European Review for Medical and Pharmacological Sciences 2021; 25: 6473-6479

Prognostic role of pre-operative serum ferritin level in stage 2 colon cancer

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Abstract. – OBJECTIVE: In this study, we aimed to evaluate the prognostic value of preoperative serum ferritin level in patients with stage 2 colon cancer who underwent curative surgery.

PATIENTS AND METHODS: The data of 120 patients who were stage 2 after curative surgery and whose ferritin levels were measured at the time of diagnosis without starting any treatment were analyzed. Demographic data such as age and gender, histopathological characteristics such as tumor size, lymphovascular invasion (LVI), perineural invasion (PNI), number of removed lymph nodes, tumor grade, and clinical and laboratory data were retrieved from the hospital medical charts or electronic medical records. In the survival analysis, the cut-off level of ferritin was accepted as 150 ng/ml, which is the upper limit determined by the World Health Organization (WHO), as a prognostic factor.

RESULTS: Fifty (41.7%) of the patients were female, 70 (58.3%) were male, and the median age was 63.5 (range 24-90) years. There was no significant difference between the low and high ferritin groups regarding age, gender, T stage, tumor localization, histological subtype, PNI, LVI, removal of less than 12 lymph nodes, and tumor size. Disease-free survival and overall survival of patients with high ferritin levels were worse than patients with low ferritin levels, but this difference did not reach statistical significance.

CONCLUSIONS: Serum ferritin level is an easily monitored, cost-effective, and reproducible marker. İn this study we found that high ferritin level was associated with poor survival, although it was not statistically significant.

Key Words:
Colon cancer, Ferritin, Prognosis, Iron.

Introduction

Iron is an indispensable nutrient for human life, and iron metabolism is altered in cancer cells. Cancer cells are more dependent on iron for proliferation compared to normal cells and are more sensitive to iron deficiency, this phenomenon is called iron dependency[1]. Ferritin is the major iron-binding protein and is found in the extracellular and intracellular space, and its extracellular form is called serum ferritin. Serum ferritin reflects the iron stores in the body, and it is used as a diagnostic marker of iron deficiency anemia in the laboratory[2]. However, ferritin is also an acute-phase protein playing a role in cellular defense against oxidative stress and inflammation. Increased serum ferritin level has also been shown to be associated with liver diseases, infections, inflammatory conditions, and malignancy[3,4]. In addition, ferritin is accepted as an oncofetal protein, and it has been shown that ferritin could be used as a tumor marker in the lung, breast, and renal-cell cancers[5-7].

Recent data show that ferritin plays an important role in processes such as cancer proliferation, angiogenesis, immunosuppression, carcinogenesis, and resistance to treatment[8-10].

In addition, higher serum ferritin levels are associated with worse survival outcomes. Therefore the ferritin protein not only functions in the transport and recycling of iron but also plays a role as a diagnostic and prognostic biomarker.

It has been shown that increased serum ferritin level indicates poor prognosis in various malignancies such as breast, lung, and pancreatic cancer[9,11-13]. Data regarding the prognostic value of high serum ferritin levels in colon cancer are controversial. Although increased serum ferritin level is a poor prognostic marker in metastatic colorectal cancer [14,15], it is accepted that it has no prognostic value in early-stage disease. Primary curative treatment in the management of

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patients with early-stage colon cancer is surgical resection. The standard treatment approach after surgery is adjuvant chemotherapy in stage 3 disease; however, there are conflicting results regarding post-surgical adjuvant therapy in stage 2 disease. Considering that stage 2 disease is a heterogeneous group, risk classification is needed to decide on adjuvant treatment in these patients. Several high-risk features may help determine which stage II patients will most benefit from adjuvant chemotherapy. However, there are no specific trials designed to answer the question of which patients with stage II colon cancer are at high risks.

In a study[16] reported from Turkey data, being over 60 years of age and having T4 tumor stage were found to be an independent risk factor in stage 2 patients. It was also shown that in this study adjuvant chemotherapy reduces the risk of recurrence in Turkish patients with stage 2 colon cancer and is an independent positive prognostic factor.

Another study[17] evaluating the effect of adjuvant chemotherapy in patients with low- and high-risk stage 2 colon cancer showed that adjuvant chemotherapy in high-risk stage 2 disease correlated with better OS and improved relapse-free survival and disease-specific survival. However, this improvement was not observed in low-risk patients.

Various prognostic factors have been described in colorectal cancers. Age, performance status, tumor sidedness, T and N stage, serum CEA, Ca.19-9 levels are defined as clinical prognostic factors; MSI, K-RAS, N-RAS, B-RAF, Her-2 status are defined as molecular prognostic factors[18]. Currently, adjuvant chemotherapy in the treatment of stage 2 disease is given depending on the clinical and pathological risk factors defined in international guidelines.

In stage 2 disease, European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines have defined high-risk factors and recommend adjuvant therapy in the presence of any of the following[19,20]. These risk factors include pT4 tumor, lymphatic/vascular invasion, poorly differentiated tumor, perineural invasion (PNI), obstruction, localized perforation, near or positive surgical margin, and less than 12 lymph node dissection. However, some population-based studies have failed to demonstrate the survival benefit of adjuvant therapy in all high-risk stage 2 colon cancers[21,22]. On the other hand, some molecular markers as microsatellite instability, which was defined as a prognostic factor, are not available in many countries and centers.

The existing risk factors are considered inadequate in the selection of adjuvant therapy, and additional prognostic factors need to be determined for the effective management of the patients.

This study aimed to evaluate the prognostic value of preoperative serum ferritin level in patients with stage 2 colon cancer who underwent curative surgery.

Patients and Methods

The medical records of 470 patients diagnosed with colon cancer between December 2012 and December 2020 at Afyon Health Sciences University Faculty of Medicine Medical Oncology Clinic were retrospectively reviewed. The data of 120 patients with stage 2 colon cancer who met the inclusion criteria were analyzed. The patients with stage 2 disease after curative surgery, whose ferritin levels were measured at the time of diagnosis before starting any therapy, and patients with complete and regular medical records and follow-up were included in the study. The exclusion criteria of the study were as follows:

a) stage 1,3 and 4 patients at the time of the diagnosis.
b) patients who received chemotherapy or radiotherapy before the analysis of ferritin level.
c) patients with a prior history of cancer and patients with asynchronous cancer.
d) patients with hepatic/renal failure or inflammatory disease that might affect serum ferritin level.
e) patients with inaccessible medical records and missing follow-up data.

Demographic data such as age and gender, histopathological characteristics such as tumor size, lymphovascular invasion (LVI), perineural invasion (PNI), number of removed lymph nodes, tumor grade, and clinical and laboratory data were retrieved from the hospital medical charts or electronic medical records.

In the survival analysis, the cut-off level of ferritin was accepted as 150 ng/ml, which is the upper limit determined by the World Health Organization (WHO), as a prognostic factor.

The overall survival (OS) and disease-free survival (DFS) were defined as the primary

end-points. OS was defined as the time from diagnosis to death (from any cause), and DFS was defined as the time from diagnosis to recurrence, metastasis, or death. The last follow-up data of the survivors were included in the analysis.

Statistical Analysis

The SPSS v. 26.0 Software (SPSS; IBM, Armonk, NY, USA) program was used in all analyses and a p-value of < 0.05 was considered statistically significant. Descriptive statistics including patient age, gender, tumor stage, histopathological type, grade, were presented as frequencies and percentages of categorical variables and median (minimum-maximum) of quantitative variables Chi-square test was used to determine the differences between groups according to serum ferritin level. The spearman rank correlation test was used to analyze the associations among continuous variables. Kaplan Meier curve was used for survival analysis, while log-rank analysis was used to compare survival differences between groups.

Results

Of 120 patients included in the study, 50 (41.7%) were female, 70 (58.3%) were male, and the median age was 63.5 (range 24-90) years. Baseline characteristics of the study group are presented in Table I. In the survival analysis, the cut-off level of ferritin was accepted as 150 ng/ml, which is the upper limit determined by the World Health Organization (WHO), as a prognostic factor.

When the patients were grouped as below 150 ng/ml and above according to the ferritin level, 98 (81.7%) cases were in the low ferritin group, and 22 (18.3%) were in the high ferritin group.

There was no significant difference between the low and high ferritin groups in terms of age, gender, T stage, tumor localization, histological subtype, PNI, LVI, removal of less than 12 lymph nodes, and tumor size (Table II). While no significant correlation was found between the ferritin level and age and tumor size, a positive correlation was found between ferritin level and hemoglobin level (rho=0.22 p=0.033). This result suggests that high ferritin levels in this study were independent of chronic disease status or inflammation.

Table I. Baseline characteristics of all stage-2 colon cancer patients.

	Patients (n = 120)
Age, years	63.5 (24-90)
Gender, n (%)	
Male	70 (58.3)
Female	50 (41.7)
BMI, kg/m^2	26.09 ± 4.6
Histology, n (%)	
Adenocarcinoma	105 (88.2)
Mucinous adenocarcinoma	14 (11.8)
Tumor location, n (%)	
Right colon	45 (37.5)
Left colon	75 (62.5)
T stage, n (%)	
T3	91 (75.8)
T4	29 (24.2)
PNI, n (%)	
Absent	97 (82.9)
Present	19 (16.2)
Unknown	1 (0.9)
LVI, n (%)	
Absent	80 (68.4)
Present	35 (29.9)
Unknown	2 (1.7)
Tumor grade, n (%)	
Unknown	5 (4.5)
Grade 1	21 (19.1)
Grade 2	78 (70.9)
Grade 3	6 (5.5)
Chemotherapy regimens, n (%)	
No	48 (40.3)
FOLFOX-XELOX	20 (16.8)
Fluorouracil-capecitabine	51 (42.9)
Tumor size grup n (%)	
< 4 cm	23 (19.2)
≥ 4 cm	97 (80.8)
Recurrens, n (%)	
Absent	103 (85.8)
Present	17 (14.2)

When the effect of ferritin level on survival was evaluated, disease-free survival and overall survival of patients with high ferritin levels were found to be worse than those with low ferritin levels, but this difference did not reach statistical significance (DFS; p=0.889, OS, p=0.115, Figure 1).

The number of cancer-related deaths was 16 in the entire study group. The mortality rate was 11.3% in the low ferritin group and 22.7% in the high ferritin group, and the difference between the groups was no statistically significant (p=0.158).

The median survival was 42 months (1-236) in the entire study group. The median survival was 52.7 (1-236) months in the low ferritin group and 43 (7-93) months in the high ferritin group.

Table II. Comparison of clinical features and baseline characteristics according to serum ferritin group in stage-2 colon cancer.

	Serum Ferritin (SF, ng/ml)		
	Low SF (n = 98)	High SF (n = 22)	*p*-value
Age, years			0.278
≥ 65	41 (41.8)	12 (54.5)	
< 65	57 (58.2)	10 (45.5)	
T stage n (%)			0.354
T3	76 (77.6)	15 (68.2)	
T4	22 (22.4)	7 (31.8)	
Gender, n (%)			0.577
Male	56 (57.1)	14 (63.6)	
Female	42 (42.9)	8 (36.4)	
Tumor location, n (%)			0.715
Right colon	36 (36.7)	9 (40.9)	
Leftcolon	62 (63.3)	13 (59.1)	
BMI, kg/m^2, n (%)			0.377
≥ 25	34 (63)	7 (50)	
< 25	20 (37)	7 (50)	
Tumor grade, n (%)			0.468
Grade 1	17 (20)	4 (20)	
Grade 2	62 (72.9)	16 (80)	
Grade 3	6 (7.1)	–	
Chemotherapy, n (%)			0.994
Yes	58 (59.2)	13 (59.1)	
No	40 (40.8)	9 (40.8)	
Tumor size, n (%)			0.639
< 4 cm	18 (18.4)	5 (22.7)	
≥ 4 cm	80 (81.6)	17 (77.3)	
Removed lymph node, n (%)			0.797
≥ 12	77 (79.4)	18 (81.8)	
< 12	20 (20.6)	4 (18.2)	
LVI, n (%)			0.720
Absent	64 (68.8)	16 (72.7)	
Present	29 (31.2)	6 (27.3)	
PNI, n (%)			0.524
Absent	77 (81.1)	20 (90.9)	
Present	17 (17.9)	2 (9.1)	
Recurrence, n (%)			0.450
Absent	83 (84.7)	20 (90.9)	
Present	15 (15.3)	2 (9.1)	

SF: serum ferritin, LVI: lymphovascular invasion; PNI: Peri-neural invasion, BMI: Body Mass.

The 3-year and 5-year survival rates were 80% and 69% in the high ferritin group, and 87% and 84% in the low ferritin group, respectively.

Discussion

In this study, the prognostic significance of serum ferritin levels in patients with stage 2 colon cancer was evaluated and it was found that high ferritin levels were associated with poor survival, although not statistically significant.

Serum ferritin levels are increased in many cancers. This increase was usually associated with a more aggressive disease course and shorter survival. In addition, the normalization of high ferritin levels in the follow-up after cancer treatment suggests that there is a response to the treatment[8].

The origin of serum ferritin in cancer patients is controversial. There are different opinions about the cause of increased serum ferritin levels in cancer patients. It is considered that the neoplasm itself might be the reason for increased serum ferritin level. The observation of higher serum ferritin levels in patients with metastatic disease compared to patients without metastasis and the decrease in serum ferritin after surgery or remission supports this opinion[23].

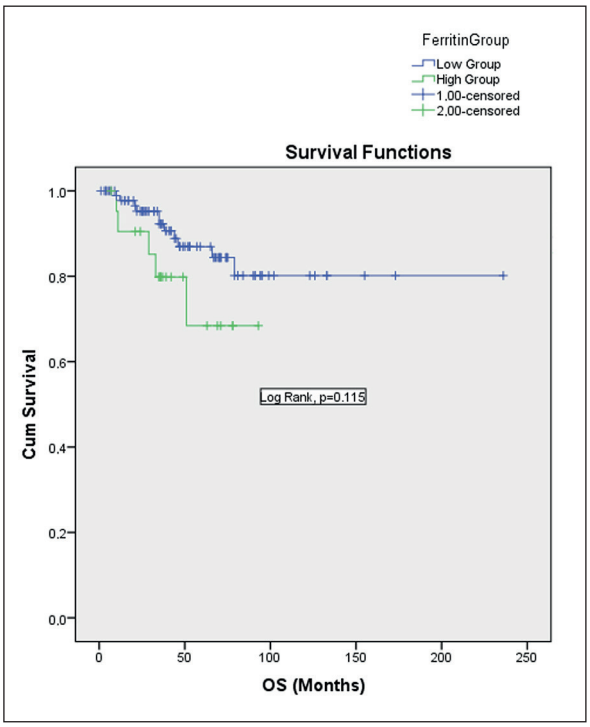

Figure 1. Kaplan-Meier curve of OS for groups by serum ferritin level. 5-year survival rates were 69% in the high ferritin group and 84% in the low ferritin group.

Recent studies[24,25] on breast cancer suggest that the increased serum ferritin might be due to a stromal reaction rather than an excessive synthesis from the tumor, this suggests that an increase in tumor-associated macrophages might be the cause of increased serum ferritin. Extracellular ferritin released from tumor-associated macrophages may stimulate tumorigenesis at various levels and indirectly induce the proliferation of tumor cells and angiogenesis and suppress lymphocyte responses[25,26].

It is also considered that chronic inflammation in cancer patients might be the cause of increased ferritin levels. The positive correlation between serum hemoglobin and serum ferritin levels detected in the present study suggests that chronic inflammation may not be the cause of increased ferritin levels.

It has been previously shown that increased ferritin level has prognostic significance in various cancers. In a study by Wang et al[27] in which they evaluated the relationship between serum ferritin levels and prognosis in patients with locally advanced pancreatic cancer receiving chemo-radiotherapy, lower progression-free and overall survival was demonstrated in patients with high ferritin levels before the therapy. In a study involving patients with advanced-stage non-small cell lung cancer, Lee et al[28] showed that high serum ferritin levels predict poor prognosis.

There is controversy regarding the prognostic significance of serum ferritin levels in both advanced and early-stage colon cancer.

In their study, Lee et al[14] evaluated the effects of various serum biomarkers on prognosis in patients with relapsing-refractory and metastatic colorectal cancer and identified high serum ferritin level as an independent prognostic factor. In the present study, patients with high serum ferritin levels exhibited a significantly poorer survival outcome.

Lorenzi et al[29] al evaluated the relationship between serum ferritin level and survival in patients with colon cancer. They showed that patients with stage 3 and who had high ferritin serum values also had a shorter survival. Similarly, high serum ferritin levels were associated with poor survival in advanced-stage patients who underwent palliative surgery.

Giessen et al[30] their study evaluating the relationship between preoperative levels of serum markers and prognosis in patients with early colon cancer, did not find any effect of serum ferritin on survival.

Only patients with stage 2 disease were included in this study, and no significant relationship was found between serum ferritin level and the well-known prognostic factors. Also, patients with high serum ferritin levels had a higher mortality rate and shorter survival, but it was concluded that there was no significant relationship with prognosis since the difference did not reach statistical significance.

In a recent prospective study involving patients with stage 1-3 colon cancer, Tingting et al[31] reported preoperative serum ferritin levels as an independent prognostic factor and showed that the mortality rate was 2.21 times higher in patients with high ferritin levels.

According to our literature review, this is the first study to evaluate the relationship between serum ferritin level and prognosis in patients with stage 2 colon cancer, but it has some limitations that might have affected the results. The first limitation is the recruitment of a small number of patients from a single center and retrospective study design. The second limitation is the short follow-up period.

Conclusions

Serum ferritin is an easily monitored, cost-effective, and reproducible marker. Available data suggest that high serum ferritin levels play a role in the etiopathogenesis of cancer and might be associated with prognosis and response to treatment. Our study found that high serum ferritin levels were associated with worse survival, although not statistically significant.

We think that the results obtained in our study may inspire more comprehensive studies that will determine the prognosis of patients with stage 2 colon cancer and evaluate its effect on the treatment decision.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

No financial support for commercial or non-commercial organizations was received.

Ethics Approval

The study was approved by the local Ethics Committee of Afyonkarahisar Health and Science University (Approval No: 2021/8 2011-KAEK-2).

Constent for Publication

All authors have approved the manuscript and consent for publication.

Authors' Contribution

Study concepts: H. Demir; Study design: H. Demir; Quality control of data and algorithms: I. Beypınar, M. Baykara, SE. Davarcı, S. Urvay; Statistical analysis: I. Beypınar; Manuscript preparation: H.Demir; Manuscript review: M. Baykara, S. Urvay, SE Davarcı; Manuscript editing: M. Baykara.

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