Risk Factors for Ferritin Depletion in Post-gastrectomy Gastric Cancer Patients with Normal Baseline Ferritin Level

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Abstract

Purpose: Decreased iron absorption is one of the most important post-gastrectomy complications. We identified risk factors for ferritin depletion in post-gastrectomy gastric cancer patients with normal baseline ferritin levels.

Material and Methods: Among 716 patients who underwent curative gastrectomy for gastric cancer during April 2009–August 2016, 445 were enrolled in the study. They were followed up for ≥3 years without recurrence and without baseline ferritin depletion (FD) (≥15 μg/L). Based on postoperative FD, the patients were divided into the ferritin non-depletion (FnD) (n=199) and FD (n=246) groups. Risk factor analysis for FD was performed using clinicopathologic and surgical factors, baseline ferritin levels, and pre-menopausal patient (PMP).

Results: PMP (FD vs. FnD=27 [13.6%] vs. 13 [5.3%], P=0.004), non-smoking history (FD vs. FnD=48 [24.1%] vs. 84 [34.1%], P=0.028), duodenal bypassing reconstruction (FD vs FnD=160 [80.4%] vs. 163 [66.3%], P=0.001) and lower baseline ferritin with cut-off 55.7 μg/L were significant risk factors for FD. Multivariate analysis revealed that PMP, type of reconstruction method, and baseline ferritin level were independent risk factors. FD in the postoperative period differed significantly according to risk categories (low-risk group: 0-1 risk factors, high-risk group: 2-3 risk factors). Regarding long-term nutritional aspects, no significant difference existed between the groups with respect to weight changes, but hemoglobin levels were significantly lower in the FD group.

Conclusion: Postoperative FD is a common post-gastrectomy complication in gastric cancer patients. PMP, food passage through the duodenum, and baseline ferritin level can be used to predict postoperative FD.

Introduction

Biennial national screening programs for gastric cancer, in Korea, enable its early detection. Although the number of early gastric cancer patients has increased, the survival rate has also improved [1, 2]. As the number of long-term survivors increases, the main interest of postoperative gastric cancer patients has moved toward quality of life, such as nutritional maintenance, rather than survival.

Iron deficiency is one of the most common nutritional issues after gastrectomy. Iron is an essential component of hemoglobin, a part of red blood cells that carry oxygen throughout the body. Iron deficiency can lead to reduced production of red blood cells, resulting in oxygen deficiency. Iron is primarily absorbed in the duodenum and the proximal jejunum. Additionally, dietary iron commonly binds to proteins and is cleaved by the action of gastric acid [3, 4]. The transit time of food through the intestine affects the time required for iron absorption. Therefore, iron absorption may be further decreased in post-gastrectomy patients.

The association of iron depletion with the extent of gastrectomy and the method of reconstruction has been investigated. The incidence of anemia is higher in patients who undergo total gastrectomy than in those who undergo subtotal gastrectomy. Furthermore, among total gastrectomy patients, those with a jejunal pouch interposition show higher iron concentration than those with Roux-en-Y reconstruction. Patients with Billroth-I subtotal gastrectomy have higher iron levels than patients with Billroth-II subtotal gastrectomy [5].

Iron absorption is multifactorial, and ferritin levels are affected by several conditions. Conditions that may cause high ferritin levels are liver disease, rheumatoid arthritis, inflammatory conditions, hyperthyroidism, and some types of cancer [6]. Preoperative gastric cancer patients sometimes show low ferritin levels due to nutritional deficiency or bleeding.

Among the variable laboratory measures that indicate iron deficiency, ferritin level is the most sensitive and specific index of iron storage, despite its multifactorial nature [7]. Thus, ferritin levels and other factors that may affect its levels, such as nutritional status, need to be investigated. Some post-gastrectomy patients have a ferritin deficiency, but they do not have anemia. This may be the result of various coexisting circumstances [8].

While previous studies have regarded ferritin level as an incidental factor of post-gastrectomy anemia, we only focused on ferritin depletion (FD). This study aimed to investigate ferritin levels in post-gastrectomy patients, as well as their influencing factors. To rule out the effects of inflammatory conditions or postoperative recurrence on changes in ferritin levels, we only included patients with normal baseline ferritin levels who were followed up every 6 months for 3 years postoperatively without gastric cancer recurrence.

Material And Methods

Study Design and Patients

This retrospective study evaluated 716 patients who underwent gastrectomy for gastric cancer by a single surgeon at Yeouido St. Mary's Hospital between March 2009 and July 2016. Among them, we excluded 172 patients with disease-free survival shorter than 36 months because of recurrence or follow-up loss (n = 160), patients who underwent preoperative chemotherapy (n = 5), patients who underwent wedge resection (n = 3), and patients who received a total gastrectomy (n = 4). Among the remaining 544 patients, we further excluded 99 patients with baseline ferritin levels < 15 μg/L, and patients who were not available for follow-up ferritin levels. Baseline ferritin level was defined as the ferritin level preoperatively, or 6 months postoperatively.

Finally, 445 patients were included in the study. They were divided into the ferritin non-depletion (FnD) (n = 199) and FD (n = 246) groups according to the postoperative ferritin level. The patients were managed according to routine postoperative care plans and were followed every 6 months for 3 years. Early gastric cancer patients were followed up annually, while advanced gastric cancer patients were followed up every

6 months for 2 years. Body weight, hemoglobin level, and ferritin level at postoperative 12, 18, 24, 36, 48, and 60 months were measured at each visit.

Data Collection and Variable Definitions

The patients' baseline clinicopathological characteristics, including smoking and alcohol history, surgical procedures, extent of resection, and type of anastomosis, were investigated. FD was defined as a follow-up ferritin level < 15 μg/L at any period, regardless of recovery after depletion. Surgical resection was categorized as distal, total, proximal, and pylorus-preserving gastrectomy. Meanwhile, surgical reconstruction was classified as Roux-en-Y, Billroth-I, Billroth-II, double tract, lower esophageal sphincter-preserving esophagogastrostomy, and gastrogastrostomy.

Risk Factor Analysis

Univariate risk factors for FD were identified through between-group comparisons of the clinicopathologic characteristics. Reconstruction type and baseline ferritin levels were included in the analysis. Other factors included were smoking history, alcohol history, and pre-menopausal patient (PMP), arbitrarily defined as female patients younger than 55 years. Reconstruction methods after gastrectomy were divided into duodenal passing and duodenal bypassing type, according to the possibility of food passage through the duodenum. The duodenal passing method consisted of Billroth-I, jejunal pouch interposition, and double tract anastomosis. The duodenal bypassing type consisted of Billroth-II, Roux-en-Y, and uncut Roux-en-Y anastomosis. Baseline ferritin levels were also analyzed as an influencing factor for postoperative FD.

Significant risk factors in the univariate analysis were entered into the multivariate analysis to identify independent risk factors. To determine the effect of FD on long-term nutritional issues, body weight and hemoglobin levels were compared, between the two groups, annually until 5 years postoperatively. The independent risk factors were then used to categorize the patients into the high-risk (2–3 risk factors) and low-risk (0–1 risk factors) groups, according to the number of risk factors and the trend of FD during the follow-up period.

Statistical Analyses

Between-group comparisons were performed using Student's t-test for continuous variables and the chi-squared and Fisher's exact tests for nominal variables. Receiver operating characteristic curve (ROC) was used to estimate the optimal cutoff value of baseline ferritin level predictive of postoperative FD. Multivariate analysis was performed using a logistic regression model. The rate of FD was compared between the low- and high-risk groups using Kaplan-Meier analysis and log-rank test. All analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) software package. Statistical significance was set at $p < 0.05$.

Results

In total, 167 patients (37.5%) were male and 278 (62.5%) were female. The baseline patient characteristics are summarized in Table 1. The median ages of patients in the FD and FnD groups were 61.4 and 63.3 years, respectively. There were no significant between-group differences in sex, age, body mass index, and Eastern Cooperative Oncology Group performance status between the FD and FnD groups. The PMP rates were significantly different between the FD and FnD groups (13.6% vs 5.3%, $p = 0.004$). The number of never-smokers was significantly higher in the FD group than in the FnD group (75.9% vs. 65.9%, $p = 0.028$). Furthermore, the rate of Billroth-I, jejunal pouch interposition, and double tract anastomosis was significantly higher in the FD group than in the FnD group (80.4% vs 66.3%, $p = 0.001$).

Table 1
Clinicopathologic characteristics of Ferritin depletion group & Ferritin non-depletion group

Variables		**Ferritin depletion** **(N = 199)**	**Ferritin non-depletion** **(N = 246)**	**P-value**
Age (year)		61.4 ± 11.3	63.3 ± 11.4	0.078
Sex	Male	86 (43.2%)	81 (32.9%)	0.033
	Female	113 (56.8%)	165 (67.1%)	
ASA	1	124 (62.3%)	130 (52.8%)	0.104
	2	69 (34.7%)	103 (41.9%)	
	3	6 (3.0%)	13 (5.3%)	
Menstruation	PMP	27 (13.6%)	13 (5.3%)	0.004
	non-PMP	172 (86.4%)	233 (94.7%)	
BMI (kg/m^2)		24.0 ± 3.4	24.0 ± 3.2	0.927
Smoking	Never-smoker	151 (75.9%)	162 (65.9%)	0.028
	Ex- or current- smoker	48 (24.1%)	84 (34.1%)	
Postoperative chemotherapy		32 (16.1%)	27 (11.0%)	0.150
CEA (ng/mL)		3.3 ± 8.8	7.0 ± 67.1	0.410
CA19-9 (U/mL)		15.2 ± 22.4	11.0 ± 14.6	0.030
Type of surgery	laparoscopic	180 (90.5%)	230 (93.5%)	0.313
	open	19 (9.5%)	16 (6.5%)	
Type of gastrectomy	DSG	170 (85.4%)	210 (85.4%)	0.049
	PG	9 (4.5%)	17 (6.9%)	
	PPG	0 (0.0%)	5 (2.0%)	
	TG	20 (10.1%)	14 (5.7%)	
Resection	STG	179 (89.9%)	232 (94.3%)	0.123
	TG	20 (10.1%)	14 (5.7%)	
Lymph node dissection	D1+	115 (57.8%)	164 (66.7%)	0.068
	D2	84 (42.2%)	82 (33.3%)	
Type of reconstruction	Billroth I	29 (14.6%)	60 (24.4%)	0.017

Variables		Ferritin depletion (N = 199)	Ferritin non-depletion (N = 246)	P-value
	Billroth II	136 (68.3%)	143 (58.1%)	
	Roux-en-Y	17 (8.5%)	15 (6.1%)	
	Uncut Roux-en-Y	7 (3.5%)	5 (2.0%)	
	Double tract anastomosis	9 (4.5%)	12 (4.9%)	
	JPI	1 (0.5%)	1 (0.4%)	
	LES LAPG	0 (0.0%)	5 (2.0%)	
	Gastrogastrostomy	0 (0.0%)	5 (2.0%)	
Reconstruction	duodenum passing	39 (19.6%)	83 (33.7%)	0.001
	duodenum bypass	160 (80.4%)	163 (66.3%)	
Operation time (min)		215.8 ± 55.6	212.2 ± 52.5	0.485
Expected blood loss (mL)		168.5 ± 182.4	168.9 ± 192.3	0.982
Tumor location	Lesser curvature	68 (34.2%)	102 (41.5%)	0.008
	Greater curvature	41 (20.6%)	34 (13.8%)	
	Anterior wall	29 (14.6%)	44 (17.9%)	
	Posterior wall	54 (27.1%)	66 (26.8%)	
	Circular	7 (3.5%)	0 (0.0%)	
T stage*	Tis	0 (0.0%)	2 (0.8%)	0.529
	T1a	87 (43.7%)	116 (47.2%)	
	T1b	61 (30.7%)	77 (31.3%)	
	T2	21 (10.6%)	24 (9.8%)	
	T3	23 (11.6%)	18 (7.3%)	
	T4a	7 (3.5%)	9 (3.7%)	
N stage*	N0	159 (79.9%)	203 (82.5%)	0.694
	N1	19 (9.5%)	26 (10.6%)	
	N2	13 (6.5%)	9 (3.7%)	
	N3a	7 (3.5%)	7 (2.8%)	

Variables		Ferritin depletion (N = 199)	Ferritin non-depletion (N = 246)	P-value
	N3b	1 (0.5%)	1 (0.4%)	
No. of retrieved lymph nodes		36.3 ± 12.9	34.8 ± 12.9	0.215
No. of metastatic lymph nodes		0.8 ± 2.2	0.7 ± 2.8	0.774
Postoperative complications		43 (21.6%)	51 (20.7%)	0.914
Pre-operative Ferritin level	≥ 55.7 ug/L	98 (49.2%)	199 (80.9%)	0.017
	< 55.7 ug/L	101 (50.8%)	47 (19.1%)	

Values are presented as mean ± standard deviation or number (%).

PMP = potential menstruation patient; non-PMP = non-potential menstruation patient;

DSG = distal subtotal gastrectomy; PG = proximal gastrectomy; PPG = pylorus-preserving gastrectomy; TG = total gastrectomy; STG = subtotal gastrectomy;

JPI = jejunal pouch interposition; LES LAPG = lower esophageal sphincter-preserving laparoscopy-assisted proximal gastrectomy;

*According to the 8th Union for International Cancer Control/American Joint Committee on Cancer TNM system.

The optimal cutoff value of baseline ferritin level for predicting FD was 55.7 μg/L, with a sensitivity of 51.3% and specificity of 80.9% (Fig. 1, $p < 0.001$). The number of patients with baseline ferritin levels < 55.7 μg/L was significantly higher in the FD group than in the FnD group (50.8% vs 19.1%, $p = 0.017$). There were no significant between-group differences in the extent of resection, final pathologic stage, or adjuvant chemotherapy. Multivariate analysis showed that PMP (OR = 2.24 (95% CI: 1.07–4.85)), duodenal bypassing of food (OR = 2.72 (95% CI: 1.68–4.52)), and baseline ferritin level < 55.7 μg/L (OR = 4.53 (95% CI: 2.89–7.22)) were significant independent risk factors of postoperative FD (Table 2). Kaplan-Meier and log-rank tests for time-based FD showed significant differences between the low- and high-risk groups (Fig. 2, $p < 0.001$).

Table 2
Univariate analysis and multivariate analysis of risk factors for ferritin depletion after gastrectomy

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Non-PMP	1	Ref	1	Ref
PMP	2.81 (1.44–5.78)	0.003	2.24 (1.07–4.85)	.035
Ex- or current- smoker	1	Ref	1	Ref
Never-smoker	0.61 (0.40–0.93)	0.022	0.84 (0.53–1.33)	0.457
Duodenum passing	1	Ref	1	Ref
Duodenum bypass	2.09 (1.35–3.26)	< 0.001	2.72 (1.68–4.52)	< 0.001
Tumor location				
Lesser curvature	1	Ref	1	Ref
Greater curvature	1.81 (1.05–3.14)	0.034	1.52 (0.84–2.76)	0.169
Anterior wall	0.99 (0.56–1.73)	0.968	0.79 (0.42–1.41)	0.408
Posterior wall	1.23 (0.76–1.97)	0.396	0.93 (0.55–1.55)	0.763
Circular	8636719.29	0.977	4336960.21	0.976
Pre-operative Ferritin level ≥ 55.7 ug/L	1	Ref	1	Ref
Pre-operative Ferritin level < 55.7 ug/L	4.36 (2.88–6.70)	< 0.001	4.53 (2.89–7.22)	< 0.001
PMP = potential menstruation patient; non-PMP = non-potential menstruation				

Long-term nutritional monitoring factors including post-operative body weight and hemoglobin level up to post-operative 5 years were analyzed. While there were no significant differences found in post-operative body weight between two group, post-operative hemoglobin level was significantly lower in FD group compared to FnD group from post-operative 1 year (Table 3).

Table 3
Long-term body weight and hemoglobin change

Variables		Ferritin depletion (N = 199)	Ferritin non-depletion (N = 246)	P-value
Body weight (kg)	preoperative	62.5 ± 10.9	64.3 ± 11.6	0.094
	postoperative, 1year	56.3 ± 9.9	58.7 ± 10.5	0.031
	postoperative, 2years	56.6 ± 9.9	58.2 ± 10.6	0.159
	postoperative, 3years	57.0 ± 9.8	58.9 ± 10.8	0.093
	postoperative, 4years	56.5 ± 9.7	58.7 ± 11.0	0.040
	postoperative, 5years	56.2 ± 9.3	59.4 ± 10.4	0.004
Hemoglobin (g/dL)	preoperative	13.3 ± 1.6	13.6 ± 1.7	0.086
	postoperative, 1year	12.8 ± 1.3	13.3 ± 1.5	< 0.001
	postoperative, 2years	12.8 ± 1.4	13.4 ± 1.6	< 0.001
	postoperative, 3years	12.6 ± 1.5	13.5 ± 1.6	< 0.001
	postoperative, 4years	12.4 ± 1.5	13.4 ± 1.6	< 0.001

Values are presented as mean ± standard deviation or number (%).

Discussion

Nutritional problems are among the most important problems post curative gastrectomy. This study found that preoperative ferritin level, premenopausal women and duodenal bypassing reconstruction were independent risk factors for FD among the patients with normal baseline ferritin levels.

Iron is closely related to the hematopoietic process, and iron deficiency is a major cause of anemia after gastrectomy [9]. However, iron status after gastrectomy varies widely among patients. To evaluate iron supplementation after gastrectomy, we focused on ferritin levels. Ferritin is a blood protein that stores and releases iron; thus, it reflects the amount of iron stored [10]. Dietary iron is absorbed through the polarized intestinal epithelial cells of the duodenum and proximal jejunum. Iron exists in an oxidized form, which has low water solubility and is not available in vivo; thus, it should be stored in a ferritinbound form. Ferritin levels positively correlate with total body iron stores under steady-state conditions, and can be used as the most convenient laboratory test to estimate iron stores [11].

A ferritin level lower than the normal level indicates an iron deficiency. Bleeding, such as menstruation, may also result in lower ferritin levels [12]. High ferritin levels could indicate high iron storage. However, inflammatory conditions, infection, postoperative state, liver disease, rheumatoid arthritis, some types of cancer, and hyperthyroidism may also elevate ferritin levels [13]. In this study, we focused on changes in the ferritin level in association not only with gastrectomy type or reconstruction method, but also with the patients' characteristics (e.g., PMP status, smoking history, and baseline ferritin level). PMP patients are at higher risk of iron deficiency than men and menopausal women. Smoking is also known to increase ferritin levels [14]. We also found that the baseline ferritin level was an influencing factor of postoperative FD. Specifically, a baseline ferritin level < 55.7 µg/L was a significant risk factor for FD. Multivariate analysis also showed that PMP, food bypass through the duodenum, and low baseline ferritin levels increased the risk of FD in both the high-risk and low-risk groups.

There have been several studies on the incidence of iron deficiency after gastrectomy, but none on the risk factors for FD, which was the focus of this study. Iron depletion after gastrectomy is a long-standing subject of interest regarding the nutritional aspect after gastrectomy. Kim et al. reviewed the medical records of 558 patients who underwent curative gastrectomy [15]. They found that the cumulative incidence of iron deficiency gradually increased with time, postoperatively. Furthermore, Billroth-I anastomosis was the best reconstruction strategy for preventing iron deficiency. Lee et al. found that Billroth-II anastomosis and female sex were associated with a higher prevalence of iron deficiency among 381 patients [16]. The authors defined iron deficiency as a ferritin level < 30 µg/L. In contrast, we defined FD as a ferritin level < 15 µg/L, which may have attributed to a lower incidence of iron depletion. We followed the World Health Organization Guideline regarding the use of ferritin concentrations to assess iron status in individuals and populations, which may be useful for determining whether patients are critically ill.

With respect to the influence of sex on ferritin levels, some studies divided patients into male and female groups. However, in the real world, the risk of iron depletion is similar between postmenopausal female and male patients. Thus, we only included patients with ferritin levels > 15 µg/L, regardless of sex. Furthermore, possible menstruation status was included in the categorization, thereby increasing statistical power. Gastrectomy reconstruction method has been a highly researched topic in the field of gastric cancer, especially distal or proximal gastrectomy. Korean guidelines for gastric cancer treatment show that there is no significant difference in the survival or quality of life benefit, except for bile reflux, in Billroth-I, Billroth-II, and Roux-en-Y anastomosis for distal gastrectomy.

Studies on iron depletion anemia have suggested that duodenal bypassing anastomosis is inferior to duodenum passing anastomosis [16]. This study shows that any type of duodenal food passage can prevent iron depletion. Additionally, we found that the low-risk group is a candidate for duodenal bypass anastomosis. Therefore, our risk stratification method can be used to determine the appropriate type of anastomosis needed. Among patients in which proximal gastrectomy is indicated; most have early gastric cancer in the proximal portion of the stomach. In such patients, the decision for the type of surgical procedure depends on the extent of resection needed. Total gastrectomy usually only has one anastomosis choice, duodenal bypassing. Meanwhile, other surgical options such as esophagogastrostomy, lower esophageal sphincter-preserving proximal gastrectomy, and double tract anastomosis allow food to pass through the duodenum [17]. Proximal gastrectomy is strongly recommended for patients at risk of iron depletion.

The clinical implications of FD need to be considered. With respect to long-term nutritional factors, there was no significant difference in postoperative body weight between the FD and FnD groups, whereas postoperative hemoglobin level was significantly lower in the FD group from the postoperative 1 year period. We need to further evaluate the implications of risk factors in iron supplement strategies. Iron deficiency is one of the most important nutritional problems in post-gastrectomy patients. Although many studies have investigated iron depletion in gastrectomy patients, our study shows the natural response or change in iron depletion among long-term survivors of gastric cancer after gastrectomy. We only included patients with normal baseline ferritin levels who were followed up for 3 years, without gastric cancer recurrence.

This study had limitations. First, this was a retrospective study, and PMP was arbitrarily defined as females < 55 years. There could have been patients < 55 years who underwent hysterectomy or were post-menopausal. Prospective studies on the menopausal status of PMP patients are needed to investigate its impact on ferritin levels. However, PMP was found to be an independent risk factor for FD. Second, ferritin might be influenced by inflammatory conditions such as sepsis or postoperative complications, and these conditions were not considered in this study. Although we evaluated the incidence of FD, we did not compare the mean with the standard deviation. As a result, the data on the impact of other inflammatory conditions on FD may be limited. Third, we did not consider other iron-related parameters, such as transferrin and iron-binding capacity, serum iron, and total iron, which also give an indication of iron status or iron activation ability. Further studies using other relevant parameters are required in the future.

In conclusion, postoperative FD is highly common after gastrectomy for gastric cancer. The patient’s risk factors (e.g., PMP, food passage through the duodenum, and baseline ferritin level) can be used to predict postoperative FD, thereby allowing physicians to determine the need for iron supplementation.

Abbreviations

FD: ferritin depletion, FnD: ferritin non-depletion, PMP: pre-menopausal patient.

Declarations

Ethics approval and consent to participate

Ethical approval was achieved from institutional review board

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

Not applicable

Funding

Not applicable

Authors' contributions

DJK, WK designed and made the concept of this study, JHJ analyzed and interpreted the patient data. JHJ and WK were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Ethical Standards

All procedures followed were in accordance with the ethical standards of the responsible institutional review committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflicts of interest

The authors report there are no competing interests to declare.

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References

1. Information Committee of Korean Gastric Cancer Association. Korean Gastric Cancer Association nationwide survey on gastric cancer in 2014. J Gastric Cancer. 2016;16:131–40.

2. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer. 2019;19:1–48.
3. Gulec S, Anderson GJ, Collins JF. Mechanistic and regulatory aspects of intestinal iron absorption. Am J Physiol Gastrointest Liver Physiol. 2014;307:G397-409.
4. Al-Nasser A, Alzerwi N, Hussain MSM, Bukhari KO, Almodhaiberi H, Ali BI. Nutritional demand after gastric surgery. Clin Surg. 2019;4:2465.
5. Lim CH, Kim SW, Kim WC, Kim JS, Cho YK, Park JM, et al. Anemia after gastrectomy for early gastric cancer: long-term follow-up observational study. World J Gastroenterol. 2012;18:6114–9.
6. Theil EC. Ferritin: the protein nanocage and iron biomineral in health and in disease. Inorg Chem. 2013;52:12223–33.
7. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372:1832–43.
8. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014;6:748–73.
9. Musallam KM, Taher AT. Iron deficiency beyond erythropoiesis: should we be concerned? Curr Med Res Opin. 2018;34:81–93.
10. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. J Intern Med. 2020;287:153–70.
11. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. Blood Rev. 2009;23:95–104.
12. Kocaoz S, Cirpan R, Degirmencioglu AZ. The prevalence and impacts heavy menstrual bleeding on anemia, fatigue and quality of life in women of reproductive age. Pak J Med Sci. 2019;35:365–70.
13. Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW, British Society for H. Investigation and management of a raised serum ferritin. Br J Haematol. 2018;181:331–40.
14. Lee CH, Goag EK, Lee SH, Chung KS, Jung JY, Park MS, et al. Association of serum ferritin levels with smoking and lung function in the Korean adult population: analysis of the fourth and fifth Korean National Health and Nutrition Examination Survey. Int J Chron Obstruct Pulmon Dis. 2016;11:3001–6.
15. Kim JH, Bae YJ, Jun KH, Chin HM. Long-term trends in hematological and nutritional status after gastrectomy for gastric cancer. J Gastrointest Surg. 2017;21:1212–9.
16. Lee JH, Hyung WJ, Kim HI, Kim YM, Son T, Okumura N, et al. Method of reconstruction governs iron metabolism after gastrectomy for patients with gastric cancer. Ann Surg. 2013;258:964–9.
17. Sun KK, Wu YY. Current status of laparoscopic proximal gastrectomy in proximal gastric cancer: technical details and oncologic outcomes. Asian J Surg. 2021;44:54–8.

Figures

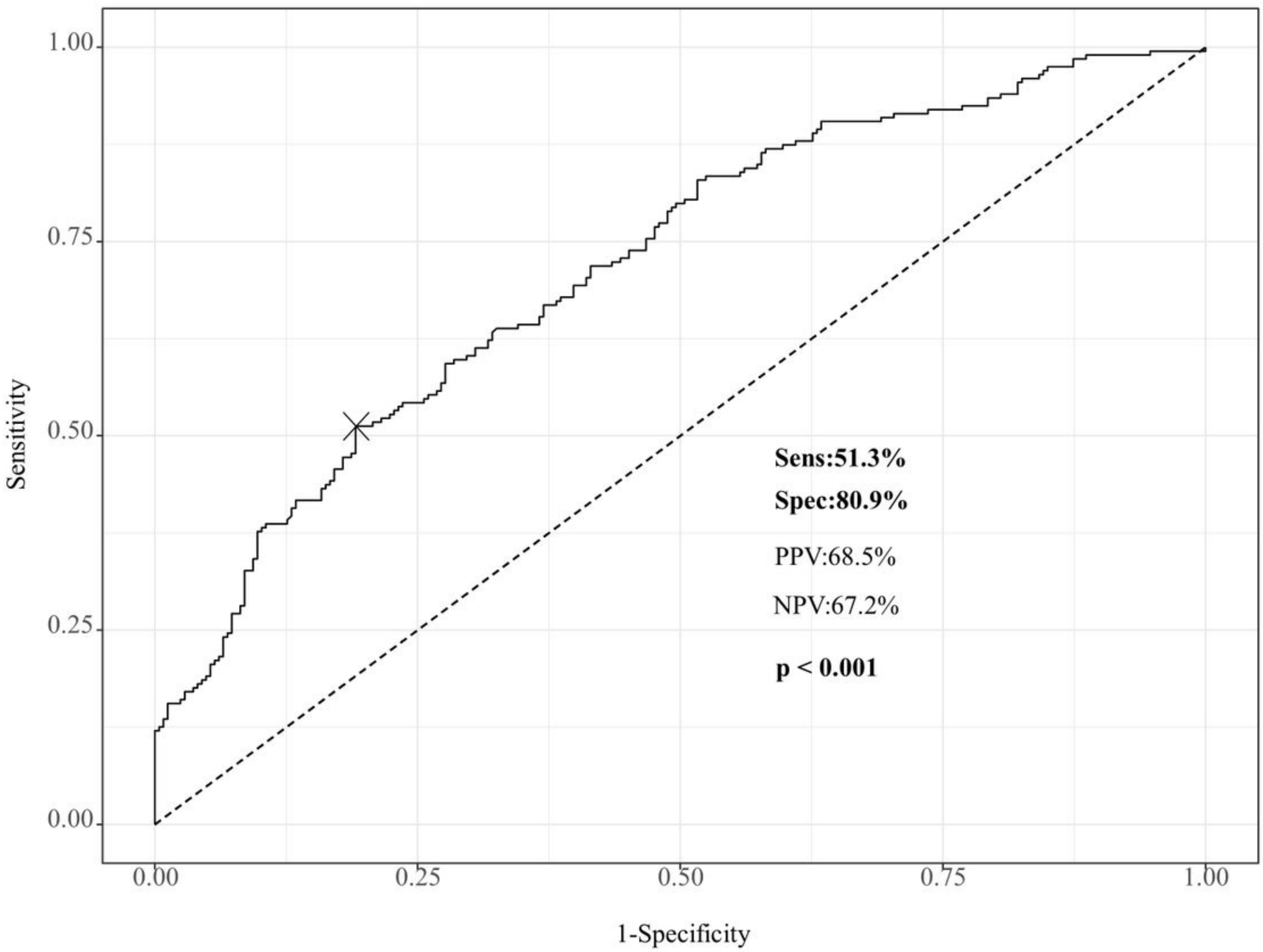

Figure 1

ROC curve for evaluating optimal cut-off value of preoperative ferritin level which can estimate the ferritin deficiency

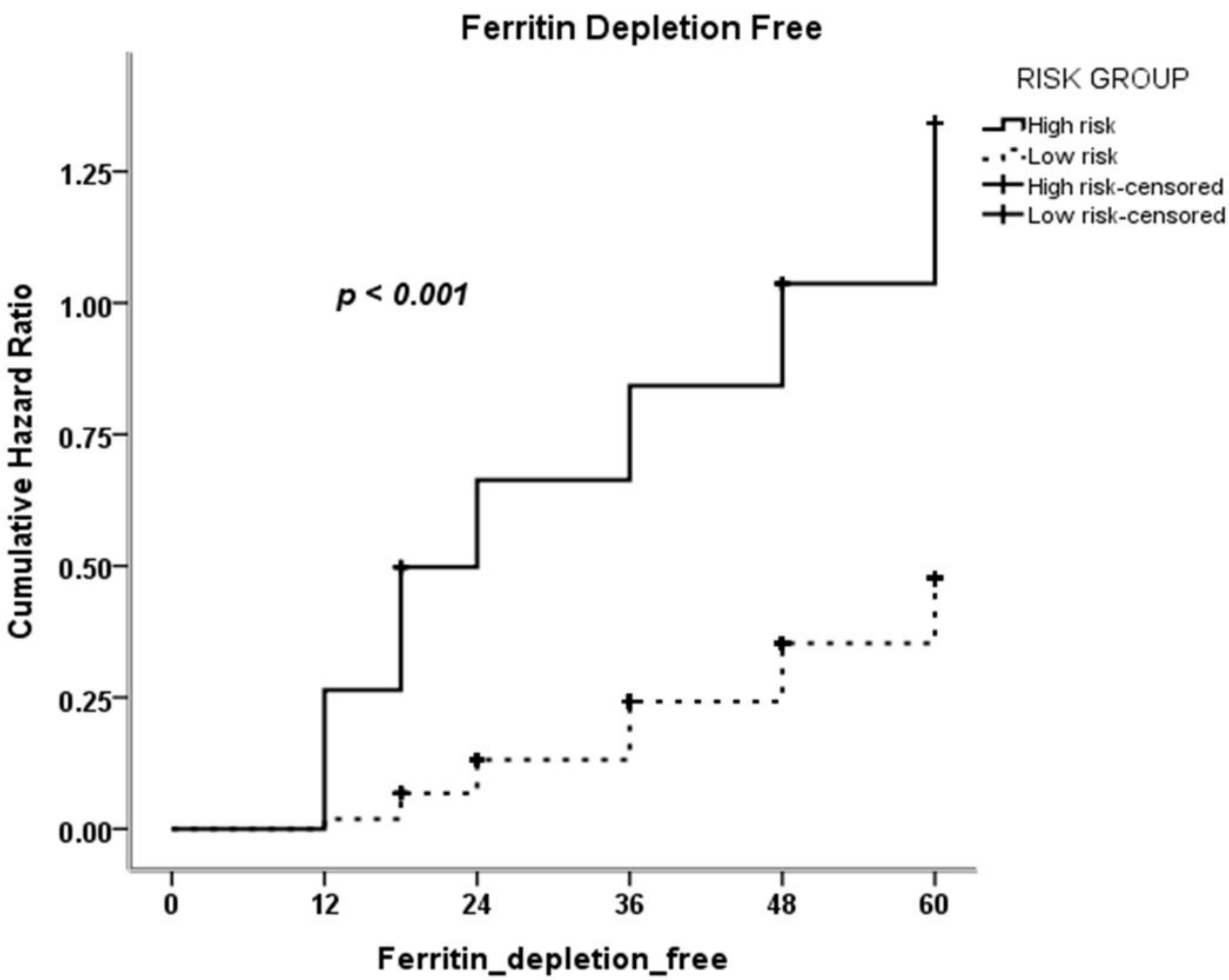

Figure 2

Kaplan-Meier analysis of the cumulative incidence of Ferritin depletion after gastrectomy for gastric cancer