

# Clinical features and outcomes in 38 dogs with cholelithiasis receiving conservative or surgical management

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## Abstract

**Background:** Ursodeoxycholic acid is used in human medicine for litholytic management of choleliths, but the efficacy of medical management in dogs with cholelithiasis is unknown.

**Objectives:** To describe the clinical features and outcomes of dogs with cholelithiasis, focusing on cases that received medical treatment, and to identify patient factors that influenced decision-making for surgical or medical management.

**Animals:** Thirty-eight dogs with cholelithiasis identified on abdominal ultrasonography (AUS).

**Methods:** Medical records of dogs with cholelithiasis on AUS between 2010 and 2019 were retrospectively reviewed. Cases were classified as symptomatic ( $n = 18$ ) or incidental ( $n = 20$ ) and divided into medically treated ( $n = 13$ ), surgically treated ( $n = 10$ ), and no treatment ( $n = 15$ ) groups. Biochemical variables and cholelith location were compared between symptomatic and incidental groups using Mann-Whitney  $U$  and chi-squared tests, respectively. Survival times were compared using Kaplan-Meier survival analysis.

**Results:** Symptomatic cases had higher alkaline phosphatase ( $P = .03$ ), gamma-glutamyl transferase ( $P = .03$ ), and alanine transferase ( $P = .02$ ) activities than did incidental cases. A higher proportion of symptomatic cases (44.4%) had choledocholithiasis than did incidental cases (0%;  $P = .003$ ). Seventy percent of surgically managed dogs, 7.7% of medically managed dogs, and 0% of nontreated dogs had choledocholiths at presentation. Seventeen dogs had follow-up AUS: cholelithiasis completely resolved in 4/8 medically treated, 5/7 of surgically treated, and 1/2 nontreated dogs. Median survival time was 457.4 days, with no significant difference between incidental and symptomatic dogs.

**Conclusions and Clinical Importance:** Medical treatment can be effective for management of cholelithiasis in dogs, with clinical presentation and cholelith location playing important roles in treatment decision-making.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUS, abdominal ultrasonography; CBD, common bile duct; EHBDO, extrahepatic biliary duct obstruction; GGT,  $\gamma$ -glutamyl transferase; UDCA, ursodeoxycholic acid.

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## KEYWORDS

biliary tract, cholecystectomy, cholelith, gall bladder, ursodeoxycholic acid

## 1 | INTRODUCTION

Cholelithiasis is an uncommon condition in dogs, with a recent study identifying a prevalence of 0.97%.<sup>1</sup> Geriatric, female, small breed dogs are overrepresented in studies of cholelithiasis in dogs.<sup>2-4</sup> Clinical signs are often nonspecific and include abdominal pain, vomiting, anorexia, icterus, polyuria, and polydipsia, but the frequency of symptomatic cholelithiasis is low<sup>1,2,5,6</sup> with 1 study reporting 13.1% of dogs to be symptomatic. Ursodeoxycholic acid (UDCA) is a synthetic hydrophilic bile acid that minimizes hepatocellular and oxidative damage resulting from bile acid retention in the liver by displacing hydrophobic bile acids. It also has choleric and anti-inflammatory actions in the gallbladder.<sup>7-9</sup> It is used commonly in people for medical dissolution and prevention of cholelithiasis,<sup>8,10,11</sup> but only a single case report documents dissolution of choleliths in a dog treated with UDCA.<sup>5</sup>

Few previous descriptive studies of medical management of cholelithiasis in dogs are available, resulting in limited evidence from which to base treatment decisions on.<sup>1,2</sup> Additional studies in dogs are needed to develop a consensus for treatment.

The aims of our retrospective study were to describe outcomes of medically and surgically managed dogs and to identify patient factors that influence decision-making for surgical or medical management.

## 2 | MATERIALS AND METHODS

The medical records of dogs diagnosed with cholelithiasis from 2010 to 2019 at The Queen's Veterinary School Hospital, University of Cambridge were retrospectively evaluated. Cases were identified by searches of the Hospital's imaging database for key word tags (liver–gb stones, cholelith, gallstones) to identify imaging reports in which cholelithiasis was described. Data collected included signalment (sex, neuter status, age), clinical signs, physical examination findings, clinical pathology data (including results of CBC [Sysmex XT-2000iV automated hematology analyzer; Sysmex XN-1000 automated hematology analyzer, Sysmex Corporation, Kobe, Japan] and blood biochemistry [Olympus AU400 chemistry analyzer; Olympus AU480 chemistry analyzer, Olympus, Tokyo, Japan]), abdominal ultrasonography (AUS) findings, results of liver and gallbladder histopathology, bile cytology, bile culture, treatment, and outcome (including follow-up AUS and biochemistry results). The reference intervals for all assessed CBC and blood biochemistry values are identical between respective CBC and biochemistry analyzers; therefore, results are presented as values rather than multiples of upper reference limits. Inclusion criteria required an ultrasonographic diagnosis of cholelithiasis consistent with published criteria.<sup>12</sup> Dogs with incomplete or absent medical

records were excluded. Medical records were considered incomplete when no clinical records or imaging reports from the time of diagnosis were available for analysis. Follow-up information was obtained in 35 cases by contacting the registered owner to ask about outcome and for permission to contact their primary care practice for clinical records. The study was approved by the Ethics and Welfare committee of the Department of Veterinary Medicine, University of Cambridge, reference CR435.

Ultrasound examinations were performed in all cases by board-certified radiologists or under their supervision. Ultrasonography was performed in all cases using either a Philips HDI 5000 (Philips, Eindhoven, the Netherlands), Philips EPIQ 7 (Philips), or Esaote MyLab Eight XP (Esaote, Genoa, Italy) machine.

Follow-up biochemistry was performed at variable time points, and therefore data were categorized into 6 time intervals after presentation: 0.5 to 1 months, 1 to 3 months, 3 to 6 months, 6 to 12 months, 12 to 24 months, and >24 months.

Presence of concurrent endocrinopathies was recorded. Cases were diagnosed either before referral or during investigations at the investigators' institution. Dogs were considered to have hyperadrenocorticism if an ACTH stimulation test or low-dose dexamethasone suppression test was positive along with compatible clinical signs. Dogs were considered to have hypothyroidism if a historical diagnosis (with consistent serum total thyroxine and thyroid stimulating hormone concentrations) had been made before referral. Dogs were considered to have primary hyperparathyroidism when ionized hypercalcemia was present with increased parathyroid hormone concentration and a parathyroid mass visible on ultrasound examinations and other causes of hypercalcemia had been ruled out during clinical investigations at the investigators' institution. Dogs were considered to have diabetes mellitus when presented with fasting hyperglycemia, in combination with glucosuria and compatible clinical signs.

Cases were subdivided into symptomatic and incidental cholelithiasis. Dogs were classified as symptomatic if they had clinical signs attributable to cholelithiasis (eg, vomiting, abdominal pain, inappetence, lethargy, icterus), ultrasonographic abnormalities of the gallbladder or biliary tree (increased gallbladder wall thickness or echogenicity, common bile duct [CBD] dilatation, cystic duct dilatation), and blood biochemistry abnormalities consistent with cholelithiasis (increases in hepatobiliary variables, cholesterol, or bilirubin)<sup>1,3,5</sup> and when no alternative disease process could account for the clinical presentation. Cases were classified as incidental when their clinical signs were not attributable to cholelithiasis, with ultrasonographic evidence of an otherwise normal biliary tract and no biochemical abnormalities attributable to cholelithiasis, or when clinical signs and biochemical abnormalities could be attributed to another disease process. Criteria were modeled on a recent study of cholelithiasis in dogs.<sup>1</sup>

Cases also were divided into 3 treatment categories: surgical, medical, and no treatment. Cases included in the surgical group underwent surgical intervention for cholelithiasis, cases in the medical group all received UDCA (Destolit, Norgine, UK) without surgical intervention for cholelithiasis, and cases in the no treatment group did not receive any specific treatment for cholelithiasis. One case reported here also has been described in a case report, whereas the remainder has not been reported previously.<sup>5</sup>

## 2.1 | Statistical analysis

Categorical data were anonymized and recorded, with each category presented descriptively. Continuous data (including age in years, CBC and blood biochemistry results, treatment doses and duration) were recorded and values for median and range were calculated for each variable.

Because both groups consisted of  $\leq 20$  cases, nonparametric 2-tailed Mann-Whitney *U* tests were performed to compare age, CBC, and blood biochemistry variables between symptomatic and incidental groups. Proportions of dogs with choledocholiths were compared between symptomatic and incidental groups using Chi-squared tests with Yates correction. Data regarding location, number, and radiopacity of choleliths, breed, and neuter status were presented descriptively.

Age, breed and neuter status, CBC and biochemistry results, treatment doses and duration, location and number of choleliths, radiopacity of choleliths, and ultrasonographic progression of cholelithiasis at follow-up for each treatment group were presented descriptively.

The Kaplan-Meier method was used to calculate survival curves from observed survival times and a log rank test was performed to determine if differences in survival distribution existed between symptomatic and incidental cases. All statistical analyses were performed using SPSS version 26 and Graphpad QuickCalcs. Results were considered significant if  $P < .05$ .

## 3 | RESULTS

### 3.1 | Signalment

Cholelithiasis was identified in 38 dogs. These included 22 breeds and 2 mixed-breed dogs. Cavalier King Charles Spaniels (CKCS; 10.5%,  $n = 4$ ) were the most commonly identified breed, followed by Dachshunds (7.9%,  $n = 3$ ), Jack Russell Terriers (7.9%,  $n = 3$ ), Labradors (7.9%,  $n = 3$ ), Cocker Spaniels (5.2%,  $n = 2$ ), Miniature Schnauzers (5.2%,  $n = 2$ ), Whip-pets (5.2%,  $n = 2$ ), and Yorkshire Terriers (5.2%,  $n = 2$ ).

Sex and neuter status were recorded in all cases. There were 14 neutered males, 13 neutered females, 6 intact males, and 5 intact females. Median age at diagnosis was 9.54 years (range, 0.25-12 years).

### 3.2 | Clinical presentation

Eighteen dogs (47.4%) had symptomatic cholelithiasis, and 20 cases (52.6%) were classified as incidental. The median age at presentation of dogs with incidental cholelithiasis (10.4 years) was significantly higher than that of dogs with symptomatic cholelithiasis (8.75 years;  $P = .01$ ).

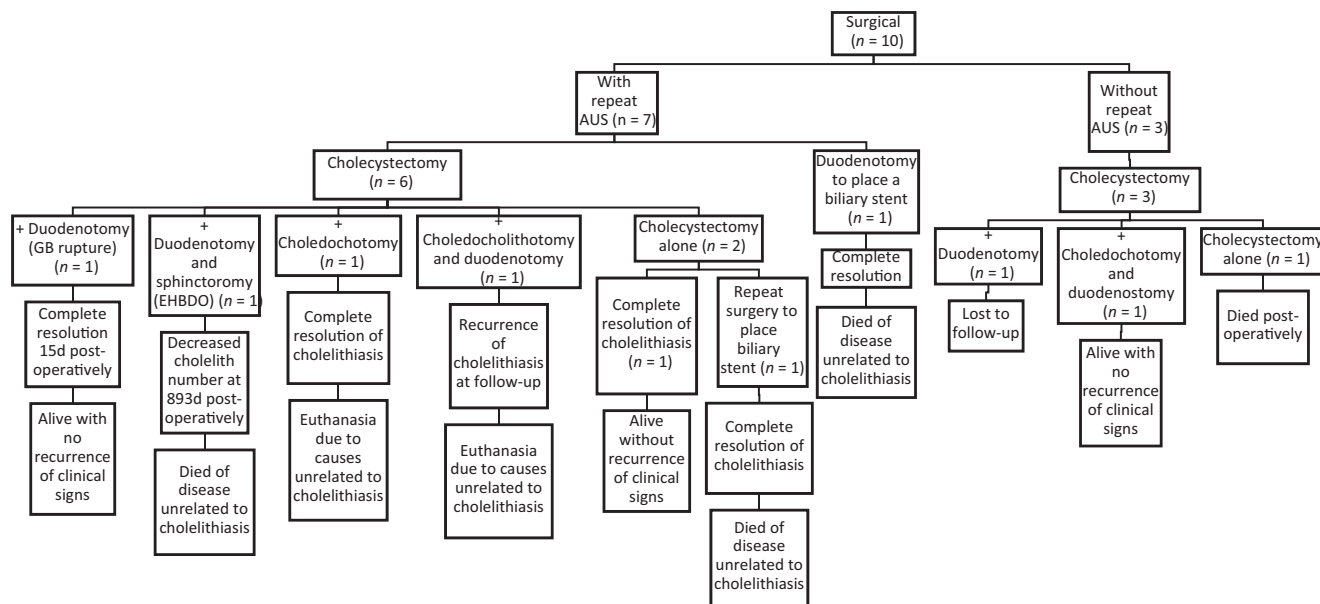
Clinical signs of symptomatic dogs are presented in Table 1. The primary disease processes of dogs with incidental cholelithiasis were neoplasia ( $n = 8$ ), other hepatobiliary ( $n = 3$ ), endocrine ( $n = 3$ ), autoimmune ( $n = 2$ ), neurological ( $n = 2$ ), gastrointestinal ( $n = 1$ ), and reproductive ( $n = 1$ ). Three dogs with incidental cholelithiasis had concurrent endocrinopathies that were not the primary presenting complaint.

### 3.3 | Concurrent endocrinopathy

Eight dogs were presented with concurrent endocrinopathies. Two dogs had symptomatic cholelithiasis and concurrent endocrinopathies:

**TABLE 1** Clinical signs at presentation in symptomatic dogs

|   | Clinical sign                                | Number | Percentage of clinically affected dogs |
|---|--|--------|--|
| Clinical signs reported in dogs presenting with symptomatic cholelithiasis ( $n = 18$ ) | Vomiting                                     | 13     | 72.2%                                  |
|   | Decreased appetite                           | 10     | 55.5%                                  |
|   | Lethargy                                     | 8      | 44.4%                                  |
|   | Diarrhea                                     | 6      | 33.3%                                  |
|   | Icterus                                      | 5      | 27.8%                                  |
|   | Abdominal pain                               | 4      | 22.2%                                  |
|   | Weight loss                                  | 3      | 16.7%                                  |
|   | Polyuria/Polydipsia                          | 1      | 5.6%                                   |
|   | Pollakiuria, stranguria, hematuria, nocturia | 1      | 5.6%                                   |
|   | Thinning of haircoat                         | 1      | 5.6%                                   |
|   | Deafness                                     | 1      | 5.6%                                   |
|   | Shifting lameness                            | 1      | 5.6%                                   |



**FIGURE 1** A diagram illustrating the outcomes of dogs in the surgical treatment group. AUS, abdominal ultrasonography; d, days; EHBDO, extrahepatic biliary duct obstruction; GB, gall bladder

primary hyperparathyroidism ( $n = 1$ ) and hypothyroidism ( $n = 1$ ). The remaining 6 dogs had incidental cholelithiasis and hyperadrenocorticism ( $n = 3$ ), primary hyperparathyroidism ( $n = 1$ ), and diabetes mellitus ( $n = 2$ ).

### 3.4 | Clinical pathology

Results of CBC at presentation were available for 35 dogs. No significant differences in hematological variables (Table 2) were found between symptomatic and incidental groups.

Blood biochemistry results at presentation were available for 37 dogs (Table 3). Activities of alkaline phosphatase (ALP;  $P = .03$ ),  $\gamma$ -glutamyl transferase (GGT;  $P = .03$ ), and alanine aminotransferase (ALT;  $P = .02$ ) were significantly higher in symptomatic cases than in incidental cases. No significant differences were found in bilirubin or cholesterol concentrations or aspartate aminotransferase (AST) activity between symptomatic and incidental groups.

### 3.5 | Diagnostic imaging

Imaging findings are summarized in Table 4. In the incidental group, choleliths were reported solely within the gallbladder in 19/20 (95%) cases, no dogs in the incidental group had choledocholithiasis. A significantly higher proportion of symptomatic dogs (44.4%) had choledocholiths than incidental dogs (0%;  $X^2 = 8.744$ ,  $df = 1$ ,  $P = .003$ ). Seven of 10 (70%) surgically managed dogs, 1/13 (7.7%) medically managed dogs, and 0/15 (0%) nontreated dogs had choledocholiths.

Abdominal radiography was performed in 22 dogs. Five dogs had evidence of mineral density and 17 dogs had radiolucent cholelithiasis (Table 4). Both dogs with primary hyperparathyroidism had radiopaque choleliths.

### 3.6 | Treatment groups

Ten dogs (26.3%) underwent surgical management for cholelithiasis, 13 dogs (34.2%) were medically treated using UDCA, and 15 dogs (39.5%) received no specific treatment.

### 3.7 | Surgical management

All surgically treated dogs were symptomatic for cholelithiasis. The median age was 9.33 years (range, 4.5–11.0 years).

Nine dogs underwent cholecystectomy, with additional choledochotomy ( $n = 1$ ), duodenotomy ( $n = 2$ ), choledocholithotomy and duodenotomy ( $n = 1$ ), duodenotomy and sphincterotomy ( $n = 1$ ) and choledochotomy and duodenostomy ( $n = 1$ ), and 1 dog underwent solely duodenotomy to place a biliary stent (Figure 1). Cholelith composition was not determined in these cases.

Two dogs were managed using UDCA for 43 days and 72 days, respectively, before surgery and before developing gallbladder rupture and extrahepatic biliary duct obstruction (EHBDO), respectively.

Liver histopathology results were available for 9 dogs, of which 8 had gallbladder histopathology results available (Supporting Information).

**TABLE 2** Complete blood count results at presentation, range is in brackets

| Measurement (reference interval)                                   | All dogs (n = 35)          | Symptomatic (n = 15)        | Incidental (n = 20)         | P   | Medically treated (n = 11)  | Surgically treated (n = 9) | No treatment (n = 15)      |
|--|----------------------------|-----------------------------|-----------------------------|-----|-----------------------------|----------------------------|----------------------------|
| WBC ( $6 \times 10^9/L$ - $17 \times 10^9/L$ ) (n = 35)            | 10.82 (6.6-34.27) (n = 35) | 13.77 (6.97-21.68) (n = 15) | 9.695 (6.6-21.68) (n = 20)  | .06 | 9.06 (6.63-21.03) (n = 11)  | 17.7 (6.97-34.27) (n = 9)  | 9.9 (6.6-21.68) (n = 15)   |
| Neutrophils ( $3 \times 10^9/L$ - $11.5 \times 10^9/L$ ) (n = 35)  | 7.78 (3.41-26.06) (n = 35) | 10.72 (4.52-19.39) (n = 15) | 6.115 (3.41-19.39) (n = 20) | .05 | 6.555 (4.04-15.44) (n = 11) | 14 (4.61-26.06) (n = 9)    | 6.16 (3.41-19.39) (n = 15) |
| Lymphocytes ( $1 \times 10^9/L$ - $4.3 \times 10^9/L$ ) (n = 35)   | 1.8 (0.5-6.4) (n = 35)     | 2.1 (0.6-3.7) (n = 15)      | 1.5 (0.5-3.7) (n = 20)      | .07 | 1.95 (1.2-6.4) (n = 11)     | 2.1 (0.6-5.82) (n = 9)     | 1.5 (0.5-3.7) (n = 15)     |
| Monocytes ( $0.2 \times 10^9/L$ - $1.5 \times 10^9/L$ ) (n = 35)   | 0.78 (0.09-3.67) (n = 35)  | 0.82 (0.09-2.16) (n = 15)   | 0.74 (0.2-2.16) (n = 20)    | .88 | 0.49 (0.09-1.79) (n = 11)   | 0.85 (0.27-3.67) (n = 9)   | 0.78 (0.2-2.16) (n = 15)   |
| Eosinophils ( $0.1 \times 10^9/L$ - $1.3 \times 10^9/L$ ) (n = 35) | 0.2 (0-1.65) (n = 35)      | 0.2 (0.02-1.65) (n = 15)    | 0.205 (0-1.65) (n = 20)     | .07 | 0.25 (0-1.65) (n = 11)      | 0.13 (0.02-0.38) (n = 9)   | 0.19 (0-0.54) (n = 15)     |
| PCV (37%-55%) (n = 34)   | 45 (31-61) (n = 34)        | 45 (37-61) (n = 14)         | 45 (31-61) (n = 20)         | .72 | 43.5 (33-61) (n = 11)       | 46 (42-55) (n = 8)         | 44 (31-55) (n = 15)        |

Note: The column labeled "P" indicates the P values from Mann-Whitney U test analysis of the symptomatic and incidental groups.

Abbreviation: WBC, total white blood cell count.

**TABLE 3** Blood biochemistry values at presentation, range is in brackets

| Measurement (reference interval)      | All dogs                   | Symptomatic (n = 17)       | Incidental (n = 20)        | P (MW) | Medically treated (n = 13) | Surgically treated (n = 9) | No treatment (n = 15)   |
|---------------------------------------|----------------------------|----------------------------|----------------------------|--------|----------------------------|----------------------------|-------------------------|
| ALP (26-107 IU/L) (n = 37)            | 340 (28-7456) (n = 37)     | 1747 (28-7456) (n = 17)    | 298 (28-4015) (n = 20)     | .03    | 1302 (32-6690) (n = 13)    | 1855 (28-7456) (n = 9)     | 277 (28-1324) (n = 15)  |
| GGT (0-10 IU/L) (n = 31)              | 7 (<1-136.1) (n = 31)      | 33.7 (3.4-136.1) (n = 16)  | 6 (<1-68) (n = 15)         | .03    | 7.8 (<1-136.1) (n = 13)    | 69.15 (4-124.4) (n = 8)    | 4.5 (1.4-68) (n = 10)   |
| ALT (14-67 IU/L) (n = 37)             | 109 (19-6460) (n = 37)     | 369 (26-5257) (n = 17)     | 86 (19-6460) (n = 20)      | .02    | 181 (19-5257) (n = 13)     | 731 (55-4153) (n = 9)      | 55 (19-6460) (n = 15)   |
| AST (12-49 IU/L) (n = 30)             | 48 (18-2887) (n = 30)      | 70.5 (18-2189) (n = 15)    | 35 (22-2887) (n = 15)      | .29    | 46 (18-2189) (n = 13)      | 220 (48-962) (n = 7)       | 34.5 (25-2887) (n = 10) |
| Bilirubin (0-12 umol/L) (n = 32)      | 3.85 (1.7-274.1) (n = 32)  | 6.5 (2.1-182.3) (n = 16)   | 3.5 (1.7-274.1) (n = 16)   | .29    | 3.1 (1.7-274.1) (n = 13)   | 34.95 (3-182.3) (n = 8)    | 3.6 (2.6-60.5) (n = 11) |
| Cholesterol (3.3-6.5 mmol/L) (n = 31) | 6.85 (3.82-17.59) (n = 31) | 7.58 (4.54-17.59) (n = 15) | 6.69 (3.82-15.15) (n = 16) | .36    | 6.64 (3.82-17.59) (n = 13) | 8.13 (5.77-16.58) (n = 7)  | 6.85 (4.84-17) (n = 11) |

Note: The column labeled "P (MW)" indicates the P values from Mann-Whitney U test analysis of the symptomatic and incidental groups.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyl transferase.

Bile culture results were available for 3 dogs and all cultures yielded multiple organisms, with positive cultures for *Escherichia coli* (n = 2), *Enterococcus* spp. (n = 3), and coliform species (n = 1).

Nine dogs survived to discharge and all were treated using a median dose of 11.9 mg/kg/d (range, 8.9-14.4 mg/kg/d) UDCA

postoperatively for a median duration of 128.5 days (range, 25-1990 days). Three dogs were treated using S-adenosylmethionine (SAME)/Silybin (Denamarin, Protexin, UK) postoperatively at a median dose of 16 mg/kg/d (range, 11.9-37.7 mg/kg/d) and median duration of 14 days (range, 14-28 days). Additional postoperative medications

**TABLE 4** Location of choleliths at presentation identified with abdominal ultrasonography and concurrent opacity of choleliths on abdominal radiography

| Group                       | Location of cholelith(s) (n = 38) |                             |               | Number of choleliths (n = 36) |                |                | Opacity of cholelith on abdominal radiography (n = 22) |                |  |
|-----------------------------|-----------------------------------|-----------------------------|---------------|-------------------------------|----------------|----------------|--|----------------|--|
|                             | Gall bladder (GB) only            | Common bile duct (CBD) only | GB and CBD    | Other                         | One            | Multiple       | Radiopaque   | Radiolucent    |  |
| Total (n = 38)              | 73.7% (n = 28)                    | 7.9% (n = 3)                | 13.2% (n = 5) | 5.3% (n = 2)                  | 38.9% (n = 14) | 61.1% (n = 22) | 22.7% (n = 5)  | 77.3% (n = 17) |  |
| Symptomatic (n = 18)        | 50% (n = 9)                       | 11.1% (n = 2)               | 27.8% (n = 5) | 11.1% <sup>*,†</sup> (n = 2)  | 29.4% (n = 5)  | 70.6% (n = 12) | 36.4% (n = 4)  | 63.6% (n = 7)  |  |
| Incidental (n = 20)         | 95% (n = 19)                      | 0                           | 0             | 5% <sup>§</sup> (n = 1)       | 47.4% (n = 9)  | 52.6% (n = 10) | 9.1% (n = 1)   | 90.1% (n = 10) |  |
| Medically treated (n = 13)  | 84.6% (n = 11)                    | 7.7% (n = 1)                | 0             | 7.7% <sup>§</sup> (n = 1)     | 50% (n = 6)    | 50% (n = 6)    | 14.3% (n = 1)  | 85.7% (n = 6)  |  |
| Surgically treated (n = 10) | 20% (n = 2)                       | 20% (n = 2)                 | 40% (n = 4)   | 20% <sup>*,†</sup> (n = 2)    | 20% (n = 2)    | 80% (n = 8)    | 44.4% (n = 4)  | 55.6% (n = 5)  |  |
| No treatment (n = 15)       | 100% (n = 15)                     | 0                           | 0             | 0                             | 42.9% (n = 6)  | 57.1% (n = 8)  | 0  | 100% (n = 6)   |  |

Note: Of dogs presenting as "other", one symptomatic case had stones in the gall bladder with mineralization of the biliary tree\*, one symptomatic case had stones in the gall bladder, common bile duct, and intrahepatic bile ducts<sup>†</sup>, and one incidental case had stones within the gall bladder and intrahepatic bile ducts<sup>§</sup>.

Abbreviations: CBD, common bile duct; GB, gall bladder.

consisted of potentiated amoxicillin (n = 4), cephalexin (n = 2), marbofloxacin (n = 2), tramadol (n = 3), carprofen (n = 1), paracetamol/codeine (n = 1), PO potassium gluconate (n = 1), and omeprazole (n = 1).

### 3.8 | Medical management

Medically managed dogs were presented at a median age of 8.58 years (range, 0.25-11.7 years). Eight dogs (61.5%) were symptomatic for cholelithiasis and 5 (38.5%) were incidental cases. The median dose of UCDA administered was 11.7 mg/kg/d (range, 6.28-41.1 mg/kg/d) with a median duration of administration of 91 days (range, 30-1642 days). Five dogs were treated concurrently with SAME/Silybin at a median dose of 19.1 mg/kg/d (range, 17.9-29.4 mg/kg/d) and 7 dogs were treated concurrently using antibiotics, consisting of potentiated amoxicillin (n = 4), amoxicillin (n = 1), potentiated amoxicillin and marbofloxacin (n = 1), and metronidazole (n = 1).

Liver biopsy histopathology results were available for 2 dogs (Table S1).

Bile cytology results were available for 1 dog and disclosed septic neutrophilic cholecystitis with gram-positive bacilli.

### 3.9 | No treatment

Fifteen dogs received no specific treatment for cholelithiasis and all were incidental cases. The primary disease processes were neoplasia (n = 8), autoimmune (n = 2), neurological (n = 2), hepatobiliary (n = 1), endocrine (n = 1), and reproductive (n = 1). The median age was 10.83 years (range, 7.25-12.0 years). Histopathology results were available for one dog (Table S1).

### 3.10 | Outcomes

#### 3.10.1 | Surgical management outcome

Follow-up biochemistry results were available for 7 dogs with a median final follow-up time of 193 days (range, 27-1463 days; Table 5). Follow-up AUS was performed in 7 surgically managed dogs with a median time from presentation to final AUS of 325 days (range, 12-1461 days; Table 6). Five of seven (71.4%) dogs with imaging follow-up experienced complete resolution of cholelithiasis, and 2/7 (29.6%) did not have complete resolution.

Three dogs were alive at the time of writing, 6 were dead, and 1 was lost to follow-up (Figure 1). Median survival time was 577 days (range, 0-2266 days). One dog underwent repeat surgery to place a biliary stent 198 days after initial cholecystectomy because of lack of clinical improvement and persistently increased liver enzyme activities, suspected to be caused by chronic scarring of the sphincter, resulting in chronic biliary tract obstruction. Complete resolution of cholelithiasis was documented at imaging follow-up 134 days after the second surgery.

**TABLE 5** Median blood biochemistry results at presentation and at subsequent follow-up intervals of dogs that had repeat blood examinations

| Time interval             | Presentation               | 0.5-1 month               | 1-3 months                                  | 3-6 months                 | 6-12 months                             | 12-24 months | >24 months              |
|---------------------------|----------------------------|---------------------------|---|----------------------------|---|--------------|-------------------------|
| <b>Medical treatment</b>  |                            |                           |   |                            |   |              |                         |
| ALP (IU/L)                | 1302 (32-6690) (n = 13)    | 1917 (102-6953) (n = 4)   | 475 (130-7711) (n = 7)                      | 175 (144-6173) (n = 3)     | 4147 (39-8255) (n = 2)                  | n/a          | 85 (n = 1)              |
| ALT (IU/L)                | 181 (19-5257) (n = 13)     | 307.5 (26-1604) (n = 4)   | 143.66-1220) (n = 7)                        | 257 (105-543) (n = 3)      | 517.5 (245-790) (n = 2)                 | 32 (n = 1)   | 196 (n = 1)             |
| AST (IU/L)                | 46 (18-2189) (n = 13)      | 323 (18-628) (n = 2)      | 68.5 (29-161) (n = 6)                       | 39 (22-46) (n = 3)         | 81 (69-93) (n = 2)                      | n/a          | 40 (n = 1)              |
| GGT (IU/L)                | 7.8 (<1-136.1) (n = 13)    | 63.1 (3.4-122.8) (n = 2)  | 12.4 (3.4-80.8) (n = 6)                     | 9 (5.6-26.3) (n = 3)       | 187 (n = 1)                             | n/a          | 5.2 (n = 1)             |
| Bilirubin (μmol/L)        | 3.1 (1.7-274.1) (n = 13)   | 25.85 (2.4-49.3) (n = 2)  | 4.95 (3.1-45.1) (n = 6)                     | 3 (2.6-3.2) (n = 3)        | 86.65 <sup>a</sup> (72.7-100.6) (n = 2) | n/a          | 2.7 (n = 1)             |
| Cholesterol (mmol/L)      | 6.64 (3.82-17.59) (n = 13) | 4.915 (4.54-5.29) (n = 2) | 7.685 (2.75-12.23) (n = 6)                  | 9.34 (4.63-9.63) (n = 3)   | 11.785 (11.57-12) (n = 2)               | n/a          | 4.51 (n = 1)            |
| <b>Surgical treatment</b> |                            |                           |   |                            |   |              |                         |
| ALP (IU/L)                | 1855 (28-7456) (n = 9)     | 254 (53-4279) (n = 3)     | 490.5 (82-1277) (n = 4)                     | 104 (97-111) (n = 2)       | 60.5 (35-1211) (n = 4)                  | 64 (n = 1)   | 144 (138-150) (n = 2)   |
| ALT (IU/L)                | 731 (55-4153) (n = 9)      | 184 (74-294) (n = 2)      | 721.5 (35-2169) (n = 4)                     | 67.5 (49-86) (n = 2)       | 103 (57-215) (n = 4)                    | 32 (n = 1)   | 119.5 (113-126) (n = 2) |
| AST (IU/L)                | 220 (48-962) (n = 7)       | 166 (n = 1)               | 85 (44-189) (n = 3)                         | n/a                        | 75 (45-105) (n = 2)                     | n/a          | 44 (n = 1)              |
| GGT (IU/L)                | 69.15 (4-124.4) (n = 8)    | 170.55 (63-278.1) (n = 2) | 34.1 (3.7-46.1) (n = 3)                     | n/a                        | 4.6 (<1-54.5) (n = 3)                   | n/a          | 5.4 (n = 1)             |
| Bilirubin (μmol/L)        | 34.95 (3-182.3) (n = 8)    | 39.5 (12.4-66.6) (n = 2)  | 4.6 (2.4-21.1) (n = 3)                      | n/a                        | 8.9 (3.1-46.9) (n = 3)                  | n/a          | 3.3 (n = 1)             |
| Cholesterol (mmol/L)      | 8.13 (5.77-16.58) (n = 7)  | 18.45 (n = 1)             | 9.4 (7.94-12.48) (n = 3)                    | n/a                        | 3.99 (2.23-5.75) (n = 2)                | n/a          | 4.7 (n = 1)             |
| <b>Nontreatment</b>       |                            |                           |   |                            |   |              |                         |
| ALP (IU/L)                | 277 (28-1324) (n = 15)     | 110 (n = 1)               | 11 955.5 (104-23 807 <sup>b</sup> ) (n = 2) | 11794 <sup>b</sup> (n = 1) | 220.5 (203-238) (n = 2)                 | 488 (n = 1)  | n/a                     |
| ALT (IU/L)                | 55 (19-6460) (n = 15)      | 151 (n = 1)               | 409.5 (74-745) (n = 2)                      | 420 (n = 1)                | 110 (105-115) (n = 2)                   | 175 (n = 1)  | n/a                     |
| AST (IU/L)                | 34.5 (25-2887) (n = 10)    | n/a                       | 85 (38-132) (n = 2)                         | 49 (n = 1)                 | 50.5 (44-57) (n = 2)                    | 19 (n = 1)   | n/a                     |
| GGT (IU/L)                | 4.5 (1.4-68) (n = 10)      | n/a                       | 626 (<1-626) (n = 2)                        | 222.6 (n = 1)              | 8 (3.6-12.4) (n = 2)                    | 32.2 (n = 1) | n/a                     |
| Bilirubin (μmol/L)        | 3.6 (2.6-60.5) (n = 11)    | n/a                       | 5.6 (3.8-7.4) (n = 2)                       | 2.7 (n = 1)                | 3.35 (2.4-4.3) (n = 2)                  | 2.1 (n = 1)  | n/a                     |
| Cholesterol (mmol/L)      | 6.85 (4.84-17) (n = 11)    | n/a                       | 10.65 (7.78-13.52) (n = 2)                  | 8.22 (n = 1)               | 7.82 (5.42-10.22) (n = 2)               | 5.39 (n = 1) | n/a                     |

Note: Dogs were checked at irregular intervals and so all variables were not always evaluated. "n" is the number of dogs with available blood biochemistry results at each time interval. Some dogs died, were euthanized, were lost to follow-up, or did not have results at every time interval, hence the "n" varies from interval to interval.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

<sup>a</sup>The sample for one dog was hemolyzed, skewing the bilirubin value.

<sup>b</sup>One dog had a marked increase in ALP after treatment with prednisolone for mast cell tumor.

**TABLE 6** Progression of cholelithiasis from presentation to follow-up of dogs with subsequent abdominal ultrasonography examinations after detection of choleliths (n = 17)

|                            | Complete resolution | Decrease in cholelith size or number | Static        | Increase in cholelith size or number | Recurrent                  | Median duration of imaging follow up (range) (days) |
|----------------------------|---------------------|--------------------------------------|---------------|--------------------------------------|----------------------------|---|
| Medically treated (n = 8)  | 50% (n = 4)         | 12.5% (n = 1)                        | 12.5% (n = 1) | 25% (n = 2)                          | n/a                        | 79 (37-833)   |
| Surgically treated (n = 7) | 71.4% (n = 5)       | 14.3% (n = 1)                        | 0             | 0                                    | 14.3% <sup>a</sup> (n = 1) | 325 (12-1461)                                       |
| No treatment (n = 2)       | 50% (n = 1)         | 0                                    | 50% (n = 1)   | 0                                    | n/a                        | 159.5 (81-238)                                      |

<sup>a</sup>This patient underwent cholecystectomy, cystotomy, and partial cystectomy. At presentation, multiple choleliths were present in the gallbladder and a single cholelith in the common bile duct, at follow up there were multiple choleliths present in the common bile duct.

One dog with primary hyperparathyroidism that underwent cholecystectomy had evidence of recurrent choledocholithiasis at 41 days postsurgery and subsequently was treated using UDCA without recurrence of symptomatic cholelithiasis and was euthanized 577 days after presentation for causes unrelated to cholelithiasis.

The single dog with a decrease in cholelith number at final imaging follow-up was presented initially with multiple cholecystoliths, choledocholiths, and choleliths within the intrahepatic ducts, and the presence of a single cholelith within the intrahepatic ducts was documented at follow-up 892 days postoperatively.

All 5 dogs that survived to discharge and that were dead at the time of writing were euthanized because of, or died of, disease unrelated to cholelithiasis.

### 3.10.2 | Medical management outcome

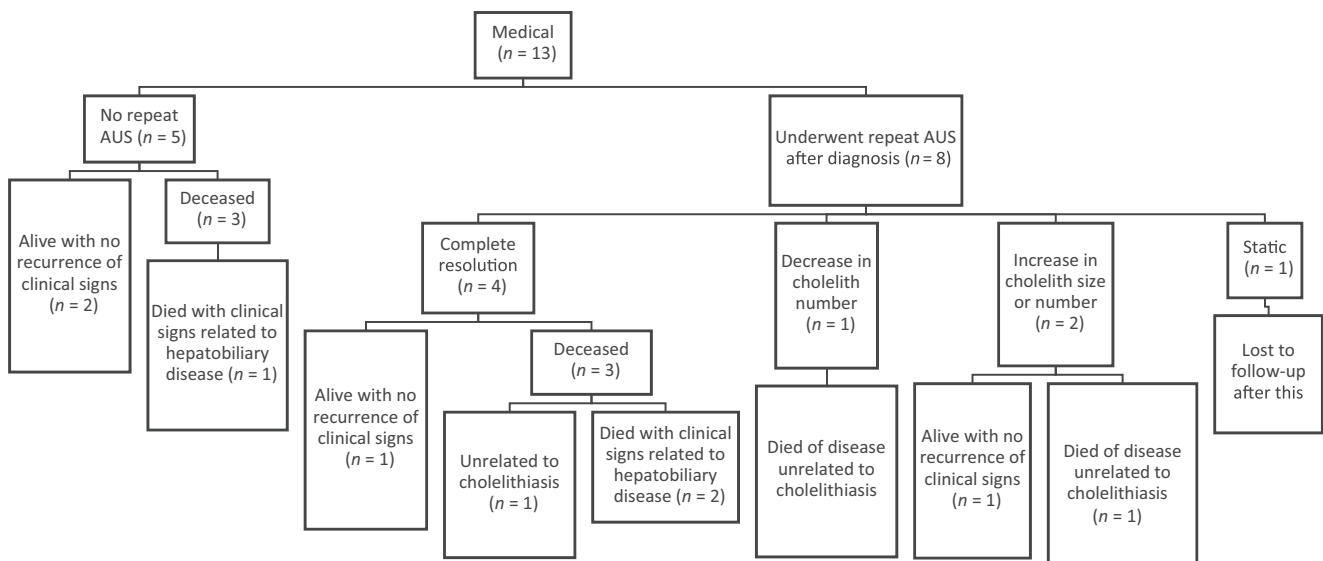
Follow-up biochemistry results were available for 10 dogs with a median follow-up time of 67.5 days (range, 29-833 days; Table 5).

Follow-up AUS was performed in 8 dogs with a median time from presentation to final AUS of 79 days (range, 37-833 days; Table 6). Fifty percent of medically managed dogs with repeat AUS had complete resolution of cholelithiasis and 12.5% had a decrease in cholelith number.

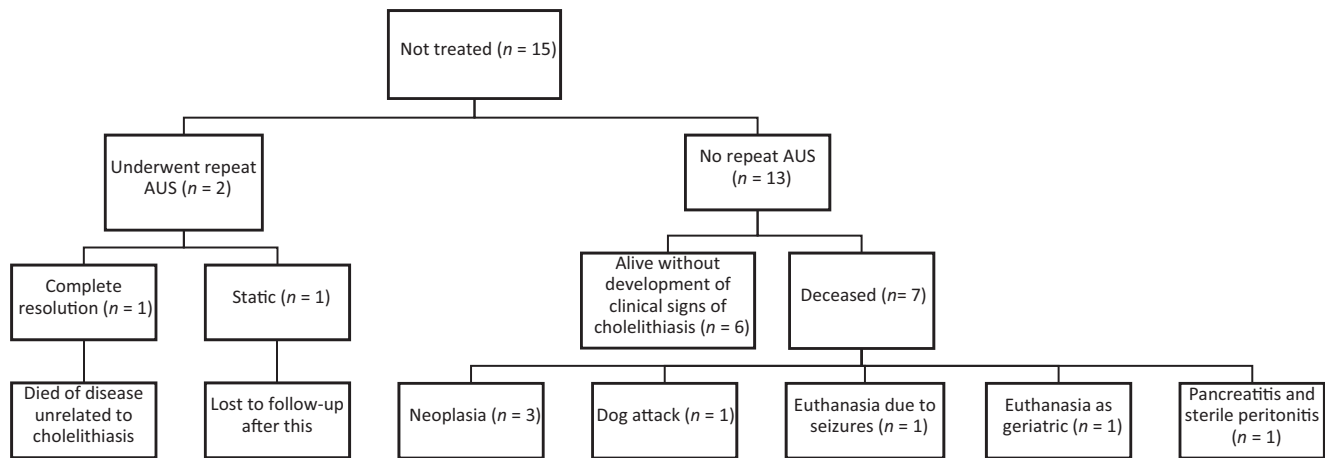
Four dogs were alive at the time of writing, 8 were dead, and 1 was lost to follow-up (Figure 2). Median survival time was 498.5 days (range, 56-2457 days).

Recurrence of clinical signs that could be attributable to cholelithiasis was seen in 1 symptomatic dog with multiple cholecystoliths after 314 days, which improved with PO antibiotic and IV fluid treatment, but repeat AUS was not performed.

Of 3 dogs that died with signs of hepatobiliary disease, 1 was diagnosed with multiple acquired portosystemic shunts and had no evidence of cholelithiasis at final imaging follow-up 64 days before death and another underwent necropsy (Table S1) at which no choleliths were noted. The final dog was presented with weight loss and icterus and euthanized 158 days after detection of cholelithiasis because of suspicion of necrotizing pancreatitis or pancreatic

**FIGURE 2** A diagram illustrating the outcomes of dogs in the medical treatment group. AUS, abdominal ultrasonography





**FIGURE 3** A diagram illustrating the outcomes of the dogs in the nontreatment group. AUS, abdominal ultrasonography

neoplasia, but necropsy was not performed. No evidence was found that ongoing cholelithiasis in this subset of patients directly contributed to death.

### 3.10.3 | Outcome of nontreatment group

Follow-up biochemistry results were available for 6 dogs with a median final follow-up time of 85.5 days (range, 3-461 days; Table 5). Follow-up AUS was performed in 2 dogs with a median time from presentation to final AUS of 160 days (range, 81-238 days; Table 6). One dog with repeat AUS had complete resolution of cholelithiasis. Six dogs were alive, 8 were dead, and 1 was lost to follow-up (Figure 3). Median survival time was 399.5 days (range, 3-2191 days). One dog died with signs of hepatobiliary disease, having been presented with hepatocellular carcinoma, and was euthanized 10 days after cholelith detection because of development of neurological signs. No dogs were reported to have either developed or died with clinical signs attributable to cholelithiasis.

### 3.11 | Survival

Median survival time of all dogs was 457.4 days (range, 0-2457 days). Four symptomatic dogs were alive at the time of writing, 12 had died, and 2 were lost to follow-up. The median survival time of symptomatic cases was 498 days (range, 0-2457 days). Nine dogs in the incidental group were alive at the time of writing and 11 had died, but the cause and time of death in 1 dog was unknown. The median survival time of dogs in the incidental group was 434 days (range, 3-2191 days). No significant difference was found in survival distribution between the symptomatic and incidental groups ( $\chi^2 = 0.044$ ,  $df = 1$ ,  $P = .83$ ; Figure 4).

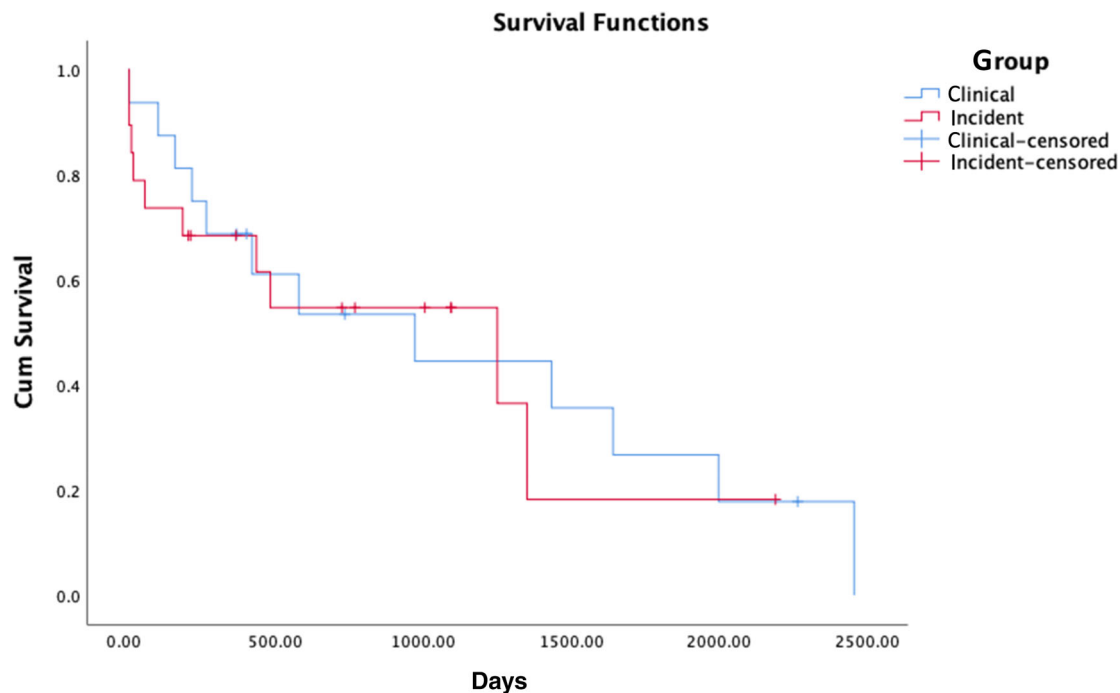
## 4 | DISCUSSION

Previous reports of medical management of cholelithiasis in dogs have documented persistence of cholelithiasis despite clinical

improvement.<sup>1-3,6</sup> In contrast to choleliths in humans, which are primarily cholesterol-based, choleliths in dogs usually are composed of calcium carbonate, cholesterol, and bilirubin.<sup>4</sup> Ursodeoxycholic acid commonly is utilized in the management of some affected humans, but surgery usually is recommended for symptomatic patients.<sup>13</sup> Literature describing use of UDCA in dogs with cholelithiasis is limited,<sup>1,2,5,6</sup> and no published guidelines guide treatment in veterinary medicine, as compared to human medicine.<sup>13</sup> In the absence of such guidelines, factors that appeared to influence treatment choice included clinical presentation, cholelith location, and hepatobiliary enzyme activities.

Similar to previous reports, older, small-breed dogs were overrepresented in our study with a high prevalence in CKCS.<sup>2,4,14</sup> We did not identify a significant sex predisposition, similar to a previous study.<sup>1</sup> These findings contrast with those in the human medical literature where females have a higher incidence of cholelithiasis, suspected to be associated with the effects of estrogen to enhance cholesterol synthesis and decrease bile acid synthesis.<sup>11,15-19</sup> This effect likely does not influence the pathophysiology in dogs because they commonly are neutered, and cholelith composition differs from that in humans.<sup>4</sup>

Interestingly, 8 dogs were presented with concurrent endocrinopathies, with 1 surgically treated dog with primary hyperparathyroidism developing cholelith recurrence. Both hyperparathyroid dogs had radiopaque choleliths, and therefore it is reasonable to assume hypercalcemia could have contributed to development of cholelithiasis in these dogs. This conclusion is supported by the fact that humans with cholelithiasis have an increased incidence of hypercalcemia<sup>20</sup> and previous reports that analyzed cholelith composition in dogs found calcium to be a major component.<sup>2,21</sup> Although debate exists as to whether an association between hyperparathyroidism and cholelithiasis occurs in humans, 3 studies have reported an increased incidence of hyperparathyroidism,<sup>20,22,23</sup> but this relationship has not been investigated in dogs. Hypercholesterolemia associated with endocrinopathies such as hyperadrenocorticism or hypothyroidism could have predisposed dogs in our study to develop cholelithiasis, given that hyperlipidemia, hypothyroidism, and hyperadrenocorticism have



**FIGURE 4** A Kaplan-Meier curve comparing survival times between dog clinically affected by cholelithiasis and dogs with incidentally detected cholelithiasis. Censored indicates that an event (death) did not occur in the time the dog has been followed up

been found in some studies to be associated with the presence of gallbladder mucocoeles.<sup>24,25</sup> Given the well-known associations between endocrinopathies and gallbladder dysfunction,<sup>25</sup> we recommend that future research be performed to investigate incidence rates of cholelithiasis in dogs with concurrent metabolic and endocrine diseases.

A novel finding of our study is that symptomatic dogs were significantly younger than dogs in the incidental group. Similarly, in the human medical literature, younger age is a factor associated with symptomatic cholelithiasis.<sup>16,17</sup> Age therefore should be considered when assessing dogs with cholelithiasis because younger dogs in our study appeared more likely to have symptomatic cholelithiasis. Almost 50% of dogs in our study were considered symptomatic, contrasting with previously published findings of just 13.1%.<sup>1</sup> In the human and veterinary medical literature, most cases of cholelithiasis are reported to be incidental,<sup>1,2,6,11,16,17</sup> with clinical signs often seen with concurrent cholecystitis, associated with biliary obstruction or gallbladder rupture.<sup>3,5</sup> The most frequently identified clinical signs in symptomatic dogs in our study were vomiting, decreased appetite, lethargy, diarrhea, icterus, and abdominal pain, similar to previous reports.<sup>1,6</sup>

Although symptomatic dogs in our study had higher ALP, ALT, and  $\gamma$ -glutamyltransferase (GGT) activities than did incidental dogs, we failed to detect significant differences in AST activity, or bilirubin or cholesterol concentrations. This observation contrasts with the findings of a previous study<sup>1</sup> that documented significant increases in AST, ALT, and GGT activity, and bilirubin and cholesterol concentrations in symptomatic dogs. Failure to detect significant differences in bilirubin and cholesterol concentrations and AST activity in our study may have been a consequence of the small number of dogs in the incidental group. Our findings and those of the

aforementioned study suggest some correlation between biochemistry abnormalities and the symptomatic status of patients with cholelithiasis, and therefore dogs with cholelithiasis and associated biochemical abnormalities warrant careful evaluation. It is important, however, to be aware that nonspecific blood biochemistry changes have been reported in dogs with ultrasonographic evidence of apparent biliary obstruction.<sup>5</sup>

Choleliths were identified within the gallbladder in 92.1% of cases, a proportion similar to the previously reported 94%.<sup>1</sup> The important findings that 100% of the nontreatment group and 95% of the incidental group had cholecystolithiasis alone could indicate that the presence of choleliths, in the absence of gallbladder wall abnormalities and CBD dilatation, may not be associated with clinical signs. However, 1 surgically managed dog with cholecystolithiasis required surgical intervention because of gallbladder rupture. An interesting aspect of our study is that all dogs observed to have choledocholiths were symptomatic. This finding may be related not only to bile duct obstruction but also to the fact the CBD is well-innervated<sup>26</sup> and obstruction caused by choledocholithiasis likely is painful. This consideration combined with the important finding that a high proportion of surgically treated dogs had choledocholithiasis, suggests that cholelith location plays an important role in determining treatment modality. The only dog with choledocholithiasis without surgical intervention had a single choledocholith that was not causing complete EHBDO and had unremarkable serum biochemical changes other than mild hypercholesterolemia. Therefore, medical management was deemed a reasonable option, and was successful in this case.<sup>5</sup> Further research is required to determine which factors should influence the decision to intervene with surgical vs medical management.

All surgically managed dogs were symptomatic for cholelithiasis and a large proportion were documented to have choledocholiths. The median results of ALP, GGT, ALT, and AST activities and bilirubin concentration in this cohort were markedly increased above reference intervals, which offer insight into historical treatment decision-making and suggest that biochemistry results may have influenced treatment choice in this cohort. However, because of the retrospective nature of our study and lack of statistical comparison with a control group we can only speculate. Despite the risk of postoperative morbidity and mortality, long-term prognosis appeared to be favorable in surgically treated dogs, with complete resolution of cholelithiasis in 5 of 7 dogs with follow-up AUS. Both cases without complete resolution of cholelithiasis on AUS remained asymptomatic postoperatively and died of causes unrelated to cholelithiasis. Although previously published data suggests that dogs undergoing cholecystectomy have better outcomes than medically treated dogs,<sup>3</sup> further research is required to establish conclusive evidence of superiority.

Four medically treated dogs in our study had resolution of cholelithiasis at follow-up AUS, and a single dog had a decrease in cholelith number. This finding has not been reported in the literature describing use of UDCA in dogs with cholelithiasis,<sup>1-3</sup> other than the single case included in a previous study.<sup>5</sup> Interestingly, 2 dogs with complete resolution had radiolucent choleliths, indicating calcium was not a major component of these choleliths, but no cases had composition analysis performed, representing a limitation of our study. In human medicine, clear guidelines and inclusion criteria exist to determine which patients with cholelithiasis are likely to benefit from treatment using UDCA, with success rates varying from 60% to 90%.<sup>27</sup> However, no guidelines exist in veterinary medicine, and despite widespread use of UDCA in veterinary medicine for the treatment of hepatobiliary disease,<sup>28,29</sup> only 2 case reports documenting its efficacy exist.<sup>5,7</sup> Ursodeoxycholic acid is a potent choleresic,<sup>9</sup> and resolution of cholelithiasis could be accounted for by passing of choleliths because of the choleresic action of UDCA rather than litholysis. It also cannot be discounted that when decreases in cholelith size or number were seen, smaller choleliths could have passed, and new, smaller choleliths subsequently could have formed and be misinterpreted as a decrease in size or partial dissolution of the previous cholelith. Despite this, our findings suggest UDCA can be safely used in the medical management of some dogs, which should inform future prospective studies investigating the use of UDCA for management of cholelithiasis in dogs.

Medical management was not effective in all cases. In 3 dogs, cholelithiasis did not resolve, although 2 had an improvement in clinical signs and the third was euthanized because of development of suspected histiocytic sarcoma 56 days after detection of cholelithiasis. Two surgically managed dogs were treated with UDCA for 43 days and 72 days before surgery and before developing gallbladder rupture and EHBDO, respectively, highlighting the importance of careful case selection and vigilant monitoring. Because of the retrospective nature of our study, it is not possible to predict which cases will respond to medical management, and future research should focus on identifying factors influencing this outcome.

Dogs in the nontreatment group all had choleliths solely within the gallbladder, were asymptomatic, and had lower median hepatobiliary laboratory test results at presentation than did both other treatment groups. None of the dogs progressed to require surgical or medical intervention or was reported to have died of causes attributable to cholelithiasis. The favorable survival time of the nontreatment group indicates that the decision not to treat cholelithiasis was not detrimental. It is reasonable to conclude from the findings of our study and previous studies<sup>1,2</sup> that dogs with choleliths in the gallbladder only, without clinical signs attributable to cholelithiasis (or clinical signs attributable to another disease process), with relatively normal serum biochemical findings and without ultrasonographic evidence of changes to the gallbladder wall, cystic duct, or CBD are unlikely to progress to require intervention, given that untreated cases were followed for a median of 399.5 days (range, 3-2191 days) without requiring intervention. A proportion (3%) of asymptomatic dogs, however, may go on to become symptomatic when untreated,<sup>1</sup> and cholelithiasis always carries a risk of progression from clinically silent to clinically relevant. Given the paucity of literature in veterinary medicine, it is impossible to accurately predict which, if any, of these patients eventually will become symptomatic or require treatment, and further research should be performed to identify patient factors that increase the risk of clinical events.

Our study had some limitations. First, its retrospective nature meant that only incomplete data were available in some cases, with variations in clinical evaluation, case management, and timing of follow-up. Patients in the medically treated group did not have consistent treatment plans, with variations in daily dose, dosing regimen, and duration of treatment with UDCA, along with a variety of additional drugs and concurrent diseases. It is possible that dose, frequency, or duration of administration of UDCA could affect cholelith progression, and future prospective studies should aim to determine if protocols differ in efficacy. The lack of a control group with which to compare progression of cholelithiasis represents another limitation, and it cannot be proven that UDCA affected progression of cholelithiasis or whether this finding is a result of a type II error. Nevertheless, our study has shown UDCA can be safely used in the treatment of dogs with cholelithiasis. Future research should include a randomized placebo-controlled prospective study to assess the efficacy of UDCA in cholelithiasis patients. Another limitation is that information regarding liver and gallbladder histopathology, bile cytology, and culture was not available for all cases because of the retrospective nature of the study. The possibility that underlying liver or gallbladder pathology may have contributed to development of cholelithiasis and outcome in these cases exists, with histopathological evidence of concurrent cholangiohepatitis and cholecystitis reported in cats and dogs with cholelithiasis<sup>1,2,30</sup> and with chronic cholecystitis identified in the majority of dogs for which histopathology results were available in our study. Diet is a factor that may influence progression of cholelithiasis and was not investigated in our study. Information regarding diet type, caloric intake, feeding patterns, and habits was not available in sufficient detail because of the retrospective nature of our study. In human medicine, diet is an important factor in the management of

cholelithiasis,<sup>10</sup> with low-cholesterol diets often recommended. Diet may have played a role in the development of cholelithiasis in some of our patients, and a change in diet could have contributed to improvement of cholelithiasis, but this remains unknown. Also, cholelith size was not routinely recorded in our study, and therefore analysis of cholelith size in relation to clinical presentation, treatment modality, and outcome could not be performed. Cholelith size may be important given that in human medicine the presence of choleliths >10 mm is associated with a higher risk of clinical events<sup>17</sup> and choleliths <5 mm respond most effectively to UDCA.<sup>10,11,27</sup>

A further limitation of our study and of previous studies investigating medical management of cholelithiasis is that composition analysis is rarely performed, with cholelith composition being a major factor affecting efficacy of UDCA in management of cholelithiasis in humans. Despite the lack of composition analysis in our study, 77% of dogs in which abdominal radiography was performed had radiolucent choleliths. This finding indicates that cholelith composition was not purely calcium-based<sup>31,32</sup> in the majority of these dogs, and instead it is possible that cholesterol-based choleliths were more prevalent.

It is also possible that the cholerectic action of UDCA aids passing of choleliths, in which case composition would be less important. This possibility may contribute to the variation in results between our study in which apparent dissolution of choleliths was observed and in previous studies where cholelithiasis was persistent.<sup>1,2</sup> A final limitation of our study is that complete follow-up was not available for every case, with 3 cases lost to follow-up and only 2 nontreated cases undergoing repeat AUS. Therefore, it is possible that important data were not acquired that may have influenced our findings.

In conclusion, we documented resolution or improvement of cholelithiasis in several dogs treated with UDCA. This finding suggests that, with careful case selection, UDCA may be a safe and effective tool for management of cholelithiasis in dogs. Our study suggests that patients presenting with marked increases in ALP, ALT, and GGT activity with or without ultrasonographic evidence of choledocholiths and with or without symptomatic cholelithiasis can be considered for surgical intervention, whereas medical management should be considered in patients without choledocholithiasis. Future prospective studies are required to develop management guidelines similar to those used in human medicine. Development of evidence-based guidelines for management of cholelithiasis in dogs would enable improved outcomes for patients and offer more reliable prognoses for clinicians, especially given the lack of consensus regarding medical management of cholelithiasis in dogs.

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#### CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

#### OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Approved by the Ethics and Welfare committee of the Department of Veterinary Medicine, University of Cambridge, reference CR435.

#### HUMAN ETHICS APPROVAL DECLARATION

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

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#### REFERENCES

1. Ward PM, Brown K, Hammond G, et al. Cholelithiasis in the dog: prevalence, clinical presentation, and outcome. *J Am Anim Hosp Assoc*. 2020;56(3):152. doi:10.5326/JAAHA-MS-7000
2. Kanemoto H, Fukushima K, Tsujimoto H, et al. Intrahepatic cholelithiasis in dogs and cats: a case series. *Can Vet J*. 2017;58(9):971-973.
3. Kirpensteijn J, Fingland RB, Ulrich T, et al. Cholelithiasis in dogs: 29 cases (1980-1990). *J Am Vet Med Assoc*. 1993;202(7):1137-1142.
4. Lee S, Kweon O-K, Kim WH. Associations between serum leptin levels, hyperlipidemia, and cholelithiasis in dogs. *PLoS One*. 2017;12(10):e0187315.
5. Allan F, McCallum KE, Genain M-A, et al. Dissolution of cholelithiasis in a Cavalier King Charles Spaniel receiving conservative management with ursodeoxycholic acid. *Vet Rec Case Rep*. 2020;8(3):e001206.
6. Ward R. Obstructive cholelithiasis and cholecystitis in a keeshond. *Can Vet J*. 2006;47(11):1119-1121.
7. Meyer DJ, Thompson MB, Senior DF. Use of ursodeoxycholic acids in a dog with chronic hepatitis: effects on serum hepatic tests and endogenous bile acid composition. *J Vet Intern Med*. 1997;11(3):195-197. doi:10.1111/j.1939-1676.1997.tb00090.x
8. Guarino MP, Carotti S, Sarzano M, et al. Short-term ursodeoxycholic acid treatment improves gallbladder bile turnover in gallstone patients: a randomized trial. *Neurogastroenterol Motil*. 2005;17(5):680-686. doi:10.1111/j.1365-2982.2005.00683.x
9. Yanaura S, Ishikawa S. Cholerectic properties of ursodeoxycholic acid and chenodeoxycholic acid in dogs. *Jpn J Pharmacol*. 1978;28(3):383-389.
10. Reshetnyak VI. Concept of the pathogenesis and treatment of cholelithiasis. *World J Hepatol*. 2012;4(2):18-34.
11. Di Ciaula A, Portincasa P. Recent advances in understanding and managing cholesterol gallstones. *F1000Res*. 2018;24(7):F1000 Faculty Rev-1529.
12. Thrall DE. *Textbook of Veterinary Diagnostic Radiology*. 6th ed. St. Louis, MO: Elsevier; 2013.
13. Tazuma S, Unno M, Igarashi Y, et al. Evidence-based clinical practice guidelines for cholelithiasis 2016. *J Gastroenterol*. 2017;52(3):276-300.
14. Lee S, Lee A, Kweon O, Kim WH. Changes in pre- and postoperative serum leptin concentrations in dogs with gallbladder mucocele and cholelithiasis. *BMC Vet Res*. 2019;15(1):215. doi:10.1186/s12917-019-1964-z
15. Lavoie J-M. Dynamics of hepatic and intestinal cholesterol and bile acid pathways: the impact of the animal model of estrogen deficiency and exercise training. *World J Hepatol*. 2016;8(23):961-975.
16. McSherry CK, Ferstenberg H, Calhoun WF, et al. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. *Ann Surg*. 1985;202(1):59-63.

17. Shabanzadeh DM, Sørensen LT, Jørgensen T. A prediction rule for risk stratification of incidentally discovered gallstones: results from a large cohort study. *Gastroenterology*. 2016;150(1):156-167.
18. Di Ciaula A, Wang DQ-H, Portincasa P. An update on the pathogenesis of cholesterol gallstone disease. *Curr Opin Gastroenterol*. 2018;34(2):71-80.
19. Pak M, Lindseth G. Risk factors for cholelithiasis. *Gastroenterol Nurs*. 2016;39(4):297-309.
20. Berger M, Dy B, McKenzie T, Thompson G, Wermers R, Lyden M. Rates of hypercalcemia and hyperparathyroidism among patients with porcelain gallbladder. *Am J Surg*. 2020;220(1):127-131.
21. Baker SG, Mayhew PD, Mehler SJ. Choledochotomy and primary repair of extrahepatic biliary duct rupture in seven dogs and two cats. *J Small Anim Pract*. 2011;52(1):32-37. doi:10.1111/j.1748-5827.2010.01014.x
22. Broulik PD, Haas T, Adámek S. Analysis of 645 patients with primary hyperparathyroidism with special references to cholelithiasis. *Intern Med*. 2005;44(9):917-921.
23. Bhadada SK, Bhansali A, Shah VN, Behera A, Ravikiran M, Santosh R. High prevalence of cholelithiasis in primary hyperparathyroidism: a retrospective analysis of 120 cases. *Indian J Gastroenterol*. 2011;30(2):100-101. doi:10.1007/s12664-011-0101-0
24. Kutsunai M, Kanemoto H, Fukushima K, Fujino Y, Ohno K, Tsujimoto H. The association between gall bladder mucocoeles and hyperlipidaemia in dogs: a retrospective case control study. *Vet J*. 2014;199(1):76-79.
25. Mesich MLL, Mayhew PD, Paek M, et al. Gall bladder mucocoeles and their association with endocrinopathies in dogs: a retrospective case-control study. *J Small Anim Pract*. 2009;50(12):630-635. doi:10.1111/j.1748-5827.2009.00811.x
26. Kyösola K. Adrenergic and cholinergic innervation of the supraduodenal common bile duct. *Am J Gastroenterol*. 1978;70(2):179-183.
27. Stawarski A, Iwańczak B, Iwańczak F. Predisposing factors and results of pharmacological treatment using ursodeoxycholic acid of gallbladder stones in children. *Pol Merkur Lekarski*. 2006;20(116):199-202.
28. Bexfield N, Watson P. Treatment of canine liver disease. *In Pract*. 2009;31(3):130-135.
29. Otte CMA, Penning LC, Rothuizen J, Favier RP. Retrospective comparison of prednisolone and ursodeoxycholic acid for the treatment of feline lymphocytic cholangitis. *Vet J*. 2013;195(2):205-209.
30. Eich CS, Ludwig LL. The surgical treatment of cholelithiasis in cats: a study of nine cases. *J Am Anim Hosp Assoc*. 2002;38(3):290-296. doi:10.5326/0380290
31. Trotman BW, Petrella EJ, Soloway RD, Sanchez HM, Morris TA III, Miller WT. Evaluation of radiographic lucency or opaqueness of gallstones as a means of identifying cholesterol or pigment stones: correlation of lucency or opaqueness with calcium and mineral. *Gastroenterology*. 1975;68(6):1563-1566.
32. Yu J-K, Pan H, Huang S-M, et al. Calcium content of different compositions of gallstones and pathogenesis of calcium carbonate gallstones. *Asian J Surg*. 2013;36(1):26-35.

### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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