Original Article

Prevalence of Gastrointestinal Findings Responsible for Anemia in Different Groups of Anemic Patients: Retrospective Study from a Large Tertiary Hospital

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Background: Gastrointestinal (GI) evaluation with bidirectional endoscopy is recommended in patients with iron deficiency anemia (IDA). In practice, however, 2 other settings are anemic patients with some clinical clues and patients who have only anemia. Diagnostic yield of bidirectional endoscopy in the latter 2 settings are unknown.

Materials and Methods: All patients who underwent bidirectional endoscopy for anemia during 2011 to 2016 were reviewed. Patients were divided into 3 groups (group A, definite IDA; group B, anemia with some clues; group C, anemia without definite proof of IDA or any clinical clue). Prevalence of significant lesions and details were analyzed.

Results: Three hundred twenty-five patients were enrolled (43 in group A, 95 in group B and 187 in group C). Significant GI lesions were found in 62.8%, 32.6% and 24.1% and cancers were found in 16.3%, 10.5% and 2.7%, respectively. From EGD, 39.5% of patients in group A, 18.9% of group B, and 15.5% of group C had significant GI lesions and the most common lesion was erosive gastroduodenitis. From colonoscopy, 14% of group A, 7.4% of group B, and 7.0% of group C had significant GI lesions and the most common lesion was colonic carcinoma. Dual lesions were found in 9.3%, 6.3%, and 1.6% of group A, B, and C, respectively. Multivariate analyses showed no predictor for significant GI lesions in group B, but reveled hemoglobin <9 g/dL to be significant predictor in group C (odds ratio 6.07, 95% confidence interval 1.1 to 33.9, $p = 0.04$).

Conclusion: Significant GI lesions detected by bidirectional endoscopy in patients with definite IDA, anemia with some clinical clues of GI blood loss, and unconfirmed IDA without any clinical clue of GI blood loss were 63%, 33% and 24%, respectively. Erosive gastroduodenitis and colonic carcinoma were the most common significant upper and lower GI lesions, respectively. Patients with Hb <9 g/dL predicted significant lesions in anemia patients without IDA confirmation.

Keywords: Anemia, Endoscopy, Evaluation, Gastrointestinal

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Many studies worldwide have shown that 40 to 70% of patients with iron deficiency anemia (IDA) would have significant gastrointestinal (GI) lesions responsible for anemia detected via esophagogastroduodenoscopy (EGD) and colonoscopy (i.e. bidirectional endoscopy)[1-7]. Importantly, one retrospective study showed that significant GI lesions were low in anemia patients without confirmation of IDA; 8% by EGD and 4% from colonoscopy or barium enema[5]. Thus, current recommendations all suggest GI endoscopy in patients with unexplained definite IDA[8,9], and bidirectional endoscopy is the recommended option[10].

In general practice, anemic patients who are consulted for GI evaluation can be divided into 3 groups; 1) definite IDA, 2) anemia with some clues for GI blood loss (e.g. minimal GI symptoms, equivocal melena, etc.) and 3) unconfirmed IDA without clinical clues of GI blood loss. According to the current recommendations, the latter 2 groups would be inappropriate candidates for GI evaluation because the prevalence of GI lesions would probably be low and may not outweigh the costs and risks of bidirectional endoscopy. However, studies on these latter 2 groups remain lacking.

Many previous studies have shown association between significant GI lesions and some clinical correlations in various groups of study population in patients with IDA, for example, age[11], presence of GI symptoms[12], NSAIDS or anti-platelet use[2,12], family history of GI malignancy[12], positive fecal occult blood test (FOBT)[2,4,12], and hemoglobin (Hb) <9 g/dL[11]. However, there was limited study about the predictors for the patients with unconfirmed IDA. Yet, GI evaluation might have some roles to apply to some specified subgroups of patients whom IDA has not been confirmed.

This study aims to determine the prevalence of GI lesions using bidirectional endoscopy in different types of

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anemic patients who are referred for GI evaluation. Moreover, we aim to define clinical clues that predict the presence of significant GI lesions, particularly in patients without a confirmation of IDA.

Materials and Methods

Study population

All patients >18 years old who underwent sameday bidirectional endoscopy for the indication of anemia at the endoscopic center, Siriraj Hospital, during January 2011 to October 2016 were enrolled in this study. Anemia was defined by the World Health Organization as a Hb concentration ≤13 g/dL for men and ≤12 g/dL for women[13].

Patients were divided into 3 groups. Patients with definite IDA (group A) were described as those who had anemia, together with at least one of the following laboratory investigations: a serum iron ≤45 µg/dL with a transferrin saturation ≤15%, a serum ferritin concentration ≤30 µg/L, peripheral blood smear revealed hypochromic microcytic red cells which responded to iron supplement[2]. Patients with some clues of GI blood loss (group B) were defined as those with anemia, accompanied by at least one of the following clinical presentations: non-specific minimal GI symptoms (upper, lower GI symptoms or both), equivocal overt GI bleeding (dark stool) and acute onset of anemia. The rest of the patients without confirmation of IDA or any clinical clue were categorized into group C.

Exclusion criteria included history of overt GI bleeding or obvious non-GI blood loss (e.g. hypermenorrhea) within the last 3 months, strict vegetarian, history of gastrectomy, known GI cancers, chronic kidney disease stage 3 to 5 (GFR <30 mL/min/1.73 m^2), pregnancy, thrombocytopenia (<50,000/mm^3), coagulopathy (INR >4), and incomplete medical records.

Significant GI lesions

The definitions of significant GI lesions that were likely to be the causes of anemia by bidirectional endoscopy were those proposed by Rockey, et al[3]. For EGD, they were: carcinoma, esophagitis with erosions or ulceration involving >5% of distal 5 cm of esophagus, erosive gastritis or duodenitis (>50 erosions ≥1 mm in diameter with white bases encircled by erythema), a gastric or duodenal ulcers ≥1 cm in diameter or 2 ulcers ≥0.5 cm in diameter, adenomatous polyp ≥1.5 cm in diameter, ≥5 vascular ectasia or ≥8 mm in diameter. For colonoscopy, they were: carcinoma, adenomatous polyp ≥1.5 cm in diameter, ≥5 vascular ectasia or ≥8 mm in diameter, active colitis, colonic ulcer ≥1 cm in diameter.

Other lesions were considered to be significant lesions for anemia when there was agreement from 2 expert endoscopists (TS and SP).

Data collection

The research protocol was approved by the Institution Review Board of the Faculty of Medicine Siriraj Hospital.

The medical records, including clinical data and laboratory data such as complete blood count, renal function test, and liver function test, together with finding of bidirectional endoscopy as well as pathological report of all patients were reviewed and recorded in the case record form.

Statistical analysis

Statistical analysis was done using R statistical system with built-in library. Descriptive statistic was used suitably. Qualitative variables were described by frequency and percentage. Quantitative variables were described by means and standard deviations. Univariate analysis of the association between clinical parameters and significant GI lesions in Group B and C were analyzed by Chi-square or Fischer-exact test for categorical variable and student t-test for continuous variables. Multivariate logistic regression analysis was conducted on factors which had p-value <0.1 by univariate analyses in order to find an independent factors. Statistical significance was considered when $p<0.05$.

Results

Overall, there were 325 patients, who were divided into 43 patients in group A, 95 patients in group B and 187 patients in group C.

Patient characteristics

The patient characteristics of the 3 groups were similar regarding to age, gender, comorbidities and medication uses. The mean Hb levels were 8.0±1.8, 8.6±2.0, and 9.4±1.9 in patients of group A, B, and C, respectively ($p<0.001$). Cardiovascular diseases (30.5%) and chronic kidney disease stage 3 (24.3%) were the 2 most common comorbidities among the patients. One or more ulcerogenic drugs were used about a half among patients in each group; 46.5%, 48.4%, and 43.3% in group A, B, and C, respectively. The details of demographic data are shown in Table 1.

Prevalence of significant GI lesions

Significant GI lesions were found in 27 of the 43 patients in group A (62.8%), 31 of the 95 patients in group B (32.6%), and 45 of the 187 patients in group 3 (24.1%) ($p<0.001$). The differences were statistically significant between group A and B ($p = 0.002$), group A and C ($p<0.001$), but were similar between group B and C ($p = 0.164$).

From EGD, 17 (39.5%) patients in group A, 18 (18.9%) in group B, and 29 (15.5%) in group C had significant GI lesions, whereas from colonoscopy, 6 (14%) patients in group A, 7 (7.4%) in group B, and 13 (7.0%) in group C had significant GI lesions. Dual lesions were found in 4 (9.3%), 6 (6.3%), and 3 (1.6%) patients in group A, B, and C, respectively (Table 2).

Endoscopic findings

Details of the endoscopic findings of all patients are shown in Table 3. Erosive gastritis/duodenitis and colonic carcinoma were the most common significant GI lesions detected by EGD (15.6%) and colonoscopy (5.5%),

Table 1. Characteristics of the 325 patients

Characteristics	Group A (n = 43)	Group B (n = 95)	Group C (n = 187)	*p*-value
Age (years), mean (SD)	66 (11)	67 (12)	66 (12)	0.847
Gender, female	27 (62.8)	58 (61.1)	125 (66.8)	0.608
Hemoglobin level (g/dL), mean (SD)	8.0 (1.8)	8.6 (2.0)	9.4 (1.9)	<0.001
GI symptoms	12 (27.9)	63 (66.3)	0	<0.001
Upper GI	6 (14.0)	24 (25.3)	0	0.204
Lower GI	5 (11.6)	28 (29.5)	0	0.039
Both	1 (2.3)	11 (11.6)	0	0.144
Comorbidities				
Cardiovascular diseases	13 (30.2)	33 (34.7)	53 (28.3)	0.544
Cirrhosis	3 (7.0)	6 (6.3)	17 (9.1)	0.694
Chronic kidney disease stage 3	8 (18.6)	27 (28.4)	44 (23.5)	0.428
Gynecologic disorders	5 (11.6)	3 (3.2)	6 (3.2)	0.040
Connective tissue diseases	2 (4.7)	3 (3.2)	4 (2.1)	0.639
Hematologic disorders	3 (7.0)	5 (5.3)	16 (8.6)	0.603
Any	25 (58.1)	57 (0.6)	106 (56.7)	0.867
Medications				
NSAIDs	9 (20.9)	9 (9.5)	17 (9.1)	0.070
Anti-platelets	14 (32.6)	35 (36.8)	55 (29.4)	0.448
Anticoagulants	4 (9.3)	8 (8.4)	15 (8.0)	0.962
Ulcerogenic drugs	20 (46.5)	46 (48.4)	81 (43.3)	0.706
Proton pump inhibitors	15 (34.9)	24 (25.3)	39 (20.9)	0.143

GI = gastrointestinal, NSAIDs = non-steroidal anti-inflammatory drugs, SD = standard deviation
Data are shown in n (%), unless specified

Table 2. Prevalence of significant GI lesions of the 325 patients

Lesions	Group A (n = 43)	Group B (n = 95)	Group C (n = 187)	*p*-value
Significant lesions	27 (62.8)	31 (32.6)	45 (24.1)	<0.001
By EGD	17 (39.5)	18 (18.9)	29 (15.5)	<0.001
By colonoscopy	6 (14)	7 (7.4)	13 (7.0)	0.023
Dual lesions	4 (9.3)	6 (6.3)	3 (1.6)	0.026
Insignificant lesions	15 (34.9)	64 (67.4)	137 (73.3)	<0.001
Normal	1 (2.3)	0	5 (2.7)	-

EGD = Esophagogastroduodenoscopy

respectively. Moreover, these 2 lesions accounted for the most significant GI lesions in each group. To illustrate, erosive gastritis/duodenitis was detected in 34.9%, 14.7% and 11.7%, while colonic carcinoma was detected in 14.0%, 7.4% and 2.7% of patients in group A, B and C, respectively.

GI carcinomas

The details of GI carcinomas are shown in Table 4. The prevalence was 16.3%, 10.5% and 2.7% in patients group A, B and C, respectively. Gastric cancer showed much lower prevalence than colonic cancer in every group. All carcinoma found in group C (5 patients) were colonic and all had hemoglobin level less than 9 g/dL. One showed positive FOBT while others did not have FOBT done.

Predictors of significant GI lesions in patient without confirmed IDA

Univariate analyses of the clinical characteristics associated with significant GI lesions of patient in group B and group C are demonstrated in Table 5 and Table 6, respectively. By the multivariate analyses, there was no independent predictor for significant GI lesions in group B, whereas in group C, hemoglobin level <9 g/dL was the only predictor for significant GI lesions (odds ratio [OR] 6.07, 95% CI 1.1 to 33.9, $p = 0.04$). Positive FOBT showed highly suggestive trend for significant GI lesions (OR 11.1, 95% CI 0.9 to 125.7, $p = 0.052$).

Discussion

GI evaluation is the standard recommendation to search for the cause of anemia in patients with definite IDA[8,9]. However, in general practice, anemic patients who are consulted for GI endoscopy can be divided into 3 groups; patients with definite IDA, patients with anemia and some clinical clues of GI blood loss, and the last group, patients with just anemia. The yields and benefits of performing

Table 3. Details of endoscopic findings of the 325 patients

	Group A (n = 43)	Group B (n = 95)	Group C (n = 187)	Total (n = 325)
EGD				
Significant lesions				
Reflux esophagitis, LA grade C-D	0	1 (1.1)	1 (0.5)	2 (0.6)
Erosive gastritis or duodenitis	15 (34.9)	14 (14.7)	22 (11.7)	51 (15.6)
Gastric ulcer or duodenal ulcer	4 (9.3)	5 (5.3)	7 (3.7)	16 (4.9)
Gastric carcinoma	1 (2.3)	3 (3.2)	0	4 (1.2)
Large gastric polyp >1.5 cm	1 (2.3)	0	1 (0.5)	2 (0.6)
Severe portal hypertensive gastropathy	0	1 (1.1)	1 (0.5)	2 (0.6)
Angiodysplasia	1 (2.3)	1 (1.1)	1 (0.5)	3 (0.9)
Insignificant lesions				
Reflux esophagitis LA grade A-B	1 (2.3)	4 (4.2)	3 (1.6)	8 (2.5)
Esophageal or gastric varices	3 (7.0)	2 (2.1)	11 (5.9)	16 (4.9)
Nonerosive gastritis or duodenitis	16 (37.2)	53 (55.8)	112 (59.9)	181 (55.7)
Small gastric or duodenal ulcer	1 (2.3)	8 (8.4)	14 (7.5)	23 (7.1)
Small gastric polyps	4 (9.3)	10 (10.5)	20 (10.7)	34 (10.5)
Mild portal hypertensive gastropathy	0	1 (1.1)	4 (2.1)	5 (1.5)
Small subepithelial lesions	0	2 (2.1)	2 (1.1)	4 (1.2)
Intestinal metaplasia	0	1 (1.1)	4 (2.1)	5 (1.5)
Others*	5 (11.6)	22 (23.2)	34 (18.2)	61 (18.8)
Colonoscopy				
Significant lesions				
Colonic carcinoma	6 (14.0)	7 (7.4)	5 (2.7)	18 (5.5)
Large adenomatous polyp >1.5 cm	2 (4.7)	3 (3.2)	2 (1.1)	7 (2.2)
Large inflammatory polyp >1.5 cm	0	0	3 (1.6)	3 (0.9)
Angiodysplasia	2 (4.7)	2 (2.1)	2 (1.1)	6 (1.8)
Active colitis	0	1 (1.1)	0	1 (0.3)
Colonic ulcer >1 cm	3 (7.0)	0	3 (1.6)	6 (1.8)
Insignificant lesions				
Small colonic polyp <1.5 cm	22 (51.2)	46 (48.4)	84 (44.9)	152 (46.8)
Diverticulum	5 (11.6)	19 (20.0)	38 (20.3)	62 (19.1)
Lipoma	1 (0.5)	0	0	1 (0.3)
Hemorrhoids	10 (23.3)	24 (25.3)	50 (26.7)	84 (25.8)
Small colonic ulcer <1 cm	2 (4.7)	3 (3.2)	2 (1.1)	7 (2.2)
Pseudomelanosis coli	2 (4.6)	3 (3.2)	7 (3.7)	12 (3.7)
Mild colitis	0	0	3 (1.6)	3 (0.9)

EGD = esophagogastroduodenoscopy, LA = Los Angeles
Data are shown as n (%)
* Others included esophageal papilloma, candida esophagitis, Barrett's esophagus, mild esophagitis, scleroderma esophagus, hiatal hernia or paraesophageal hernia, diverticulum and pseudomelanosis duodenii or ileii.

Table 4. Prevalence of cancers of the 325 patients

GI carcinomas	Group A (n = 43)	Group B (n = 95)	Group C (n = 187)	*p*-value
Gastric carcinoma	1 (2.3)	3 (3.2)	0	0.059
Colonic carcinoma	6 (14.0)	7 (7.4)	5 (2.7)	0.009
Total	7 (16.3)	10 (10.5)	5 (2.7)	0.001

endoscopy among the latter 2 groups were previously unknown.

The present study demonstrated significant differences in the prevalence of significant GI lesions among the 3 types of anemic patients. 63% of patients with definite IDA, 33% of anemic patients with some clinical clues of GI blood loss and 24% of anemic patients with neither confirmed IDA nor clinical clues of GI blood loss. Hemoglobin less than 9 g/dL and positive FOBT were predictors of significant lesions in patients with 'just' anemia without confirmed IDA or any clinical clue.

The prevalence of significant GI lesions in patients

Table 5. Univariate analysis of clinical characteristic associated with significant GI lesions in patients with anemia with some clinical clues of GI blood loss

Clinical characteristics	Significant lesions (n = 31)	Insignificant lesions or normal (n = 64)	Univariate analysis	
			Odds ratio (95% CI)	*p*-value
Age (years), mean (SD)	66 (13)	67 (12)	-	0.982
Gender, female	21 (67.7)	37 (57.8)	1.53 (0.63 to 3.89)	0.352
Hemoglobin level (g/dL)				
Mean (SD)	8.7 (2.1)	8.6 (2.0)	-	0.762
<9 g/dL	16 (51.6)	31 (48.4)	1.14 (0.32 to 2.10)	0.772
GI symptoms	24 (77.4)	39 (60.9)	2.20 (0.85 to 6.21)	0.111
Equivocal overt GI bleeding	8 (25.8)	22 (34.4)	0.66 (0.24 to 1.68)	0.400
Acute onset of anemia	2 (6.5)	5 (7.8)	0.57 (0.08 to 2.55)	0.498
Comorbidities				
Cardiovascular diseases	6 (19.4)	27 (42.2)	0.33 (0.11 to 0.87)	0.028
Cirrhosis	3 (9.7)	3 (4.7)	2.18 (0.38 to 12.42)	0.349
Chronic kidney disease stage 3	6 (19.4)	21 (32.8)	0.49 (0.16 to 1.32)	0.173
Gynecologic disorders	0	3 (4.7)	-	0.221
Connective tissue diseases	0	3 (4.7)	-	0.221
Hematologic disorders	1 (3.2)	4 (6.3)	0.50 (0.02 to 3.57)	0.536
Any comorbidity	15 (48.4)	42 (65.6)	0.49 (0.20 to 1.17)	0.108
Medication uses				
NSAIDs	2 (6.5)	7 (10.9)	0.56 (0.08 to 2.50)	0.484
Anti-platelets	8 (25.8)	27 (42.2)	0.48 (0.18 to 1.19)	0.121
Anti-coagulants	1 (3.2)	7 (10.9)	0.27 (0.01 to 1.63)	0.304
Ulcerogenic drugs	10 (32.3)	36 (56.3)	0.37 (0.15 to 0.89)	0.028
Proton pump inhibitors	9 (29.0)	15 (23.4)	1.34 (0.49 to 3.49)	0.556
Menopause*	17/18 (94.4)	28/30 (93.3)	1.21 (0.11 to 27.30)	0.878
Family history of colorectal cancer**	2/4 (50.0)	4/12 (33.3)	2.00 (0.18 to 22.63)	0.551
H. pylori infection***	10/29 (34.5)	16/56 (28.6)	1.32 (0.49 to 3.43)	0.575
Positive FOBT****	8/11 (72.7)	14/19 (73.7)	0.95 (0.18 to 5.64)	0.954

CI = confidence interval, FOBT = fecal occult blood test, GI = gastrointestinal, NSAIDs = non-steroidal anti-inflammatory drugs, SD = standard deviation
Data are shown as n (%) unless specified.
* Menstrual status was available in 48 patients
** Family history of colorectal cancer was available in 16 patients
*** Investigation for *H. pylori* infection was done in 85 patients
**** FOBT was done in 30 patients

with definite IDA in the present study (63%) is close to the results of many previous studies (40 to 70%)[1,3-7], including our previous study[2]. The prevalence of gastric carcinoma (2%) and colorectal carcinoma (14%) in such patients are also closed to those of previous studies (1 to 5% and 10 to 13%, respectively)[2-5]. These results confirm the role bidirectional endoscopy in patients with definite IDA.

In anemic patients with some clinical clues of GI blood loss, the prevalence for significant GI lesions was indifferent to those with unconfirmed IDA without any clinical clues of GI blood loss. In this group of patients, there has been no previous study reporting its prevalence as it may not be an appropriate indication for bidirectional endoscopy. The result of the present study suggests that bidirectional endoscopy may not be appropriate to perform on all patients with some clinical clues of GI blood loss. Although the prevalence of gastric carcinoma and colonic carcinoma in this group was 3.2% and 7.4%, respectively, these results were indifferent to patients with definite IDA. Thus, this may be controversial that bidirectional endoscopy may be beneficial in detecting cancer. Clinical predictors would be helpful in this group of anemic patients. Unfortunately, the present study could not identify any of them. Besides, the prevalence of significant GI lesion in this group in the present study may be too high which described by the higher in comorbidities and medication use in this tertiary care.

The last group is patients with unconfirmed IDA and without any clinical clues of GI blood loss. The prevalence of significant GI lesions in this group of patients (24%) was slightly higher than that of the previous study by Powell, et al (8% from EGD and 7% from barium enema or colonoscopy)[5]. The striking difference was among the significant GI lesions from EGD (16% versus 8%)[5]. The different patients' factors probable affect the results since erosive gastroduodenitis was the major upper GI lesion by EGD. Patients in our study had high rate of antiplatelet and ulcerogenic drug uses that could increase the incidence of erosive gastroduodenitis. Comorbid illnesses like

Table 6. Univariate analysis of clinical characteristic associated with significant GI lesions in patients with unconfirmed IDA and without any clinical clues of GI blood loss

Clinical characteristics	Significant lesions (n = 45)	Insignificant lesions or normal (n = 142)	Univariate analysis	
			Odds ratio (95% CI)	*p*-value
Age (years), mean (SD)	68 (12)	65 (12)	-	0.115
Gender, female	25 (55.6)	100 (70.4)	0.52 (0.26 to 1.05)	0.065
Hemoglobin level (g/dL)				
Mean (SD)	9.2 (1.7)	9.4 (1.9)	-	0.466
<9	21 (46.7)	47 (33.1)	1.77 (0.89 to 3.50)	0.099
Comorbidities				
Cardiovascular diseases	17 (37.8)	36 (25.4)	1.79 (0.87 to 3.63)	0.107
Cirrhosis	5 (11.1)	12 (8.5)	1.35 (0.41 to 3.89)	0.589
Chronic kidney disease stage 3	9 (20.0)	35 (24.6)	0.76 (0.32 to 1.69)	0.522
Gynecologic disorders	0	6 (4.2)	-	0.161
Connective tissue diseases	2 (4.4)	2 (1.4)	3.26 (0.38 to 27.80)	0.220
Hematologic disorders	2 (4.4)	14 (9.9)	0.43 (0.07 to 1.60)	0.258
Any comorbidity	28 (62.2)	78 (54.9)	1.35 (0.68 to 2.73)	0.390
Medication uses				
NSAIDs	1 (2.2)	16 (11.3)	0.18 (0.01 to 0.92)	0.066
Anti-platelets	12 (26.7)	43 (30.3)	0.84 (0.38 to 1.74)	0.643
Anti-coagulants	5 (1.1)	10 (7.0)	1.65 (0.49 to 4.93)	0.381
Ulcerogenic drugs	18 (40.0)	63 (44.4)	0.84 (0.42 to 1.64)	0.606
Proton pump inhibitors	10 (22.2)	29 (20.4)	1.11 (0.48 to 2.45)	0.796
Menopause*	19/21 (90.5)	74/86 (86.0)	1.54 (0.38 to 10.44)	0.589
Family history of colorectal cancer**	1/5 (20)	7/30 (23.3)	0.82 (0.04 to 6.80)	0.869
H. pylori infection***	11/29 (37.9)	32/123 (26.0)	1.01 (0.44 to 2.20)	0.982
Positive FOBT****	9/10 (90.0)	25/41 (61.0)	5.76 (0.95 to 111.44)	0.081

CI = confidence interval, FOBT = fecal occult blood test, GI = gastrointestinal, NSAIDs = non-steroidal anti-inflammatory drugs, SD = standard deviation
Data are shown as n (%) unless specified
* Menstrual status was available in 107 patients.
** Family history of colorectal cancer was available in 35 patients.
*** Investigation for *H. pylori* infection was done in 152 patients.
**** FOBT was done in 51 patients

cardiovascular diseases, cirrhosis and chronic kidney disease, which are well-known risks for peptic ulcer and erosive gastritis[14-19] were also prevalent in our study. Surprisingly, the present study showed that 2.7% of patients in this group had cancers, all of which were colorectal cancer (CRC). Although this CRC prevalence was higher than the usual rates of colorectal cancer detected by screening colonoscopy in average-risk persons (1 to 2%)[20,21], it was not very outrageous because the rate of CRC as high as 3.4% in CRC screening study had also been reported[22]. The mean age of the patients in this group was 66 years, which was higher than most studies (57 to 59 years)[20-22], hence might affect the rate of CRC[23,24]. We explored the 5 CRC detected in this group and found that all had large T3 tumors and hemoglobin below 9 g/dL (data not shown). We suspected that if all these 5 patients had iron study done, they would definitely have had IDA. Thus, the role of endoscopy in this group of patients might be equivalent to CRC screening. Taken together, patients with unconfirmed IDA and without any clinical clue of GI blood loss are not candidates for bidirectional endoscopy, but rather for colonoscopy for CRC screening if the patients' age reach 50 years. EGD added little benefit because it detected only gastroduodenitis and there was no gastric cancer.

The present study demonstrated the only one predictor for the detection of significant GI lesion in the patients with unconfirmed IDA without any clinical clue of GI blood loss, hemoglobin level less than 9 g/dL, which was similarly identified in some previous studies[11,25]. Positive FOBT showed highly suggestive trend for significant GI lesion (OR 11 and *p*-value = 0.052) but it was not statistically significant by multivariate analysis due to the insufficient number of samples to show the difference. Positive FOBT might have some benefit since all patients whose colonic cancers were detected, demonstrated hemoglobin level less than 9 g/dL, one showed positive FOBT, but unfortunately the other four did not perform FOBT. These two factors may not be strong enough to prompt a decision to perform bidirectional endoscopy in patients with unconfirmed IDA without any clinical clue of GI blood loss; notwithstanding, they could only suggest that patient with hemoglobin less than 9 g/dL may have more benefit from a GI evaluation than

those with hemoglobin more than 9 g/dL.

There are some controversial issues on the definitions of IDA and significant GI lesions which are accountable to being a cause for anemia. For IDA in the present study, the authors used the definition of IDA by iron study together with well-accepted criteria from the hematologist by ferritin level and peripheral blood smear. For significant GI lesions, the authors used a well-established definition by Rockey et al[3] together with other lesions on which at least two GI experts agreed that they could cause anemia.

The limitations of the present study were the facts of retrospective chart review. Some additional clinical presentations might be present without record. Furthermore, the present study was conducted in tertiary center so the results may be different from other hospitals and make it difficult to generalize the results. Last, there were no data on small bowel investigation (e.g. capsule endoscopy) in patients with negative bidirectional endoscopy.

Conclusion

The prevalence of significant GI lesions by bidirectional endoscopy in patients with definite IDA, anemia with some clinical clues of GI blood loss, and unconfirmed IDA without any clinical clue of GI blood loss were 63%, 33% and 24%, respectively. Erosive gastroduodenitis was the most common, significant upper GI lesion and CRC was the most common, significant lower GI lesions in all groups. Patients with definite IDA should undoubtedly undergo bidirectional endoscopy. Patients with anemia and some clinical clues of GI blood loss had the prevalence of significant GI lesions and cancers in the middle, thus the decision to perform endoscopy is reasonable. GI evaluation for anemic patients without definite diagnosis for IDA is not advised except for CRC screening in average-risk individuals.

What is already known on this topic?

Gastrointestinal evaluation by EGD and colonoscopy is recommended in patients with unexplained definite IDA.

What this study adds?

Patients with anemia and some clinical clues of GI blood loss had lower, but unignorably significant GI lesions, than definite IDA patients. GI evaluation for anemic patients without confirmation of IDA and no clinical clues had low diagnostic yield, of which were mostly gastroduodenitis and CRC that were similar to CRC screening.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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