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# Anemia, iron deficiency, and cobalamin deficiency in cats with chronic gastrointestinal disease

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## Abstract

**Background:** Iron deficiency and cobalamin deficiency, as sequelae to chronic gastrointestinal (GI) disease, could result in anemia and increased morbidity in cats with chronic enteropathies.

**Objective:** To evaluate iron deficiency in cats with chronic GI disease and its relationship with hypocobalaminemia, anemia, and disease severity.

**Animals:** Twenty client-owned cats with primary GI disease.

**Methods:** Prospective, cross-sectional study. Cats were enrolled at the time of evaluation for chronic GI disease, after exclusion of comorbidities. CBC with reticulocyte indices, iron metabolism (serum iron and ferritin concentrations, total iron binding capacity [TIBC]), serum methylmalonic acid (MMA), cobalamin, and folate concentrations, pancreatic lipase and trypsin-like immunoreactivity, and disease severity were evaluated.

**Results:** Anemia (hematocrit <30%), iron deficiency, and cobalamin deficiency were diagnosed in 4/20, 7/20, and 8/20 cats, respectively. Hematocrit ($r_s$ = –.45; $P$ < .05) and body condition score ($r_s$ = –.60; $P$ < .01) negatively correlated with MMA. Median TIBC was lower in cats with increased vs normal MMA (218 μg/mL; range, 120-466 μg/mL vs 288 μg/mL; range, 195-369 μg/mL; $P$ = .02). Hematocrit ($r_s$ = .51; $P$ = .02), reticulocyte MCV ($r_s$ = .52; $P$ = .02), reticulocyte hemoglobin content ($r_s$ = .71; $P$ < .001), and percent transferrin saturation ($r_s$ = .79; $P$ < .0001) positively correlated with serum iron concentration.

**Conclusions and Clinical Importance:** Functional iron deficiency was common in cats with chronic GI disease. Associations between hypocobalaminemia, iron parameters, and hematologic parameters warrant further investigation on the impact of iron deficiency on chronic GI disease morbidity in cats.

KEYWORDS

chronic enteropathy, feline, ferritin, functional iron deficiency, methylmalonic acid

**Abbreviations:** %TSAT, percent transferrin saturation; BCS, body condition score; CHr, reticulocyte hemoglobin content; FID, functional iron deficiency; GI, gastrointestinal; Hct, hematocrit; IBD, inflammatory bowel disease; MCV, mean corpuscular volume; MMA, methylmalonic acid; TIBC, total iron binding capacity.

## 1 | INTRODUCTION

Iron deficiency is a common sequela to chronic gastrointestinal (GI) disease in humans, affecting 80% to 90% of people diagnosed with inflammatory bowel disease (IBD) and Crohn's disease.[1] Prevalence of iron deficiency is increased in humans with active vs inactive Crohn's disease.[2] Iron deficiency can be characterized as functional (FID) or absolute, and both can be present concurrently in people with IBD.

Functional iron deficiency in humans with IBD occurs as a consequence of systemic inflammation, documented by increased local and systemic inflammatory cytokine production.[3,4] Inflammatory cytokines lead to cellular internalization of ferroportin, driven by amplified hepcidin production.[5] Ferroportin is an iron export protein located on the basolateral membrane of GI cells, as well as reticuloendothelial cells.[4,6] Effectively, GI cell internalization and subsequent ferroportin degradation result in defective GI iron absorption. Reticuloendothelial cell iron stores are increased, but this iron cannot to be exported into the bloodstream (ie, FID).[1,2] Absolute iron deficiency results because of decreased intake and malabsorption. Concurrent cobalamin deficiency, which is common in humans with IBD, exacerbates malabsorption by GI villus blunting and crypt atrophy.[7]

Whether iron deficiency is functional or absolute, anemia can develop, because iron is not available for erythropoiesis. Anemia can be further exacerbated because inflammation increases red blood cell phagocytosis and decreases circulating red blood cell life span.[5] Anemia also is common in humans with chronic GI disease, affecting up to 80% of people with IBD and Crohn's disease.[6] Individuals with Crohn's disease who are anemic have increased disease morbidity. Furthermore, treatment of anemia in these individuals is directly correlated with improvement in disease severity scores, suggesting that correction of anemia may result in improved quality of life.[1] Although iron deficiency is not the only cause of anemia in humans with IBD, current recommendations in human medicine include measurement of serum iron and cobalamin concentrations in anemic IBD patients.[2,6]

Although the same associations between iron deficiency and anemia have not been established in cats with IBD, studies have shown a high prevalence of cobalamin deficiency in cats with chronic GI disease,[8,9] as well as increased GI inflammatory cytokines.[3] Furthermore, anemia has been documented as a risk factor for longer duration of hospitalization and increased all-cause mortality in sick cats.[10]

Our objectives were (a) to determine the prevalence of iron deficiency in cats with chronic GI disease and (b) to evaluate its relationship with anemia and cobalamin status. We hypothesized that FID-related anemia would be common in cats with chronic GI disease. Furthermore, it was expected that cats with hypocobalaminemia would have lower serum iron concentrations and higher prevalence of anemia than normocobalaminemic cats.

## 2 | METHODS AND MATERIALS

Ours was a prospective, cross-sectional study designed to enroll a population of cats with primary GI disease presented to the Kansas State University Veterinary Health Center over the course of 1 year (January 2019-December 2019). Cats were considered for inclusion in the study based on a minimum of 4 weeks' duration of clinical signs consistent with GI disease including, vomiting, diarrhea, weight loss, and dysrexia, and exclusion of non-GI causes of clinical signs. Before study inclusion and at the time of presentation for GI disease, all cats had a serum biochemistry profile, CBC, urinalysis, and abdominal ultrasound examination performed as part of a standard diagnostic evaluation for primary GI disease. A serum total T4 concentration measurement was required within 3 months of presentation and after onset of GI signs. Cats that were diagnosed with uncontrolled hyperthyroidism, exocrine pancreatic insufficiency or other systemic diseases were excluded from the study. Cats with increased pancreatic lipase immunoreactivity were not excluded. Additionally, any cats that had received cobalamin supplementation, hematopoietic stimulant administration (eg, darbepoetin), iron administration, or blood transfusion within the previous month were excluded from the study. Cats that met the inclusion criteria had additional blood collected for additional tests (folate, cobalamin, pancreatic lipase immunoreactivity, trypsin-like immunoreactivity), serum methylmalonic acid concentration (MMA), serum iron and ferritin concentrations, total iron binding capacity (TIBC), and CBC with reticulocyte indices (if not already performed on the same day). All cats had body condition scoring (BCS),[11] muscle condition scoring, and fecal scoring[12] performed by a single investigator (MCJ). Owners were required to fill out a questionnaire for disease severity scoring,[13] which included complete diet, supplement, and medication history (Supporting Information Data S1). The Institutional Animal Care and Use Committee (IACUC) at Kansas State University approved the study protocol (#4155).

### 2.1 | Blood sampling, storage, and analysis

Whole blood was collected by peripheral venipuncture from each cat. Whole blood (0.5 mL) was placed into an EDTA tube, and CBC with reticulocyte indices was performed immediately in-house using a commercial analyzer (Advia 2120i Hematology System, Siemens HealthCare GmbH, Munich, Germany). The remaining blood was collected into serum tubes, allowed to clot and then centrifuged at 1500*g* for 20 minutes at room temperature. Serum was separated and allocated into 2 separate, additive-free tubes for the remaining tests. Serum for parameters of iron metabolism was stored at 4°C and assays performed within 1 week. Serum ferritin concentration was measured using a feline-specific ELISA. Serum iron concentration and TIBC were measured using spectrophotometry. All serum iron analyses were performed by the Kansas State University Veterinary Diagnostic Laboratory using commercial analyzers (Hitachi Cobas c501, Roche Diagnostics, Basel, Switzerland). Serum for GI tests and serum MMA concentration was frozen (−20°C) and shipped within 24 hours of collection to a commercial laboratory (Texas A&M Gastrointestinal Laboratory, College Station, Texas).

### 2.2 | Statistical analysis

Data were evaluated for normality using the Shapiro-Wilk test. Data are reported as mean ± SD and median (range) for normally distributed and nonnormally distributed data, respectively. Population characteristics (sex, age, weight, BCS, and duration and severity of clinical signs) were evaluated using descriptive statistics. The Mann-Whitney *U* test was used to compare severity scores, serum cobalamin and MMA concentrations, and CBC parameters in cats with low vs normal serum iron concentrations and severity scores, iron indices, and CBC parameters in cats with normal vs high serum MMA concentrations, respectively. Spearman's correlation ($r_s$) was used to compare duration of clinical signs, serum MMA concentration, iron indices, and CBC parameters. Strength of correlation was defined as previously described (0-0.09 = negligible, 0.1-0.39 = weak, 0.4-0.69 = moderate, 0.7-.89 = strong, 0.9-1.0 = very strong).[14]

For statistical analysis, cats with serum cobalamin concentrations <150 ng/L or >1000 ng/L were recorded as 150 or 1000, respectively. Cats were considered hypocobalaminemic if they had serum MMA concentration above the reference range, regardless of serum cobalamin concentration. Cats were considered anemic if they had a hematocrit (Hct) <30%. Cats that did not have GI histopathology performed for disease severity scoring received a score of 0 for that category. For all statistical analyses, $P < .05$ was considered significant.

Statistical analysis was performed using GraphPad Prism (Version 8.4.3, GraphPad Software) and SPSS for Windows (Version 27, IBM SPSS Inc).

## 3 | RESULTS

### 3.1 | Study population

After initial diagnostic testing and exclusion of non-GI disease, 20 client-owned cats (8 spayed females and 12 castrated males) met the inclusion criteria for chronic enteropathy and were enrolled after obtaining informed owner consent. At the time of presentation, mean age was 9.2 ± 3.6 years, weight was 4.5 ± 1.0 kg, and BCS was 5/9 ± 1.96. Sixty-five percent (13/20) of the cats had normal muscling to mild muscle atrophy, whereas 4 cats had moderate muscle atrophy and 3 had severe muscle atrophy. Definitive diagnoses included lymphoplasmacytic enteritis (n = 2), eosinophilic enteritis (n = 1), small cell lymphoma (n = 4), large cell lymphoma (n = 1), and undefined (n = 12).

### 3.2 | Characteristics of clinical signs

Median duration of clinical signs at the time of presentation was 6.5 months (range, 1-24 months). The most common clinical sign at presentation was vomiting in 95% (n = 19) of the cats, followed by weight loss in 65% (n = 13) and diarrhea in 55% (n = 11). Twelve (60%) cats were considered to have moderate to severe vomiting, characterized by vomiting ≥2 times per week. Similarly, 12 cats were considered to have moderate to severe weight loss, with loss of ≥5% body weight and 6 of those cats had lost >10% body weight. Mean disease severity score was 6.6/19 ± 2.9. Body condition score was moderately negatively correlated with MMA ($r_s = -.60$; $P < .01$; 95% confidence interval [CI], −0.83 to −0.020) and moderately positively correlated with Hct ($r_s = .53$; $P = .02$; 95% CI, 0.096 to 0.79). Neither disease duration nor severity was correlated with other hematologic parameters, iron indices, or serum MMA concentration.

### 3.3 | Hematologic parameters

Anemia was present in 4 cats. Mean Hct was 34 ± 5.0%. Anemia was classified as nonregenerative in all affected cats, with a median reticulocyte count of 31 500 reticulocytes/μL (range, 16 000-71 000 reticulocytes/μL). Mean corpuscular volume (MCV) ranged from 33 to 54 fL (reference range, 41-51 fL), with a median of 46 fL. Two cats had MCVs below the reference range, but were not anemic.

### 3.4 | Cobalamin and methylmalonic acid

Median serum cobalamin concentration was 728 ng/L (range, 150-1000 ng/L), with 7 cats having serum cobalamin concentrations below the normal reference range. Median serum MMA concentration was 755 nmol/L (range, 174-14 753 nmol/L), with 8 cats having serum MMA concentration above the normal reference range. Of these 8 cats, 3 had normal serum cobalamin concentrations despite having increased serum MMA concentrations. Cats with decreased serum cobalamin concentrations had significantly higher serum MMA concentrations than did cats with normal serum cobalamin concentrations (median, 2641 nmol/L; range, 538-14 753 nmol/L vs median 713 nmol/L; range,174-2032 nmol/L; $P = .03$). Hematocrit was moderately negatively correlated with MMA ($r_s = -.45$; $P < .05$; 95% CI, −0.75 to 0.0050). The TIBC was significantly lower in cats with increased vs normal serum MMA concentration (median, 218 μg/mL; range, 120-466 μg/mL vs median, 288 μg/mL; range,195-369 μg/mL; $P = .02$), and serum MMA concentrations moderately negatively correlated with TIBC ($r_s = -.57$; $P = .008$; 95% CI, −0.81 to −0.16).

### 3.5 | Parameters of iron metabolism

Median serum iron and ferritin concentrations, TIBC, and percent transferrin saturation (%TSAT) were 78 μg/dL (range, 30-294 μg/dL), 289 ng/mL (range, 145-794 ng/mL), 253 μg/mL (range, 120-466 μg/mL), and 31% (range, 11-66%), respectively. Seven cats had decreased serum iron concentrations. No cats had decreased serum ferritin concentrations; 2 cats had increased serum ferritin concentrations. The TIBC was decreased in 5 cats, including 2 cats with decreased serum iron concentrations and 3 cats with normal serum iron concentrations; serum ferritin

concentration was normal in 4 of these cats, and increased in 1 cat. Four cats had decreased %TSAT.

Hematocrit ($P$ = .03), hemoglobin ($P$ = .02), and reticulocyte hemoglobin content (CHr; $P$ = .02) were significantly lower in cats with low serum iron concentration as compared with cats with normal serum iron concentrations. Serum iron concentration moderately positively correlated with Hct ($r_s$ = .51; $P$ = .02; 95% CI, 0.072 to 0.78), reticulocyte MCV ($r_s$ = .52; $P$ = .02; 95% CI, 0.090 to 0.078), and ferritin ($r_s$ = .45; $P$ < .05; 95% CI, −0.0060 to 0.75). Correlation between serum iron concentration and CHr ($r_s$ = .71; $P$ < .001; 95% CI, 0.38 to 0.88) and %TSAT ($r_s$ = .79; $P$ < .0001; 95% CI, 0.52 to 0.91) was strong. Percent saturation was significantly lower in cats with low vs normal or increased serum iron concentrations ($P$ = .01). Hematologic parameters in cats with low vs normal serum iron concentrations are shown in Table 1. Iron parameters in cats with normal vs increased serum MMA concentrations are shown in Table 2.

## 4 | DISCUSSION

Our prospective study reports the prevalence of iron deficiency, anemia, and cobalamin deficiency in a population of cats with chronic GI disease. Hypocobalaminemia is commonly recognized in cats with chronic GI disease, and prevalence in our study is similar to that of previous reports.[8,9,15-19] However, we also evaluated the relationship among parameters of iron metabolism, serum cobalamin concentrations, and hematologic parameters in cats with chronic GI disease. Both iron parameters and serum MMA concentration correlated with several clinical findings and hematologic parameters. Therefore, iron status warrants further investigation in cats with chronic GI disease.

Iron deficiency was diagnosed in 35% cats in our study based on decreased serum iron concentrations. Iron deficiency secondary to chronic GI disease can be absolute or functional. Iron is absorbed exclusively into enterocytes via divalent metal cation transporter-1, located on the apical enterocyte surface.[20] Therefore, malabsorptive GI disease can result in decreased iron absorption. In addition, disease states characterized by increased inflammatory cytokines, such as interleukin-6, result in down regulation of ferroportin and decreased transport of iron into the systemic circulation.[4,5] Distinguishing between FID and absolute iron deficiency can be challenging. Iron indices can help differentiate FID (decreased %TSAT with normal to increased serum ferritin concentration) from absolute iron deficiency (decreased %TSAT with decreased serum ferritin concentration).[1,2,4] Based on these criteria, all iron deficient cats in our study were classified as having FID, because all cats had serum ferritin concentrations within or above the reference range.

However, the above classification is not necessarily conclusive, in part because of ferritin's role as a positive acute phase protein. Furthermore, absolute iron deficiency and FID can exist concurrently in an individual. Disease states, such as IBD, can increase enterocyte turnover and decrease GI mucosal ferritin stores.[21] Decreased dietary intake or GI bleeding can further decrease the amount of iron available for absorption by the GI tract or result in overt iron loss, respectively. Although quantification of GI iron loss is challenging, many cats in our study had evidence of malabsorptive disease, characterized by increased serum MMA concentrations. Therefore, some cats in our study also may have had a component of absolute iron deficiency, with falsely increased serum ferritin concentrations secondary to inflammatory disease.

Reticulocyte indices have been cited as indicators of iron deficiency in veterinary and human medicine.[22-28] In dogs, CHr, percentage of hypochromic reticulocytes, percentage of reticulocytes with low CHr, percentage of reticulocytes with high CHr, and reticulocyte MCV have been associated with iron deficiency.[22,24-26] Much less information is available in cats, with a single study of cats identifying an association between iron deficiency and CHr.[24] In humans, CHr

**TABLE 1** Hematology parameters of 20 cats with chronic gastrointestinal disease, grouped by cats with decreased (N = 7) or normal (N = 13) serum iron concentrations

| | Cats with decreased serum iron | | Cats with normal serum iron | | |
|---|---|---|---|---|---|
| Variable | Median | Range | Median | Range | *P* value |
| Hematocrit (%) | 32 | 23-38 | 35 | 29-42 | .03 |
| MCV (fL) | 45 | 34-49 | 46 | 42-54 | .23 |
| MCHC (g/dL) | 33.8 | 33-36 | 34.8 | 33-36 | .27 |
| Hemoglobin (g/dL) | 10.7 | 8-13 | 11.8 | 10-14 | .02 |
| Absolute Reticulocyte (M/μL) | 37 000 | 26 000-71 000 | 29 000 | 16 000-60 000 | .15 |
| MCVretic (fL) | 55 | 43-68 | 62 | 50-70 | .11 |
| CHr (pg) | 16.7 | 13-18 | 18 | 16-21 | .02 |
| CHm (pg) | 15.8 | 12-17 | 16.2 | 15-17 | .19 |
| Percent hypochromic reticulocytes (%) | 6 | 2.4-9.5 | 2.9 | 1.0-11.6 | .09 |
| Percent macrocytic reticulocytes (%) | 1 | 0-3.7 | 1.7 | 0.1-12.6 | .4 |
| Percent microcytic reticulocytes (%) | 0 | 0-0.1 | 0 | 0-1 | .88 |

Abbreviations: CHm, cellular hemoglobin content; CHr, reticulocyte hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; $MCV_{retic}$, reticulocyte mean corpuscular volume.

**TABLE 2** Iron indices in 20 cats with chronic gastrointestinal disease, grouped by cats with normal (N = 12) or elevated (N = 8) serum methylmalonic acid concentrations

| | Cats with normal MMA | | Cats with elevated MMA | | |
|---|---|---|---|---|---|
| Variable | Median | Range | Median | Range | *P* value |
| Iron (μ/dL) | 88 | 30-164 | 72 | 34-294 | .73 |
| Ferritin (ng/mL) | 289 | 159-613 | 278 | 145-794 | .91 |
| Total iron binding capacity (μ/mL) | 288 | 195-369 | 218 | 120-466 | .02 |
| Percent transferrin saturation (%) | 27 | 11-66 | 39 | 26-63 | .15 |

Abbreviation: MMA, methylmalonic acid.

below specified cut-offs most reliably predicts response to iron supplementation.[27] Similarly, our study showed CHr to be most predictive of iron deficiency, with lower CHr corresponding to cats with decreased serum iron concentrations. Notably, this indicator does not appear specific for absolute iron deficiency, because all of these cats had FID. Similar to dogs, MCV did not appear to either predict or rule out iron deficiency in our population of cats, reinforcing the importance of evaluating reticulocyte parameters in conjunction with standard CBC measurements.

Anemia was diagnosed in 4 to 14 of 20 cats in our study based on Hct <30% or hemoglobin concentration below the laboratory reference range, respectively. Anemia was categorized as nonregenerative in all cats, based on a reticulocyte count within the normal reference range. Functional iron deficiency leads to anemia because of decreased iron availability for hematopoiesis. Anemia can be further exacerbated in disease states, because of the negative impact of systemic inflammation on RBC survival.[28] Therefore, the clinical finding of chronic disease coupled with the diagnosis of FID in our study population is the likely cause of anemia in these cats.

The combination of anemia and FID has important clinical relevance for cats with GI disease. Although the impact of anemia on disease prognosis has not been evaluated in this specific population, anemia has been shown to increase all-cause mortality in hospitalized cats.[10] Furthermore, anemia directly increases morbidity associated with GI disease in humans.[6,29] Not all cats with FID in our study were anemic. This finding is similar to what is observed in humans, in whom iron deficiency is diagnosed in 80% to 90% of people with chronic GI disease, with or without concurrent anemia,[1] and disease activity is independently related to iron deficiency in some forms of disease.[4] Therefore, the finding of these 2 interrelated biochemical alterations in the cats in our study could provide new strategies for disease monitoring and treatment in cats with chronic GI disease.

Cobalamin deficiency, based on increased serum MMA concentration, was identified in 8/20 cats in our study population. This finding is similar to what has been reported in previous studies of cats that reported prevalences of 30% to 80%,[8,9,15-19,30] supporting routine evaluation of serum cobalamin concentration and therapeutic intervention in cats with chronic GI disease. Methylmalonyl-CoA mutase is a cobalamin-dependent enzyme that catalyzes the transformation of succinyl-CoA from MMA. When intracellular cobalamin deficiency occurs, methylmalonyl-coenzyme A (CoA) mutase is unable to catalyze this transformation, resulting in increased circulating MMA. Serum MMA concentration, therefore, can be used as an additional marker of cobalamin status at the cellular level. Our study supported previous findings that serum MMA concentration is a more sensitive indicator of cellular cobalamin status than serum cobalamin concentration,[30,31] because serum cobalamin concentration alone would have failed to identify 3 of the 8 cats that were hypocobalaminemic. These results support initial evaluation of both serum MMA and cobalamin concentrations when considering biochemical markers of cobalamin deficiency.[30-32]

The relationship among cobalamin deficiency, anemia, and iron deficiency in cats with GI disease is complex. Clinically relevant ileal disease can lead to villus atrophy and subsequent malabsorptive disease, resulting in decreased cobalamin absorption. In a cyclical process, hypocobalaminemia and secondary histopathologic changes, including GI epithelial megaloblastosis and increased mucosal turnover, lead to further malabsorptive disease and may aggravate clinical signs.[7,21] In our study, MMA negatively correlated with both Hct and TIBC. Because MMA also negatively correlated with BCS, it is possible these findings are simply related to severity of disease and overall increased systemic inflammation, leading to FID. However, MMA was not correlated with either disease severity score or duration of clinical signs, and thus GI malabsorption contributing to both cobalamin deficiency and iron deficiency is possible. Cobalamin status was significantly associated with Hct and MCV in a previous study,[19] with increased serum MMA concentration associated with anemia. Mean corpuscular volume was not significantly related to increased serum MMA concentration our study, which may be a consequence of low statistical power to detect a relationship, because 163 cats were enrolled in the previous study.[19]

Our study had several limitations as an observational study. Diagnosis of the underlying cause of enteropathy was not required for enrollment. Rather, our study was designed to evaluate the presence of iron deficiency and anemia in cats with chronic GI disease. Specific relationships among disease processes and cobalamin status have been established in cats, [8] and similar relationships may exist among specific diseases and iron status. This possibility limits extrapolation of study conclusions to specific diseases, and additional studies would be needed to determine whether our study's conclusions are applicable to specific causes of chronic GI disease in cats (eg, IBD vs small cell lymphoma). In addition, our study had a small number of cats, and

although significant correlations were observed between MMA and hematologic and iron parameters, the wide 95% CIs observed for some variables warrant further evaluation in a larger population of cats. Our study also required exclusion of a number of common diseases of cats that are often comorbidities, and may make our findings less representative of many cats evaluated in clinical practice. However, these exclusions were necessary to standardize the study population and ensure results were a consequence of chronic GI disease. In addition, findings of iron deficiency and anemia directly affect GI-associated morbidity in humans, many of whom have comorbidities. Comorbidities likely would increase the observed prevalence of anemia and FID in affected cats. Our study did not evaluate markers of systemic inflammation in enrolled cats, but rather relied on the combination of ferritin, iron, and %TSAT to distinguish FID from absolute iron deficiency. One cat included in our study was diagnosed by ultrasound-guided aspirates and cytology with large cell lymphoma. Although this cat had intra-abdominal lymphadenopathy, suggesting systemic involvement, and potential impact of systemic inflammation on iron metabolism cannot be excluded, ultrasound examination disclosed severe gastric wall thickening (0.8 mm) with loss of wall layering, and the cat presented with signs (vomiting and hemorrhagic diarrhea) consistent with primary GI disease. Inclusion of markers, such as serum amyloid A protein or interleukin-6, would help more clearly define the severity of systemic inflammation and its relationship to disease severity and presence of FID. Lastly, we did not evaluate the effect of iron deficiency or anemia on GI disease prognosis or the impact of treatment on morbidity or outcome, but rather reported the relationship among cobalamin, iron status, and hematologic parameters in cats with chronic GI disease. The severity of anemia noted in these cats was mild, consistent with many chronic disease processes,[13,33,34] and did not warrant direct treatment (eg, blood transfusion). Therefore, future prospective studies will be necessary to elucidate the benefit of iron supplementation and determine the best treatment protocol.

In conclusion, we evaluated the interrelationship of hematologic parameters, iron deficiency, and cobalamin status in cats with chronic GI disease. Functional iron deficiency, anemia, and cobalamin deficiency were common in this population of cats. Furthermore, alterations in iron and cobalamin occurred without concurrent anemia, suggesting that evaluation of iron status and MMA should be included in the diagnostic evaluation of cats with chronic GI disease. Routine CBC parameters do not appear to effectively assess for iron deficiency, suggesting that reticulocyte indices should be included as part of a complete hematologic evaluation. Future prospective studies are needed to determine the effect of iron deficiency and anemia on outcome in cats with chronic GI disease, as well as determine the most effective treatment protocols.

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## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the Kansas State University IACUC committee (protocol number 4155).

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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