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Influence of normograde versus retrograde catheterization of bile ducts in dogs treated for gallbladder mucocele

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Abstract

Objective: To determine the influence of normograde (NG) versus retrograde (RG) catheterization of the cystic duct and common bile duct (CBD) in dogs with gallbladder mucoceles (GBM) treated with open cholecystectomy.

Study design: Retrospective study.

Animals: Dogs ($n = 117$) with GBM.

Methods: Medical records were reviewed for signalment, history, clinical laboratory and diagnostic imaging findings, details of surgery including catheterization method, complications, and outcome. Long-term follow-up data were obtained by telephone or electronic communication. Relationships between catheterization method and clinical variables and outcome were evaluated.

Results: Dogs catheterized RG were more likely to experience any postoperative complication ($p = .0004$) including persistence of gastrointestinal signs ($p = .0003$). Survival to discharge and long-term survival did not differ by group ($p = .23$ and $p = .49$). Total bilirubin (TB) decreased by 70.3% after NG catheterization compared to 39.1% after RG catheterization ($p = .03$) and increased in 14.9% dogs catheterized NG and 38.0% dogs catheterized RG ($p = .004$). The presence of a diplomate surgeon at surgery resulted in decreased incidences of any perioperative or postoperative complication ($p = .003$ and $p = .05$).

Conclusion: Retrograde catheterization was associated with more postoperative concerns than NG catheterization, but similar survival times. Surgery should be performed by diplomates experienced in biliary surgery to minimize complications.

Clinical significance: Although both NG and RG techniques to catheterize the cystic duct and CBD are options for treatment of GBM with low mortality,

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results of this study provide some evidence to recommend NG over RG catheterization.

1 | INTRODUCTION

Gallbladder mucocele (GBM) is one of the most common biliary diseases in dogs, characterized by distension of the gallbladder (GB) by a semisolid mass of tenacious, mucin-laden bile.[1-10] Extension of gelatinous bile into the cystic duct, common bile duct (CBD), and hepatic ducts may occur, causing varying degrees of extrahepatic biliary obstruction (EHBO).[1,2,5,6,11] The etiology of GBM is incompletely understood but thought to be multifactorial.[1,12,13] Gallbladder dysmotility may result in functional obstruction of the cystic duct and CBD, or mechanical obstruction of the ducts by mucus, choledocholithiasis, or pancreatitis may cause bile stasis.[12,14-16] Bile stasis leads to prolonged exposure of the GB epithelium to cytotoxic bile salts.[1,2,17,18] Increased mucus secretion occurs, and, in some cases, cystic mucinous hyperplasia of the GB.[1,2,6,9,10,12,17-21] Fibrinosuppurative and necrotizing, hemorrhagic cholecystitis may develop with GBM and cause transmural ischemia and GB rupture.[2,5,17,19,20,22] Cholecystectomy addresses the defective GB wall and is the most appropriate treatment for GBM.[1,6,12,16,18] Patency of the cystic duct and CBD can be determined by surgical catheterization and flushing of the ducts to remove material obstructive to bile flow.[1,6,9-12,16,19-25]

Flushing of the cystic duct and CBD can be accomplished by normograde (NG) or retrograde (RG) catheterization.[6,9-12,16,20,25] Normograde catheterization requires removal of GB contents via cholecystotomy or cholecystectomy prior to catheterization. Careful packing of the hepatic fossa is necessary to prevent contamination of the abdomen with bile.[6,9,16,20] Removal of the GB prior to catheterization precludes cholecystoenterostomy, and careful intraoperative assessment of biliary pathology is required. In dogs having a sharp angle between the infundibulum and cystic duct, NG catheterization can be challenging to perform. Retrograde catheterization requires antimesenteric duodenotomy to access the major duodenal papilla (MDP) which may prolong surgical duration, create a site for potential dehiscence, or adversely affect gastrointestinal motility.[2,6,9-12,16,20] Reported complications associated with RG catheterization include postoperative pancreatitis, GB necrosis, hepatic abscessation, and duodenal dehiscence or perforation.[1,11,12,20]

The objective of this study was to determine the influence of NG versus RG catheterization of the cystic duct and common bile duct (CBD) in dogs with gallbladder mucoceles (GBM) treated with open cholecystectomy. We hypothesized that RG catheterization would be associated with increased risk for postoperative complications.

2 | MATERIALS AND METHODS

Search of the medical records databases at the University of Illinois and Purdue University Veterinary Teaching Hospitals was performed for dogs that underwent cholecystectomy for treatment of GBM from January 1, 2006 to December 31, 2016. Dogs were included if results of abdominal imaging (ultrasonography [US] or computed tomography [CT]) or histologic findings consistent with GBM were obtained, treatment consisted of open cholecystectomy with catheterization of the cystic duct and CBD, and method of catheterization was included in the surgery report. Dogs were excluded if cholecystectomy was performed laparoscopically, the surgery report did not clearly define the method of catheterization, more than one method of catheterization was used, or histopathologic findings of the GB were not consistent with GBM.

Data retrieved included age and body weight at presentation; gender and reproductive status; breed; rectal temperature, pulse rate, respiratory rate at presentation; preoperative clinical signs and duration; and presence and type of medical comorbidities. Method of abdominal diagnostic imaging, abnormal findings, and clinical interpretation by a board-certified veterinary radiologist were also recorded. Surgery and anesthesia reports were evaluated for intraoperative findings, visual evidence of GB rupture, presence or absence of focal or diffuse bile peritonitis (BP), method by which the cystic duct and CBD were catheterized, and total anesthesia and surgery times. The presence of a diplomate surgeon at surgery was also documented. Results of complete blood count and serum biochemistry profiles from the preoperative and postoperative periods were recorded. Clinical laboratory values recorded from preoperative were the results of the last sample taken before cholecystectomy and included alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) enzyme activities as well as total serum bilirubin (TB) concentrations. Laboratory values recorded from postoperative were the results of the last sample taken after cholecystectomy but

prior to discharge. Liver enzyme activities and TB were noted to be within or above reference range (RR) of the respective institution and were compared between groups. Percent change of liver enzyme activities and TB from pre- to postoperative were compared between groups. Results of GB histology and aerobic and anaerobic bacterial culture and sensitivity testing of GB contents were recorded. Duration of postoperative hospitalization and complications were recorded. Complications that occurred during or within 24 h of surgery were considered perioperative. Complications that occurred between 24 h and 14 days after surgery were considered postoperative. Clinical signs were considered persistent >24 h postoperative. If a dog died or was euthanized, cause of death or reason for euthanasia and date of death were recorded. For dogs that were discharged from the hospital, long-term follow-up data were obtained by telephone or electronic mail with the primary veterinarian or owner. The date of last follow-up was recorded.

2.1 | Statistical analysis

Continuous data were assessed for normality using histograms, skewness, kurtosis, and Shapiro–Wilk tests and described using median and interquartile range (IQR) if non-normally distributed. Frequencies and percentages were used to describe categorical data. Associations between surgical catheterization technique and categorical variables were assessed using Fisher's exact tests. Kruskal–Wallis tests were used to test between differences in continuous variables based on surgical catheterization technique. Statistical significance was set at alpha = 0.05, and t analysis was performed using a commercial software package (SAS software, Version 9.4, SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Signalment

One-hundred-seventeen dogs met the inclusion criteria, and demographics and operative variables of the study population are summarized in Table 1. Fifty-five (47.0%) dogs were treated at the University of Illinois at Urbana-Champaign, and 62 (53.0%) were treated at Purdue University. Sixty-seven (57.3%) dogs underwent NG catheterization of the cystic duct and CBD and 50 (42.7%) dogs underwent RG catheterization. The most common catheterization technique was NG 47/55; 85.4%) at the University of Illinois and RG (42/62; 67.7%) at Purdue University ($P < .001$).

3.2 | Clinical findings

Fifty-four (46.2%) dogs were presented with clinical signs including lethargy, vomiting, regurgitation, anorexia, ptyalism, diarrhea, icterus, and weight loss. Nineteen of 117 (16.2%) dogs had one or more endocrinopathies including hyperadrenocorticism, hypothyroidism, or diabetes mellitus, including 9/67 (13.4%) dogs catheterized NG and 10/50 (20.0%) dogs catheterized RG.

One-hundred-fifteen of 117 (98.3%) dogs had advanced abdominal imaging interpreted by a board-certified radiologist. Abdominal US was performed in 112/117 (95.7%) dogs. Common US changes included stellate GB (63/112; 53.6%), biliary sludge (33/112; 29.5%), CBD distension (27/112; 24.1%), and hyperechoic mesentery localized to the hepatic fossa (32/112; 28.6%). Abdominal CT with IV contrast (iohexol, 300 mg/mL) was performed in 5/117 (5.1%) dogs. Gallbladder enlargement was observed in 3/5 dogs, hyperattenuating GB contents in 4/5 dogs, and CBD distension between 7 and 15 mm in 2/5 dogs. A combination of imaging modalities was performed in 64/117 (54.7%) dogs.

3.3 | Perioperative and intraoperative details

Diplomate surgeons were present during cholecystectomy in 100/117 (85.5%) dogs, including 54/67 (80.6%) dogs catheterized NG and 46/50 (85.2%) dogs catheterized RG ($p = .16$). Median [IQR] anesthesia time was 167.5 [67.5] minutes for dogs catheterized NG compared to 205 [102.0] minutes for dogs catheterized RG ($p = .015$). Median [IQR] surgery time was 110 [40.0] minutes for dogs catheterized NG compared to 134 [75.0] minutes for dogs catheterized RG ($p = .040$). Elective cholecystectomy was performed in 69/117 (59.0%) dogs, including 41/67 (61.2%) dogs catheterized NG and 28/50 (56.0%) dogs catheterized RG. Emergency cholecystectomy was performed in 48/117 (41.0%) dogs, including 26 (38.8%) dogs catheterized NG and 22 (44.0%) dogs catheterized RG ($p = .7$).

Bile peritonitis acquired preoperatively was noted in 42/117 (35.9%) dogs at surgery, including 22/67 (32.8%) dogs catheterized NG and 20/50 (40%) dogs catheterized RG. Of these, 10/42 dogs (23.8%) had positive cultures taken at surgery including 4 dogs catheterized NG and 6 dogs catheterized RG. Gallbladder rupture was identified at surgery in 32/117 (27.3%) dogs, including 20 (30.0%) dogs catheterized NG and 12 (24%) dogs catheterized RG ($p = .48$). Distension of the cystic duct and CBD with thick, gelatinous bile was noted in all dogs at surgery. With cranial traction on the GB or hepatic fossa and caudal traction on the duodenum, red rubber catheters (Kendall, Covidien, Dublin, Ireland) were used to

TABLE 1 Characteristics of 117 dogs treated for gall bladder mucocele with open cholecystectomy and normograde or retrograde bile duct catheterization

		Normograde (NG) ($n = 67$)		Retrograde (RG) ($n = 50$)		
Variable	**Category**	***n***	**%**	***n***	**%**	***p*-value**
Institution	Illinois	47	70.1	8	16.0	<.001
	Purdue	20	29.9	42	84.0	
Breed[a]	Mixed breed	7	10.4	13	26.0	.01
	Cocker spaniel	9	13.4	7	14.0	
	Shetland sheepdog	10	14.9	0	0.0	
	Other	41	61.2	30	60.0	
Reproductive status	Male castrated	30	44.8	20	40.0	.61
	Female spayed	33	49.3	27	54.0	
	Male intact	2	3.0	3	6.0	
	Female intact	2	3.0	0	0.0	
Emergency surgery	Yes	26	38.8	22	44.0	.7
	No	41	61.2	28	56.0	
Gall bladder rupture	Yes	20	29.9	12	24.0	.48
	No	47	70.2	38	76.0	
Preoperative Peritonitis	Yes (non-septic)	18	26.9	14	28.0	.57
	Yes (septic)	4	6.0	6	12.0	
	No	45	67.2	30	60.0	
Culture result- bile	Positive	21	31.3	17	34.0	.78
	Negative	43	64.2	32	64.0	
Diplomate present	Yes	54	80.6	46	92.0	.16
	No	10	14.9	2	4.0	
Variable		**Median**	**IQR**	**Median**	**IQR**	***p*-value**
Age at surgery (months)	Median (IQR)	111.0	40.0	129	36.0	.14
Body weight (kg)	Median (IQR)	11.2	11.0	9.9	11.5	.27
Surgery time (min)	Median (IQR)	110.0	40.0	134	75.0	.040
Anesthesia time (min)	Median (IQR)	167.5	67.5	205	102.0	.015
Days until discharge	Median (IQR)	4.0	2.0	5.0	3.0	.12

Abbreviation: IQR, interquartile range.
[a]Breeds that were represented with over 10 dogs in the entire study population.

cannulate and flush the cystic duct and CBD of dogs in both groups. The size of catheter and method of catheterization were chosen at the discretion of the primary surgeon, and catheters ranged in size from 5 to 10 Fr. Liver biopsy was performed in 102/117 (87.2%) dogs, including 57 (85.1%) dogs catheterized NG and 45 (90%) dogs catheterized RG.

3.4 | Perioperative complications

Perioperative complications are summarized in Table 2 and included difficulty catheterizing the cystic duct or CBD, rupture of the GB during surgery, and clinically relevant hypotension or hemorrhage. Perioperative complications occurred in 38/117 (32.5%) dogs, including 23/67 (34.3%) dogs catheterized NG and 15/50 (30.0%) dogs catheterized RG ($p = .69$). Six (5.1%) dogs, 3 in each group, suffered multiple perioperative complications ($p = .71$). Difficulty catheterizing the cystic duct and CBD was noted in the surgery report of 2 dogs, one from each group. Seven (6.0%) dogs had intraoperative rupture of the GB including 5 dogs catheterized NG and 2 dogs catheterized RG. Fourteen (12.0%) dogs had intraoperative hypotension, including 8 dogs catheterized NG and 6 dogs catheterized RG. Four (3.4%) dogs experienced clinically

TABLE 2 Outcomes of 117 dogs categorized by common bile duct (CBD) catheterization method

		Normograde (NG) (n = 67)		Retrograde (RG) (n = 50)		
Variable		***n***	**%**	***n***	**%**	***p*-value**
Perioperative complications						
Any complication		22	32.8	14	28.0	.69
Multiple complications		3	4.5	3	6.0	.71
Hemorrhage	Yes	3	4.5	1	2.0	.63
	No	64	95.5	49	98.0	
Hypotension	Yes	8	11.9	6	12.0	.99
	No	59	88.1	44	88.0	
Intraoperative gall bladder rupture	Yes	5	7.5	2	4.0	.7
	No	62	92.5	48	96.0	
Difficulty catheterizing the CBD	Yes	1	1.5	1	2.0	.43
	No	66	98.5	49	98.0	
Postoperative complications						
Any complication		22	32.8	33	66.0	.0004
Multiple complications		12	17.9	15	30.0	.12
Pancreatitis	Yes	8	11.9	8	16.0	.53
	No	59	88.1	42	84.0	
Postoperative bile peritonitis	Yes	6	9.0	6	12.0	.59
	No	61	91.0	44	88.0	
	Septic	3	4.5	4	8.0	.81
	Non-septic	3	4.5	2	4.0	
CBD obstruction	Yes	1	1.5	0	0.0	1
	No	66	98.5	50	100.0	
Hypotension	Yes	5	7.5	7	14.0	.25
	No	62	92.5	43	86.0	
Persistent gastrointestinal signs	Yes	6	9.0	18	36.0	.0003
	No	61	91.0	32	64.0	
Other postoperative complication[a]	Yes	9	13.4	16	32.0	.02
	No	58	86.6	34	68.0	

Abbreviation: IQR, interquartile range.

[a]Anemia; hypoxemia; heart failure; pulmonary edema; pleural effusion; aspiration pneumonia; cardiopulmonary arrest; suspicion for acute kidney injury, and suspicion for acute respiratory distress syndrome, systemic inflammatory response syndrome, disseminated intravascular coagulation, and/or multiorgan dysfunction syndrome.

relevant hemorrhage, including 3 dogs catheterized NG and 1 dog catheterized RG. All dogs survived surgery.

3.5 | Postoperative findings

Postoperative complications were diagnosed based on clinical laboratory findings and diagnostic imaging and are also summarized in Table 2. Postoperative complications included complications related to the biliary tract such as postoperative pancreatitis, BP, and persistent CBD obstruction (n = 1; NG) and complications not specifically related to the biliary tract including persistent hypotension, persistent gastrointestinal signs >24 h postoperative including vomiting, regurgitation, diarrhea, ptyalism, and anorexia, and "other" systemic postoperative complications such as anemia (n = 4); hypoxemia (n = 3); heart failure (n = 3); pulmonary edema (n = 2); pleural effusion (n = 2); aspiration pneumonia (n = 1); cardiopulmonary arrest (n = 2); suspicion for acute kidney injury (n = 2), and suspicion for acute respiratory distress syndrome, systemic inflammatory response

syndrome, disseminated intravascular coagulation, and/or multiorgan dysfunction syndrome ($n = 3$).

Fifty-five (47.0%) dogs experienced any postoperative complication, including 22 (32.8%) dogs catheterized NG and 33 (66.0%) dogs catheterized RG ($p = .0004$). Twenty-seven (23.1%) dogs experienced multiple postoperative complications, including 12/67 (17.9%) dogs catheterized NG and 15/50 (30.0%) dogs catheterized RG ($p = .12$). Concerning complications related to the biliary tract, 16/117 (13.7%) dogs experienced postoperative pancreatitis, including 8/67 (11.9%) dogs catheterized NG and 8/50 (16.0%) dogs catheterized RG ($p = .25$). Bile peritonitis was diagnosed postoperatively by abdominal fluid cytology ± bacterial culture in 12 (10.3%) dogs, including 6 dogs catheterized NG and 6 dogs catheterized RG ($p = .59$). Septic BP was diagnosed postoperatively in 7/12 dogs, including 3 dogs catheterized NG and 4 dogs catheterized RG ($p = .81$). The source of bile leakage was identified in 5/12 (41.7%) dogs. Four dogs were returned to surgery, including 2 dogs catheterized NG and 2 dogs catheterized RG. One dog in the NG group that was euthanized underwent necropsy. Sites of bile leakage identified at surgery or on necropsy were the cystic duct ($n = 2$), the hepatic duct of the right medial liver lobe ($n = 2$), and the CBD ($n = 1$). Three dogs catheterized NG and 4 dogs catheterized RG diagnosed with postoperative BP died or were euthanized without additional surgery or necropsy.

Concerning complications not specifically related to the biliary tract, 12/117 (10.3%) dogs experienced persistent hypotension after surgery, including 5/67 (7.5%) dogs catheterized NG and 7/50 (14.0%) dogs catheterized RG ($p = .25$). Twenty-four (20.5%) dogs experienced persistence of gastrointestinal signs >24 h postoperatively, including 12/67 (17.9%) dogs catheterized NG and 18/50 (36.0%) dogs catheterized RG ($p = .0003$). Twenty-five (21.4%) dogs experienced "other" systemic postoperative complications, including 9/67 (13.4%) dogs catheterized NG and 16/50 (32%) dogs catheterized RG ($p = .02$).

The presence of a diplomate surgeon at surgery resulted in decreases in the incidences of any perioperative or postoperative complication ($p = .003$ and $p = .05$, respectively). However, survival to discharge and long-term survival were not affected by the presence of a diplomate surgeon ($p = .82$ and $p = .09$, respectively).

3.6 | Histopathology and microbiology results

Histopathology was diagnostic for GBM in 106/117 (90.6%) dogs, including 60/67 (89.6%) dogs catheterized NG and 46/50 (92.0%) dogs catheterized RG. Eight of 117 (6.8%) dogs had results consistent with GBM such as necrotizing or fibrinosuppurative cholecystitis, including 6 dogs catheterized NG and 2 dogs catheterized RG[1,2,4,5,9,12,17,20] In 3 dogs without histopathology or with findings of cholecystitis, preoperative imaging was consistent with GBM. Liver biopsy results were consistent with biliary hyperplasia, portal fibrosis, and hepatocellular vacuolar degeneration.

Samples for bacterial culture and sensitivity were obtained from GB contents in 113 (96.6%) dogs, including 64/67 (95.5%) dogs catheterized NG and 49/50 (98.0%) dogs catheterized RG. Results were positive in 38/113 (33.6%) dogs, including 21/64 (32.8%) dogs catheterized NG and 17/49 (34.7%) dogs catheterized RG. Common bacteria included *Bacteroides* spp., *Escherichia coli*, *Enterococcus* spp., and *Bacillus* spp.

3.7 | Laboratory findings

Preoperative ALT was above RR in 105 (89.7%) dogs, including 62/67 (92.5%) dogs catheterized NG and 43/50 (85.0%) dogs catheterized RG. Preoperative ALP was above RR in 110 (94.0%) dogs, including 66/67 (98.5%) dogs catheterized NG and 44/50 (88.0%) dogs catheterized RG ($p = .04$). Preoperative GGT was above RR in 92 (78.6%) dogs, including 53/67 (79.1%) dogs catheterized NG and 39/50 (78.0%) dogs catheterized RG. Preoperative TB was above RR in 69 (35.3%) dogs, including 46/67 (68.7%) dogs catheterized NG and 23/50 (46.0%) dogs catheterized RG ($p = .01$).

Postoperative ALT was above RR in 92 (78.6%) dogs, including 49/67 (73.1%) dogs catheterized NG and 43/50 (86.0%) dogs catheterized RG. Postoperative ALP was above RR in 97 (82.9%) dogs, including 56/67 (83.5%) dogs catheterized NG and 41/50 (82.0%) dogs catheterized RG. Postoperative GGT was above RR in 75 (64.1%) dogs, including 42/67 (62.7%) dogs catheterized NG and 33/50 (66.0%) dogs catheterized RG. Postoperative TB was above RR in 50 (42.7%) dogs, including 28/67 (41.8%) dogs catheterized NG and 22/50 (44.0%) dogs catheterized RG. From pre- to postoperative, ALT decreased by 35.8% (median; IQR = 76.8%) after NG catheterization compared to 19.0% (median; IQR = 140.6%) after RG catheterization ($p = .07$). ALP decreased by 23.5% (median; OQR = 113.2%) after NG catheterization compared to 8.9% (median; IQR = 94.2%) after RG catheterization ($p = .18$). GGT decreased by 38.5% (median; IQR = 90.0%) after NG catheterization compared to 14.8% (median; IQR = 66.2%) after RG catheterization ($p = .1$). From pre- to postoperative, TB decreased by 58.2% (median; IQR = 82.4%) after NG catheterization compared to 0.0% (median; IQR = 133.7%)

after RG catheterization ($p = .001$). Of 69 dogs with preoperative TB above RR, 46 dogs were catheterized NG and 23 dogs were catheterized RG. In this group, TB decreased by 70.3% (median; IQR = 45.3%) after NG catheterization compared to 39.1% (median; IQR = 88.1%) after RG catheterization ($p = .03$). Additionally, TB increased from pre- to postoperative in 29/117 (24.8%) dogs, including 10/67 (14.9%) dogs catheterized NG and 19/50 (38.0%) dogs catheterized RG ($p = .004$). In this group, TB increased by 61.4% (median; IQR = 250%) after NG catheterization compared to 100.0% (median; IQR = 816.6%) after RG catheterization.

3.8 | Outcome

One-hundred-one of 117 (86.3%) dogs survived to discharge, including 61/67 (91.0%) dogs catheterized NG and 40/50 (80.0%) dogs catheterized RG ($p = .23$). Time from surgery to discharge was 4 (median; IQR = 2) days for dogs catheterized NG and 5 (median; IQR = 3) days for dogs catheterized RG (range; 1–14 days) ($p = .12$). Sixteen of 117 (13.6%) dogs did not survive to discharge. Five dogs died prior to discharge, including 2 dogs catheterized NG and 3 dogs catheterized RG. Eleven dogs were euthanized prior to discharge, including 4 dogs catheterized NG and 7 dogs catheterized RG. Causes of euthanasia were similar for both groups and included severe presumptive pancreatitis, septic BP, pulmonary edema, and presumptive acute respiratory distress syndrome, systemic inflammatory response syndrome, disseminated intravascular coagulation, and/or multiorgan dysfunction.

Follow-up information of at least 6 months was available for 93/101 (92.1%) dogs that survived to discharge, including 53/61 (86.9%) dogs catheterized NG and 40/40 (100.0%) dogs catheterized RG. Sixty-two of 101 (61.4%) dogs were alive 6 months after surgery, including 38 (61.3%) dogs catheterized NG and 24 (38.7%) dogs catheterized RG. Thirty-one of 101 (30.7%) dogs died or were euthanized within 6 months postoperatively, including 15 (48.4%) dogs catheterized NG and 16 (51.6%) dogs catheterized RG ($p = .49$).

4 | DISCUSSION

For dogs undergoing open cholecystectomy for GBM with either NG or RG catheterization of the cystic duct and CBD, both techniques are options for surgeons treating GBM. Dogs catheterized RG were more likely than dogs catheterized NG to experience any postoperative complication, most notably persistence of gastrointestinal signs. Although dogs in the RG group showed less improvement than dogs in the NG group in all liver enzyme activities from pre- to postoperative, the difference was only significant for TB concentrations. The greater reduction in TB after NG catheterization compared to RG catheterization from pre- to postoperative and the persistence of gastrointestinal signs after RG catheterization might reflect tissue injury associated with RG catheterization. Duodenotomy and manipulation of the MDP and peripancreatic region during RG catheterization could contribute to prolonged mild EHBO and persistent clinical signs and elevations of TB. Importantly, although dogs catheterized RG experienced more frequent persistent gastrointestinal signs and more frequent and greater elevations in TB, survival was not adversely affected.

The treatment of choice for GBM is cholecystectomy,[1,6,9,12,16-18,25] and catheterization and flushing of the CBD is recommended by some investigators to confirm patency at surgery.[6,9-12,16,20,25] Although other investigators have reported they do not assess CBD patency intraoperatively,[1,6,18,20] techniques for evaluating patency of the cystic duct and CBD in dogs other than NG and RG catheterization include aspiration of the duodenum for bile and visual discernment of bile passage into the duodenum by detection of discoloration through an intact intestinal wall.[18] The absolute requirement for cystic duct and CBD catheterization and superiority of any catheterization technique is not yet known.[1,6,9-11,16,18]

The most commonly reported complications following biliary surgery include pancreatitis, surgical site dehiscence with BP and sepsis, and inflammatory response syndromes.[1,4,6,10-13,15,16,18,22] Complications associated with hyperbilirubinemia and surgery of the biliary tract affected dogs in both groups equally in this study and included postoperative pancreatitis, postoperative septic and non-septic BP, hypotension, and hemorrhage.[10-12,15,16,20] Pancreatitis was a major complication following cholecystectomy for dogs in both groups. Factors common to dogs in both groups that may have led to postoperative pancreatitis include hyperbilirubinemia, hemorrhage, and potential for endotoxin-mediated inflammatory responses, including hypotension causing decreased systemic perfusion and hypoperfusion of the pancreas.[10,12,15,16,20,26-28] Other factors include surgical manipulation in the right cranial abdomen, specific handling of the pancreas and duodenum, duodenal or biliary reflux, and concurrent endocrinopathies.[4,12,26-28] Although the incidence of postoperative pancreatitis was similar between groups, it is possible that some dogs experienced subclinical postoperative pancreatitis following RG catheterization, causing EHBO within the peripancreatic portion of the CBD and prolongation of elevations in TB.[5,6,10,11,15,16,25-28]

Both bile and bacterial laden fluid may leak from a dehisced duodenotomy incision or an area of compromise in the biliary tree. As most cases of BP did not undergo exploratory surgery or necropsy, we were unable to discern the source of bile leakage in all dogs. It is therefore not possible to determine what role, if any, duodenal site dehiscence played in the development of BP in RG dogs. However, as 12 dogs developed BP, 6 in each group, and the rates of postoperative septic and nonseptic peritonitis and survival did not differ between groups, it is unlikely the duodenotomy site was a significant source of surgical site dehiscence in RG dogs. In cases in which the source of bile leakage was able to be identified, the biliary tract was implicated in all cases.

Dogs catheterized RG were more likely than dogs catheterized NG to have any postoperative complication, most notably persistence of gastrointestinal signs. Although duodenotomy in dogs catheterized RG did not likely contribute to postoperative BP, it is possible that entry into the gastrointestinal tract was still an additional source of morbidity, contributing to gastrointestinal complications such as ileus, persistent vomiting, regurgitation, ptyalism, diarrhea, or anorexia.[1,6,9,29,30]

Dogs catheterized RG were also more likely to experience "other" systemic complications not specifically related to the biliary tract. Hyperbilirubinemia is a known preoperative risk factor for death in dogs undergoing biliary surgery, and TB concentrations predict shorter survival times in dogs with GB disease due to the effects of EHBO on coagulability, vascular tone, and binding of endotoxin.[4-6,13,15,18,20,22] Anesthesia and surgical times were mildly but significantly prolonged for dogs catheterized RG and may have exacerbated the inflammatory effects of hyperbilirubinemia in these unstable patients, contributing to vasculitis, volume overload, and systemic inflammatory responses.[4,6,10,11,22,29-31] The presence of a diplomate surgeon at surgery was associated with a decrease in the incidence of any perioperative and postoperative complication in dogs in this study. This underscores the requirement for experienced surgical judgment as well as proficient surgical technique in the performance of biliary tract surgery.[11,18,20]

Total bilirubin decreased from pre- to postoperative by nearly 60% for dogs catheterized NG compared to 0% for dogs catheterized RG. As more dogs catheterized NG had preoperative TB concentrations above RR compared to dogs catheterized RG, lack of randomization may have contributed to this finding. We therefore evaluated further only those dogs in both groups with preoperative elevations in TB. For these subgroups, TB decreased by over 70% after NG catheterization compared to just over 39% after retrograde catheterization. Moreover, median TB concentrations actually increased from pre- to postoperative more commonly in dogs catheterized RG, increasing by 100% in dogs catheterized RG compared to 60% in dogs catheterized NG. The greater reduction in TB after NG catheterization compared to RG catheterization and the tendency for TB to increase substantially following RG catheterization from pre- to postoperative prompts consideration of the possible tissue effects of RG catheterization. It is possible mechanical injury associated with duodenotomy and repeated or sustained manipulation of the MDP with resultant tissue edema might cause transient swelling of the MDP or compression of the CBD, prolonged mild EHBO, and persistent clinical signs and elevations of TB in dogs catheterized RG.[11,29-31] Further, displacement of bacteria from the gastrointestinal tract into the pancreatic duct, cystic duct, and hepatic ducts may occur more often with RG catheterization, leading to pancreatitis or cholangitis, respectively.[9,11,29,30] Finally, findings indicative of sustained or worsened cholestasis might be due to other hepatocellular diseases or to extension of the pathologic process underlying GBM into the intrahepatic biliary ducts or hepatic parenchyma, causing intrahepatic biliary stasis or hepatic necrosis.[1,11,25,26,28]

Although dogs catheterized RG suffered persistent gastrointestinal signs as well as persistent or worsened elevations in TB concentrations at discharge, survival was not negatively impacted. All dogs in the present study survived surgery, and survival to discharge and long-term survival did not differ between groups. Perioperative mortality (13.7%) was similar to mortality rates of 9%–19.6% reported in other recent studies.[1,3,6,8,16,18,22] Survival at 6 months following surgery in our study was 61.4% and is consistent with findings of previous studies that dogs that undergo cholecystectomy for GBM and survive the initial perioperative period have good long-term survival.[1,3,5,6]

The main limitation of this study is its retrospective nature. Lack of randomization and controls regarding treatment options and techniques as well as incomplete medical records and surgery reports are inherent to retrospective studies and may have impacted findings, therefore data were interpreted with caution. We elected to include both elective and emergent cases as surgeons operating GBM must choose whether to catheterize and catheterization technique, regardless of timing of presentation. However, including both elective and emergent cases created a more heterogeneous population of dogs. Differences in approach to diagnosis and treatment are common with multi-institutional studies, and choice of catheterization technique varied by institution and surgeon. Reference ranges for ALT, ALP, GGT, and TB differed between institutions, precluding comparison of absolute values. Calculation of the exact times from NG or RG catheterization to determination of clinical

laboratory values was not possible as surgery reports often did not include the exact time catheterization was completed, and times recorded for the end of surgery often included adjunctive procedures. Further, timestamps of clinical laboratory reports do not take into consideration any lag time between blood collection and testing of serum, which may have been significant in some cases. To normalize sampling times across groups, clinical laboratory values recorded from preoperative and postoperative for both groups were the results of the last sample taken before cholecystectomy and the last sample taken after cholecystectomy but prior to discharge, respectively. Diagnosis of postoperative pancreatitis in dogs in both groups was often presumptive based on clinical signs of gastrointestinal upset, abdominal discomfort, and US or CT findings consistent with pancreatitis. Pancreatitis is often a challenging diagnosis to standardize or confirm, and consideration should be given in future studies to routine abdominal US, together with supportive clinical laboratory testing such as canine pancreatic lipase immunoreactivity and pancreatic cytology or histopathology, when possible, to render more practical and reliable means for accurate diagnosis of pancreatitis and other postoperative complications in these cases. A diagnosis of postoperative BP was made based on clinical signs, US findings, and cytology of abdominal effusion, but the source of bile leakage was inconsistently identified due to the small number of animals undergoing additional surgery or necropsy. Finally, follow-up data were incomplete due to inability to reach some primary veterinarians or owners. Serial assessment of serum biochemical values following discharge would have permitted calculation of time to resolution of clinical laboratory abnormalities of dogs in both groups.

Findings of this study showed the incidence of postoperative complications related to the biliary tract such as pancreatitis and BP did not differ between groups, indicating both NG and RG catheterization techniques are options for surgeons treating GBM. Postoperative complications and clinical laboratory perturbations that develop or persist in dogs catheterized RG might require monitoring or treatment but are unlikely to affect survival. Such knowledge is useful for intraoperative decision-making, postoperative management, and prognostication following cholecystectomy in dogs with GBM. Experienced surgical judgment and dexterity are useful for successful treatment of GBM, and surgery should be performed or supervised by surgical diplomates experienced in biliary surgery to minimize perioperative and postoperative complications. Finally, randomized, prospective, longitudinal studies are required to determine the impact of cholecystectomy and NG or RG catheterization of the cystic duct and CBD on resolution of clinical laboratory abnormalities and survival in dogs with GBM.

AUTHOR CONTRIBUTIONS

Allison Putterman, VMD; Medical record review, acquisition, analysis, and interpretation of data, writing, drafting, and revision of the work, and final approval of the submitted manuscript. Laura E. Selmic, BVetMed (Hons), MRCVS, MPH, DACVS-SA, DECVS; Design of the work performed, statistical analysis and interpretation of data, revision of the work, and final approval of the submitted manuscript. Cameron Kindra, DVM; Medical record review, acquisition of data, and final approval of the submitted manuscript. Daniel J. Duffy, BVM&S (Hons), MS, FHEA, MRCVS, DACVS-SA, DECVS; Acquisition of data, revision of the work, and final approval of the submitted manuscript. Marije Risselada, DVM, PhD, DACVS-SA, DECVS; Acquisition of data, revision of the work, and final approval of the submitted manuscript. Heidi Phillips, VMD, DACVS-SA; Design of the work performed, acquisition and interpretation of data, writing, drafting, and revision of the work, and final approval of the submitted manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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