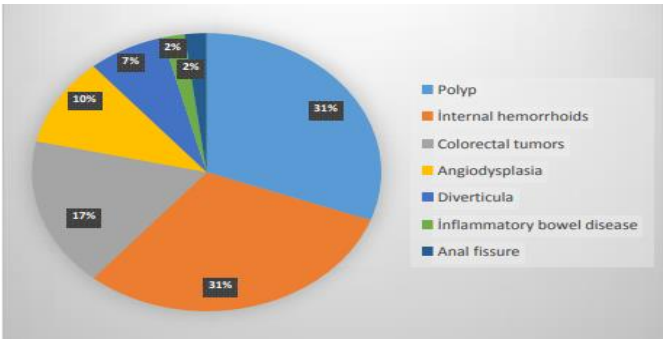

Figure 2. Colonoscopy Results in Patients with Nutritional Anemia

4. Discussion

This cross-sectional study analyzed the rate, characteristics and etiology of anemia in patients over the age of 65 at the hematology outpatient clinic. The prevalence of anemia was 18%, which was compatible with the range of 13.6-25% in other studies (9,19,20). The diagnosis of anemia was more common in women than in men with a ratio of 1.5:1. In the literature, anemia rates ranged from 9.9 to 11% in men and 10.2 to 14.2% in women (7,20). The differences in the rate of anemia between genders may be related to the number of people participating in the study, regional etiological differences and the place where the study was performed (hospital, home, etc.).

The most common symptoms in our study were fatigue (48.6%), shortness of breath (14.8%), weight loss (7.5%) and joint pain (7%); 12.3% of the patients were asymptomatic. Typical symptoms of anemia in elderly patients, such as fatigue, weakness and shortness of breath are not specific and might be multifactorial and often attributed to advancing age (21). Typical symptoms are usually less severe in older patients than expected in younger adults. When anemia first appears, most of the patients continue their usual daily activities (22). It should be noted that patients may have symptoms of anemia without active complaints or the symptoms may be similar to those of other diseases.

In our study, hemoglobin levels decreased significantly with increasing age (Table 2) and normocytic anemia (66.4%) was the most common form, similar to previous studies (11, 23). The prevalence of anemia increases after the age of 60 to 65 years and becomes more pronounced over the age of 80 (22). It has been shown that hemoglobin levels over the age of 65 decrease gradually, whether they are anemic or not (8).

Various studies have shown that there is a decrease in serum albumin concentration

between 0.08 and 0.17 g/L per year associated with aging (24, 25). Despite these age-related changes, albumin levels remain above 38 g/L in healthy elderly people until after 90 years of age, and there is no evidence of a pathological decrease in albumin levels with age. Therefore, in the case of clinical stability, albumin may be a good predictor of nutritional status in the elderly population (26). In our study, albumin levels were found to be significantly higher in patients aged 65 to 75 years compared to the 75 to 85 years and > 85 years age groups. Similar to the literature, the mean serum albumin levels decreased within normal ranges in elderly patients.

In the elderly patient population, nutritional deficiencies and chronic inflammatory disorders were the most common causes of anemia, respectively (6, 27). In our analysis, hemological malignancies were the second most prevalent condition after nutritional deficiencies. The rate of unexplained anemia (UAE) was quite low. In one of the population-based study, Guralnik et al. (7) examined the third National Health and Nutrition Examination Survey (NHANES) of 4199 community-dwelling men and women over the age of 65 years. The rate of UEA was found to be 33.6% among all anemic elderly. In another community-based study of 8744 people in Italy, the rate of UEA was 26.4% (8). In another study by Artz et al. (10), the rate of UEA was reported as 43.7% and BMBX is performed only %32 of patients. In a retrospective study conducted by Michalak et al.(9) the rate of UEA was 28.4% in 169 elderly anemic patients. Bone marrow biopsy or genetic studies could not be performed in 81.3% of these patients. Although the UEA rates were similarly high both in community and hospital-based studies, we think the low rate in our study is related to more comprehensive hematological examination of patients, including invasive procedures. BMBX rate is quite higher than other studies. This may explain why hematologic malignancies were the second most common cause of anemia in the elderly patient population in our study.

In elderly patients with IDA, blood loss from the gastrointestinal (GI) tract is mostly occult and may not be excluded by negative stool guaiac tests (28). The endoscopic examination in patients over the age of 50 years with IDA shows lesions in 33- 56% of the upper GI tract and 14-36% of the lower GI tract. In a summary of seven studies about the GI tract examination in patients with IDA over the age of 50, 721 patients were evaluated. The most common lesion in the upper GI tract was peptic ulcer (13.4%) and the rate of gastric cancer was 2%. The most common lesion in the lower GI tract was colorectal cancer (8.4%), followed by adenomatous polyps (5.5%) (29). In our study, the most common cause of upper GI pathology was chronic non-atrophic gastritis, while polyps and internal hemorrhoids were the most common causes of lower GI pathology.

The incidence of cancer increases with age and anemia is present in more than 60% of cancer patients with an increasing rate in advanced stages of cancer (30). In our study, endoscopic examinations detected gastric cancer in 1 patient and colon tumors in 17 patients. Solid organ malignancies were present in 21 patients with anemia from chronic disease. A total of 166 (27.6%) patients had hematological or solid organ malignancies. The increasing rates of malignancy with age underscore the importance of a detailed examination of the etiology of anemia in the elderly. However, in frail patients, the procedures should be done while considering the risk-benefit ratio. In addition, it is difficult to persuade patients to undergo invasive procedures such as endoscopic examinations and BMBX in this age group. In our study, endoscopic procedures could not be performed on more than half of the patients with nutritional anemia. The etiology of anemia could not be investigated in 8.3% of the patients due to their unwillingness for further invasive procedures. Despite all the analysis, the etiology of anemia could not be identified in 0.3% of our patients. In this group of patients, low serum EPO levels, decrease in testosterone level, occult inflammation, unidentified iron deficiency, clonal hematopoiesis; especially idiopathic cytopenia

of uncertain importance (ICUS) may be the cause of anemia. However, next generation sequencing (NGS) could not be used in our center at the time of this study.

As another cause of anemia in the elderly patient population Kara O et al.(31) reported the importance of polypharmacy. In a multicenter analysis of 579 geriatric patients who receive more than five drugs, Röhrig G et al.(32) reported an increased rate of anemia. In our study, 93.8% of the patients were using more than one drug, while 68.3% of the patients were using five or more drugs. The high rate of polypharmacy in the elderly anemic patient groups supports the relationship between polypharmacy and anemia.

The retrospective nature of this study and the unavailability of NGS technology for cytogenetic analysis were limitations of this study. The high rate of BMBX performed in necessary patients is the strength of the study in terms of contributing to a better understanding of the etiology of anemia in the elderly.

In conclusion, anemia in the elderly is a challenging issue due to comorbidity, polypharmacy, and problems in further examination. Since the success of the treatment is associated with the reduction of morbidity and mortality and the development of geriatric syndromes, the etiology of anemia should be investigated in detail to guide treatment. Hematological evaluation of anemia in the elderly patient population will reduce the rate of unexplained anemia. However, patient selection for invasive procedures should be based on a risk-benefit ratio in frail elderly patients.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Baskent University Ethical Committee (Approval Date/ Number: 05.07.2022 / KA22/302).
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