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Prevalence and clinical relevance of cholelithiasis in cats: A multicenter retrospective study of 98 cases

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Abstract

Background: Cholelithiasis is an uncommon and mainly incidental finding in dogs; current literature on this topic is scarce in cats.

Hypothesis: Report prevalence, clinical presentation, management, and outcome of cholelithiasis in cats.

Animals: Ninety-eight cats with cholelithiasis.

Methods: Retrospective multicenter case series. Electronic databases from 3 hospitals were searched for cats diagnosed with cholelithiasis by ultrasonography (US). Cholelithiasis was classified as incidental (IC) or symptomatic (SC) depending on clinicopathological signs, biliary tract US appearance, and presence of another disease potentially explaining the clinical presentation. Multivariate analysis was used to investigate factors associated with clinical expression of cholelithiasis and, within the SC group, survival.

Results: The observed prevalence of cholelithiasis was 0.99% (95% confidence interval [CI], 0.79%-1.19%) among cats that underwent abdominal US. Cholelithiasis was classified as IC in 41% and SC in 59%. Choleliths found in multiple locations within the biliary tract (odds ratio [OR], 8.11; 95% CI, 2.32-34.15; $P = .001$) or associated with US signs of obstruction (OR, 18.47; 95% CI, 2.13-2413.34; $P = .004$) were significantly associated with SC. Concurrent hepatobiliary diseases were suspected or confirmed in 83% of cases with SC. Forty-three cats (74%) with SC survived to discharge. Biliary tract obstruction (BTO) was negatively associated with survival (OR, 13.87; 95% CI, 1.54-124.76; $P = .001$). None of the cats with IC that had available follow-up (47%) developed clinicopathological signs related to cholelithiasis.

Conclusions and Clinical Importance: Cholelithiasis is uncommon and can be asymptomatic in cats. Symptomatic cholelithiasis frequently is associated with another hepatobiliary disease or BTO or both. Biliary tract obstruction is associated with poorer outcome.

Abbreviations: AICc, Akaike information criterion corrected; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCS, body condition score; BTO, biliary tract obstruction; CBD, common bile duct; CCH, cholangitis/cholangiohepatitis; CE, chronic enteropathy; CI, confidence interval; IC, incidental cholelithiasis; IQ, interquartile; OR, odds ratio; SC, symptomatic cholelithiasis; UDCA, ursodeoxycholic acid; US, ultrasonography.

KEYWORDS
cholelith, hepatobiliary disease, obstruction, risk factors, ultrasonography

1 | INTRODUCTION

Cholelithiasis has been reported as infrequent in dogs and cats, with most cases being diagnosed after death.[1] Advances in abdominal ultrasonography (US) have improved antemortem detection of cholelithiasis, and US has become the gold standard for the identification of choleliths in both people and small animals.[2-7] Cholelithiasis is reported in up to 20% of humans but is considered an asymptomatic and incidental finding in 80% of cases.[8-10] In contrast, prevalence reported in dogs ranges from 0.03% to 13% with a more recent prevalence of 0.97% in a population of dogs undergoing abdominal US.[6,11,12] As in humans, choleliths are considered to be asymptomatic in 53% to 87% of dogs.[6,7]

Most incidental cholelithiasis in humans remains asymptomatic throughout life and treatment is rarely required. However, ~20% of patients with cholelithiasis develop clinical signs within 20 years of detection.[11,13] When cholelithiasis becomes symptomatic, surgical management by cholecystectomy or medical dissolution using ursodeoxycholic acid (UDCA) can be attempted.[5,8] The natural course of incidental cholelithiasis has been reported once in dogs, with <8% developing clinical signs.[6] Several surgical procedures have been described for the management of cholelithiasis including cholecystectomy, cholecystotomy, cholecystoenterostomy, choledochotomy, or temporary bile duct stenting.[7,14-16] The use of UDCA for cholelith dissolution is poorly described in veterinary medicine, with 1 study reporting complete resolution of cholelithiasis in 4/8 dogs.[7,17] Its efficacy in cholelith dissolution has not been reported in cats.

Several small case series of cholelithiasis in cats have been described,[14,16,18-27] but the prevalence of cholelithiasis has never been reported in a large cohort. Because cholelithiasis was mainly associated with biliary tract obstruction (BTO) in prior publications, medical management of cats without obstruction has not been widely investigated. Moreover, to our knowledge, cholelithiasis has been reported as an incidental finding in only 2 cats and no follow-up was available.[27,28]

Because the veterinary literature on cholelithiasis in cats is scarce, our objectives were (1) to determine the prevalence of cholelithiasis in cats, (2) to describe clinicopathological features, management, and outcome, (3) to identify potential risk factors associated with clinical expression of cholelithiasis, and (4) to report prognostic factors in the subgroup of cats with symptomatic cholelithiasis (SC).

2 | MATERIALS AND METHODS

2.1 | Case selection criteria

A retrospective review of medical records from 3 veterinary teaching hospitals (Veterinary Teaching Hospital of the National Veterinary School of Alfort, Maison-Alfort, France; Veterinary Teaching Hospital of VetAgro Sup, Campus Vétérinaire de Lyon, France and Veterinary Teaching Hospital of Oniris, Nantes, France) was performed to search for cats diagnosed with cholelithiasis by US between January 2010 and December 2021. Cases were identified by searching the electronic patient database for the terms "cholelith," "cholelithiasis," "gallbladder stone," "biliary stone," and "bile stone." Cats were excluded if cholelithiasis was detected by an imaging modality other than US, or if results of abdominal US were equivocal. Abdominal US was performed by a board-certified radiologist, a senior resident, or an advanced practitioner in diagnostic imaging.

2.2 | Medical records review

Data collected from the medical records included signalment (age, breed, sex, body weight, and body condition score [BCS]), clinical signs (anorexia, vomiting, diarrhea, lethargy, and weight loss), physical examination findings (pyrexia as defined by a rectal temperature >39.2°C, jaundice, and abdominal pain) and results of clinicopathologic tests. Given that the study was multicentric, involving various analyzers and reagents for blood testing, results were recorded as "normal," "increased" or "decreased" relative to each reference interval. For the most relevant biochemical variables (alanine aminotransferase [ALT]), alkaline phosphatase [ALP]), and bilirubin), a subcategory of ">2-fold increase" relative to their upper reference limit was added to consider their amplitude of increase for the multivariate analysis. Abdominal US reports were reviewed for estimated liver size, echogenicity, and homogeneity; gallbladder volume, wall thickness, and echogenicity; intrahepatic biliary duct, cystic duct, or common bile duct (CBD) dilatation and wall thickness; estimated pancreas size and echogenicity; pancreatic duct dilatation and wall thickness; and ileus and wall thickness of the digestive tract. The location and number of choleliths were recorded. Choleliths were considered as obstructive when biliary tract obstruction (BTO) was present (BTO was defined as dilatation of intrahepatic or extrahepatic biliary ducts or both [CDB dilatation ≥5 mm] reported upstream of the cholelith on US). Results of aerobic and anaerobic bacterial cultures (on bile, liver, or gallbladder samples), cytology (on bile or liver samples), and histology (on liver, gallbladder, pancreas, and digestive tract samples) were recorded.

For each case, cholelithiasis was classified as a "symptomatic" (SC) or an "incidental" (IC) finding. Cats were considered to be symptomatic for their cholelithiasis based on a combination of clinical signs (vomiting, diarrhea, abdominal pain, lethargy, anorexia, jaundice, or some combination of these), biliary tract US abnormalities (increased thickness or echogenicity of the biliary tract walls, dilatation of the gallbladder, cystic duct, CBD, or some combination of these), biochemical evidence of biliary disease (increased blood bilirubin

concentration, or liver enzyme activities, or both), and if no other disease was identified to explain the clinical presentation.[6] Final diagnosis or diagnoses (confirmed or presumptive) and concurrent diseases were recorded for all cases. Incidental cholelithiasis was considered in cats that did not have any clinical or biochemical findings attributable to cholelithiasis or when those changes could be attributed to another disease process and for which the biliary tract did not show other US abnormalities. Classification was supervised by a board-certified internist at each institution (Ghita Benchekroun, Emilie Krafft, and Juan Hernandez in veterinary teaching hospital of the national veterinary school of Alfort, veterinary teaching hospital of VetAgro Sup and Veterinary Teaching Hospital of Oniris, respectively). When classification of a case was not straightforward, an internist from another institution also reviewed the cat's medical record, and only cases for which both clinicians agreed were included. Treatments related to cholelithiasis were reviewed, including surgical procedures, use of ursodeoxycholic acid (UDCA), type and duration of antimicrobials, and administration of corticosteroids. Outcome, either survival to discharge or death during hospitalization (euthanasia or natural death), was evaluated.

When available, follow-up information was collected. Recurrence of clinical signs and development of complications attributed to cholelithiasis were recorded. Long-term outcome was recorded until last available follow-up or death.

2.3 | Statistical analysis

Statistical analyses were performed using R 4.1.2 software (R Foundation for Statistical Computing, Vienna, Austria). Non-parametric statistics were used to describe the population. Data were examined for normal distribution using the Shapiro-Wilk test. The means of continuous normally-distributed variables were compared using a *t* test. Non-normally distributed continuous data were reported as medians and were compared using the Mann-Whitney *U* test. Biological findings were summarized as the number and percentage of cases with a measured variable above, within, or below the reference interval and were compared using Fischer's exact test. Categorical variables were expressed as number and percentage and compared using Pearson's χ^2 test or Fischer's exact test.

The overall prevalence of cholelithiasis was calculated by dividing the number of cats with evidence of cholelithiasis by the total number of cats that underwent abdominal US over the same time period.

Multivariate analysis was performed to determine potential risk factors for clinical expression of cholelithiasis and short-term survival. Data from all included cats were used to evaluate factors associated with SC. Short-term survival was defined as survival to discharge and was evaluated only in the population with SC. Because of the retrospective nature of the data leading to a considerable proportion of missing information in medical records, separate multivariate logistic regression models were fit for each of the 5 types of information collected (epidemiology, clinical signs, CBC, biochemistry, and US findings) to maximize the number of cats with no missing data in each multivariate model. All variables collected with <50% missing information were included in the corresponding complete multivariate logistic model and variable selections were performed using the MuMin (Multi-Model Inference) package in R with the automated model selection option (dredge) to calculate the corrected second-order Akaike information criterion (AICc) for all possible sub-models. The final model was chosen as the most biologically and medically relevant among all sub-models with a difference of <2 AICc compared with the 1 with the lowest AICc.[29]

In the presence of separation (when the number of cats with certain risk factors was equal to 0, respectively, in SC or non-survivors), inference of the final multivariate model was performed using the logistf package[30]; otherwise inference was performed using the glm function of R. Both linear models were checked for homoscedasticity and random distribution of residuals, and correct fit of the logistic regression was assessed using Pearson residual analysis. All variables were null-checked using a Wald test and considered significant at a *P*-value <.05.

For treatment effect, a final model then was constructed as mentioned above, including all significant risk factors for non-survival previously identified and the implementation of a medical or surgical treatment or both. To assess the impact of the inclusion of non-treated cats in the survival analysis, the corresponding models were run again after excluding them.

3 | RESULTS

3.1 | Population description and demographic data

Ninety-eight cats were included in the study, with 51 cats from Veterinary Teaching Hospital of the National Veterinary School of Alfort, 29 from Veterinary Teaching Hospital of VetAgro Sup, and 18 from Veterinary Teaching Hospital of Oniris. Over the study period, 9805 cats underwent abdominal US, which led to an overall prevalence of cholelithiasis of 0.99% (95% CI, 0.79-1.19). Cholelithiasis was classified as incidental (IC) in 40/98 (41%) and as symptomatic (SC) in 58/98 (59%) cats.

Demographic data are presented in Table 1 and breeds are given in Supplementary Materials S1. Age ($P = .35$), sex ($P = 1$), body weight ($P = .47$), and BCS ($P = .92$) were not statistically different between IC and SC on univariate analysis.

Final diagnosis in cases with SC is presented in Table 2. Forty-eight cats were diagnosed with concurrent hepatobiliary disease (either confirmed [n = 26] or presumptive [n = 22]) including cholangitis/cholangiohepatitis (CCH; n = 27; 56%), cholecystitis (n = 11; 23%), both CCH and cholecystitis (n = 9; 19%) and hepatic lipidosis (n = 1; 2%). Based on cytologic or histologic results or both, it was possible to further classify concurrent hepatobiliary disease in 16 cases: CCH was classified as neutrophilic in 11 cases, lymphocytic in 2, and mixed in 3 cases. Other concurrent diseases included pancreatitis in 6 cats (presumptive in 4 and confirmed in 2), or chronic enteropathy (CE) in 8 cats (presumptive in 6 and confirmed in 2). In 10 cats with SC, cholelithiasis

TABLE 1 Population characteristics.

	Global population (n = 98)	Cats with symptomatic cholelithiasis (n = 58)	Cats with incidental cholelithiasis (n = 40)	*P*
Age[a,b] (n = 97)	11.6 (SD: 3.58; range: 3-19)	11.4 (SD: 3.49; range: 4-19)	12.1 (SD: 3.71; range: 3-8)	.35
Sex[a,c] (n = 97)				1
Intact females	1 (1%)	1 (1.7%)	0 (0%)	
Spayed females	35 (36%)	21 (36%)	14 (36%)	
Intact males	0 (0%)	0 (0%)	0 (0%)	
Castrated males	61 (63%)	36 (62%)	25 (64%)	
Body weight[a,d] (n = 92)	4.0 kg (IQ: 3.14-5.23; range: 1.5-9)	4.1 kg (IQ: 3.1-5.35; range: 1.5-9)	3.75 kg (IQ: 3.1-5; range: 2.1-8)	.47
Body condition score[a,d] (n = 87)	4/9 (IQ: 3-5; range: 1.5-8)	4/9 (IQ: 3-6; range: 1-9)	4/9 (IQ: 3.5-5; range: 2-7)	.92

Abbreviation: IQ, interquartile range; SD, standard deviation.
[a]For each parameter (number of cases with data available).
[b]Expressed as mean (SD; range) and compared by *t*-test.
[c]Expressed as number (percentage) and compared by Fisher test.
[d]Expressed as median IQ; (range) and compared by Mann-Whitney test.

was the sole diagnosis, of which it was obstructive (BTO) in 8 cases and non-obstructive in the other 2. Biliary tract obstruction was reported in 24 cases (43%) with SC. In cats with IC, diagnosis was achieved in 39 of 40 cases (98%) and is presented in Table 3.

Details about prior medications are provided in Supplementary Materials S2.

3.2 | Clinical and biological data

Frequencies of clinical signs at presentation and physical examination findings are presented in Table 4. Lethargy, vomiting, anorexia, jaundice, and pyrexia were significantly more frequent in cats with SC than in cats with IC on univariate analysis ($P < .05$). Clinical pathology results are presented in Table 5. As anticipated based on the inclusion criteria, increased serum bilirubin concentration and liver enzyme activity, including ALT, ALP, and aspartate aminotransferase (AST), were more common in cats with SC than in cats with IC on univariate analysis ($P < .05$).

3.3 | Abdominal ultrasound findings

Number and location of choleliths are reported in Table 6. According to imaging findings, choleliths most frequently were located within the gallbladder (69 cats; 70%), CBD (42 cats; 43%), cystic duct (24 cats; 24%), and intrahepatic biliary tract (22 cats; 22%). Cats with SC more often had multiple choleliths ($P < .001$) in multiple locations ($P < .001$) than did cats with IC on univariate analysis. Choleliths located within the CBD were more commonly symptomatic, compared with other locations ($P < .001$). Biliary tract obstruction was reported in 24 cats (41%) with SC, either alone (n = 8) or in combination with another hepatobiliary disease (n = 16), and in no cats with IC ($P < .001$).

Abdominal US findings are presented in Table 7. In addition to choleliths, biliary tract, gallbladder, liver, digestive tract, and pancreatic abnormalities were identified in 53 (54%), 64 (65%), 64 (65%), 46 (47%), and 43 (44%) cats, respectively. Ultrasonographic abnormalities of the biliary tract (SC, 44/58; IC, 9/40; $P < .001$), gallbladder (SC, 47/58; IC, 17/40; $P < .001$), liver (SC, 24/58; IC, 19/58; $P < .01$), and pancreas (SC, 31/58; IC, 12/40; $P = .02$) were more common in cats with SC compared with cats with IC on univariate analysis.

3.4 | Microbiological and histopathological data

Twenty-nine cats (30%) underwent cholecystocentesis, of which 28 cases had SC and 1 had IC. Bile cytology was performed in 18 cats (18%) and bile cultures (both aerobic and anaerobic) in 28 (29%) cats. Bile cytology identified neutrophilic inflammation in 6/18 samples and bacteria in 8/18. Bacterial cultures were positive in 17/28 samples and identified 1, 2, or 3 bacterial species in 12, 4 and 1 samples respectively. Cultures were positive in all 8 samples for which bacteria were identified on cytology. Results of bacterial culture are presented in Table 8. For the single cat with IC that underwent cholecystocentesis and for 2/10 cats where the sole diagnosis was cholelithiasis, bile cytology was unremarkable, and culture was negative.

Liver, gallbladder, pancreatic, and intestinal biopsies were performed in 13, 4, 2, and 2 cats, respectively. Liver biopsy was performed in 2 cats with IC and no cats with a final diagnosis of only SC. Results are presented in Supplementary Materials S2.

3.5 | Treatment

Among the 58 cats with SC, 33 (57%) received medical treatment alone and 13 (22%) required surgical intervention, combined (9 cats) or without (4 cats) medical management. Twelve cats (21%) did not receive any treatment, of which 7 were euthanized or died shortly after arrival and the others were discharged from the hospital. Among the cats with BTO, only 7 (29%) underwent surgical intervention,

TABLE 2 Diagnosis in cats with symptomatic cholelithiasis (n = 58).

Disease category	Individual diagnosis		Number of cats
Choleliths alone (n = 10)	Cholelithiasis		2
	Cholelithiasis + BTO		8[a]
Choleliths and concurrent hepatobiliary diseases (n = 48)	CCH (n = 13)[b]	CCH	7
		CCH + BTO	2
		CCH + BTO + presumptive[c] pancreatitis	1
		CCH + neutrophilic and lymphoplasmacytic pancreatitis[b] + lymphoplasmacytic enteritis[b]	1
		CCH + presumptive[c] CE	2
	Presumptive CCH (n = 14)[c]	CCH	5
		CCH + BTO	4
		CCH + BTO + lymphoplasmacytic enteritis[b]	1
		CCH + presumptive[c] CE	2
		CCH + presumptive[c] pancreatitis	1
		CCH + presumptive[c] pancreatitis + presumptive[c] CE	1
	Confirmed cholecystitis (n = 6)[b]	Cholecystitis	3
		Cholecystitis + BTO	1
		Cholecystitis + presumptive[c] CE	1
		Cholecystitis + presumptive[c] pancreatitis	1
	Presumptive cholecystitis (n = 5)[c]	Cholecystitis	4
		Cholecystitis + BTO	1
	Confirmed CCH and cholecystitis (n = 6)[b]	CCH + cholecystitis	2
		CCH + cholecystitis + BTO	3
		CCH + cholecystitis + BTO + suppurative and lymphoplasmacytic pancreatitis[b] + lymphoplasmacytic enteritis[b]	1
	Presumptive CCH and cholecystitis (n = 3)[c]	CCH + cholecystitis	1
		CCH + cholecystitis + BTO	2
	Hepatic lipidosis		1

Abbreviations: BTO, biliary tract obstruction, defined as dilation of intrahepatic and/or extrahepatic biliary ducts (common bile duct dilation ≥5 mm) reported upstream of the cholelith on ultrasonography; CCH, cholangitis/cholangiohepatitis; CE, chronic enteropathy.
[a]Bile cytology and culture was performed in 2/10 and liver histopathology in none.
[b]Diagnoses were confirmed based on compatible cytological and/or histological and/or bacterial analyses.
[c]Clinician-stated diagnosis based on clinicopathological data and ultrasonographic findings.

10 (42%) received medical management alone, and 7 (29%) were not treated, including, respectively, 2, 2, and 4 cats without suspicion or confirmation of concurrent hepatobiliary disease.

Medical management included antimicrobials in 39 (93%), UDCA in 21 (50%), and corticosteroids in 12 (29%) cases. Medical treatments are detailed in Supplementary Materials S3. Surgeries performed included cholecystoenterostomy in 8 cats, temporary bile duct stenting in 5 cats, and cholecystectomy, cholecystotomy, and choledochotomy in 2 cats each. Two or more surgical procedures were performed in 5 cases. None of the choleliths removed were submitted for composition analysis.

Among the 40 cats with IC, only 4 (10%) were prescribed UDCA for a median of 4 weeks (range, 4-8 weeks) and none underwent surgical removal of the choleliths.

3.6 | Outcomes

Forty-three cats (74%) with SC and 30 (75%) with IC survived to discharge. When focusing on cases with SC that were treated (n = 46), 38 (83%) survived to discharge, including 9/13 with surgical treatment and 29/33 with medical management ($P = .2$).

Among the 73 cats that survived to discharge, 40 (55%) had available follow-up, including 26 cats (60%) with SC (median follow-up time, 122 days; range, 46-4262 days) and 14 (47%) with IC (median follow-up time, 173 days; range, 4-464 days). Detailed data for short and long-term outcomes are presented in Figures 1 and 2. Of the 14 cats with IC that had follow-up available for review, none developed clinicopathological signs related to cholelithiasis. Among them, 5 had US re-evaluation of the biliary tract; choleliths were still present

in 2 cats. In contrast, for cats with SC, recurrent or persistent clinicopathological signs were reported in 5/26 cases (2 surgically and 3 medically treated), of which 3 had at least 2 relapses. One cat underwent cholecystectomy, 2 cats were medically managed (UDCA in 2, antibiotic in 1 and prednisolone in 1) and 2 were euthanized on days 46 and 122.

TABLE 3 Diagnosis in cats with incidental cholelithiasis (n = 40).

Disease category	Individual diagnosis	Number of cats
Neoplasia (n = 11)	Squamous cell carcinoma	1
	Lymphoblastic leukemia	1
	Alimentary lymphoma	1
	Digestive sarcoma	1
	Pancreatic carcinoma	1
	Pancreatic adenocarcinoma	1
	Hepatic carcinoma	1
	Mast cell tumor	1
	Pulmonary carcinoma	1
	Apocrine carcinoma	1
	Hepatic metastasis from an undetermined primary cancer	1
Urinary diseases (n = 7)	Acute or chronic kidney disease	4
	Feline lower urinary tract disease	3
Digestive diseases (n = 7)	CE	7
Others (n = 14)	Systemic hypertension of unknown origin	3
	Immune-mediated anemia	2
	Diabetes mellitus	2
	Pancreatitis	2
	Portosystemic shunt	1
	Systemic bartonellosis	1
	Bronchopneumonia	1
	Pleural effusion	1
	Hypertrophic cardiomyopathy	1
Unknown (n = 1)		

Abbreviations: CE, chronic enteropathy.

3.7 | Factors associated with clinical expression of cholelithiasis

The final multivariate model included age, male sex, low and high BCS for epidemiologic variables; vomiting, lethargy, pyrexia, and jaundice for clinical variables; lymphopenia, hyperglobulinemia, and increased ALP and ALT activities for biological variables; and liver, gallbladder, and biliary tract abnormalities, multiple locations, location within gallbladder, and obstruction for US variables (Table 9). High BCS remained the only epidemiologic variable significantly associated with an increased risk of SC (OR, 3.86; 95% CI, 1.13-13.16; $P = .03$). For clinical signs, vomiting (OR, 9.89; 95% CI, 2.65-36.94; $P = .001$), pyrexia (OR, 10.52; 95% CI, 1.49-74.22; $P = .02$), and jaundice (OR, 5.79; 95% CI, 1.03-32.45; $P = .05$) were significantly associated with SC. Among biological variables, only increased ALT activity (OR, 15; 95% CI, 4.05-81.77; $P < .001$) was associated with higher risk of being symptomatic. Multiple location of the choleliths within the biliary tract (OR, 8.11; 95% CI, 2.32-34.15; $P = .001$) and BTO (OR, 18.47; 95% CI, 2.13-2413.34; $P = .004$) were the only US variables associated with SC.

3.8 | Factors associated with survival in cats with symptomatic cholelithiasis

The first multivariate model included age, male sex, low and high BCS for epidemiologic variables; weight loss and lethargy for clinical variables; neutropenia, neutrophilia, and increased serum creatinine concentration and ALP activity for biological variables; and obstruction for US variables (Table 10). Among all factors, only neutropenia (OR, 48.33; 95% CI, 2.52-8173.54; $P = .01$), neutrophilia (OR, 6.61; 95% CI, 1.13-71.22; $P = .04$), and BTO (OR, 4.14; 95% CI, 1.19-14.44; $P = .03$) were associated with increased risk of death before discharge and were included in the final model. In this last model that included

TABLE 4 Frequencies of reported clinical signs.

Clinical sign	All cats (n = 98)[a]	Cats with symptomatic cholelithiasis (n = 58)[a]	Cats with incidental cholelithiasis (n = 40)[a]	*P* (Pearson's χ^2 test)[b]
Lethargy	66 (67%)	46 (79%)	20 (50%)	**.002**
Vomiting	63 (64%)	48 (83%)	15 (36%)	**<.001**
Anorexia	60 (61%)	41 (71%)	19 (48%)	**.02**
Weight loss	44 (45%)	24 (41%)	20 (50%)	.39
Jaundice	27 (28%)	25 (43%)	2 (5%)	**<.001**
Abdominal pain	25 (26%)	18 (31%)	7 (18%)	.13
Pyrexia	15 (15%)	13 (22%)	2 (5%)	**.01**
Diarrhea	14 (14%)	8 (14%)	6 (15%)	.86

[a]For each sign: number (percentage) of cases affected.
[b]Significant *P* values are written in bold.

TABLE 5 Clinical pathology results.

Parameter[a]	Number of cats (%) with results above reference range		Number of cats (%) with results below reference range		*P* (Fischer's exact test)[c]
	Cats with symptomatic cholelithiasis[b]	Cats with incidental cholelithiasis[b]	Cats with symptomatic cholelithiasis[b]	Cats with incidental cholelithiasis[b]	
Hematocrit (n = 75)	1/47 (2%)	0/28 (0%)	16/47 (34%)	14/28 (50%)	.32
White blood cell count (n = 67)	20/40 (50%)	8/27 (30%)	1/40 (3%)	1/27 (4%)	.21
Neutrophil count (n = 55)	15/32 (47%)	8/23 (35%)	2/32 (6%)	2/23 (9%)	.64
Lymphocyte count (n = 51)	0/29 (0%)	2/22	16/29	7/22	.09
Platelet count (n = 65)	0/39 (0%)	1/26 (4%)	6/39 (15%)	4/26 (15%)	.58
Urea (n = 85)	16/52 (31%)	16/33 (48%)	1/52 (2%)	0/33 (0%)	.2
Creatinine (n = 81)	12/49 (24%)	12/32 (38%)	0/49 (0%)	0/32 (0%)	.21
Glycemia (n = 69)	14/44 (32%)	6/25 (24%)	1/44 (2%)	0/25 (0%)	.74
Total protein (n = 83)	8/53 (15%)	6/30 (20%)	2/53 (4%)	3/30 (10%)	.37
Albumin (n = 75)	2/48 (4%)	1/27 (4%)	7/48 (15%)	8/27 (30%)	.26
Globulin (n = 74)	10/48 (5%)	6/26 (23%)	2/48 (4%)	2/26 (33%)	.75
ALT (n = 89)	41/56 (89%)	4/33 (12%)	0/56 (0%)	1/33 (3%)	**<.001**
ALP (n = 86)	14/54 (26%)	0/32 (0%)	0/54 (0%)	1/32 (3%)	**<.001**
GGT (n = 40)	8/31 (26%)	0/9 (0%)	0/31 (0%)	0/9 (0%)	.16
AST (n = 19)	8/13 (62%)	0/6 (0%)	0/13 (0%)	0/6 (0%)	**.02**
Bilirubin (n = 54)	36/44 (82%)	3/10 (30%)	0/44 (0%)	0/10 (0%)	**<.01**
Ammonia (n = 5)	1/5 (20%)	—	0/5 (0%)	—	1
Preprandial bile acids (n = 4)	3/3 (100%)	0/1 (0%)	0/3 (0%)	0/1 (0%)	—
Postprandial bile acids (n = 3)	2/2 (100%)	0/1 (0%)	0/2 (0%)	0/1 (0%)	—
Sodium (n = 61)	2/38 (3%)	1/23 (4%)	12/38 (32%)	5/23 (22%)	.8
Potassium (n = 63)	3/40 (8%)	2/23 (9%)	12/40 (30%)	6/23 (26%)	1
Chloride (n = 48)	2/31 (6%)	2/17 (12%)	3/31 (10%)	2/17 (12%)	.74
Ionized calcium (n = 41)	1/23 (4%)	1/18 (13%)	4/23 (17%)	5/18 (28%)	.73
Phosphorus (n = 20)	2/11 (18%)	1/9 (11%)	3/11 (27%)	3/9 (33%)	1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase.
[a]For each parameter (number of cases with data available).
[b]For each result: number (percentage) of cases concerned.
[c]Significant *P* values are written in bold.

treatment effects, only BTO remained associated with increased risk of death (OR, 13.87; 95% CI, 1.54-124.76; $P = .001$) whereas medical management was associated with decreased risk (OR, 0.02; 95% CI, 0-0.23; $P = .001$; Table 11). Surgical management did not significantly decrease the risk of death before discharge (OR, 0.79; 95% CI, 0.14-4.44; $P = .43$). Main risk factors of death before discharge remained similar when excluding non-treated cats from the analyses (Tables 12 and 13).

4 | DISCUSSION

The prevalence of cholelithiasis in cats undergoing abdominal US was 0.99% and a majority of these cases (59%) were symptomatic. Most cats with SC survived to discharge, although BTO was identified as a poor prognostic factor. A concurrent hepatobiliary disease was suspected or confirmed in >75% of cases with SC. Notably, our study is the first to report successful medical treatment without surgical intervention in a large cohort of cats with SC, including cases with BTO, demonstrating a high rate of survival with this approach. These findings highlight that SC is not an indication for surgical treatment in itself and that diagnostic and therapeutic strategies should consider concurrent hepatobiliary disease. Incidental cholelithiasis was also common (41%) and no cat with IC went on to develop SC, indicating that biliary stones can be non-problematic.

We report an overall low prevalence of cholelithiasis in cats, comparable to that reported in dogs but much lower than in humans.[6,8,9,11,12] Symptomatic cholelithiasis was more frequent than IC in our population, in contrast to observations in dogs and humans.[6,7,10] These differences in prevalence and clinical expression could be related to different diseases leading to cholelithiasis or, more likely, to differences in the prevalence of these diseases between species. Confirmed

TABLE 6 Number and location of cholеliths.

	Cats with symptomatic cholelithiasis[a] (n = 58)	Cats with incidental cholelithiasis[a] (n = 40)	P[d]
Number of cholеliths[b]			
Single (n = 30)	10 (17%)	20 (50%)	**<.01**
Multiple (≥2) (n = 64)	46 (80%)	18 (45%)	
Not reported (n = 4)	2 (3%)	2 (5%)	
Location[c]			
Unique (n = 57)	22 (38%)	35 (88%)	**<.001**
Multiple (n = 41)	36 (62%)	5 (12%)	
Anatomic location within the biliary tract[c]			
Intrahepatic biliary tract (n = 22)	17 (29%)	5 (13%)	.06
Gallbladder (n = 69)	40 (69%)	29 (72%)	.71
Cystic duct (n = 24)	18 (31%)	6 (15%)	.08
Common bile duct (n = 42)	34 (59%)	8 (22%)	**<.001**

[a]For each parameter: number (percentage) of cases concerned.
[b]Compared with Fischer's exact test.
[c]Compared with Pearson's χ^2 test.
[d]Significant *P* values are written in bold.

TABLE 7 Pertinent abdominal ultrasonography findings.

	Cats with symptomatic cholelithiasis (n = 58)[a]	Cats with incidental cholelithiasis (n = 40)[a]	P (Pearson's χ^2 test)[c]
Biliary tract abnormalities (n = 53, 54%)[a]	44 (76%)	9 (23%)	**<.001**
Intrahepatic ducts dilation	18 (41%)	0 (0%)	
Cystic duct dilation	23 (51%)	5 (56%)[b]	
Cystic duct wall thickening	8 (18%)	0 (0%)	
Common bile duct dilation	37 (82%)	5 (56%)[b]	
Common bile duct wall thickening	13 (29%)	1 (11%)	
Gallbladder abnormalities (n = 64, 65%)[a]	47 (84%)	17 (45%)	**<.001**
Increased volume	8 (16%)	0 (0%)	
Thickened wall	39 (80%)	15 (83%)	
Increased wall echogenicity	2 (4%)	2 (11%)	
Heterogenous content	6 (12%)	1 (6%)	
Mucocele	2 (4%)	3 (15%)	
Liver abnormalities (n = 64, 65%)[a]	45 (78%)	19 (49%)	**<.01**
Hepatomegaly	25 (56%)	8 (42%)	
Increased echogenicity	17 (38%)	8 (42%)	
Decreased echogenicity	12 (27%)	4 (21%)	
Heterogeneity	14 (31%)	10 (53%)	
Digestive tract abnormalities (n = 46, 47%)[a]	24 (41%)	22 (55%)	.12
Digestive tract wall thickening	20 (80%)	21 (95%)	
Ileus	1 (4%)	1 (5%)	
Pancreas abnormalities (n = 43, 44%)[a]	31 (54%)	12 (31%)	**.02**
Enlargement	16 (52%)	3 (25%)	
Echogenicity modification	29 (94%)	11 (92%)	
Pancreatic duct dilation and/or wall thickening	6 (19%)	1 (8.3%)	

[a]For each sign: number (percentage) of cases concerned.
[b]Mild/non-relevant dilation in all cases (below 5 mm).
[c]Significant *P* values are written in bold.

or suspected causes for cholelith formation include altered bile composition, bile supersaturation, precipitation of a nucleus, mucin hypersecretion, aberrant biliary pH, biliary stasis or aberrant gallbladder motility, biliary bacterial infections, cholecystitis, cholangitis, and dietary factors.[2,19,22,31-35] In humans, cholelith composition depends on the underlying cause; most choleliths contain cholesterol and develop in relation to metabolic disorders.[4,5,13] Bilirubin choleliths predominantly originate from the gallbladder and occur with persistent hyperbilirubinemia (chronic hemolytic diseases and cirrhosis).[13] In contrast, calcium carbonate choleliths are mainly found in the CBD and are commonly associated with chronic infectious or sclerosing cholangitis.[11,13] Because most choleliths in dogs and cats are pigment stones composed of calcium carbonate or bilirubin or both, liver and biliary tract diseases are considered the most important factors in companion animals.[16,31-33,36] Although contributing to cholelith formation, these diseases also could participate directly in the clinical and biological features associated with cholelithiasis. In fact, in companion animals, clinical signs might be more attributable to underlying hepatobiliary disease than to the choleliths themselves.[31,32] Unfortunately, as none of the choleliths removed by surgery in our study were submitted for composition analysis, their composition remains speculative and no definitive conclusion can be drawn regarding their etiology.

However, several observations in our study support this hypothesis of an underlying hepatobiliary disease responsible for cholelithiasis, especially SC. Symptomatic cholelithiasis was commonly diagnosed concurrently with CCH, or cholecystitis or both, although these diagnoses were only presumptive in 22/26 cases. Pyrexia and increased ALT activity were also predictors of SC and more likely related to an

TABLE 8 Results of bile culture.

Bacteria identified	Number (percentage) of cats
Escherichia coli	10 (59%)
Enterococcus spp.	4 (24%)
Streptococcus spp.	3 (18%)
Cellulomonas spp.	1 (6%)
Enterobacter spp.	1 (6%)
Kluyvera spp.	1 (6%)
Salmonella spp.	1 (6%)
Proteus spp.	1 (6%)
Corynebacterium spp.	1 (6%)

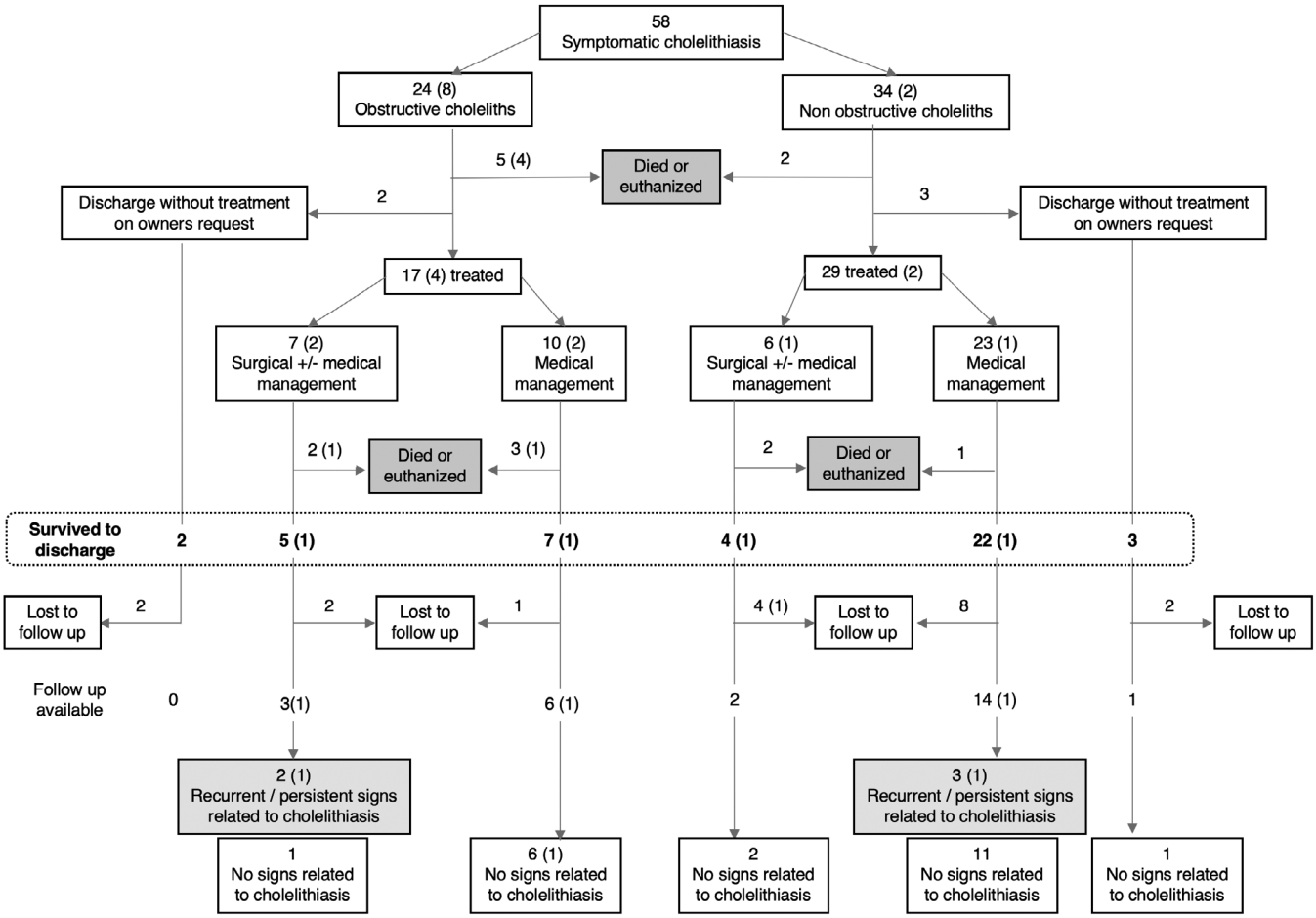

FIGURE 1 Diagram illustrating treatment and outcome in cats with symptomatic cholelithiasis. *Number in () correspond to the cases without suspicion of a concurrent hepatobiliary disease.

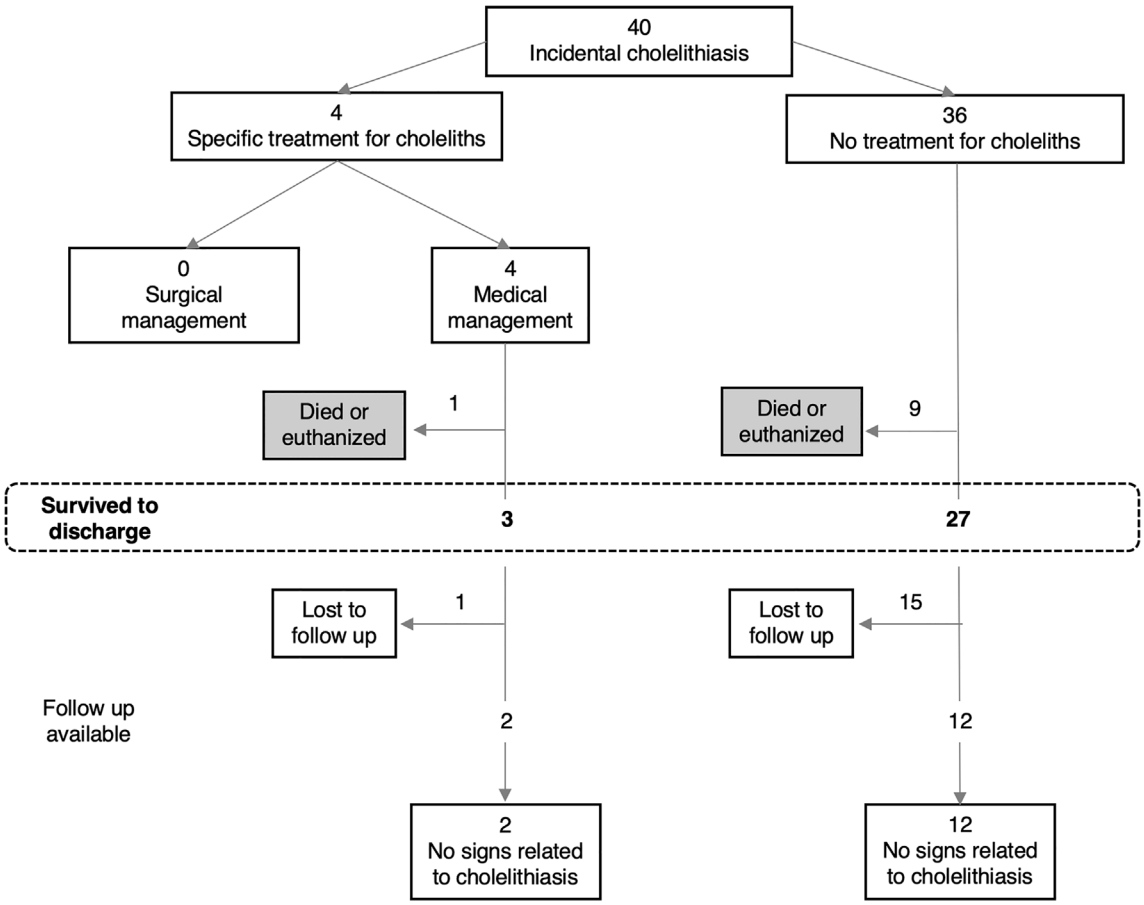

FIGURE 2 Diagram illustrating treatment and outcome in cats with incidental cholelithiasis.

underlying infectious or inflammatory process rather than cholelithiasis alone. Good outcomes also were observed without surgical removal, even in some cases with BTO, and medical treatments mainly relied on antibiotics, followed by UDCA and corticosteroids. Medical treatment in these cases likely was aimed at treating the hepatobiliary disease associated with cholelithiasis rather than the choleliths themselves. The observation of IC without progression to SC highlights the fact that choleliths may not independently cause clinical signs, and suggests that different factors might be implicated in IC.

In contrast, some authors suggest that choleliths also may be an independent cause of clinical signs, as is occasionally observed in humans.[31,32] Some findings from our study could favor this hypothesis. Indeed, 10/58 cases with SC were considered to have SC without concurrent hepatobiliary disease. However diagnostic tests beyond US to exclude comorbidities were not performed in most cases and 2 cats experienced complete resolution of clinical signs with medical management alone. Nevertheless, although concurrent hepatobiliary disease might have been overlooked in some cases, our findings raise the possibility that clinical signs may be caused directly by choleliths and subsequent BTO, as suggested in a recent review.[31] Biliary colic, where pain occurs from temporary obstruction of the biliary tract with spontaneous resolution, is also a common clinical entity in humans and still needs to be investigated in companion animals as mentioned by other authors.[4-6,32]

Some findings from our study could directly be considered in the clinical setting when managing cats with cholelithiasis. First, IC was almost as common as SC. When managing cats with choleliths, it seems therefore important to question their clinical relevance first and consider IC so as to avoid unnecessary treatment, especially immediate surgical removal. Although epidemiological data did not differentiate IC from SC, some clinicopathological data and US findings were significantly associated with SC and could be used to guide the diagnostic process. Vomiting and jaundice were associated with SC, which was expected because these signs were part of the inclusion criteria. This result still validated these 2 signs as relevant chief complaints for SC. Pyrexia, which was not an inclusion criterion for SC in our study, was also a predictor of SC. Although serum ALT, ALP, and AST activities and bilirubin concentrations were significantly increased in cats with SC compared with IC on univariate analysis, only increased serum ALT activity remained significantly associated with SC in the multivariate analysis. This finding is in contrast with results of 2 previous studies in dogs, which suggested that serum gamma glutamyl transferase (GGT) activity was significantly higher in cases with SC.[6,7] However, failure to document any significant difference in our study could be related to the low number of cats that underwent GGT activity measurement, especially in cats with IC. Finally, multiple cholelith locations and BTO were the only US variables that remained significantly predictive of SC. Although several potential risk factors for

TABLE 9 Factors associated with symptomatic cholelithiasis.

Variables	Odd ratio (OR) [95% confidence interval (CI)]	*P* value[b]
Epidemiology (n = 85)[a]		
Age	0.94 [0.82-1.07]	.34
Male sex	0.59 [0.22-1.56]	.29
BCS < 3/9	2.66 [0.93-7.62]	.07
BCS > 6/9	3.86 [1.13-13.16]	**.03**
Clinical signs (n = 83)[a]		
Vomiting	9.89 [2.65-36.94]	**.001**
Lethargy	2.68 [0.79-9.09]	.11
Pyrexia	10.52 [1.49-74.22]	**.02**
Jaundice	5.79 [1.03-32.45]	**.05**
CBC (n = 49)[a]		
Lymphopenia	2.29 [0.71-7.4]	.17
Biochemistry (n = 73)[a]		
Hyperglobulinemia	0.22 [0.03-1.18]	.08
Increased ALT	15 [4.05-81.77]	**<.001**
Increased ALP	9.76 [0.91-1334.67]	.06
US findings (n = 98)[a]		
Multiple cholelith locations	8.11 [2.32-34.15]	**.001**
Choleliths located within the gallbladder	0.5 [0.13-1.77]	.28
Liver abnormalities	3.3 [0.96-12.85]	.06
Gallbladder abnormalities	2.73 [0.82-9.66]	.10
Biliary tract abnormalities	2.27 [0.73-7.14]	.16
Biliary tract obstruction	18.47 [2.13-2413.34]	**.004**

Abbreviation: US, ultrasonography.
[a]n = number of cases with data available for all presented variables and that were entered in the corresponding multivariate logistic regression model.
[b]Odd ratios with significant *P* values are written in bold.

TABLE 10 Factors associated with risk of death before discharge.

Variables	Odd ratio (OR) [95% confident interval (CI)]	*P* value[b]
Epidemiology (n = 51)[a]		
Age	1.03 [0.84-1.26]	.75
Male sex	1.46 [0.33-6.47]	.62
BCS < 3/9	1.38 [0.29-6.51]	.68
BCS > 6/9	0.47 [0.07-3.15]	.43
Clinical signs (n = 47)[a]		
Weight loss	2.16 [0.58-8.91]	.26
Lethargy	5.6 [0.58-749.5]	.16
CBC (n = 32)[a]		
Neutropenia	48.33 [2.52-8173.54]	**.01**
Neutrophilia	6.61 [1.13-71.22]	**.04**
Biochemistry (n = 48)[a]		
Increased creatinine	3.74 [0.85-16.43]	.08
Increased ALP	0.86 [0.14-5.24]	.87
2-fold increase in ALP	4.36 [0.49-38.58]	.19
US features (n = 58)[a]		
Biliary tract obstruction	4.14 [1.19-14.44]	**.03**

[a]n = number of cases with data available for all presented variables and that were entered in the corresponding multivariate logistic regression model.
[b]Odd ratios with significant *P* values are written in bold.

TABLE 11 Risk of death before discharge according to significant risk factors and treatments (n = 58).

Variables	Odd ratio (OR) [95% confidence interval (CI)]	*P* value[a]
Surgical management	0.79 [0.14-4.44]	.79
Medical management	0.02 [0-0.23]	**.001**
Biliary tract obstruction	13.87 [1.54-124.76]	**.02**
2-fold increase in ALP	1.65 [0.18-15]	.66

[a]Odd ratios with significant *P* values are written in bold.

clinical expression of cholelithiasis were identified by multivariate analysis, further prospective studies are required to validate them and determine whether they could be useful to discriminate between IC and SC in challenging cases.

Our study is the first to describe a large cohort of cats with IC. None of the cats with IC and available follow-up developed clinicopathological features related to their cholelithiasis, and resolution of cholelithiasis was documented in 3 cats. Even though some cats with IC were not followed and most of them were followed only for a short period of time, our study suggests that IC rarely progresses to SC. In humans, treatment of asymptomatic choleliths is not always advised, and laparoscopic cholecystectomy remains reserved for patients with increased risk of development of cholelith-related symptoms and complications (patients at risk of malignancy, presence of choledocholiths, chronic hemolytic conditions, large choleliths, diabetes mellitus).[10,37] Currently, no established guidelines are available for the management of IC in dogs or cats. Progression from asymptomatic to symptomatic disease was reported in only 7.7% of affected dogs despite persistence of cholelithiasis in all cases with US follow-up.[6] Another study reported the follow-up of 20 dogs with IC either treated with UDCA (n = 5) or not treated and no dog developed clinical signs related to their cholelithiasis.[7] In our study, only 12.5% of cats with IC were prescribed medical treatment. However, because all cats remained asymptomatic and US was not repeated in all cases, no conclusion can be drawn about the necessity and efficacy of any treatment for IC in cats.

Our study also included relevant findings regarding management of SC. Survival rate to discharge among cats with SC was 74%; 69% in cases that underwent surgery and 88% in cases that received only medical management. According to the final model of multivariate analysis, BTO but not surgical management was associated with worse outcome whereas medical treatment was positively associated

TABLE 12 Factors associated with risk of death before discharge (n = 46, after exclusion of non-treated cats).

Variables	Odd ratio (OR) [95% confident interval (CI)]	*P* value[b]
Epidemiology (n = 45)[a]		
Age	0.99 [0.76-1.28]	.92
Male sex	1.91 [0.3-12.3]	.50
BCS < 3/9	0.57 [0.07-4.57]	.60
BCS > 6/9	0.57 [0.08-4.25]	.58
Clinical signs (n = 39)[a]		
Weight loss	0.56 [0.09-3]	.51
Lethargy	0.56 [0.09-3]	.28
CBC (n = 27)[a]		
Neutropenia	48.33 [2.52-8173.54]	**.01**
Neutrophilia	2.84 [0.32-35.11]	.34
Biochemistry (n = 39)[a]		
Increased creatinine	6.26 [0.85-46.23]	.07
Increased ALP	0.84 [0.07-10]	.89
2-fold increase in ALP	24.11 [1.41-413.58]	**.03**
US features (n = 45)[a]		
Biliary tract obstruction	3.61 [0.74-17.64]	.11

[a]n = number of cases with data available for all presented variables and that were entered in the corresponding multivariate logistic regression model.
[b]Odd ratios with significant *P* values are written in bold.

TABLE 13 Risk of death before discharge according to significant risk factors and treatments (n = 46, after exclusion of non-treated cats).

Variables	Odd ratio (OR) [95% confident interval (CI)]	*P* value[a]
Surgical management	0.35 [0.03-4.75]	.43
Medical management	0.01 [0-0.42]	**.02**
Biliary tract obstruction	10.52 [0.99-111.48]	.05
2-fold increase in ALP	4.4 [0.33-59.19]	.26

[a]Odd ratios with significant *P* values are written in bold.

with survival to discharge. Surgical techniques and outcomes were in accordance with the published literature.[14,16,18,21,24,27,38,39] Recurrent or persistent clinicopathological features of SC after discharge were reported in 19% of cats, which is within the range of values reported by other authors (0%-38.9%).[18,24,27] Interestingly, only half of the cats that underwent surgery had signs of BTO based on US and surgical treatment was not performed in some cases with BTO. These findings appear contrary to the current recommendations which state that surgery is only indicated in case of cystic cholelith or CBD occlusion by choleliths.[2,36,38] The reason for these therapeutic choices was unknown because of the retrospective design of our study. The fact that some cases with BTO did not undergo surgical treatment could have affected their outcome. However, our results confirmed that SC in itself is not an indication for surgical intervention and suggest that medical treatment alone can be successful in selected cases.

Ninety-three percent of cases with SC received antimicrobials as a part of their medical management. However, bile culture was performed in less than half of the cats with SC and was positive in only 63% of them. Therefore, only 29% of cases with SC (17/58) had confirmed bacterial infection and the contribution of bacterial infection remained unknown in 30 cats. Half also received UDCA, the efficacy and safety of which have been demonstrated previously in dogs.[7,17,40] Because medical treatment strategies were highly variable and often combined with surgery, it is therefore not possible to draw conclusion from our study about the utility of each medical treatment. The recommended treatment plan also should consider the presence and type of concurrent hepatobiliary disease.

Our study had several limitations because of its retrospective design. Data were lacking in some medical records, especially in cats with IC. To minimize the impact of missing information, univariate analyses were performed for each variable and multivariate models were separately fit for each of the 5 categories of variables collected in medical records. This technique permitted the calculation of OR based on the most available information for each type of risk factors and the assessment of potential confounding effects within each category of variables. However, cofounding effects among different categories could not be assessed except in the final model assessing the treatment effect. The potential bias related to missing information is important, but it is unclear if it could have led to an over or an underestimation of the OR. On one hand, missing data were more frequent in IC than in SC, which could lead to an OR overestimation. On the other hand, cats with IC and complete records may have had more severe illness (not related to cholelithiasis) than cats without complete records, which can lead to an OR underestimation. Finally, adjustment for *P*-value related to the implementation of 5 multivariate models was not performed, and thus these results should be treated with caution and interpretation should be based more on the OR values and width of their 95% CI. Because including and excluding untreated cats with SC both could have inherently biased the survival analysis, factors were analyzed first in all cats with SC. The effect of excluding untreated cats then was assessed and did not substantially change the results. Also, cats were retrospectively categorized as having IC or SC based on our understanding of their medical records, but misclassification could not be completely excluded. Moreover, investigations to identify underlying or concurrent hepatobiliary disease were absent or incomplete in most cases, as reflected by the low number of cats that underwent liver biopsy or bile analysis. Finally, follow-up was not standardized and not available in all cats. Therefore, data concerning development or recurrence of clinical signs in cats with both IC and SC must be interpreted with caution.

5 | CONCLUSION

Our retrospective study found that choleliths were an uncommon finding on abdominal US in cats. Cholelithiasis more often was

symptomatic, but IC was regularly encountered and none of the cats with IC and available follow-up became symptomatic. However, a long-term prospective study with standardized follow-up is required to confirm this result. Most cats with SC survived to discharge but BTO was identified as a poor prognostic factor. A strong association between SC and hepatobiliary disease was observed and prospective studies including cholelith composition analysis and systematic liver and bile sampling are encouraged. Other factors contributing to cholelith formation, especially in cats with IC, should also be considered in future studies.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest. Royal Canin had no role in the design or conduct of the study, assessment of the data or writing of the article.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

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

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