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# Predictors of Colorectal Cancer in Patients Referred to a Gastroenterologist for Iron Deficiency

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**Abstract :**

**Background**: Iron deficiency is a common reason for referral to a gastroenterologist.

**Objective:** To identify predictors of colorectal cancer in patients referred to a gastroenterologist for iron deficiency.

**Methods**: This was a retrospective review of consecutive patients referred to one of two gastroenterologists for assessment of iron deficiency. The office files and electronic health records were reviewed for all patients. Clinical data, such as hemoglobin level, and clinical symptoms were recorded. The final diagnosis was that of the attending gastroenterologist. Variables associated with a diagnosis of colorectal cancer by univariate analysis were entered into a multivariate logistic regression model to identify variables independently associated with the diagnosis of colorectal cancer.

**Results:** Two hundred and seventy eight patients were included in this study. One hundred and fifty-eight (56.8%) were female. Mean age was 60.7 years (☐ 16.7 years). The most common causes of iron deficiency were: menorrhagia 16.2%, colorectal cancer 14%, use of aspirin or non-steroidal agents 11.2% and regular blood donation 7.2%. In 11.5% of patients, no cause was found. In univariate analysis, lower hemoglobin, greater age, shorter duration of iron deficiency, weight loss, symptoms from anemia and NSAID use were associated with colorectal cancer. In multivariate analysis, only older age (OR=1.06; 95% CI 1.04-1.09) and symptoms from anemia (OR=2.19; 95% CI 1.20-4.0) were independently associated with colorectal cancer.

**Conclusions:** Colorectal cancer was found in 14% of patients referred to a gastroenterologist because of iron deficiency. Older age, and symptomatic anemia may help predict a diagnosis of colorectal cancer.

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## Introduction

Iron deficiency (ID) is a common indication for a gastroenterology assessment. Although many patients with ID will have a benign etiology, it may be indicative of gastrointestinal (GI) blood loss and a presentation of colorectal cancer (CRC) (1). Consequently, many patients referred to a gastroenterologist with ID will ultimately undergo a GI evaluation, including colonoscopy and esophagogastroduodenoscopy (EGD) (2). The importance of ID has been recognized by the Canadian Association of Gastroenterology (CAG), which has recommended that ID patients be seen by a gastroenterologist within 2 months (3). A recent Taiwanese study suggests that CRC patients who manifest ID anemia have a mean survival of 5.79 years when colonoscopy is performed within 30 days of ID diagnosis, compared to just 4.04 years when colonoscopy is delayed longer than 91 days (4).

There have been several publications regarding the etiology of ID in select patient groups (5-7). Older age, male gender, lower mean corpuscular volume, hemoglobin (Hb) < 90 mg/dL, abdominal symptoms, anticoagulant use, and positive fecal occult blood tests were all predictors of CRC. We set out to evaluate unselected patients referred to a gastroenterologist for ID to determine the etiologies and to assess for predictors of CRC.

## Methods

This retrospective study included consecutive patients referred for ID to one of two academic gastroenterologists at Health Sciences Centre, St. John's, NL from July 1, 2000 to January 1, 2009. The research proposal received full approval from the local Research Ethics Board.

Patients referred with ID were identified using the applicable diagnostic code recorded by the attending gastroenterologist as part of the billing process. Both gastroenterologists involved used that code exclusively for their ID patients. Only patients with confirmed ID, defined as either a serum ferritin < 30 mg/L or proven on bone marrow examination, were included. There were no exclusion criteria. An abnormal Hb was not required for entry into the study.

During the time period of the study, capsule endoscopy, CT enterography and deep enteroscopy were unavailable at our institution.

Patient records were reviewed, including the gastroenterologists' office charts and the hospital electronic medical record (EMR), which contained all procedure reports, laboratory data, radiologic and histologic test results for patients in the Eastern Health region. Data collected included patient age and gender, Hb, ferritin, duration of ID at the time of GI assessment, all diagnostic tests that were undertaken for ID, clinical data (including weight loss and symptoms of anemia), menorrhagia, regular blood donation, use of nonsteroidal anti-inflammatories (NSAIDS), and family history of CRC.

The final diagnosis for etiology of ID was determined by the attending gastroenterologist and was based on the aggregate of the clinical assessment and investigative findings. A diagnosis of CRC required histopathological confirmation. In cases where no diagnosis was immediately apparent or where a diagnosis of a benign condition was made (such as hemorrhoidal bleeding), the patient record was followed for the duration of their care by the attending gastroenterologist, and longer through the EMR if possible, to ascertain if another diagnosis subsequently became evident.

## Statistical analysis

Data were entered into SPSS version 20.0, which was used for descriptive statistics and the analysis. Univariate analysis was performed using Student's t-test or one-way ANOVA for continuous variables. Chi-squared test was used for categorical

variables.

A priori it was determined that the following variables would be assessed for a relationship with CRC: age, gender, hemoglobin, mean cell volume (MCV), ferritin, severe anemia (Hb<90 mg/dL), family history of CRC, weight loss, symptoms of anemia, use of NSAIDS, and duration of ID. Variables associated with a diagnosis of CRC on univariate analysis (p£0.10) were entered into a logistic regression model, with CRC as the dependent variable. Variables with a p-value £0.05 were identified as independent predictors of CRC.

## Results

A total of 278 patients with ID were identified during the study period. One hundred and fifty-eight (56.8%) were female and 120 (43.2%) were male. Mean patient age was 60.7 years (± 16.7 years; range 16-99 years) (Table 1).

**Table 1: Patient characteristics.**

| Characteristic | Value |
|---|---|
| Female | 158 (56.8%) |
| Age | 60.6 ± 16.7 |
| Mean Hemoglobin | 102.3 ± 22.3 g/L |
| Mean Ferritin | 10.8 ± 7.6 mmol/L |
| Mean MCV | 78.0 ± 9.5 FL |
| Mean duration ID | 20.6 ± 33.4 months |
| Anemic (whole cohort) | 0.913 |
| Male (< 140 g/L) | 0.958 |
| Female (< 120 g/L) | 0.88 |
| Weight loss | 0.101 |
| Symptoms of anemia | 0.245 |
| NSAID use | 0.356 |

The mean ferritin level was 10.8 mg/mL (± 7.6) and mean Hb was 102.3 g/L (± 22.3). The majority of the cohort had anemia, defined as Hb <120 g/L in women (88%) and < 140 g/L in males (95.8%). The mean duration of documented ID prior to first assessment by a gastroenterologist was 20.6 months with wide variation (SD 33.4 months; range 0-243 months).

CRC was identified as the cause for ID in 39 cases (14.0%). Gastric cancer was found in 2 patients (0.7%) and colonic polyps were the etiology for ID in 5 (1.8%). In 32 cases (11.5%), no cause for ID could be determined (Table 2).

**Table 2: Final Diagnosis of Iron Deficiency**

| Diagnosis (n=278) | Number (%) |
|---|---|
| Colorectal cancer | 39 (14.0) |
| No cause identified | 32 (11.5) |
| Menorrhagia | 45 (16.2) |
| ASA/NSAID | 31 (11.2) |
| Blood donation | 20 (7.2) |
| Angiodysplasia | 19 (6.8) |
| Previous gastric surgery/resection | 13 (4.7) |
| Peptic ulcer disease | 12 (4.4) |
| Hemorrhoidal bleeding | 9 (3.2) |
| Cameron's erosions | 9 (3.2) |
| Celiac disease | 8 (2.9) |
| Erosive esophagitis | 6 (2.2) |
| Inadequate dietary intake | 6 (2.2) |
| Colonic polyp | 5 (1.8) |
| Inflammatory bowel disease | 3 (1.1) |
| Gastric cancer | 2 (0.7) |
| Chronic mesenteric ischemia | 2 (0.7) |
| Portal hypertensive gastropathy | 2 (0.7) |
| Other | 15 (5.4) |

The majority of ID cases were attributed to benign etiologies, including 45 cases (16.2%) of menorrhagia, 31 (11.2%) from NSAID/ASA use, and 20 (7.2%) due to regular phlebotomy from blood donation.

Compared to patients without CRC, patients with CRC had lower mean Hb (93.9 g/L vs.103.7 g/L; p=0.01), greater mean age (71.4 years vs. 58.9 years; p<0.001), shorter duration of ID (11.6 months vs. 22.2 months; p=0.08), were more likely to have weight loss (23.1% vs. 7.9%; p=0.01), symptoms from anemia (41% vs. 21.8%; p=0.03), severe anemia (20.2% vs. 11.2%; p=0.05), and have used NSAIDs (53.8% vs. 32.6%; p=0.04). Patients with CRC had slightly higher ferritin levels than those who did not (13.4 µg/L vs. 10.4 µg/L; p=0.02) (Table 3). No differences were noted for

gender or MCV.

**Table 3: Predictors of CRC in univariate analysis**

| Parameter | CRC present | CRC absent | P Value |
|---|---|---|---|
| Hemoglobin | 93.9 g/L | 103.7 g/L | 0.01 |
| Age | 71.4 years | 58.9 years | <0.001 |
| Ferritin | 13.4 µg/L | 10.4 µg/L | 0.02 |
| Duration of ID | 11.6 months | 22.2 months | 0.08 |
| Weight loss | 0.231 | 0.079 | 0.01 |
| Symptoms of anemia | 0.41 | 0.218 | 0.03 |
| Severe anemia (Hb<90 mg/dL) | 0.202 | 0.112 | 0.05 |
| NSAID use | 0.538 | 0.326 | 0.04 |
| Blood donation | 0 | 0.121 | 0.06 |
| Menorrhagia | 0 | 0.142 | 0.03 |

Patients with CRC were less likely to be regular blood donors (0% vs. 12.1%; p=0.06) or to have menorrhagia (0% vs. 14.2%; p=0.03). However, these data were not in the medical record in 31.3% and 38.5% of cases, respectively.

Multivariate regression analysis identified greater age (OR=1.06; 95% CI 1.04-1.09), and symptoms from anemia (OR=2.19; 95% CI 1.20-4.0) as independent associated with a diagnosis of CRC (Table 4).

**Table 4: Predictors of CRC in multivariate analysis**

| Characteristic | Odds Ratio | 95% Confidence Interval |
|---|---|---|
| Age | 1.06 | 1.04-1.09 |
| Symptoms of anemia | 2.19 | 1.2-4.0 |

## Discussion

ID is a common reason for patient referral to gastroenterologists. Concern about the possibility of occult malignancy often leads to a prompt GI workup, including colonoscopy and EGD (2). In this study of 278 patients referred to one of two gastroenterologists to evaluate ID, 39 (14%) had CRC. Older patient age, and overt symptoms of anemia were associated with a greater risk of CRC.

Consistent with previous studies, the majority of ID patients (84.5%) were found to have a benign etiology (8). Menorrhagia was most common and was seen in 16.2% of all patients. NSAID and/or ASA use was the etiology in 11.2%. We noted a significant number of cases of ID (7.2%) that occurred as a result of regular blood donation.

These results may be helpful to gastroenterologists when prioritizing ID patients for endoscopic work up. Our findings suggest that younger patients with no symptoms from anemia are less likely to have CRC. Conversely, symptomatic older patients should be given highest priority for GI evaluation. Previous research suggests that although it is possible for premenopausal women to have GI pathology, the majority have no significant findings (9). Our observations were similar. In the 36 women age 45 or less, only 1 (2.8%) had malignancy (colorectal cancer).

The finding of mostly benign conditions as a cause for ID is reassuring. Although ID from menorrhagia and NSAID/ASA use has long been recognized, the finding of blood donation as the cause of 7.2% of ID cases is noteworthy because it has not been previously reported as a common cause for ID in referred patients. Our findings are consistent with research in blood donors. In a study of 836 Chinese donors, it was found that 65.3% of females and 35.1% of males who had low predonation Hb levels had ID (10). A Dutch study found that ID was present in 9.8% of female and 6.9% of male donors (11). Determining if a patient is a regular blood donor can be easily done during the interview and might help to triage referrals and guide the plan for investigation.

This study has several strengths. We identified a large cohort of patients and continued to follow many

patients for a prolonged period after the etiology of their ID had been determined. In cases where judgment was necessary to make the diagnosis, this validated the diagnosis and ensured no alternate diagnosis subsequently became apparent. There were no cases of CRC subsequently diagnosed in patients initially given a benign diagnosis. However, ongoing follow-up did identify two patients initially classified as 'no cause for ID' who later had surgically confirmed chronic small bowel ischemia, which was then presumed to have been the etiology for ID.

Although the two gastroenterologists in this study both work at an academic institution, there are few other gastroenterologists in community practice in this region of Canada. Therefore, their referral base is similar to that of most Canadian community gastroenterologists. Only these two of the five gastroenterologists at our institution used diagnostic codes that allowed for identification of patients referred for evaluation of ID. However, their practice does not differ significantly from the 3 who were not a part of this study.

The study took place before capsule endoscopy, enteroscopy, or CT enterography were available at our institution. There is evidence to suggest that had such modalities been available that a smaller proportion of cases would have been classified as 'no cause found' (12).

These results may not be representative of all cases of ID identified by primary care givers, since not all of those patients would be referred to a gastroenterologist. However, we feel these results are generalizable given the unselected nature of the patients included in the study.

We included ID patients with and without anemia. A study from Korea showed that these groups had comparable GI findings with the exception of malignant GI lesions, found in 5.1% of anemic patients compared to 0.7% of those without anemia ($p<0.01$) (13). Our results were similar as no patients without anemia had CRC compared to 15.4% of those who were anemic.

The primary weakness of this study is its retrospective design. Although this did not effect collection of the data pertaining to etiology of ID, other data were not available for all patients. The non-systematic recording of data was most problematic regarding menorrhagia and blood donation. Many patients were not asked about these issues if an obvious cause for ID was identified (such as CRC). Consequently, the association of these variables with CRC could not be reliably ascertained.

The final diagnosis for some patients was based on clinical judgment and therefore, subjective. Despite best efforts, 11.5% of patients had no etiology found for their ID. By following patients for an extended period we reduced the possibility of a malignant etiology of ID being overlooked. No such cases were identified. Similarly, a recent British study noted that of 373 ID patients with no cause found after a GI workup, only 2% were ultimately diagnosed with a GI luminal malignancy after 5 years of follow-up (14).

These findings suggest that patients referred to a gastroenterologist for evaluation of ID are more likely to have CRC if they are older and have symptoms from anemia. Such patients may benefit from expedited evaluation and prompt endoscopy. Most patients referred for ID have a benign etiology. We suggest that inquiry about regular blood donation should be made of all ID patients.

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