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Long-Term Outcomes and Prognostic Factors for Patients with Endoscopy-Negative Iron Deficiency

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Abstract

Background and Aim—Iron deficiency anemia (IDA) is a common problem among the elderly, and often no cause is identified after routine upper endoscopy and colonoscopy exams. The purpose of this study was to determine the long-term outcomes and predictors of gastrointestinal pathology and death in patients with endoscopy-negative IDA.

Methods—This was a retrospective review of consecutive endoscopy negative-IDA patients during 2002–2004 at the VA San Diego Healthcare System.

Results—Mean age was 69.3 years (range 42–93), and included 105 men and nine women. Mean length of follow-up was 65.1 months. IDA resolved in 56 patients. None of these patients developed evidence of any clinically significant gastrointestinal pathology. The remaining 58 patients had persistent anemia ($n = 47$) or recurrent anemia ($n = 11$). Only 2/47 patients with persistent anemia were found to have clinically significant but benign gastrointestinal pathology during follow-up. In contrast, 6/11 patients with recurrent anemia were subsequently found to have gastrointestinal pathology. Deaths during follow-up occurred in 7 (12.5 %) patients with resolved anemia, compared with 20 (34.5 %) patients with recurrent or persistent anemia ($p = 0.006$). Significant independent predictors of death included persistent or recurrent anemia, anti-platelet or anticoagulant use, and congestive heart failure.

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Conflict of interest None.

Conclusions—Patients with iron deficiency anemia and negative upper endoscopy and colonoscopy often have a favorable outcome, especially if the anemia resolves with treatment. In patients with recurrent anemia a malignancy within reach of standard endoscopy and colonoscopy are possible, and repeating these procedures is warranted before consideration of further investigations.

Keywords

Iron deficiency anemia; Colonoscopy; Endoscopy; Colorectal cancer

Introduction

Iron deficiency anemia (IDA) is a common problem among the elderly, and in the developed world it is commonly a result of gastrointestinal blood loss in adult men and postmenopausal women [1, 2]. Patients are often referred for endoscopic evaluation, however, in 10–41 % of patients no clear cause of their anemia is identified [1–4]. The cause of iron deficiency in patients with a negative endoscopic evaluation may be related to dietary deficiencies, malabsorption, or unidentified small intestinal lesions; or it may be multifactorial and related to any of these causes with or without concomitant anemia of chronic disease due to other comorbid disease. The concern for these patients is that a clinically significant lesion in the gastrointestinal track may have been missed by the initial examinations or present in the small bowel, which may not be routinely examined.

Currently, there are few guidelines for the evaluation and management of IDA. One guideline from the British Society of Gastroenterology recommends that all male patients and postmenopausal females with IDA should undergo an upper endoscopy and colonic assessment [5]. In addition, rectal examination, urine testing and screening for celiac disease should be performed. If these tests are negative, then iron stores should be replete and hemoglobin checked every 3 months for one year, then again after a year. Small bowel evaluation is not recommended unless the patient becomes transfusion-dependent or has overt gastrointestinal bleeding. There are only a few studies examining the long-term outcomes of asymptomatic patients with IDA and negative initial endoscopic evaluation [6–8], and only one of these studies included patients that received colonoscopy as part of the initial evaluation. The risk factors for recurrent or persistent IDA as well as the long-term clinical consequences of these conditions are unknown. These data are needed to inform how aggressive further work-up should be in those who have no source of GI blood loss identified after initial evaluation. Further data would be helpful to answer the question of whether one should undergo repeat endoscopy and/or small bowel investigation versus only treatment with iron replacement and observation.

The Veterans Health Administration (VHA) is the largest integrated healthcare provider in the United States, serving almost 5.5 million patients in 2008 [9]. Many VHA patients are elderly and have more comorbidities than the general population [10]. The objective of this study was to follow a cohort of patients in a VHA population, with documented IDA, who have had initial negative upper and lower GI investigations in order to determine long-term

clinical outcomes, and to identify risk factors for those with recurrent or persistent IDA and/or significant GI pathology.

Materials and Methods

Patients who underwent both an upper endoscopy and colonoscopy for IDA during calendar years 2002 and 2004 at the VA San Diego Healthcare System in San Diego, CA were identified retrospectively with the VA electronic medical record system. Anemia was defined as hemoglobin less than 13 g/dL or hematocrit less than 40 % in men, and hemoglobin less than 12 g/dL or hematocrit less than 35 % in women. Iron deficiency is confirmed if serum ferritin is less than 15 ng/mL or iron/total iron-binding capacity ratio less than 15 %. Clinical and demographic data were collected for all patients. Patients were excluded if they were found to have a definite cause for their anemia found on the initial esophagogastroduodenoscopy (EGD) and colonoscopy (peptic ulcer disease, gastric resection, severe erosive esophagitis or gastritis, all malignant neoplasms, polyps $\geq$ 1 cm, colitis/inflammatory bowel disease, angiodysplasia, and celiac disease).

Results for all endoscopic or radiological procedures, comorbidities, medications at presentation, iron therapy, transfusions, results of further GI investigations, including small bowel examinations and repeat endoscopies, and detection of significant GI pathology if any, were collected by chart review. Hemoglobin values were followed subsequent to the index endoscopy exams, and patients were categorized into three groups: *resolved anemia* if subsequent hemoglobin tests became normal; *persistent anemia* if subsequent hemoglobin values remained in the anemic range; or *recurrent anemia* if subsequent hemoglobin values became normal transiently and then declined.

Disease groups were compared on demographic and clinical variables at baseline using *t* tests for means and chi-square/Fisher's exact tests for proportions. Univariate and multivariate analyses were conducted using SPSS (IBM Corporation, Armonk, NY). The study was approved by the Institutional Human Research Protections Program and the Research and Development Committee.

Results

One hundred fourteen patients who had negative upper endoscopy and colonoscopy for the evaluation of IDA were identified. Basic demographics are presented in Table 1. The mean age was 69.3 years at presentation (range 42–93), and included 105 men (92.1 %) and 9 women (7.9 %). The length of follow-up ranged from 1 to 96 months with a mean of 65.1 months. Celiac disease was excluded in 72 patients by duodenal histology. At presentation, 77 patients were on aspirin and/or NSAID therapy, four patients were on warfarin and three were on clopidogrel. There were three patients who were on both aspirin and clopidogrel, and one was on both aspirin and warfarin. Hematocrit ranged from 14.8 to 40 % with a mean of 31.6 % at initial evaluation. Median ferritin level at initial evaluation was 11 ng/mL, and median iron/total iron-binding capacity ratio was 7.4 %.

Significant differences ($p < 0.05$) of basic demographics between the group of patients with resolved anemia versus persistent/recurrent anemia are presented in Table 1. Compared with

patients with resolved anemia, those who had persistent or recurrent anemia were older, had more FOBT positive tests on presentation, lower baseline iron, required more transfusions, and more frequently underwent repeat endoscopy. Patients with persistent/recurrent anemia also had significantly more diabetes, coronary artery disease, malignancies, subsequent GI pathology, and deaths. Patients with persistent anemia were more likely to have significant comorbidities, such as chronic renal disease, diabetes, coronary artery disease, CHF, and COPD, compared to patients with either resolved or recurrent anemia. Patients with recurrent anemia were significantly more likely to have follow-up endoscopy and significant GI pathology demonstrated than patients with persistent anemia ($p = 0.001$, Table 1).

After the initial negative EGD and colonoscopy, 30 patients (26 %) underwent subsequent small bowel follow-through series, 9 (7.9 %) underwent capsule studies, and 21 (18.4 %) underwent repeat EGD or colonoscopy during the follow-up period. Subsequent endoscopies were done for various reasons, including recurrent anemia or the development of symptoms, such as GI bleeding, early satiety, or weight loss. The findings of subsequent endoscopies in these patients are indicated in Table 2. Because of the retrospective nature of this study, there was no standardized method for exclusion of celiac sprue. The majority of patients received duodenal biopsies to exclude sprue, and of 43 patients without biopsies, seven had serologic tests for celiac disease that were negative. A total of 31 % of patients were not tested for celiac disease; however, throughout the period of follow-up no clinical diagnosis of celiac disease was made.

The iron deficiency anemia resolved in 56 patients (49.1 %). Of this group, three underwent capsule studies, and aside from one patient who had duodenitis found on capsule, the rest were normal studies. Three underwent repeat endoscopy, which were negative. Over an average follow-up period of 69.5 months, none of these patients developed evidence of any clinically significant gastrointestinal pathology. The remaining 58 (50.9 %) patients had persistent anemia ($n = 47$) or recurrent anemia ($n = 11$). Only eight out of 47 of the patients with persistent anemia subsequently had repeat EGD and/or colonoscopy, and no significant lesions were found. In the persistent anemia group three patients underwent capsule studies, and one patient was found to have small bowel angioma, while the other capsule studies were negative. Over an average period of 60.4 months of follow up, only 2/47 (4.3 %) were found to have gastrointestinal pathology. These included one patient with the small bowel angioma and one with a gastric ulcer.

Of 11 patients with recurrent anemia, three required blood transfusions, and all underwent repeat EGD or colonoscopy. In the recurrent anemia group, 6/11 (54 %) were subsequently found to have gastrointestinal pathology, and it included one patient with duodenal cancer, two with colorectal cancer, two with gastric ulcers, and one with gastric angiodysplasia. The three patients who were subsequently found to have GI malignancy (small bowel and colorectal cancers) did not have other significant comorbidities aside from hypertension. These patients did not require blood transfusions. Their ferritin levels were less than 12, and iron saturation was less than 5 % at the time of initial evaluation.

Current guidelines recommend small bowel investigation if the patient becomes transfusion-dependent or had recurrent symptoms [5]. In our study, eight patients became transfusion-

dependent. Five of these patients underwent SBFT, which were all normal. Two patients underwent capsule endoscopy, with one patient found to have small bowel angiodysplasia. In all, a total of 30 patients in our study underwent SBFT, which were all normal, and nine patients underwent capsule endoscopy; only two with significant findings: one patient with duodenitis and one patient with small bowel angiodysplasia.

During follow-up, there were 27 deaths (23.7 %) overall. The causes of death included the following: anoxic brain injury ($n = 1$), dementia ($n = 2$), myocardial infarction ($n = 1$), complications of CHF ($n = 5$), acute cardiac arrest ($n = 2$), massive pulmonary embolus ($n = 1$), severe COPD ($n = 1$), sepsis of unclear source. ($n = 2$), pneumonia ($n = 1$), advanced metastatic prostate cancer ($n = 1$), and metastatic hepatocellular carcinoma ($n = 1$). Of the three patients who were subsequently found to have GI malignancy, two were placed on hospice for metastatic disease from colorectal and duodenal adenocarcinoma, while the remaining patient with colorectal cancer remains alive during the period of follow-up. The cause of death was unclear in seven patients; however, there was no indication of malignancy or gastrointestinal bleeding in the immediate history prior to death.

Multivariate and univariate logistic regression analyses with p value < 0.05 were performed for predictors of death (Tables 3, 4). Univariate predictors of death that were significant include anti-platelet or anticoagulant use, CHF, COPD, persistent or recurrent anemia. In the multivariate analysis independent predictors of death included anti-platelet or anticoagulant use, CHF, and persistent or recurrent anemia.

Discussion

Iron deficiency anemia (IDA) is a problem commonly found in elderly patients. In 10–41 % of patients, no clear etiology of IDA can be found. The cause may have been missed at the initial endoscopy or colonoscopy, located in the small bowel, or related to underlying chronic comorbidities. Providers often recommend that these patients undergo further evaluation with small bowel studies, such as small bowel follow-through, small bowel enteroscopy, and capsule endoscopy. In the literature to date, only three studies have followed the long-term outcome of patients with negative upper and lower GI evaluations for IDA. Two of these studies included patients who received a barium enema rather than colonoscopy as part of the initial evaluation of IDA. Sahay and Scott followed 83 patients (31 male, 62 female, mean age 61 years) in the United Kingdom for a mean of 6 years, who had negative evaluations with upper endoscopy, small bowel biopsy and barium enemas [6]. Over the course of follow-up, possible causes for anemia were found in 17 patients, including NSAIDs use, menstruation, gastrectomy, and poor nutrition. No other causes of anemia were found in the other patients. McLoughlin and Tham followed 69 patients (54 female, 15 male, mean age 65.8 years) in South Australia for a median of 5 years and 10 months, all of whom had negative EGD and negative lower GI evaluation (4 patients had colonoscopy, 58 had barium enema, 7 had barium enema with sigmoidoscopy) [8]. In 57 patients (83 %), the IDA resolved. Twelve patients developed persistent anemia, among which six required long-term iron or blood transfusions. Seventeen patients had transient recurrence of anemia. Two patients who previously had a barium enema were found to have colorectal malignancies during 9–91 months of follow-up. One patient was diagnosed with

gastric cancer 42 months after initial examination, and one patient was diagnosed with a small bowel adenocarcinoma that was successfully treated with surgery 13 months after first presentation. Hence, these data emphasize the importance of using colonoscopy for evaluation of patients with iron deficiency rather than barium enema and follow-up studies in patients who do not have resolution of anemia. Gordon et al. [7] followed 69 patients (43 male, 26 female, mean age 68 years) for a mean of 39 months, who had initial negative colonoscopy, EGD or upper GI series. Additionally, some patients went on to have small bowel follow-through series and small bowel biopsies. In 49 patients (71 %), the IDA resolved. Recurrence of anemia occurred in five patients, in whom subsequent GI evaluations were performed and found negative, and whose anemia subsequently resolved with iron supplementation. Only one patient was identified to have anemia because of a GI source (duodenal angioectasia), and no other GI pathologies were found. The overall results were felt to be generally favorable, and they recommended that further GI evaluations should be reserved for those whose anemia is refractory to iron replacement or those who do not have co-concomitant conditions that may contribute to anemia of chronic disease.

Our study is comprised of an elderly Veteran, primarily male cohort, and is the largest study to date. The purpose of this study was to document long-term follow-up in patients with endoscopic-negative iron deficiency in routine clinical practice. A minority of patients had endoscopic follow-up after initial endoscopies, and hence a long-term follow-up is used to determine if any significant gastrointestinal pathology would manifest over time. Of the 114 patients in our study, IDA resolved in 56 (49.1 %) patients. This is lower compared to the prior studies by Gordon et al. and McLoughlin and Tham, at 71 and 83 %, respectively. It is unclear why this is so, but one might consider the multiple medical comorbidities of the Veteran population, or medication compliance issues as factors. These 56 patients in general had a favorable outcome, and their IDA resolved with iron supplementation and did not recur during the follow-up period. None of these patients were found to develop any significant gastrointestinal pathology or malignancy over a mean follow-up of 69.5 months. In contrast, 58 (50.9 %) patients had a persistent or recurrent anemia. Patients with persistent or recurrent anemia were more likely to be older, have lower baseline iron and transfusion requirements, and have underlying comorbid diseases such as chronic renal disease, diabetes, coronary artery disease, COPD, and malignancy. Interestingly, patients with recurrent IDA during follow-up were significantly more likely to have GI pathology compared with patients with persistent IDA. There were no other significant predictors of GI pathology on follow-up. Deaths during follow-up occurred in 7 (12.5 %) patients with resolved anemia, compared with 20 (34.5 %) patients with recurrent or persistent anemia ($p = 0.006$). The overall mortality rate was 23.7 % in our study, which was higher than the McLoughlin and Tham [9] study (22 %), and lower than the Gordon et al. [8] study (39 %). This significant mortality rate is likely a reflection of the underlying chronic medical conditions that are present in our elderly Veteran population. Significant predictors of death on univariate analysis of death in our study include antiplatelet or anticoagulant use, CHF, COPD, and persistent or recurrence of anemia. Multivariate analysis indicated that antiplatelet or anticoagulation use, CHF, and persistent or recurrent anemia were independent predictors of death in follow-up. These data indicate that comorbidities likely contribute to worsening anemia over time and contribute to increased mortality risk.

Three patients with recurrent anemia were later diagnosed with a GI malignancy in the follow-up period, one with duodenal cancer and two with cecal cancer. All of these were within reach of standard endoscopy and colonoscopy, and developed in patients with prior negative endoscopic studies. Of the patients with subsequent GI pathology, the patient with the duodenal cancer was diagnosed 5 years after an essentially normal EGD, and is most likely unrelated to the initial episode of IDA. He had not previously undergone other small bowel investigations such as small bowel follow-through or capsule study. He had a repeat EGD after new anemia was noted and he developed symptoms of hematochezia. Two patients were found to have cecal adenocarcinomas, one within 19 months of initial investigations, and one within 5 years of initial investigations. The former patient had a negative colonoscopy, although noted to have poor prep. It is possible that had the patient had an earlier repeat colonoscopy given his poor prep, that the tumor would have been diagnosed earlier. The latter patient was found to have four diminutive tubular adenomas on the initial colonoscopy (deemed not significant enough to cause the degree of his IDA at the time). He was found on the routine repeat colonoscopy 4 years later to have a cecal tubulovillous polyp with adenocarcinoma, which was resected. These findings reflect the known limitations of colonoscopic exams especially for detection of right-sided lesions, and with recent attention to proper colonoscopic technique [11, 12] and implementation of improved “split” colon preps [13], the error rate of future colonoscopies may be lower.

Of note, long-term follow-up of patients reported by McLoughlin and Tham included patients who were found to have colon cancer despite previous negative barium enema exams [8]. These data suggest that high quality endoscopic exams are needed for evaluation of patients with IDA, and that if anemia re-occurs the patients should be evaluated with repeat endoscopy and colonoscopy before considering other diagnostic modalities. Overall our group of patients with persistent anemia on average had a lower baseline iron, required more transfusions, and had more concomitant medical conditions such as chronic kidney disease, diabetes, coronary artery disease, and COPD. These comorbidities likely contributed to anemia of chronic disease, which persisted once iron stores were replaced. The group of patients with recurrent anemia was significantly more likely to have significant GI pathology demonstrated as a cause of the recurrent anemia. A more rigorous study design to examine the adequacy of endoscopy in IDA would be to prospectively repeat these procedures in all patients with endoscopy-negative iron deficiency, with special attention to adequate technique, including the possible use of side-viewing duodendoscopes to visualize the medial side of the duodenum. Our data suggests that the yield of this protocol would be small and limited to patients with persistent or recurrent anemia.

In patients with IDA, small bowel investigations may be considered after upper and lower endoscopic investigations do not reveal a possible bleeding lesion. In our study, routine small intestinal examinations were not performed in all patients, but no cases of small intestinal malignancy occurred beyond the reach of standard endoscopic exams over an average follow-up of 65.1 months. Combining the results of the present study and the three prior series of endoscopy negative IDA reported to date [6–8] (total $n = 335$), only one patient (0.2 %) was found to have a small intestinal malignancy unreachable by standard endoscopy during the follow-up time periods [8]. These data call into question the routine

use of small bowel imaging or capsule studies for evaluation of the small intestine of patients with IDA without documented occult (guaiac positive) or overt GI bleeding who have had negative high quality endoscopic studies. Previous studies have shown that the diagnostic yield of small bowel contrast studies for IDA, such as small bowel follow-through (SBFT) and enteroclysis, are low, 0–6.5 % [1, 4] and 0–21 % [2, 14], respectively. Small intestinal capsule endoscopy provides a higher yield of possible causes of iron deficiency. In one study, the diagnostic yield of wireless capsule endoscopy in patients with unexplained IDA was shown to be 57 % [15]. In another study, the diagnostic yield of significant capsule findings was 37 % in patients referred for IDA, and in the majority of the patients, their anemia had resolved during the follow-up period [16]. The large majority of lesions diagnosed by capsule endoscopy are angiodysplasia or benign erosions and ulcerations, and treatment of these lesions has not been shown to be necessary for asymptomatic iron deficiency patients. Apostolopoulos et al. and Sheibani et al. reported the diagnosis by capsule endoscopy of small bowel tumors in 2/51 (3.9 %) and 0/57 patients in their series of patients with endoscopy negative iron deficiency, respectively. In the former study the small bowel tumors were also demonstrated in both patients by enteroclysis. Recently, Milano et al. reported on the findings of routine capsule endoscopy and CT enteroclysis in 45 patients (mean age 55 years) with endoscopy negative IDA in a referral academic center in Chieti, Italy [17]. They found neoplasms in five (11.1 %) patients, with an equal diagnostic accuracy for capsule endoscopy vs. CT-enteroclysis. This was a young referral cohort, and they did not report the clinical characteristics (presence of symptoms, degree of anemia, clinical bleeding) or long-term outcomes of these patients; hence, applicability to the current series is unknown. Ateriovenous malformations and other benign lesions were the most common findings, and a possible etiology was found in 37/45 patients using both capsule endoscopy and enteroclysis. Therefore, to date there are little data to support routine use of small bowel imaging for evaluation of endoscopy negative IDA in elderly patients without occult or overt GI bleeding or other alarm symptoms.

In conclusion, our study supports and extends the findings of prior studies that the majority of elderly patients with IDA who have negative high quality upper endoscopy and colonoscopy generally have a favorable outcome, especially if the anemia resolves with treatment. Those with persistent stable anemia despite negative initial investigations frequently have multiple concomitant chronic medical conditions. In patients with recurrent anemia a malignancy within reach of standard endoscopy and colonoscopy is possible, and repeat of these procedures in a setting of high quality (with consideration of side viewing duodenoscopy also) is warranted. The overall data, to date, appear to support prior guidelines [5], and in this older population with multiple comorbid diseases, reserving small bowel studies for those patients with severe or transfusion-dependent anemia or documented occult (guaiac positive) or overt GI bleeding.

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References

1. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med*. 1993; 329:1691–1695. [PubMed: 8179652]
2. Kepczyk MT, Kadakia CS. Prospective evaluation of gastrointestinal tract in patients with iron deficiency anemia. *Dig Dis Sci*. 1995; 40:1283–1289. [PubMed: 7781448]
3. McIntyre AS, Long RG. Prospective survey of investigations in outpatients referred with iron deficiency anaemia. *Gut*. 1993; 34:1102–1107. [PubMed: 8174963]
4. Gordon SR, Smith RE, Power GC. The role of endoscopy in the evaluation of iron deficiency anemia in patients over the age of 50. *Am J Gastroenterol*. 1994; 89:1963–1967. [PubMed: 7942718]
5. Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. *Gut*. 2000; 46:IV1–IV5. [PubMed: 10862605]
6. Sahay R, Scott BB. Iron deficiency anaemia—how far to investigate? *Gut*. 1993; 34:1427–1428. [PubMed: 8244114]
7. Gordon S, Bensen S, Smith R. Long-term follow-up of older patients with iron deficiency anemia after a negative GI evaluation. *Am J Gastroenterol*. 1996; 91:885–889. [PubMed: 8633576]
8. McLoughlin MT, Tham TC. Long-term follow-up of patients with iron deficiency anaemia after a negative gastrointestinal evaluation. *Eur J Gastroenterol Hepatol*. 2009; 21:872–876. [PubMed: 19282769]
9. Chao HH, Schwartz AR, Hersh J, et al. Improving colorectal cancer screening and care in the Veterans Affairs Healthcare system. *Clin Colorectal Cancer*. 2009; 8:22–28. [PubMed: 19203893]
10. Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at veterans affairs medical centers sicker? A comparative analysis of health status and medical resource use. *Arch Intern Med*. 2000; 160:3252–3257. [PubMed: 11088086]
11. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med*. 2010; 362:1795–1803. [PubMed: 20463339]
12. Lee RH, Tang RS, Muthusamy VR, et al. Quality of colonoscopy withdrawal technique and variability in adenoma detection rates (with videos). *Gastrointest Endosc*. 2011; 74:128–134. [PubMed: 21531410]
13. Kilgore TW, Abdinoor AA, Szary NM, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc*. 2011; 73:1240–1245. [PubMed: 21628016]
14. Moch A, Herlinger H, Kochman ML, et al. Enteroclysis in the evaluation of obscure gastrointestinal bleeding. *AJR Am J Roentgenol*. 1994; 163:1381–1384. [PubMed: 7992733]
15. Apostolopoulos P, Liatsos C, Gralnek IM, et al. The role of wireless capsule endoscopy in investigating unexplained iron deficiency anemia after negative endoscopic evaluation of the upper and lower gastrointestinal tract. *Endoscopy*. 2006; 38:1127–1132. [PubMed: 17111335]
16. Sheibani S, Levesque BG, Friedland S, et al. Long-term impact of capsule endoscopy in patients referred for iron-deficiency anemia. *Dig Dis Sci*. 2010; 55:703–708. [PubMed: 19941072]
17. Milano A, Balatsinou C, Filippone A, et al. A prospective evaluation of iron deficiency anemia in the GI endoscopy setting: role of standard endoscopy, videocapsule endoscopy, and CT-enteroclysis. *Gastrointest Endosc*. 2011; 73:1002–1008. [PubMed: 21396638]

Table 1

Demographics for all patients, patients with resolved anemia, and patients with persistent or recurrent anemia

Demographic	All patients	Resolved anemia	Persistent or recurrent anemia	<i>p</i> value vs. persistent/recurrent anemia	Recurrent anemia	Persistent anemia	<i>p</i> value
Total, <i>N</i>	114	56	58		11	47	
Age, years $\pm$ SD	69.3 $\pm$ 10.8	66.7 $\pm$ 11.3	71.9 $\pm$ 9.9	0.010	70.1 $\pm$ 10.3	72.3 $\pm$ 9.8	0.513
Sex, <i>N</i> (%)							
Male	105 (92.1)	49 (87.5)	56 (96.6)	0.091	11 (100)	45 (95.7)	0.654
Female	9 (7.9)	7 (12.5)	2 (3.4)		0 (0)	2 (4.3)	
Follow-up, months $\pm$ SD	65.1 $\pm$ 23.7	69.5 $\pm$ 18.9	60.9 $\pm$ 27.1	0.053	63.2 $\pm$ 24.5	60.4 $\pm$ 27.9	0.759
Hct, mean $\pm$ SD	31.6 $\pm$ 5.0	32.5 $\pm$ 5.2	30.8 $\pm$ 4.7	0.065	30.5 $\pm$ 4.9	30.8 $\pm$ 4.7	0.860
FOBT positive, <i>N</i> (%)	16 (14.0)	2 (3.6)	14 (24.1)	0.002	4 (36.4)	10 (21.3)	0.433
Baseline iron, mean $\pm$ SD	33.4 $\pm$ 21.4	37.7 $\pm$ 25.0	29.4 $\pm$ 16.5	0.040	22.5 $\pm$ 8.0	31.0 $\pm$ 17.6	0.021
Ever required transfusion, <i>N</i> (%)	15 (13.2)	3 (5.4)	12 (20.7)	0.024	3 (27.3)	9 (19.1)	0.681
Repeat endoscopy, <i>N</i> (%)	22 (19.3)	3 (5.4)	19 (32.8)	0.001	11 (100.0)	8 (17.0)	0.001
Capsule endoscopy, <i>N</i> (%)	9 (7.9)	3 (5.4)	6 (10.3)	0.490	3 (27.3)	3 (6.4)	0.075
Aspirin or NSAID use, <i>N</i> (%)	77 (67.5)	37 (66.1)	40 (69.0)	0.741	10 (90.9)	30 (63.8)	0.146
Antiplatelet or anticoagulant use, <i>N</i> (%)	7 (6.1)	2 (3.6)	5 (8.6)	0.439	1 (9.1)	4 (8.5)	0.665
Ever smoker, <i>N</i> (%)	73 (64.0)	35 (62.5)	38 (65.5)	0.951	6 (54.5)	32 (68.1)	0.305
Ever drinker, <i>N</i> (%)	60 (52.6)	29 (51.8)	31 (53.4)	0.796	8 (72.7)	23 (48.9)	0.200
Hepatitis, <i>N</i> (%)	13 (11.4)	9 (16.1)	4 (6.9)	0.149	1 (9.1)	3 (6.4)	0.580
Chronic kidney disease, <i>N</i> (%)	17 (14.9)	3 (5.4)	14 (24.1)	0.007	1 (9.1)	13 (27.7)	0.265
HTN, <i>N</i> (%)	78 (68.4)	35 (62.5)	43 (74.1)	0.181	10 (90.9)	33 (70.2)	0.257
Diabetes, <i>N</i> (%)	37 (32.5)	13 (23.2)	24 (41.4)	0.038	4 (36.4)	20 (42.6)	0.491
Coronary artery disease, <i>N</i> (%)	28 (24.6)	7 (12.5)	21 (36.2)	0.003	2 (18.2)	19 (40.4)	0.185
CHF, <i>N</i> (%)	10 (8.8)	2 (3.6)	8 (13.8)	0.094	1 (9.1)	7 (14.9)	0.525
COPD, <i>N</i> (%)	25 (21.9)	8 (14.3)	17 (29.3)	0.053	0 (0.0)	17 (36.2)	0.024
Malignancy, <i>N</i> (%)	25 (21.9)	5 (8.9)	20 (34.5)	0.001	5 (45.5)	15 (31.9)	0.487
GI pathology found, <i>N</i> (%)	8 (7.0)	0 (0.0)	8 (13.8)	0.006	6 (54.5)	2 (4.3)	0.001
Death, <i>N</i> (%)	27 (23.7)	7 (12.5)	20 (34.5)	0.006	5 (45.5)	15 (31.9)	0.487

p values are listed for significant differences between the resolved anemia group and the group of patients with persistent or recurrent anemia. *T* test was used for means and chi-square/Fisher's exact tests for proportions

Table 2

Findings in 21 patients with repeat endoscopic procedures over time following initial negative endoscopies for cause of iron deficiency

Patient #	Gender/ age	Anemia resolved, persistent, recurrent	Findings at first subsequent endoscopic procedure	Days between initial and subsequent procedures
39	M/87	Persistent	EGD: normal; colonoscopy: normal	556
68	M/62	Persistent	EGD: normal; colonoscopy: normal	414
73	M/60	Persistent	EGD: Barrett's esophagus; colonoscopy: normal	546
83	M/69	Recurrent	EGD: bleeding gastric ulcer ^a	1,393
41	M/69	Recurrent	EGD: hiatal hernia; colonoscopy: diverticulosis	135
43	M/63	Recurrent	EGD: hiatal hernia; colonoscopy: diverticulosis; enteroscopy: normal	67
51	M/71	Recurrent	EGD: hyperplastic polyp; colonoscopy: normal EGD: esophagitis, gastric ulcers ^a	441 1,171
59	M/59	Recurrent	EGD: gastropathy ^a	463
64	M/62	Recurrent	EGD: normal; capsule: normal	1,204
37	M/76	Recurrent	Colonoscopy: normal EGD: normal; colonoscopy: cecal adenoma ^a	57 555
86	M/59	Recurrent	EGD: duodenal adenocarcinoma ^a	1,765
92	M/87	Recurrent	Colonoscopy: cecal tubulovillous polyp with adenocarcinoma ^a	1,483
96	M/81	Recurrent	EGD: normal EGD: gastric ulcer and one AVM ^a	35 445
111	M/61	Recurrent	EGD: small gastric ulcer ^a	29
58	M/63	Persistent	EGD: mild antral gastritis; colonoscopy normal	212
61	M/66	Persistent	EGD: new Mallory-Weiss tear	179
3	M/63	Persistent	EGD: hiatal hernia; colonoscopy: diverticulosis	2,463
12	M/61	Resolved	EGD: hiatal hernia; colonoscopy: diverticulosis	1,023
15	M/63	Persistent	Colonoscopy: normal	1,527
18	M/84	Resolved	Colonoscopy: diverticulosis and hyperplast polyps	1,297
106	M/63	Resolved	EGD: normal; colonoscopy: normal	120

^aSignificant GI pathology

Table 3

Univariate predictors of death

Predictor	OR	95 % CI	<i>p</i> value
Age	1.040	0.99–1.08	0.060
Hct < 30	1.705	0.695–4.182	0.244
Aspirin or NSAID use	1.187	0.464–3.036	0.720
Anti-platelet or anticoagulant use	9.659	1.755–53.166	0.009
Current or past smoker	1.025	0.393–2.669	0.960
Current or past drinker	0.607	0.250–1.475	0.270
Hepatitis	2.244	0.667–7.550	0.192
CKD	1.420	0.451–4.470	0.548
HTN	1.842	0.671–5.054	0.235
DM	1.613	0.659–3.945	0.295
CAD	2.222	0.870–5.678	0.095
CHF	5.929	1.533–22.931	0.010
COPD	3.585	1.376–9.337	0.009
Malignancy	1.023	0.361–2.893	0.966
Persistent or recurrent anemia	3.684	1.412–9.616	0.008
Persistent	3.281	1.205–8.934	0.020
Recurrent	5.833	1.400–24.297	0.015
Required transfusion	2.476	0.792–7.741	0.119
Repeat endoscopy	1.680	0.603–4.682	0.321
GI pathology found	2.050	0.457–9.205	0.349

OR odds ratio, *CI* confidence interval

Values in bold are statistically significant

Table 4

Multivariate analysis for predictors of death, including univariate predictors with p value <0.10 (age, anti-platelet or anticoagulant use, CAD, CHF, COPD, persistent/recurrent anemia)

Predictor	OR	95 % CI	p value
Anti-platelet or anticoagulant use	9.133	1.503–55.506	0.016
CHF	4.738	1.121–20.024	0.034
Persistent or recurrent anemia	3.088	1.118–8.532	0.030

OR odds ratio, CI confidence interval

Values in bold are statistically significant