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Anemia in Individuals over Age 80: Unattended Issue in Clinical Practice

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Objectives: To assess the current state of anemia evaluation in the elderly over 80 years of age.

Methods: Patients who were more than 80 years old and visited Dongguk University Ilsan Hospital from April 2005 to February 2014 were included. Statistical analysis were assessed using the logistic regression model.

Results: Total 548 patients, who had anemia according to WHO criteria, were identified. The median age was 85 years old (range, 82 to 99 years) and median hemoglobin level was 11.0 g/dL (range, 2.7 to 12.9 g/dL). Twenty-eight, 468, and 52 patients were classified as microcytic anemia, normocytic anemia, and macrocytic anemia, respectively. Among them, 397 patients (72.4%) did not undergo proper evaluation for the cause anemia i.e., 8 cases (28.5%) of microcytic anemia, 361 cases (77.1%) of normocytic anemia, and the 28 cases (53.84%) of 52 macrocytic anemia patients. The remaining 151 patients (27.6%) had completed the evaluation, and 24 patients (15.9%) were diagnosed as solid malignancies. In the assessment of iron deficiency anemia, hemoglobin levels, and age had no effect on whether or not to perform esophagogastroduodenoscopy.

Conclusion: This finding showed that physicians often neglected anemia in individuals over 80 years of age. Though these patients have limited life expectancy, physicians should carefully discriminate the sub-population who will be benefit from adequate evaluation and treatment. **(Ewha Med J 2016;39(3):69-75)**

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Key Words
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Introduction

Anemia, defined by Word Health Organization (WHO) as a hemoglobin concentration below 13 g/dL in adult male and 12 g/dL in adult female [1], is prevalent in the elderly [2]. Its prevalence is expected to increase with aging of the general population. According to the Third National Health and Nutrition Examination Survey (NHANES III), the incidence of anemia is reported at a rate of >20% [3]. In Korea, the incidence of anemia in patients over the age of 70 years is reported as 11.1% in men and 18% in women according to Korea Health Statistics 2013: Korea National Health and Nutrition Examination Survey (KNHANES VI-1) [4]. Health expenditure is gradually increasing related to anemia and incidence of anemia has elevating trend in men, as shown by analysis of National Health Insurance Service of Korea data [5].

In fact, several recent studies support that anemia is an emerging problem in elderly patients. Anemia in elderly is associated with poor nutritional state, lower physical performance and muscle strength and increased morbidity and mortality [6-9]. Even hemoglobin at the lower normal limit showed the functional decline on tests of walking speed, balance, and abil-

ity to rise from a chair [10]. Also, low hemoglobin itself has a harmful health effect, especially in patients with congestive heart failure, cancer, human immunodeficiency virus infection, and several other medical conditions [11,12].

Cause of anemia in the elderly is categorized as nutritional anemia (one third of the cases), anemia of renal insufficiency (8%) or chronic inflammation (20%), myelodysplastic syndrome and other causes [3]. In the real world, many cases of anemia in the elderly are likely of mixed or unexplained etiology. Age related comorbidities and chronic inflammation with aging are the cause of unexplained anemia. Other factors including erythropoietin insensitivity, changes in molecular mechanisms underlying hematopoietic stems cells should reveal the pathophysiology of obscure anemia in the elderly population [13].

Besides the pathophysiology of anemia in the elderly, physicians should be able to discriminate the cause of the treatable subpopulation such as anemia caused by nutritional deficiency and recommend further evaluation with awareness of negative impact of anemia in the elderly. However, to date, there is little data on the level of evaluation, which reflects the physicians' low awareness of anemia in the elderly, especially over the age of 80 years.

Despite these emerging issues, anemia in the elderly is often overlooked in Korea. Korea has the most rapidly growing elderly population, so issues about how much evaluation is what can be done need to be solved. Proper evaluation of causes of anemia is essential in correcting anemia, whereas performing evaluation and management in the elderly with limited life expectancy causes discomfort and risk from medical procedures, especially in the unfit or frail population.

We conducted a study to determine how much diagnostic evaluation was performed for anemia in individuals aged 80 years and over, and aimed to raise physicians' awareness.

Methods

1. Study population

This study was a medical record-based retrospective study. We reviewed medical records of all patients aged more than 80 years old with anemia, who visited Dongguk University Ilsan Hospital from April 2005 to February 2014. Initial complete blood count on first visit was the standard for enrollment in this study. Patients who had a recent history with one of these were excluded: major bleeding, operation, and infection. After sorting, a total of 548 patients aged over 80 years were included.

2. Clinical and laboratory evaluations

For all patients with anemia, we investigated their past medical history (heart disease, solid tumor, hematologic malignancy, stroke, etc.) to examine Charlson comorbidity index. We recorded the patient's age, sex, comorbidities, hemoglobin, and mean corpuscular volume (MCV). Also, to investigate the relationship between the cause of anemia and malignancy, the number of patients with anemia related to malignancy was recorded.

Once anemia was confirmed, then microcytic, normocytic, and macrocytic anemia was categorized according to MCV. Definition of anemia was based on the WHO definition (hemoglobin level <13 g/dL in men and <12 g/dL in women) and the classification according to MCV value followed the usual definition (microcytic anemia, MCV<80 fL; normocytic anemia, MCV 80–100 fL; and macrocytic anemia, MCV>100 fL).

We conducted a laboratory review for evaluation of differential diagnosis of each category of anemia. Three algorithms used with main reference to help identify the etiology for anemia [6]. First, serum ferritin level, blood urea nitrogen/creatinine, and peripheral blood smear were regarded as essential components of evaluation of microcytic anemia. For normochromic anemia, peripheral blood smear, reticulocyte count, vitamin B12 and folate level, serum ferritin, blood urea nitrate/creatinine, lactate dehydrogenase, and bilirubin were basic complements for differential diagnosis. Meanwhile, endoscopy examination was used for underlying etiology of iron deficiency anemia among patients with iron deficiency anemia from the subpopulation of microcytic or normocytic anemia.

In the algorithms for diagnosis of macrocytic anemia, peripheral blood smear and reticulocyte count was the fundamental checklist in initial assessment. If reticulocyte counts were higher than 2%, several laboratory parameters lactate dehydrogenase, indirect bilirubin, haptoglobin, and direct Coombs test) were required. In case of normal range reticulocyte, vitamin B12 or folate level was used to diagnose deficiency.

3. Statistical analysis

The results were presented as medians and ranges. The factors affecting the evaluation of endoscopy in patients with iron de-

ficiency anemia and vitamin B12 level measurement in patients with macrocytic anemia were assessed using the logistic regression model. Univariate analysis and multivariate analysis were done with adjustment for potential confounding factors. $P<0.05$ was considered statistically significant. Statistical analyses were performed using SAS ver. 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

1. Study population

A total of 548 patients aged over 80 years were diagnosed as anemia. One hundred and seventy-six patients and 126 patients were initial visitors to the Emergency Room and Department of Internal Medicine. The median age was 85 years (range, 82 to 99 years) and 55.3% were men. Median hemoglobin level was 11.0 g/dL (range, 2.7 to 12.9) and Charlson comorbidity index was 5.7 points (range, 4 to 12 points). When the patients were divided by the hemoglobin (Hb) level, the majority of patients were Hb>10 g/dL (76.4%) and the least of patients were Hb<6 g/dL (2%) (Table 1).

2. Anemia classification

Among 548 patients, as divided by MCV, 28, 468, and 52 patients were classified as microcytic anemia (MCV<80 fL), normocytic anemia (MCV 80–100 fL), and macrocytic anemia (MCV>100), respectively. Most of enrolled patients (85.4%) showed as normocytic anemia. When classified according to identified cause as shown by NHANES III [14], acute inflammation, other, and iron deficiency anemia (IDA) followed the remaining portion (Fig. 1).

3. Degree of evaluation for anemia

Three-hundred and ninety-seven patients (72.4%) did not undergo proper evaluation for the etiology of anemia after revealing anemia confirmed by complete blood count finding, including 8 of 28 (28.5%) microcytic anemia patients, 361 of 468 (77.1%) normocytic anemia patients, and the 28 of 52 (60.4%) macrocytic anemia patients.

Iron deficiency anemia was the most common cause of microcytic anemia (15 patients; 75%). Fifty-two patients (48.6%)

Table 1. Baseline characteristics of enrolled elderly patients with anemia (n=548)

Characteristic	Value
Age (yr)	86.5 (82–99)
Hemoglobin (g/dL)	11.0 (2.7–12.9)
Hb<6	11 (2.0%)
6≤Hb<8	29 (5.3%)
8≤Hb<10	99 (18.1%)
10≤Hb	409 (74.6%)
Albumin (g/dL)	3.5 (1.2–4.8%)
Body weight (kg)	52.1 (26.7–94.3)
Height (cm)	157.5 (133–182)
Comorbidity	
Cardiac disease	142 (25.9%)
Cerebrovascular disease	87 (15.9%)
Dementia	61 (11.1%)
Pulmonary disease	33 (6.0%)
Prior malignancy	48 (14.2%)
Charlson comorbidity index (score)	5.7 (4–12%)

Values are presented as median (range) or number (%).

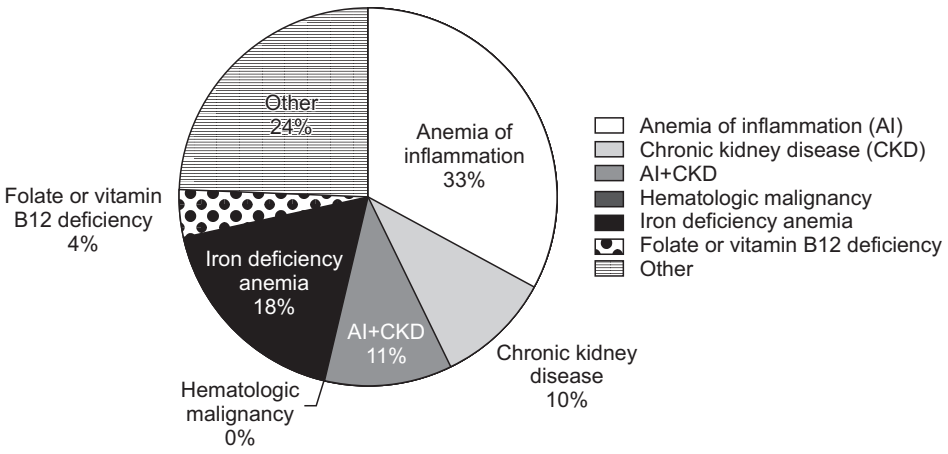

Fig. 1. Classification of anemia according to identified cause as shown by National Health and Nutrition Survey (NHANES) III.

Table 2. Cause of anemia according to mean corpuscular volume value

Variable		Male	Female	Total (%)
Microcytic (n=20)	Iron deficiency anemia	10	5	15 (75.0)
	Anemia of chronic kidney disease	3	0	3 (15.0)
	Anemia of chronic inflammation	1	1	2 (10.0)
	Thalassemia	0	0	0 (0.0)
Normocytic (n=107)	Iron deficiency anemia	6	6	12 (11.2)
	Anemia of chronic kidney disease	10	5	15 (14.0)
	Anemia of chronic inflammation	35	17	52 (48.6)
	Hemolysis	2	0	2 (1.9)
	Recent blood loss	12	2	14 (13.1)
	Unexplained	9	3	12 (11.2)
Macrocytic (n=24)	Vitamin B12 or folate deficiency	5	1	6 (25.0)
	Hemolysis	2	1	3 (13.0)
	Recent blood loss	8	1	9 (38.0)
	Unexplained	4	2	6 (25.0)

Table 3. Number of patients with anemia related to malignancy

Variable		Male	Female	Total (%)
Microcytic (n=20)	Related to solid tumor	5	0	5 (25.0)
	Related to hematologic malignancy	0	0	0 (0.0)
Normocytic (n=107)	Related to solid tumor	7	6	13 (12.1)
	Related to hematologic malignancy	3	1	4 (3.7)
Macrocytic (n=24)	Related to solid tumor	1	0	1 (4.1)
	Related to hematologic malignancy	0	0	0 (0.0)

of normocytic anemia were composed with anemia of chronic disease and 9 patients (38.0%) of macrocytic anemia were composed with recent blood loss. Five patients (20%) of microcytic anemia were related to malignancy, 17 patients (15.9%) of normocytic anemia, and 1 patient (4.1%) of macrocytic anemia, respectively (Tables 2, 3).

The likelihood between performance of endoscopic procedures and parameters like age and Hb level did not have any significance in iron deficiency anemia patients (adjusted odd ratio of age>85, 1.639 [95% confidence interval, 0.291 to 9.224], Hb>8.6, 0.988 [95% confidence interval, 0.193 to 5.064]) (Tables 4, 5). In contrast, frequency of vitamin B12 level test was definitely higher in the group with lower Hb (≤ 8.6) (adjusted odd ratio of Hb>8.6, 5.773 [95% confidence interval, 1.102 to 30.230]) in macrocytic anemia patients.

Discussion

This retrospective study on elderly patients demonstrated that proper evaluation was not performed in a major proportion of patients. Especially, over half of patients with normocytic anemia and macrocytic anemia did not undergo basic laboratory examination for further work-up.

In fact, anemia is a unique diagnosis for which underlying etiology should be determined. Anemia in the elderly is now recognized as an emerging issue, since anemia itself, even of mild grade, compromises patient's wellbeing.

Several studies reported the etiology of anemia in the elderly. First of all, anemia caused by nutritional deficiency that comprises ~30% of elderly anemia, can be easily reversed by appropriate management [14,15]. However, in contrast, if a serious condition like myelodysplastic syndrome or gastrointestinal tract cancer is suspected, prompt referral to specialist is needed. Therefore, proper evaluation is required to identify the cause of anemia [16].

NHANES III classified anemia of the elderly into 4 main categories of nutrient deficiencies (iron, folate, and vitamin B12), anemia secondary to renal disease, anemia of chronic inflam-

Table 4. Multivariate analysis of factors associated with performance of endoscopic procedures in patients with iron deficiency anemia

Variable	Endoscopy	
	OR (95% CI)*	Adj-OR (95% CI)†
Age (yr)		
≤85 (reference)	1.000	1.000
>85	1.633 (0.310–8.607)	1.639 (0.291–9.224)
Hemoglobin		
Hemoglobin≤8.6	1.125 (0.236–5.371)	0.988 (0.193–5.064)
Hemoglobin>8.6 (reference)	1.000	1.000

OR, odd ratio; CI, confidence interval; Adj-OR, adjusted odd ratio.
*Estimated from the logistic regression model with each covariates (unit model).
†Estimated from the logistic regression model with all covariates (full model).

Table 5. Multivariate analysis of factors associated with performance of vitamin B12 or folate measurement in patients with macrocytic anemia

Variable	Vitamin B12 or folate	
	OR (95% CI)*	Adj-OR (95% CI)†
Age (yr)		
≤85 (reference)	1.000	1.000
>85	1.494 (0.430–5.191)	1.355 (0.348–5.277)
Hemoglobin		
Hemoglobin≤8.6	5.714 (1.414–23.097)	5.773 (1.102–30.230)
Hemoglobin>8.6 (reference)	1.000	1.000

OR, odd ratio; CI, confidence interval; Adj-OR, adjusted odd ratio.
*Estimated from the logistic regression model with each covariates (unit model).
†Estimated from the logistic regression model with all covariates (full model).

mation/disease, and in the absence of other identifiable cause, unexplained anemia. Our study showed 33% of patients with anemia of inflammation, 22% patients with nutrient deficiencies, and 21% patients with chronic kidney disease.

In the subgroups of microcytic anemia, only 20 of 28 patients (71.4%) was properly evaluated with clinical and hematologic examination. Ferritin is essential to distinguish other causes of microcytic anemia. In this study, 75% of microcytic anemia was diagnosed as iron deficiency anemia, 15% was anemia of chronic kidney disease, 10% was anemia of chronic disease, and no patient was diagnosed as thalassemia.

Iron deficiency anemia (IDA) and the later phase of the anemia of chronic disease are microcytic. When focusing on iron deficiency anemia, most cases are due to gastrointestinal blood losses due to drugs, peptic ulcer disease, stomach cancer, and colon cancer. Whether physicians should proceed with endoscopy for determining the etiology of IDA in caring for the elderly, is a somewhat difficult decision. Even though endoscopy is essential, it is an invasive procedure especially with bowel preparation required for colonoscopy and carries some risk associated with sedation. Regarding a recent study about current clinical practice for octagenarians and nonagenarians with IDA, frequent omission of endoscopy for IDA occurred in enrolled patients (59%) [17]. This study analyzed factors associated with likelihood of performance of endoscopic procedures, and indicated that gastrointestinal symptoms were the significant factor for performing endoscopic procedures. Other parameters like comorbidity index, polypharmacy, use of anticoagulants, and several lab parameters (Hb<9.7 g/dL and ferritin≤12 ug/L) did not affect the endoscopy procedure. Age (<85 yr) or Hb (8.6 g/dL) was not significant factors for performing endoscopy in our study (Table 4).

Meanwhile, the interesting finding from a study of iron deficiency anemia in Octogenarians and Nonagenarians, benefit of surgery in cases of colon cancer as the cause of IDA, was not apparent until approximately 1.3 years. Thus, authors suggested that the primary benefit of an examination for IDA for them would be the earliest possible identification of colon cancer to optimize the quality of life and survival by preventing poorer prognosis.

Because a very small number of patients (12 patients, 75%) underwent endoscopy for revealing an etiology of IDA in this study, we could not diagnose and follow-up of gastrointestinal malignancy, as in the earlier study. However, here are noticeable examples. Among the 2 microcytic anemia patients, one was an 86-year-old female patient who was diagnosed as microscopic anemia without further evaluation, including ferritin, reticulocyte count and endoscopy. Three months later, on re-visit due to dizziness, rectal cancer was found and the patient expired. Another 87-year-old female patient whose initial hemoglobin was 4.8 was properly evaluated including endoscopy and diagnosed as ischemic colitis. She fully recovered with adequate therapeutic intervention. Surely, development of predictive model is needed to determine whether the elderly individual is considered fit or willing to undergo comprehensive evaluation with management.

In the subgroups of normocytic anemia, there was a large proportion of patients who were not assessed. This may be influenced by physicians' lack of awareness of the impact of mild anemia. In this study, more than 70% of patients had hemoglobin over 10 g/dL, anemia with inflammation was the most common cause of normocytic anemia. Diagnosis of this type of anemia is quite difficult, because of the lack of an adequately sensitive and specific test to measure the type of cytokine-mediated chronic inflammation that is associated with bone marrow suppression. Furthermore, laboratory data alone cannot distinguish anemia of inflammation or other cause of anemia of chronic disease such as infection, rheumatologic disorders, malignancy, and other chronic illnesses.

Anemia of chronic inflammation was suspected in more than 20% of cases in NHANES III, either in isolation or in conjunction with renal insufficiency [3]. Thus, it is recommended that physicians should classify anemia by more strict standards to find the correctable cause. Renal insufficiency, another easily treatable cause of anemia in the elderly, accounts for approximately 8% of the NHANES III cases. In this study, further evaluation of normocytic anemia was found lacking in most cases, which is a concern that needs to be addressed.

Macrocytic anemia accounted for a relatively small portion in this study. Especially, hematologic malignancies are nearly undetected. Other research indicates that extensive, careful evaluation is required to diagnose myelodysplastic syndrome (MDS) and hematologic malignancy in elderly patients.

In addition, vitamin B12, folate deficiency is a reversible cause of macrocytic anemia. In this study, when hemoglobin levels were lower than 8.6 g/dL, vitamin B12 was measured with significant frequency (Table 5). It appears that physicians recognize the possibility of vitamin B12 deficiency relatively well.

In approximately one third of older patients with anemia, the cause of the anemia cannot be found; their anemia is unexplained anemia or anemia of unknown cause [3,18,19]. In this study, because of improper assessment of cause of anemia, we were unable to measure the frequency of this type of anemia.

There were several limitations in this study. First, this was a retrospective study to reveal the level of evaluation of anemia in elderly age over 80, so there were several limitations to analyze the diagnosis and outcome relationship. In future, extensive research to identify causes for anemia in future domestic elderly groups is required. Second, we reviewed medical chart from one institution, which could lead selection bias.

In conclusion, this study demonstrated that anemia in the elderly was an unattended problem in the clinical situation. Physicians need to keep in mind that identifying the cause of anemia in the elderly is important and requires prompt evaluation and management with proper referral to specialist, if needed.

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