Utility of Serum Ferritin as A Predictor of Colorectal Cancer in Elderly Patients

Yaşlı Hastalarda Kolorektal Kanser Tanısında Serum Ferritin Düzeyinin Yeri

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Abstract

Objective: Ferritin is an indicator of iron deficiency. Colorectal cancer is an important cause of morbidity and mortality in older subjects. The aim of this study was to determine the value of serum ferritin and ferritin-transferrin saturation in the diagnosis of colorectal cancer in older subjects.

Materials and Methods: older patients who had undergone upper and lower gastrointestinal endoscopic examination were included into the study. Serum iron profile and C-reactive protein were also recorded. Patients were then evaluated by three different ferritin levels according to their iron profiles: method 1: ferritin < 50 µg/L; method 2: ferritin < 100 µg/L; method 3: ferritin+transferrin saturation index. The relationship between existence of colorectal cancer and serum ferritin level was investigated.

Results: 528 patients had normal upper and lower endoscopic findings. 72 patients had colorectal carcinoma with normal upper gastrointestinal findings. Method 1 (ferritin<50 µg/L) predicted 58.4% of patients with colorectal carcinoma with a sensitivity and specificity of 63% (95% CI:52-74) and 53% (95% CI: 48-57) respectively. However, sensitivity [91% (95% CI:82-96)] of method 3 was greater than method 1 and 2 with a AUROC value of 70.4%. There was no difference by means of median ferritin levels. Median transferrin saturation index was significantly higher in group I (Normal subjects) compared to patients in group II (Colorectal cancer patients) (17.5 vs 8%, p<0.001).

Conclusion: Serum ferritin <50 µg/L and <100 µg/L have rather low diagnostic yield in the decision making of colonscopic examination for colorectal carcinoma. However, ferritin <100 µg/L and TSI <16% values can be more useful in selecting older patients for colonoscopic examination.

Keywords: Anemia, Colorectal Carcinoma, Colonoscopy, Ferritin

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Öz

Amaç: Ferritin demir eksiklğinin bir belirtecidir. Kolorektal kanser yaşlı bireylerde önemli bir morbidite ve mortalite sebebidir. Bu çalışmnaın amacı yaşlı bireylerde serum ferritin ve ferritin-transferrin saturasyonunun kolorektal kanser tanısındaki yerini önemini belirlemektir.

Gereç ve Yöntemler: Çalışmaya üst ve alt gastrointestinal endoskopi sonucu olan 65 yaş ve üstü 600 hasta alınmıştır. Serum demir profili ve C-reaktif protein değerleri incelenmiştir. Hastalar ferritin düzeylerine göre üç gruba ayrılmıştır: metod 1: ferritin < 50 µg/L; metod 2: ferritin < 100 µg/L; metod 3: ferritin+transferrin saturasyon indeksi. Her üç metod ile kolorektal kanser varlığı ile serum ferritin düzeyi arasındaki ilişki araştırılmıştır.

Bulgular: 528 hastanın üst ve alt gastrointestinal endoskopi bulguları normaldir. 72 hastada kolorektal kanser saptanırken, bu hastaların hepsinde üst gastrointestinal endoskopi bulguları normal olarak bulunmuştur. Metod 1 (ferritin<50 µg/L) kolorektal kanser varlığını %58.4 oranında tahmin etmiştir (Duyarlılık ve özgünlük sırasıyla %63 ve %53'tür). Buna karşın metod 3'ün duyarlılığı [91% (95% CI:82-96)] metod 1 ve 2'den daha yüksek olup AUROC değeri %70,4'tür. Her üç grupta da median ferritin düzeyleri arasında fark bulunamamıştır. Median transferrin saturasyon indeksi grup I'de (Normal hastalar) grup II'ye (Kolorektal kanserli hastalar) göre daha yüksektir (17.5 vs 8%, p<0.001).

Sonuç: Serum ferritin düzeyi <50 µg/L ve <100 µg/L değerlerinde kolonoskopik incelemeye karar vermekte düşük tanısal değere sahiptir. Buna karşılık serum ferritin düzeyi <100 µg/L ve transferrin saturasyon indeksi <%16 ise yaşlı bireylerde kolonoskopik incelemeye karar vermekte daha yararlı olarak bulunmuştur.

Anahtar Kelimeler: Anemi, Kolorektal Kanser, Kolonoskopi, Ferritin

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Introduction

The geriatric age group is defined by World Health Organization as individuals over 65 years of age. In 2010, the population over the age of 65 constitutes 8% of the world population with 524 million. However, this number is expected to reach 1.5 billion by 2050, making up 16% of the world population. This table reveals that the problems of elderly patients will become more and more important day by day (1). Anemia is defined by the World Health Organization as less than 13 g/dL in men and 12 g/dL in women. Anemia is a common clinical problem in the geriatric age group, with a prevalence of 17%. The most important cause of anemia in the elderly patient group is "chronic disease anemia" due to underlying diseases. Anemia due to nutritional reasons comes after chronic disease anemia in elderly patients and it has been shown that the second most common cause is iron deficiency anemia (IDA). As in all age groups, the etiology of anemia should be investigated in geriatric patients. Patients with unexplained iron deficiency are considered for an evaluation of the gastrointestinal (GI) tract because IDA appears in GI cancer due to occult blood loss. However, anemia is not sensitive enough as a diagnostic tool for GI cancer, because a high proportion of patients with GI cancer (50%) do not have anemia at the time of tumour diagnosis(2-4). Colorectal carcinoma is the second most common malignant disease in women and the third in men worldwide, and causes 10% of cancer-related deaths. The median age of the disease is 70 years age and it is also important for the elderly patient group. Colorectal carcinoma is an important cause of mortality and morbidity and mostly encountered in anemic and non-anemic elderly symptomatic patients, irrespective of the iron status (5,6). Many laboratory values are helpful in the diagnosis of iron deficiency. Serum ferritin is an accurate and noninvasive test for the diagnosis of IDA due to iron loss, and is often used in clinical practice while deciding which patients need colonoscopy (7,8). Most studies use ferritin < 20 - 50 ng/mL as an indicator of iron deficiency anemia (9-13). However, in the clinical settings, iron deficiency anemia is often present despite normal levels of ferritin, especially in older patients and/or in patients with comorbidities. Ferritin is an acute phase reactant and it is also elevated by various conditions including, chronic inflammation, infectious diseases and malignancies. Since these clinical problems are more common in elderly patients than other age groups, the availability of ferritin in the geriatric age group becomes even more limited (14). Therefore, the transferrin saturation index calculated using serum iron and total iron binding capacity helps ferritin in the diagnosis of IDA and more important in elderly patients (15-19). In addition, iron deficiency can be presented in patients with ferritin levels of 51 - 100 ng / mL because ferritin behaves as an acute phase reactant (20, 21). It was reported that patients with anemia and serum ferritin level 51 – 100 ng/mL have the same prevalence of colonic neoplasia as those with serum ferritin level ≤ 50 ng/mL (21). In this context, the decision to order a colonoscopy in older patients should not only be considered in patients with anemia or iron deficiency. Moreover, several guidelines recommend screening for patients between 76 and 85 years of age should be tailored according to the patients' special conditions (23, 24). However, colorectal cancers bleed in a silent manner, and decrease in serum ferritin occurs before serum hemoglobin level. Depending upon this knowledge, while some authors suggested the measurement of serum ferritin may provide a screening test for colorectal cancer (25), some others reported that serum ferritin has no value as a screening test for colorectal cancer (26). Therefore, the goal of this research was to explore whether different ferritin levels has a value in the prediction of colorectal carcinoma and if exists, to define associated factors in older patients.

Materials and Methods

This study was designed as a single-center and the data were obtained retrospectively. In this study, medical charts of patients aged > 65 years who had been referred for upper and lower GI endoscopic examination for various reasons during the last five years were reviewed. Endoscopic procedures performed in the endoscopy unit of Ankara University Faculty of Medicine, Department of Gastroenterology were retrospectively screened and patients over 65 years of age were selected. Patients with a history of colorectal cancer, previous colon surgery, inflammatory bowel diseases, incomplete

colonoscopy, systemic diseases and upper GI lesions that may cause iron deficiency such as peptic ulcer disease, gastric cancer, previous gastric surgery, esophagitis, esophageal varices and celiac disease were excluded from the study. Laboratory parameters including C - reactive protein (CRP), whole blood count, ferritin, serum iron, total iron binding capacity and transferrin saturation were also extracted from medical records. Patients who lacked laboratory tests and had laboratory values longer than 12 weeks before the endoscopic procedure or whose iron profile and CRP values were not on the same date were not included in the study. The study was approved by the Local Ethical Committee (Ethical Committee of Ankara University Faculty of Medicine, approval number: 06-242-16).

Patients:

Patients were stratified into two groups: Group I: patients with normal upper and lower GI findings (n = 528), Group II: patients with normal upper GI findings and colorectal carcinoma (n = 72). All patients included into this study were then evaluated by using three different ferritin levels in order to establish sensitivity and specificity for predicting colorectal carcinoma irrespective of the presence of anemia (Anemia definition determined by World Health Organization was accepted as 13 g/dL for men and 12 g/dL for women): Method 1: ferritin < 50 μg/L, Method 2: ferritin < 100 μg/L, Method 3: combination of ferritin and transferrin saturation index (TSI) (patients who had ferritin < 50 μg/L were evaluated irrespective of TSI, however, patients who had ferritin > 50 μg/L transferrin saturation index < 16 % was used) (19). Thus, the best method to suggest the evaluation of colon cancer, which is an important cause of morbidity and mortality, was searched for patients in the geriatric age group. The study protocol was approved by the local ethics committee of the related institution.

Statistics:

Statistical analysis was performed by using SPSS 16.0 (SPSS, Chicago, IL, USA) for Windows version 10. The Shapiro – Wilk test was used to test of normality. Results were expressed as mean ± SD (range) unless otherwise stated, and nominal variables were expressed as n and (%). Significance of the differences in hemoglobin level, mean corpuscular volume, ferritin, transferrin saturation index and CRP between groups were compared by using the Student's t - test, and significance of the differences in median values were investigated by the Mann – Whitney U - test. Nominal variables were evaluated by Pearson's chi-square χ - test or Fisher's exact test. Receiver operating characteristic (ROC) curves were used to describe and compare the performance of diagnostic values of ferritin level in predicting colorectal carcinoma. A P - value of < 0.05 was considered statistically significant.

Results

Six-hundred patients aged > 65 - year-old were included into the study and were evaluated by stratifying into two groups: Group I: patients with normal upper and lower GI findings (n = 528), Group II: patients with normal upper GI findings and colorectal carcinoma (n = 72). Demographic characteristics and laboratory parameters of study participants were illustrated in Table 1. Median TSI was significantly higher in group I compared to patients in group II [17.5 (2 - 86) vs 8 (2 - 69) %, p < 0.001]. However, although median ferritin level was higher in group I, this was not statistically significant [51 (3 - 294) vs 24.5 (2 - 346) μg/dL, P = 0.11]. When method I was used (ferritin < 50 μg/L), ROC curve analysis suggested that this method predicted 58.4% of patients with colorectal carcinoma with a sensitivity and specificity of 63% (95% C I: 52 - 74) and 53% (95% CI: 48 - 57) respectively (PPV: 15, 95% CI:12 – 18; NPV:91, 95% CI:88 - 93). However, sensitivity [91% (95% CI:82 - 96)] of method 3 was greater than method 1 and 2 with a AUROC value of 70.4% (Table 2). We compared 12 colon cancer patients who have been predicted only by method 3 to 54 patients predicted by using both methods 2 and 3 by means of serum CRP levels. Serum CRP levels were found to be higher in patients predicted by method 3 [86.8 mg/L (min – max: 4.4 - 197) vs 22 mg/L (min – max: 1 - 182), P < 0.001].

Table 1

Demographic Characteristics and Laboratory Parameters of Study Participants

	Group - 1 (n = 528)	Group - 2 (n = 72)	P
Age, years (mean ± SD)	71.09 ± 6.08	71.43 ± 6,67	P = 0.85
Gender (female/male)	270 / 258	35 / 37	P = 0.68
Hemoglobin (g/dL) (mean ± SD)	12.5 ± 1.8	11.7 ± 1.9	P < 0.001
Mean Corpuscular Volume (fL) (mean ± SD)	86.8 ± 6.6	76.7 ± 7.7	P < 0.001
Ferritin (µg/dL) [median (min - max)]	51 / 3 - 294	24.5 / 2 - 346	P = 0.11
Transferrin Saturation Index (%) [median (min - max)]	17.5 / 2-86	8 / 2 - 69	P < 0.001
C reactive protein (mg/L) [median (min - max)]	3.1 / 1-183	17 / 1-197	P < 0.001

Table 2

AUROC, Sensitivity, Specificity, PPV And NPV of Three Different Ferritin Levels Used in This Study

	AUROC	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Method - 1	58.4	63 (52 - 74)	53 (48 - 57)	15 (12 - 18)	91(88 - 93)
Method - 2	49.6	79 (69 - 86)	20 (16 - 23)	11(9 - 14)	87 (84 - 90)
Method - 3	70.4	91 (82 - 96)	49 (44 - 53)	19 (16 - 23)	97 (96 - 98)

(AUROC: area under receiver operating curve, PPV: positive predictive value, NPV: negative predictive value)

Discussion

The current study reports the utility of different values of ferritin in the prediction of colon carcinoma in older patients. Our study shows that, sensitivity and specificity of ferritin < 50 µg/L and ferritin > 50 µg/L are rather low in predicting colorectal carcinoma. However, if a combination of ferritin and TSI is used, sensitivity and specificity of this method reaches 91% and 49% respectively with an AUROC of 70.4%.

In clinical practice, the correlation of IDA and malignancy is well known. In a retrospective study, Ho et al investigated 101 colorectal carcinoma patients (mean age: 65.3 years) and reported that IDA is a common clinical manifestation of patients with colorectal carcinoma, and occurred more frequently in females, patients with right colon tumor and with larger tumor size (27). They measured serum ferritin in only 25 out of 101 patients and low ferritin level (< 40 µg/L) was found in 15 (60%) of them. The prevalence of colon carcinoma in patients with IDA was reported to be as 12%. Çoban et al investigated 1388 patients over 65 years by means of IDA and colon carcinoma was diagnosed in 8 (8.3%) out of 106 patients with IDA (28) and concluded that patients should be thoroughly investigated regarding a possible association with GI malignancy. However, in this case it is possible to miss non-anemic patients with colorectal carcinoma. In this context, Joosten et al examined 359 older patients aiming to determine the relationship between the prevalence of colorectal cancer and serum iron profile (6). They found that the prevalence of colorectal carcinoma was not different among patients with a serum ferritin level < 50 µg/L, between 50 - 100 µg/L and 100 > µg/L. There was also no difference between anemic and non-anemic patients. They concluded that colonoscopic examination in older subjects should not be only considered in patients with iron deficiency and/or anemia, but should be also considered in patients with vague symptoms and suggested that normal serum ferritin and hemoglobin levels are not reliable parameters to exclude colorectal carcinoma. In addition, this study reveals that the use of ferritin alone due to the presence of colorectal cancer or other underlying chronic diseases is not very effective even if the cut-off values changed. (6). In a study by Tingting et al in 514 patients with colorectal cancer, high serum ferritin levels were found to be associated with perineural invasion of colorectal cancer, and a significant relation was found between high serum ferritin and increased mortality. This situation emerges as a result of the high ferritin value in people with colorectal cancer. This reveals the limitation of serum ferritin alone in predicting colorectal cancer(29).

As serum ferritin is an acute phase reactant, high levels of serum ferritin cannot completely rule out iron deficiency (30). Serum ferritin can be falsely high even in patients with iron deficiency as in the case of older patients with comorbidities and also malignancy itself may cause higher levels of ferritin. In order to address this discrepancy, we compared 12 colon cancer patients who have been predicted only by method 3 to 54 patients predicted by using both methods 2 and 3 by means of serum CRP levels. Serum CRP levels were found to be significantly higher in patients predicted by method 3 [86.8 mg/L (min - max: 4.4 - 197) vs 22 mg/L (min – max: 1 - 182), P < 0.001]. Sawhey et al investigated 414 patients for anemia and 323 non anemic subjects for cancer screening purposes by means of colonoscopic examination (22). While 7.2% of subjects with ferritin 51 - 100 µg/L had colonic neoplasia, 7.9% of subjects with ferritin level ≤ 50 had colonic neoplasia. They concluded that, a ferritin cutoff of 100 µg/L can be used to determine the need for colonoscopy in men with anemia. In our study, we used three different methods in order to determine which patients need colonoscopic examination. Method I (ferritin < 50 µg/L) diagnosed 46 (63.9 %) out of 72 patients with colorectal carcinoma. Method 2 (ferritin < 100 µg/L) diagnosed 57 (79.2%) out of 72 patients and method 3 (ferritin + TSI) reached a diagnostic value of 91.7% (66 out of 72 patients).

In conclusion, our study suggests that serum ferritin values; ferritin < 50 µg/L and ferritin < 100 µg/L have rather low value in the decision making of colonscopic examination for colorectal carcinoma. However, ferritin < 100 µg/L and TSI < 16% values can be more useful in selecting older patients for colonoscopic examination.

Finally; the iron profile method and values to be used for colorectal carcinoma, especially in the geriatric age group, are not clearly defined in the literature. In this sense, this study is important because it sets the usefull method to be used in elderly patients. However, although the number of patients is sufficient, the low number of patients with colorectal cancer appears to be the limitation of the study.

Conclusion

Colorectal cancer is an important cause of morbidity and mortality in geriatric patients. Although anemia is an accompanying symptom, some patients may develop colorectal cancer without anemia. We think that the use of the third method (ferritin and TSI together) will create an important awareness for these patients.

Ethics Committee Approval: The study was approved by the Ethical Committee of Ankara University Faculty of Medicine, approval number: 06-242-16.

Informed Consent: Written consent was obtained from the participants.

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