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Gastroduodenal ulceration in dogs with liver disease

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Abstract

Background: Liver disease is frequently cited as a cause of gastroduodenal ulceration (GDU) in dogs but studies regarding GDU and liver disease are limited.

Objectives: To document the presence of GDU in dogs with liver disease.

Animals: Forty dogs that underwent liver biopsy, computed tomographic (CT) angiography or both at the University of Florida Small Animal Hospital to diagnose congenital or acquired liver disease.

Methods: Cross-sectional study. Dogs had gastroduodenoscopy performed with photographic and video documentation in a standardized fashion. Lesions (hemorrhage, erosions, ulcers) in the esophagus, stomach, and duodenum were scored based on a grading scale. Presence of esophageal varices was recorded. Dogs were categorized into 4 groups according to cause of liver disease (inflammatory disease, cirrhosis, congenital, other). Presence or absence of ulcers, erosions or both as well as total endoscopic scores were compared among groups.

Results: Forty dogs were enrolled with the following distribution: 13 congenital, 13 inflammatory, 3 cirrhosis, and 11 other. Four dogs had GDU (10%; 95% confidence interval [CI], 3%-24%) and 6 dogs had erosions (15%; 95% CI, 6%-30%). No difference was found in total endoscopic score ($P = .21$) or in the proportion of dogs with ulcers, erosions or both versus those without ($P = .25$) among the groups.

Conclusions and Clinical Importance: Gastroduodenal ulceration was found in 10% of dogs with liver disease in this population. Additional studies are warranted to confirm these findings in larger numbers of dogs with specific disease etiologies.

KEYWORDS
esophageal varices, hepatic disease, hepatic shunt, ulcers

1 | INTRODUCTION

Gastroduodenal ulceration (GDU) in dogs has been associated with drugs, neoplasia, inflammatory gastrointestinal disease, and systemic diseases such as hepatic disease.[1] The recent American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on rational use of gastrointestinal protectants acknowledges that evidence for hepatic disease as a cause of GDU is limited and that information on the prevalence of GDU in dogs with hepatic disease is lacking.[2] A retrospective review of 43 cases of GDU in dogs found that the most common suspected underlying causes were treatment with

Abbreviations: APF, arterioportal fistula; CT, computed tomography; EV, esophageal varices; GDU, gastroduodenal ulceration.

nonsteroidal anti-inflammatory drugs (NSAIDs), treatment with corticosteroids, and hepatic disease.[3] Of the 12 dogs with hepatic disease, 6 had received either NSAIDs or corticosteroids, and the duodenum and pylorus were the most common locations for ulceration.[3] In dogs with intrahepatic portosystemic shunts, 17% were reported to have had GDU before corrective procedures in a previous study, but additional information about these cases was not published.[4] A retrospective study of dogs with noncirrhotic portal hypertension (now termed primary portal vein hypoplasia with portal hypertension) reported 3/19 dogs were euthanized because of perforated duodenal ulcers, but this study did not discuss concurrent medications and exposure to ulcerogenic drugs was not reported in this population.[5]

The mechanism for GDU associated with liver disease in dogs is unknown. The most common causes of gastrointestinal bleeding in humans with cirrhosis are gastroesophageal varices and portal hypertensive gastropathy, the presence and severity of which correlate with the severity of portal hypertension.[6] Esophageal or gastric varices have only been identified rarely in naturally-occurring liver disease in dogs. No reports of naturally-occurring portal hypertensive gastropathy in dogs have been published,[7] and a single small case series described esophageal and gastroesophageal varices in dogs with portal hypertension for a variety of reasons.[8] Experimentally-induced canine models of portal hypertension are commonly used, and esophageal varices, gastric varices, and portal hypertensive gastropathy can be present in these models.[9,10] It is possible that the prevalence of these complications in dogs with naturally- occurring portal hypertension is underestimated simply because of lack of specific investigation.

Undetected and untreated GDU can cause substantial morbidity and mortality in dogs.[3,4] Knowledge of diseases that carry the highest risk for GDU will allow earlier detection, treatment, and possibly prevention of GDU and related complications. Our objective was to evaluate for the presence of GDU in dogs with various types of liver disease and describe clinical characteristics in these patients.

2 | MATERIALS AND METHODS

2.1 | Study population

Forty dogs were prospectively recruited from the patient population at the University of Florida Small Animal Hospital. Inclusion criteria were (1) clinical suspicion of liver disease warranting liver biopsy or advanced imaging; (2) dogs undergoing anesthesia for liver biopsy, portosystemic shunt correction, or contrast computed tomography (CT) to evaluate for vascular anomalies; and (3) no contraindication to extension of anesthesia time, at the discretion of the attending clinician or anesthesiologist. Cases were excluded (1) if a congenital vascular anomaly was not present on CT scan and liver biopsy was not planned or (2) if the dog had received medications that might cause or treat GDU (NSAIDs, corticosteroids, or acid suppressants) within the past 14 days. The study was approved by the University of Florida Institutional Animal Care and Use Committee and the University of Florida Veterinary Hospital Research Review Committee. Informed consent was obtained before enrollment.

2.2 | Data collection

All dogs underwent general anesthesia for the clinically-indicated procedure (liver biopsy, contrast CT scan, or portosystemic shunt correction). Gastroduodenoscopy was performed before or after the primary procedure (at the discretion of the attending clinician) by 1 of 3 board-certified internal medicine specialists (AO, AG, KC) in a standardized fashion based on European Society of Gastrointestinal Endoscopy Guidelines.[11] Video and standardized photographic documentation were obtained in each case (Figure 1). The endoscope then was withdrawn after removal of remaining air. During each procedure, the stomach was insufflated as needed to permit full view of the mucosa. Food, hair, or debris obscuring the mucosa was irrigated with water as thoroughly as possible to allow visualization of the entire stomach to the greatest extent possible.

After completion of the study, each investigator scored each dog's endoscopic photographs and video individually without any identifying details. If the investigators' scores did not agree, the images and video were reviewed by all investigators as a group and a consensus score agreed upon. For scoring purposes, the stomach and duodenum were divided into 5 different regions as previously described[12]: (a) proximal duodenum to the major duodenal papilla, (b) pylorus and pyloric antrum, (c) incisura angularis, extending along the lesser curvature, (d) greater curvature, from the cardia to pyloric antrum, and (e) cardia, extending from

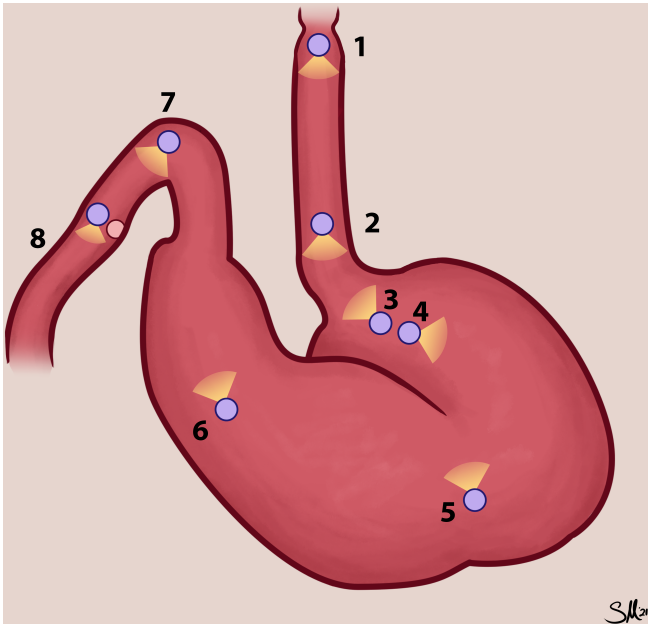

FIGURE 1 Diagram showing locations of standardized images collected during endoscopic evaluation of the esophagus, stomach, and proximal duodenum in 40 dogs with liver disease. (1) Upper esophageal sphincter. (2) Lower esophageal sphincter. (3) Cardia/fundus. (4) Greater curvature/fundus. (5) Incisura angularis. (6) Pyloric antrum. (7) Proximal duodenum. (8) Major duodenal papilla

TABLE 1 Endoscopic scoring system

Score	Description
1	Normal
2	1 mucosal hemorrhage
3	2–5 mucosal hemorrhages
4	>5 mucosal hemorrhages
5	1 erosion
6	2–5 erosions
7	>5 erosions
8	1 ulcer
9	2 ulcers
10	≥3 ulcers
11	Perforating ulcer

Note: Scoring system used for each of the 6 regions evaluated.

the greater curvature region to the lesser curvature that was not included with the incisura angularis. Each area was scored as previously described[13] (Table 1). In addition, a single score was given for the entire esophagus.

The score for each region was based on the most severe score assigned to that region, and the total score for each dog was calculated using the sum of scores from each region. For example, if >5 mucosal hemorrhages (score of 5) and an ulcer (score of 8) were present in region 4, the score for region 4 used to calculate the total score was 8. A total score of 6 indicated no lesions in any area. As previously described,[12] a mucosal hemorrhage was defined as petechia or ecchymosis with an intact mucosa, an erosion as a superficial defect of the mucosa, and an ulcer as a mucosal defect associated with width, depth, and a raised margin.

After histopathologic or imaging diagnosis of liver disease by the attending pathologist or radiologist, respectively, dogs were placed into 1 of the following groups: (1) inflammatory disease without cirrhosis (acute, chronic), (2) cirrhosis, (3) congenital vascular anomalies (including extrahepatic portosystemic shunt (EHPSS), intrahepatic portosystemic shunt (IHPSS), primary portal vein hypoplasia with or without portal hypertension, hepatic arteriovenous malformation, or arterioportal fistula [APF]), or (4) other (including vacuolar hepatopathy, nodular hyperplasia, necrosis, neoplasia, copper hepatopathy without associated inflammation). Histopathologic classification was based on the World Small Animal Veterinary Association Guidelines.[14] If the histopathologic classification was unclear, the investigators consulted with the attending pathologist to reach a conclusion.

A CBC and serum biochemistry profile were performed within 2 weeks before endoscopy in 38/40 and 34/40 patients, respectively. Of the remaining dogs, 1/2 had a CBC and 5/6 had a serum biochemistry profile performed within 1 month before endoscopy and the remaining dog had a CBC and serum biochemistry panel 2 months before endoscopy. The latter dog had a PCV and abbreviated liver chemistry panel the day before endoscopy that were used in assessment of anemia and hypoproteinemia. The dog with a CBC within a month before endoscopy also had a PCV the day before endoscopy that was used for assessment of anemia. Additionally, 29/40 dogs had abdominal ultrasound reports available for review and 20 dogs had CT reports available for review. A median of 14 days (range, 1-180 days) elapsed between ultrasound and endoscopy and a median of 0 days (range, 0-255 days) between CT and endoscopy. Ten of 29 dogs had ultrasonography within 1 week of endoscopy, and 14 of 20 dogs had a CT scan within 1 day of endoscopy. Medical records were evaluated for clinical indications of GDU, including: (1) presence or recent history of melena or hematemesis, (2) panhypoproteinemia, (3) regenerative anemia without evidence of hemolysis, (4) acute nonregenerative anemia likely to be caused by gastrointestinal bleeding, (5) iron deficiency anemia, (6) suspected ulceration on abdominal ultrasound, or (7) thrombocytosis. Dogs were classified as being panhypoproteinemic if serum albumin and globulin concentrations were below the lower end of the reference interval and as anemic if the PCV was below the lower end of the reference interval. Anemia was characterized as regenerative if the reticulocyte count was >65 000/μL (upper limit of reference interval) and as suspicious for iron deficiency if the anemia was characterized as microcytic, hypochromic, and regenerative or if reticulocyte indices were reported as suspicious for iron deficiency during CBC review by a clinical pathologist. Additionally, clinical evidence of portal hypertension during the clinical evaluation was recorded, including: (1) acquired portosystemic shunts visualized grossly or by diagnostic imaging examination, (2) presence of peritoneal effusion characterized as a transudate or modified transudate with serum albumin concentration ≥2.0 g/dL with no other defined cause, or (3) ultrasonographic evidence[7] of hepatofugal blood flow, decreased portal blood flow velocity (<10 cm/s), dilated left gonadal vein, or portal vein-to-aorta ratio <0.65 in the absence of a single congenital portosystemic shunt based on CT evaluation.

2.3 | Statistical analysis

Demographic data is presented using descriptive statistics. Proportions are presented with their binomial exact 95% confidence intervals (CI). The proportions of dogs with (1) erosions, (2) ulcers, and (3) erosions or ulcers were compared using Fisher's exact tests among the 4 categories of liver disease (inflammatory disease without cirrhosis, cirrhosis, congenital portovascular anomalies, other). Data was tested for normality using the D'Agostino & Pearson test and parametric or nonparametric tests were used as indicated. Total endoscopic score was compared among the 4 liver disease categories using a Kruskal-Wallis test. Total endoscopic score also was compared between the congenital liver disease dogs and all other dogs using a Mann-Whitney *U* test. The proportion of dogs with anemia that did and did not have GDU were compared using a Fisher's exact test. Statistical analysis was performed using Graphpad Prism v.9 and SPSS and $P < .05$ was considered significant. Because of low numbers, statistical analysis was not performed to evaluate for site dependent differences in occurrence of erosions or ulcers in each disease category.

TABLE 2 Liver disease category/subcategory

Liver disease category	Histopathologic diagnosis or subcategory	Number of dogs
Inflammation (n = 13)	Chronic hepatitis with increased copper	8
	Chronic cholangitis	1
	Chronic hepatitis with *Heterobilharzia americana*	1
	Chronic hepatitis without increased copper	3
Cirrhosis (n = 3)	Cirrhosis	3
Congenital portovascular anomaly (n = 13)	Intrahepatic portosystemic shunt	3
	Extrahepatic portosystemic shunt	9
	Arterioportal fistula	1
Other (n = 11)	Neoplasia (hepatocellular carcinoma)	2
	Reactive hepatopathy	2
	Vacuolar hepatopathy	2
	Necrosis	2
	Copper hepatopathy without inflammation	2
	Hepatic lobular atrophy	1

3 | RESULTS

Forty dogs were included in the study, with a median age of 5.3 years (range, 0.6-11.8 years), median weight of 14.3 kg (range, 2.6-46.1 kg) and sex distribution of 19 female spayed, 4 female intact, 15 male neutered, and 2 male intact. There were 13 dogs with chronic inflammatory liver disease, 3 dogs with cirrhosis, 13 dogs with congenital portovascular anomalies, and 11 dogs with other liver disease (Table 2). The inflammatory liver disease group had a median age of 8.4 years (range, 2.5-12 years) and weight of 23.6 kg (range, 4-32.8 kg) and had a breed distribution of 4 mixed breeds, and included 1 each of Greyhound, Goldendoodle, American Bulldog, Dalmatian, Chihuahua, Havanese, and Cairn Terrier. The cirrhosis group had a median age of 10.5 years (range, 8-10.5 years) and weight of 30.6 kg (range, 29-46 kg), of which 2 were Doberman Pinschers and 1 was a Labrador Retriever. In the congenital portovascular anomaly group, the median age was 2.75 years (range, 0.6-7 years), weight was 8.5 kg (range, 2.6-46.1 kg), and the breed distribution included 5 Miniature Schnauzers, 3 mixed breeds, and 1 each of Bernese Mountain Dog, English Bulldog, Shih Tzu, Havanese, and Great Pyrenees. The other group had a median age of 5 years (range, 2-11.5 years), median weight of 9.8 kg (range, 5.6-34.4 kg), and included 4 mixed breeds, and 1 each of Bichon Frise, Lhasa Apso, Australian Shepherd, Standard Poodle, Belgian Malinois, Labradoodle, and Labrador Retriever.

In our study, 35/40 dogs had liver biopsy either on the day of endoscopy or during surgery for correction of a portovascular anomaly.

TABLE 3 Number of dogs with ulcers and/or erosions by group

Category	Ulcer(s)	Erosion(s)	Ulcer or erosion(s)
Inflammation (n = 13)	0	2	2
Cirrhosis (n = 3)	1	2	2[a]
Congenital (n = 13)	1	1	2
Other (n = 11)	2	1	3
P-value[b]	.16	.12	.25

[a]One dog had both erosions and ulcers.
[b]*P*-value reflects comparison of proportion of dogs with ulcers, erosions, or ulcers and/or erosions between the 4 groups.

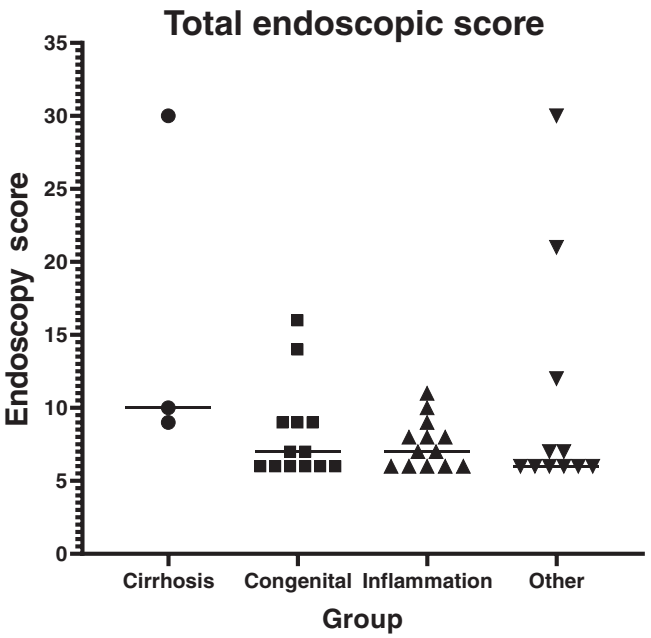

FIGURE 2 Scatter plot of total endoscopic score in 40 dogs with liver disease by disease group. The horizontal lines denote the median score for each group. A score of 6 indicates no endoscopic lesions

Of the 5 dogs without biopsy, 3 dogs had IHPSS and had percutaneous transvenous coil embolization during which liver biopsy is not routinely performed, 1 dog had an APF and did not have further diagnostic evaluation or surgical correction, and 1 dog had an EHPSS and did not return for surgery.

Overall, 4/40 dogs (10%; 95% CI, 3%-24%) had ulceration and 6/40 (15%; 95% CI, 6%-30%) had erosions. One dog had erosions and ulcers and was included in both categories. Overall, 9/40 (23%; 95% CI, 11%-39%) had erosions or ulcerations detected. Group comparisons are presented in Table 3. No significant difference was found in proportions of dogs positive for ulceration, erosion, or ulceration or erosion among the groups. Specific conditions in 1 each of the dogs with ulcers were cirrhosis, congenital extrahepatic portosystemic shunt, hepatocellular carcinoma, and hepatic necrosis. In dogs with erosions, specific conditions were cirrhosis in 2 dogs (1 of which also had ulcers), and in 1 dog each chronic hepatitis caused by *Heterobilharzia americana*, chronic hepatitis with

increased copper, congenital intrahepatic portosystemic shunt, and vacuolar hepatopathy.

The median (range) total endoscopic score was 7[6-11] in the inflammation group, 10 (9-30) in the cirrhosis group, 7[6-16] in the congenital group, and 6 (6-30) in the other group, with no significant difference detected among the groups ($P = .21$; Figure 2; Table S1). Also, no significant difference was detected when comparing median total endoscopic score in the congenital group (7; range, 6–16) versus all other dogs (7; range, 6-30; $P = .74$).

One dog had esophageal varices observed. This dog was diagnosed by CT angiography with an APF (cranial mesenteric artery to extrahepatic portal vein) and multiple acquired portosystemic shunts secondary to suspected portal hypertension. This dog did not have erosions or ulcers.

No dogs had a confirmed history of melena or hematemesis and no dogs were panhypoproteinemic, but 11 dogs had hypoalbuminemia (median, 2.4 g/dL; range, 1.9-2.8 g/dL). Eight dogs (20%) were anemic (median Hct, 36.6%; range, 28%-39.6%; reference range, 40%-56%), of which 5 had congenital portovascular anomalies, 1 had cirrhosis, 1 had inflammation without cirrhosis, and 1 had other disease (hepatocellular carcinoma). The CBCs for these dogs were performed the day before or morning of endoscopy in 7 dogs and 10 days before in 1 dog. A reticulocyte count, performed 10 days before endoscopy, was available for 1 anemic dog (177 600/μL; reference range, 8000-65 000/μL). Two of the 8 anemic dogs had GDU, 1 with neoplasia (regenerative anemia; CBC 10 days before endoscopy) and 1 with a congenital extrahepatic portovascular anomaly (no reticulocyte count available; CBC 1 day before endoscopy). One anemic dog (no reticulocyte count available; CBC the day of endoscopy) with a congenital intrahepatic portovascular anomaly had erosions. No difference was found in the proportion of dogs with anemia that did (3/8) or did not (5/8) have GDU ($P = .35$). Reticulocyte counts and indices were not available for most anemic dogs, therefore characterization of anemia as suspicious for iron deficiency was not possible. Additionally, 1 dog with erosions had mild thrombocytosis (452 000/μL; reference range, 134 000-396 000/μL; CBC 1 day before endoscopy).

Of 29 dogs with ultrasound reports available for review, none had GDU suspected on ultrasound examination, including 3 of 4 dogs with ulcers present during endoscopic examination. The 3 dogs with GDU and ultrasound reports available had ultrasound examination performed 7, 9, and 16 days before endoscopy. Evidence of portal hypertension was limited to 4 dogs. Two had multiple acquired portosystemic shunts identified on CT scan, 1 with APF and 1 with cirrhosis, and neither had GDU present. One dog with an EHPSS had hepatofugal blood flow noted on ultrasound examination and had a portal vein-to-aorta ratio of 0.56. One dog had a low protein transudate in the abdomen, and gallbladder and pancreatic edema on CT suspected to be secondary to portal hypertension, and this dog had ulcers and erosions. The majority of dogs (27/29) with ultrasound reports available did not have documented evaluation for presence of hepatofugal blood flow, decreased portal blood flow velocity (<10 cm/s), dilated left gonadal vein or a portal vein-to-aorta ratio <0.65.

4 | DISCUSSION

We found that 4/40 (10%) of dogs with a variety of hepatic diseases had GDU present at the time of endoscopy. Five additional dogs had erosions present and 1 dog had erosions and an ulcer, for a total of 9/40 (23%) having erosions or ulcers. No difference was found in the proportion of dogs with erosions or ulcers among the liver disease categories designated in the study and no difference in total endoscopic score was found among the groups.

Although commonly listed as a cause of GDU in dogs, the overall prevalence of GDU in dogs with hepatic disease and the disease specific prevalence are unknown. A recent retrospective study of 82 dogs with GDU confirmed by direct visualization at endoscopy, surgery, or necropsy did not report hepatic disease as a suspected cause in any dogs, although 50% of dogs did not have an identified cause and information on the thoroughness of investigation into hepatic disease as a specific cause was not presented.[15] Another study evaluated predisposing factors in dogs with necropsy-confirmed GDU using a retrospective case-control design. The authors found 31% of dogs with GDU had hepatobiliary disease compared to 23% of control dogs without GDU that had hepatobiliary disease, and in univariable analysis the presence of hepatobiliary disease was not associated with GDU.[16] Although our study cannot be directly compared to prior studies because of differences in study design and lack of a control population, it does provide information about the prevalence of GDU in a group of dogs with a variety of liver diseases that were not receiving specific treatment for GDU.

Given that humans with cirrhosis may have gastroesophageal varices and portal hypertensive gastropathy leading to gastrointestinal bleeding, we sought to evaluate whether dogs with evidence of portal hypertension more commonly had GDU. Because only 4 dogs had evidence of portal hypertension, 1 of which had GDU, meaningful conclusions could not be drawn. One dog with evidence of portal hypertension presumed to be a result of an APF between the cranial mesenteric artery and portal vein had nonbleeding esophageal varices present. To our knowledge, this type of vascular anomaly has not been reported in dogs previously. Varices are not well described in the veterinary literature, but 1 case series included a dog with an intrahepatic arterioportal communication that had multiple types of varices.[8] A recent retrospective study of 25 dogs with esophageal varices, predominantly diagnosed by CT, included 9 cases with hepatic disease and confirmed or presumed portal hypertension as the cause.[17] In our study, only 20 dogs had CT scans available for review, and thus some esophageal varices may have not been detected.

In our study population, clinical signs, laboratory findings, and abdominal ultrasound findings were not consistently indicative of GDU. The latter is not totally surprising because studies have reported sensitivities of abdominal ultrasound examination for nonperforated GDU in dogs ranging from 30-65%.[15,18] Because not all of the dogs in our study had ultrasound examination immediately before endoscopy, it is also possible that ulcers detected at endoscopy were not present at the time of the ultrasound examination. The exclusion of dogs receiving acid suppressant medication may have biased our study

population toward dogs without clinical signs or laboratory abnormalities suggestive of GDU. However, multiple studies evaluating GDU in dogs highlight the lack of clinical signs (vomiting, melena, hematochezia, hematemesis) or laboratory findings (anemia, hypoalbuminemia, panhypoproteinemia) compatible with clinical bleeding in the majority of dogs despite the presence of substantial mucosal injury.[13,15,19-21] In these studies, melena, anemia, hypoalbuminemia or increased BUN concentration usually were present only in dogs with severe ulceration or perforation.[20,22] One large study included 82 dogs with confirmed GDU and found that only approximately 30% had specific signs of GDU such as hematemesis or melena.[15]

A limitation of our study is that histopathology was not performed to detect microscopic ulceration or to exclude underlying microscopic gastrointestinal disease as a cause for the endoscopic findings. Additionally, fecal flotation and assessment of parasite preventative treatment was not performed, but no gross evidence of parasites was seen during endoscopic examination. Based on clinicopathologic assessment, no evidence of systemic disease associated with gastric ulceration or erosion was identified, but cases were not specifically tested for hypoadrenocorticism. Other limitations include the small numbers of cases in each category of liver disease, and only 4 dogs with suspected portal hypertension. The limited number of dogs with cirrhosis or intrahepatic shunts may be particularly important because these specific types of hepatic disease have been suggested to be more commonly associated with GDU.[4] As mentioned previously, we also excluded dogs receiving gastric acid suppressant medications. This design feature largely excluded dogs suspected or diagnosed with IHPSS because current protocol in our hospital is to start gastric acid suppression early in these patients based on findings reported previously.[4] However, this approach also may have excluded dogs that had past clinical signs of gastrointestinal bleeding and, therefore, those with highest risk of GDU. Additionally, we did not have a healthy control population, and the prevalence of lesions such as erosions or hemorrhages in healthy pet dogs is not known. Studies utilizing healthy research dogs have found hemorrhages and erosions on endoscopic examination in some dogs before administration of medications for the study or in those of the placebo group.[23,24] Therefore, it is possible that some of the mild mucosal changes such as hemorrhages or erosions could be unrelated to liver disease.

In conclusion, we found that 10% of dogs with hepatic disease had endoscopic evidence of GDU and 23% had erosions, ulcerations, or both. Clinical, laboratory, and diagnostic imaging findings were not consistently indicative of the presence of these lesions. Given the wide variety of causes of hepatic disease and small numbers of dogs in each group, further investigation of dogs in specific disease groups thought to be at higher risk, such as those with congenital IHPSS, portal hypertension, and dogs already on gastric acid suppressants or mucosal protectant medications, still is needed to determine if these populations are at higher risk of GDU.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label antimicrobial use.

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

Approved by the University of Florida IACUC (protocol# 201609626) and the University of Florida Veterinary Hospitals Research Review Committee (# 2016-016).

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 in the online version of the article at the publisher's website.

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