

# Association between biliary tree manipulation and outcome in dogs undergoing cholecystectomy for gallbladder mucocele: A multi-institutional retrospective study

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## Abstract

**Objective:** To determine whether catheterization of the common bile duct (CBD) is associated with outcome in dogs undergoing cholecystectomy for gallbladder mucocele and to determine whether this association is modified by the catheterization method.

**Study design:** Multi-institutional retrospective cohort study.

**Animals:** Dogs (n = 252) that underwent cholecystectomy for gallbladder mucocele.

**Methods:** Dogs were identified via electronic medical record review at four veterinary teaching hospitals. Baseline dog characteristics, surgical findings, and methods including normograde vs retrograde CBD catheterization, intraoperative outcomes, and postoperative outcomes and complications were recorded. Variables were compared between dogs with and without catheterization.

**Results:** Catheterized dogs had higher American Society of Anesthesiologists scores ( $P = .04$ ), higher total bilirubin ( $P = .01$ ), and were more likely to have dilated CBD at the time of surgery ( $P < .01$ ). Incidence of major and minor intraoperative complications was similar between the two groups. Surgical time was longer for the catheterized group ( $P = .01$ ). The overall incidence of postoperative complications was similar between the groups; however, postoperative pancreatitis was associated with performing CBD catheterization ( $P = .01$ ). This association was retained as an independent association in a

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multivariable model that addressed baseline group differences ( $P = .04$ ). Likelihood of developing postoperative pancreatitis was not different between normograde and retrograde catheterization ( $P = .57$ ).

**Conclusion:** Catheterization of the CBD was associated with development of postoperative pancreatitis. This was not influenced by the method of catheterization.

**Clinical significance:** The requirement for catheterization of the CBD during open cholecystectomy in dogs should be carefully considered, particularly in dogs without evidence of biliary obstruction because the procedure may induce postoperative pancreatitis.

## 1 | INTRODUCTION

Gallbladder mucoceles (GBM) represent one of the most common indications for biliary tract surgery in dogs.<sup>1,2</sup> Surgical intervention via cholecystectomy is considered the treatment of choice for dogs with symptomatic GBM.<sup>3</sup> There are, however, notable perioperative complications associated with canine biliary surgery, including hypotension, systemic inflammatory response, pancreatitis, disseminated intravascular coagulation, pulmonary thromboembolism, multiple organ dysfunction including respiratory and renal failure, anemia, and death.<sup>1,2,4</sup> Mortality rates associated with cholecystectomy in dogs remain high, with a recently reported 20% failure to survive to hospital discharge in dogs undergoing nonelective cholecystectomy.<sup>5</sup>

Intraoperative catheterization and flushing of the common bile duct (CBD) has been suggested to form a crucial component of performing a cholecystectomy to confirm patency of the CBD; normograde catheterization via cholecystostomy and retrograde catheterization via duodenotomy have been described.<sup>6</sup> Proposed benefits of intraoperative flushing include reduced risk of compromised bile flow postoperatively because of residual bile plugs or choleliths.<sup>7</sup> There is some uncertainty, however, about the absolute requirement for routine catheterization and flushing of the biliary system.<sup>8</sup> Researchers in one study found no significant association between catheterization and postoperative outcome; however, this study was limited to 43 dogs.<sup>2</sup> Authors of another report described similar outcomes between 10 catheterized dogs and 38 dogs that received no catheterization; however, the impact of biliary tree catheterization in this context was not the primary focus of the study.<sup>6</sup> Cannulation of the major duodenal papilla with subsequent injection of saline as well as various contrast mediums into the pancreatic duct caused pancreatitis in all dogs in an experimental model for endoscopic retrograde cholangiopancreatography.<sup>9</sup> This finding raises concerns

that dogs undergoing CBD catheterization and flushing during cholecystectomy for GBM may be experiencing morbidity from the procedure that has not yet been accurately attributed. Equally, the benefit of catheterization and flushing has not been well established and may be restricted to a subset of dogs with specific indications.

To the best of the authors' knowledge, previously published studies have not specifically sought to establish the risks and benefits associated with biliary catheterization in a large number of dogs undergoing cholecystectomy for GBM. This would be a prerequisite for implementing a randomized controlled trial to investigate outcomes after this intervention. The objective of this study was to determine whether catheterization of the biliary tree was associated with outcome in dogs undergoing cholecystectomy for GBM and whether the method of catheterization, normograde or retrograde, was influential on outcome. Based on clinical impression as well as the studies previously mentioned, our hypothesis was that no difference in positive or negative outcomes would be noted between catheterization vs no catheterization of the CBD.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

This was a retrospective cohort study in which we evaluated associations between catheterization and flushing of the CBD and intraoperative and postoperative outcomes in dogs that underwent a cholecystectomy after diagnosis of GBM. Dogs were identified by electronic record search, and record review was conducted by two investigators (H.J.P. and S.L.) at four veterinary teaching institutions (Cornell University Hospital for Animals, Ontario Veterinary College, Michigan State University Veterinary Medical Center, North Carolina State Veterinary Hospital). Dogs were considered eligible for inclusion when a GBM

had been diagnosed by abdominal ultrasound or by computed tomography, dogs had undergone cholecystectomy between January 29, 2008 and October 11, 2018, and a full surgical report and outcome information to the time of hospital discharge was on file. Dogs were subsequently excluded when the cholecystectomy was performed laparoscopically, choleliths, were identified in the biliary tree by imaging or at the time of surgery, a neoplastic diagnosis of the biliary tree was reached, or a choledochal stent was placed.

## 2.2 | Data collection

Information was collected on intraoperative outcomes, including intraoperative death; iatrogenic injury to a hepatic duct, CBD, or cystic duct; and hemorrhage. The surgical time was also recorded. For dogs in which sequential serum total bilirubin data were available, the rate of postoperative change of total bilirubin was calculated as (preoperative measurement closest to surgery – postoperative measurement longest from surgery) / (hours from surgery to postoperative measurement) and recorded. New onset postoperative complications were defined and recorded as follows.

1. Requirement for oxygen support: the dog was assessed as requiring oxygen support by oxygen cage or nasal catheter in the postoperative period.
2. Pancreatitis: diagnosis was made on the basis of clinical signs (vomiting, atypical abdominal pain, anorexia) and characteristic ultrasonographic/laboratory findings (elevated specific canine pancreatic lipase  $\pm$  pancreatic enlargement, hypoechoic regions within the pancreas, hyperechoic peripancreatic fat).
3. Acute kidney injury: urine output  $<1$  mL/kg/hour, serum creatinine increase  $>1.5$  times baseline, or serum creatinine increase  $>0.3$  mg/dL from baseline.
4. Persistent biliary stasis: failure of serum total bilirubin to decrease below preoperative values during the hospitalization period combined with a poor clinical response to surgery (persistent anorexia and nausea).
5. Euthanasia or death within the hospitalization period: Dogs qualifying for multiple categories were assigned to the category that was assessed to be the most severe problem by the attending clinician. The duration of the hospital stay and the time from surgery to the last recorded follow-up with the dog was also recorded.

Baseline characteristics data were also collected, including age; sex; breed; duration of clinical signs; admission illness severity based on acute patient physiologic and laboratory evaluation score (10 variable when

data were available, otherwise 5 variable)<sup>10</sup>; American Society of Anesthesiologists (ASA) score<sup>11</sup>; admission serum total bilirubin and alanine aminotransferase levels; whether multiple procedures were performed at the time of surgery; and whether bile peritonitis, gallbladder rupture, or CBD dilation was identified by abdominal exploration.<sup>10,11</sup> Finally, details of the CBD catheterization procedure, such as success and method of access (normograde vs retrograde), were recorded.

According to pilot data ( $n = 20$ ), the estimated rate of decline of serum total bilirubin after cholecystectomy in uncatheterized dogs would be  $0.05 \pm 0.07$  mg/dL/hour. Detecting an increase in this rate of decline to 0.1 mg/dL/hour would require a minimum of 32 dogs per group to achieve 80% power at 5% significance.

## 2.3 | Statistical analysis

Because this was a nonrandomized study, case selection bias was anticipated. It was expected that this would result in baseline differences between the catheterized and uncatheterized groups that might in turn predispose the groups to differences in outcome. Data on these differences were collected to facilitate an adjusted as well as an unadjusted analysis. Missing data were not imputed, and the proportion of missing data points for any variable with missing data was reported.

Group differences in categorical data were tested by using the  $\chi^2$  test when cell numbers were  $> 5$  or by using Fisher's exact test when cell numbers were  $< 5$ . Continuous data were evaluated for normal distribution by using the Shapiro Wilk test and were reported as mean  $\pm$  SD when they were normal and reported as median (interquartile range) when they were not normal. Group differences in continuous normal data were tested by using Student's  $t$  test, and group differences in nonnormal data were tested by using the Mann Whitney  $U$  test.

The unadjusted odds ratio (OR) for developing postoperative pancreatitis in the catheterized group was calculated by using exact univariable logistic regression and the likelihood ratio test. The OR after adjusting for between group differences in potential confounders was calculated by using multivariable logistic regression. Proportions were reported with 95% CI when this was assessed as likely to have clinical utility. Data were analyzed in Stata 15 (StataCorp, College Station, Texas).

## 3 | RESULTS

In total, GBM was diagnosed in 262 dogs (Ontario Veterinary College  $n = 92$ , Cornell University  $n = 63$ , Michigan

State University  $n = 56$ , North Carolina State University  $n = 51$ ) by using abdominal ultrasound or computed tomography (CT), and these dogs underwent surgery during the study period. Five dogs were subsequently excluded because the procedure had been performed laparoscopically, and five dogs that were identified with palpable choleliths in the biliary tree at surgery were also excluded because this represented an absolute indication to catheterize and flush the biliary tree. Neither neoplastic diagnosis nor placement of a choledochal stent was determined in any dog. Among the remaining 252 dogs, 245 dogs underwent open exploratory surgery as the planned intervention, while seven surgeries were

converted to open procedures during laparoscopic cholecystectomy. Intraoperative data were available for all dogs. Postoperative data were unavailable for three dogs because they died intraoperatively.

Dogs were divided into groups in which catheterization and saline flushing of the biliary tree was attempted or performed ( $n = 157$ ) and those in which there no catheterization of the biliary tree was performed ( $n = 95$ ). In eight of the uncatheterized dogs, intraoperative duodenal needle aspirate was used to confirm the presence of bile (based on a gross visual appearance consistent with bile) in the duodenum. The baseline characteristics and intraoperative findings in these two groups were recorded

**TABLE 1** Baseline characteristics and intra-operative findings for dogs receiving cholecystectomy for gallbladder mucocele ( $n=252$ )

Characteristic	Catheterized, $n = 157$	Uncatheterized, $n = 95$	P value
Sex, $n$			
Intact female	2	2	
Spayed female	77	48	
Intact male	5	1	
Neutered male	73	44	.739
Age, years	$10 \pm 2.6$	$10.2 \pm 2.6$	.681
Breed, $n$			
Mixed	33	24	
Shetland sheepdog	20	11	
Cocker spaniel	18	7	
Miniature schnauzer	7	10	
Beagle	7	7	
Other	72	36	.263
Clinical signs duration, duration, days	4 (2-7)	3 (2-8)	.83
Data not available, $n$	7	11	
APPLE score mortality probability risk, %.	6.9 (2.7-16.0)	4.4 (1.7-10.6)	.12
APPLE data not available, $n$	47	42	
ASA score $\pm$ SD	$3.06 \pm 0.73$	$2.87 \pm 0.67$	.04
ASA data not available, $n$	17	5	
Icteric at admission PE (%)	36.3	20	.01
to Admission TBILI, mg/dL	2.3 (0.6-5.2)	0.4 (0.1-3.1)	<.01
TBILI data not available, $n$	20	8	
U/L to Admission ALT, U/L	859 (210-1531)	471 (123-1344)	.01
ALT data not available, $n$	22	9	
Concurrent procedure, %	27.4	32.6	.38
Bile peritonitis, %	4.5	5.3	.77
Gallbladder rupture, %	23.1	14.7	.16
CBD dilation, %	57.3	36.8	<.01

Means are reported as mean $\pm$ SD. Medians are reported as median (interquartile range).

Note:  $N = 252$ .

Abbreviations: ALT, alanine aminotransferase; APPLE, acute patient physiologic and laboratory evaluation; ASA, American Society of Anesthesiologists; CBD, common bile duct; PE, physical examination; TBILI, total bilirubin.

**TABLE 2** Details of catheterization method procedural success, intra-operative injuries to the biliary tree, and post-operative pancreatitis incidence by catheterization method (n=157)

CBD catheterization method	Attempts made, n	Failures, n	Hepatic duct injury, n	Cystic duct injury, n	CBD injury, n	Postoperative pancreatitis, n	Surgical time, median, min
Normograde	87	2	0	4	1	7	103
Retrograde	59	3	1	4	0	7	118
Normograde & retrograde	11	0	1	0	0	0	130

Note: N = 157.

Abbreviations: CBD, common bile duct.

(Table 1). In brief, the catheterized dogs were more unstable with higher ASA scores ( $P = .04$ ), had more severe cholestasis ( $P = .01$ ), and were more likely to have

dilated CBD identified either by preoperative imaging or intraoperatively ( $P < .01$ ). Similar proportions of each group had been hospitalized for management prior to

**TABLE 3** Outcome data by catheterization group for dogs receiving cholecystectomy for gallbladder mucocele (n=252)

Outcome	Catheterized, n = 157	Uncatheterized, n = 95	P value
Major intraop complications			
Cardiac arrest, n	1	2	
Hepatic duct tear, n	2	0	
Common bile duct tear, n	1	1	
Total, n (%)	4 (2.6)	3 (3.2)	>.99
Minor intraop complications			
Cystic duct tear, n	8	6	
Gallbladder rupture, n	5	2	
Hemorrhage, n	7	0	
Total, n (%)	20 (12.7)	8 (8.4)	.408
Surgical time, minutes	110 (85-130)	75 (60-105)	<.01
Postoperative rate of change in TBILI, mg/dL/hour	-0.05 ± 0.08	-0.05 ± 0.07	0.64
TBILI data not available, n	59	50	
Postop complications, n			
Oxygen support required	5	2	
Pancreatitis	14	1	
AKI	8	8	
Persistent biliary stasis	2	1	
Euthanasia	6	4	
Death	4	3	
Total	39	19	.38
Days from surgery until discharge.	3.7 ± 2.3	3.0 ± 1.8	.02
Follow-up available for a minimum of 30 d postdischarge, n (%)	68 (43)	35 (37)	.07

Note: N = 252.

Abbreviations: AKI, Acute Kidney Injury; ALT, alanine aminotransferase; APPLE, acute patient physiologic and laboratory evaluation; ASA, American Society of Anesthesiologists; CBD, common bile duct; intraop, intraoperative; PE, postop, postoperative; Sx, TBILI, total bilirubin. For continuous data means are reported as mean±SD. medians are reported as median (interquartile range).

**TABLE 4** Multivariable model for prediction of postoperative pancreatitis outcome

Variable	OR	95% CI	P value
CBD catheterization	8.1	1.1-63.9	.04
ASA score	1.6	0.8-3.4	.20
Presence of icterus on admission	0.8	0.2-2.4	.64
Presence of CBD dilation	1.6	0.5-5.0	.45

Note: N = 249.

Abbreviations: ASA, American Society of Anesthesiologists; CBD, common bile duct; OR, odds ratio.

referral (in the catheterized group, 70/157 [44.6%] and in the uncatheterized group, 42/95 [44.2%]). Among the 157 dogs in which catheterization was attempted, there were no cases in which it was ultimately unsuccessful. However, two normograde catheterizations required conversion to retrograde catheterization, and three retrograde catheterizations required conversion to normograde catheterization. The details of the method of catheterization of the 157 catheterized cases were recorded (Table 2). While flushing with sterile saline was reported in all cases, there was limited extractable information regarding flush volumes and pressures. There was no difference in surgical time between dogs that received normograde vs retrograde catheterization ( $P = .16$ ).

The incidence of major and minor intraoperative complications was similar between the uncatheterized and catheterized groups. The surgical time was a median of 35 minutes longer in the catheterized group ( $P = .01$ ). The rate of postoperative change in serum total bilirubin levels was similar between the two groups, with a mean decrease of 0.05 mg/dL/hour for both groups ( $P = .64$ ). The overall incidence of postoperative complications was not different between the two groups ( $P = .38$ ), with an overall incidence risk of 58 of 252 (23%; 95% CI = 18%–28.7%); however, 14 of 15 dogs in which postoperative pancreatitis was diagnosed were in the catheterized group (OR = 9.02, 95% CI = 1.3-387.6,  $P = .01$ ). In a multivariable model in which the baseline group differences on illness severity, icterus, and CBD dilation were controlled for analytically, the association between undergoing CBD catheterization and postoperative pancreatitis remained (adjusted OR = 8.1 (95% CI = 1.1-63.9,  $P = .04$ )). The details of the outcome data by catheterization group and the multivariable model used to obtain the adjusted OR were recorded (Tables 3 and 4).

Catheterized dogs remained in the hospital for an average of 0.7 days longer compared with uncatheterized dogs ( $P = .02$ ). When outcomes were differentiated by the method of catheterization, whether normograde or

retrograde, no difference in pancreatitis incidence was detected between the normograde and retrograde groups (7/85 vs 7/56;  $P = .41$ ). No difference was identified in intraoperative biliary tree injury between the two methods (5/87 vs 5/59;  $P = .53$ ). No incidence of dehiscence of the enterotomy site made for retrograde catheterization was reported in any dog. No dog required conversion to a cholecystoenterostomy. No cases were surgically retreated for persistent biliary obstruction.

## 4 | DISCUSSION

The objective of this study was to determine whether catheterization of the CBD during open cholecystectomy for a GBM was associated with outcome as well as to determine whether catheterizing via a normograde vs a retrograde technique affected outcome. Catheterization of the CBD was associated with an increased risk of pancreatitis in both unadjusted analysis and after statistical control of group differences. Catheterization was also associated with longer surgical time. Catheterization was not associated with a more rapid rate of decline of serum bilirubin levels postoperatively. The method of catheterization, specifically normograde vs retrograde, did not appear to have a differential association with subsequent development of pancreatitis.

In-hospital mortality risk in this study was relatively low at 17 of 252 (6.7%) and was comparable to other recent studies with mortality risks ranging between two of 43 (4.7%)<sup>2</sup> and six of 70 (8.5%)<sup>5</sup>; this may reflect a trend toward earlier treatment of dogs in which GBM has been diagnosed.

An association between pancreatitis and GBM has been previously reported.<sup>12</sup> Proposed mechanisms include hyperlipidemia and corticosteroid hormones contributing to both disease processes as well as bile stasis within the biliary tree secondary to pancreatitis influencing GBM formation. It is possible that dogs with GBM are hormonally predisposed to developing pancreatitis, with the pancreatitis event precipitated by CBD flushing.

There is a close anatomic association between the pancreatic duct and the CBD in the dog. The pancreatic duct conjoins with the CBD at the level of the duodenal papilla, while the accessory pancreatic duct opens via a separate orifice more aborad within the duodenum; cross connection pathways between the pancreatic and accessory pancreatic ducts are highly variable in morphology but are typically present.<sup>13</sup> The pancreatic duct is protected in the normal state from reflux of bile and duodenal contents by an independent crescentic sphincter muscle.<sup>14</sup> Manual reflux of bile into the pancreatic duct is a well-described experimental method for induction of

severe acute pancreatitis in the canine. In this model, the CBD is catheterized at the duodenal papilla and then occluded manually proximally. Slow injection of autologous bile follows, such that reflux of bile into the pancreatic duct system is achieved; this intervention has been shown in multiple studies to reliably induce acute necrotizing pancreatitis with secondary multiple organ dysfunction syndrome of a variable degree of severity.<sup>15</sup> Unfortunately, it appears possible that the common surgical practice of saline flushing of the CBD with supraphysiologic pressures during cholecystectomy for GBM may inadvertently cause reflux of biliary secretions into the pancreatic duct resulting in the association with acute pancreatitis identified in this study. An alternate hypothesis is that the placement of a catheter may result in trauma to the major duodenal papilla, resulting in inflammation and transient occlusion of the pancreatic duct orifice at this site. A similar mechanism has been hypothesized as an explanation for postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in man. In this syndrome, an increased number of injections as well as increased cannulation difficulty has been associated with pancreatitis.<sup>16</sup> This procedure also reliably induces pancreatitis in a canine model, with a 100% incidence of histologic inflammation of the pancreas after ERCP.<sup>9</sup> Repeated handling of the pancreas during catheterization and/or inadvertent cannulation of the pancreatic duct are potential additional mechanisms.

No other outcome differences were found between the catheterized and uncatheterized groups other than a shorter surgical time. Given the increased odds of developing pancreatitis with no apparent beneficial outcome of the measured variables in this study, these findings challenge some of the current dogma that flushing of the CBD when performing a cholecystectomy for GBM is critical. To the contrary, our study data provide evidence that routine flushing of the CBD in cases with GBM may not be beneficial and can be associated with morbidity. Acute pancreatitis has a high mortality rate in veterinary medicine, ranging from 27%–58%, underscoring the significance and clinical relevance of the development of this complication.<sup>17</sup> Thus, catheterization and flushing of the CBD should be used judiciously and only when clinically warranted in select cases, such as when imaging findings raise concerns for concurrent cholelithiasis, biliary tree dilation consistent with biliary obstruction is identified, or there is suspicion for biliary tree perforation. In these cases, the risk of leaving obstructive disease untreated must offset concerns regarding the morbidity of the intervention.

In the field of biliary surgery performed in man, this issue is similarly controversial, although some notable differences apply. Cholecystectomy is typically performed

laparoscopically and for management of cholelithiasis.<sup>18</sup> Concurrent intraoperative imaging of the biliary tree to assess for obstructive choleliths may be performed electively or routinely, depending on the treatment center. Imaging is typically performed by endoscopic cannulation of the duodenal papilla and retrograde contrast fluoroscopy; this has been reported to carry a 3.5% risk of inducing pancreatitis<sup>19</sup> but may also be performed by laparoscopic ultrasound.<sup>20</sup> When choleliths are identified, they are preferably managed by minimally invasive techniques, including basket retrieval via the duodenal papilla after sphincterotomy, transcystic basket retrieval, laparoscopic choledochotomy, or laser lithotripsy.<sup>21</sup> Flushing expulsion is rarely performed because of the risk of pancreatic and biliary tree injury.<sup>21</sup> There is active research on the introduction of minimally invasive techniques into the field of veterinary choledocholithiasis management.<sup>22</sup>

Limitations of this study result primarily from its retrospective and nonrandomized nature. Differences between the groups, such as the catheterized group having a higher ASA score, more severe cholestasis, and dilation of the CBD, could have confounded the results despite attempts at analytic control with the use of a multivariable model. Type II error is possible, with failure to identify further differences between the two groups as well as wide CI for the strength of any associations that were identified. In addition, information or selection bias is possible because of reliance on retrospective data and surgical reports. Assignment of dogs to the “pancreatitis” outcome was based on clinical diagnosis recorded in the medical record by the supervising clinicians at the time of the patient’s hospitalization. The tests applied to determine this diagnosis were applied variably depending on the clinicians involved, the clinical presentation, and the owner’s financial resources. It is also possible that some of the dogs in which pancreatitis was diagnosed postoperatively had pancreatic inflammation prior to their surgical procedure.

Overall, the major difference between the catheterized and uncatheterized groups was an increased odds of developing postoperative pancreatitis in the catheterized group. This finding challenges the concept that catheterization and flushing of the CBD is an essential step for all dogs undergoing open cholecystectomy for GBM. While catheterization of the CBD should still be pursued in light of specific concerns such as lack of integrity or patency of the CBD, routine catheterization in dogs undergoing a cholecystectomy for GBM should be questioned because of possible morbidity. An informed consent randomized clinical trial is warranted to further elucidate the potential benefits and risks of flushing the

CBD in dogs undergoing a cholecystectomy for GBM because of potential postoperative morbidity.

## ACKNOWLEDGMENTS

### AUTHOR CONTRIBUTIONS

Piegols HJ, DVM: Acquisition of data, interpretation of data, drafting of the work, revision of the work, and final approval of the article; Hayes GM, BVSc, PhD, MRCVS, DACVS, DACVECC: Design of work, acquisition of data, analysis of data, interpretation of data, drafting of the work, revision of the work, and final approval of the article; Lin S, DVM: Acquisition of data; Singh A, DVM, DVSc, DACVS: Acquisition of data, revision of the work, and final approval of the article; Langlois DK, DVM, DACVIM: Acquisition of data, revision of the work, and final approval of the article; Duffy DJ, BVM&S, MS, FHEA, MRCVS, DACVS-SA, DECVS: Acquisition of data, revision of the work, and final approval of the article.

This paper is dedicated in loving memory of Samantha Lin.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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**How to cite this article:** Piegols HJ, Hayes GM, Lin S, Singh A, Langlois DK, Duffy DJ. Association between biliary tree manipulation and outcome in dogs undergoing cholecystectomy for gallbladder mucocele: A multi-institutional retrospective study. *Veterinary Surgery.* 2021;50:767-774. <https://doi.org/10.1111/vsu.13542>