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Feline cholangitis: a necropsy study of 44 cats (1986–2008)

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Forty-four cats diagnosed with moderate to severe cholangitis at necropsy are described. The population comprised 0.86% of all feline necropsies performed during the 22-year study period. Liver specimens were classified as acute neutrophilic cholangitis (ANC), chronic neutrophilic cholangitis (CNC), lymphocytic cholangitis (LC) or chronic cholangitis associated with liver fluke infestation (CC) based on the World Small Animal Veterinary Association (WSAVA) classification scheme. ANC (seven) and CNC (33) comprised the majority of cases. In contrast to previous descriptions, overlap was seen in clinical findings between ANC and CNC subtypes. Results suggest that liver enzyme activity may not predict degree of inflammation. Severity of inflammation varied between liver sections in individual cats, underscoring the need to obtain biopsy samples from multiple sites. Inflammatory bowel disease (50%), pancreatitis (60%), or both (32%) commonly accompanied cholagitis. We conclude that cholangitis is not a common cause of feline mortality. Most cats that succumb to cholangitis have ANC or CNC, and concurrent disease contributes to death in many.

Cholangitis is one of the most common hepatobiliary diseases of cats.[1–3] Previous veterinary literature has used varying terminology to describe this disease process.[3–5] Recently, the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group suggested standardized criteria for diagnosis of liver diseases of dogs and cats.[5] These criteria have been applied to clinical cases of canine hepatitis and feline cholangitis.[6,7] The standards define three main forms of cholangitis which are recognized to occur in feline patients: neutrophilic cholangitis (NC), lymphocytic cholangitis (LC), and chronic cholangitis associated with liver fluke infestation (CC). Histological findings associated with each type have been previously described.[5]

Previous descriptions of the clinical features of feline cholangitis have highlighted differences between the various forms.[4,8,9] Comparison of cats with acute and chronic cholangiohepatitis has suggested that cats with acute disease are younger and more likely to have fever, weight loss, neutrophilia and a left shift.[9] Cats with chronic disease are reported to have higher serum total bilirubin concentration and alkaline phosphatase activity.[9] Recent data identified few differences in the clinical findings between cats with different types of cholangitis when classified using the WSAVA standards.[7] In the data evaluating clinical outcomes of cats with cholangitis, the prognosis appears to be generally good for all forms, including median survival times greater than 1 year in two studies.[9,10] It has been suggested that cats with poor outcomes may have concurrent disease contributing to mortality.[9]

Discussion regarding extra-hepatic disease in cats with cholangitis centers around inflammatory disease of the pancreas, the gastrointestinal (GI) tract and to a lesser degree, the kidneys.[4,11–16] Cats with cholangitis are more likely to have pancreatitis and inflammatory bowel disease (IBD) than cats without cholangitis.[11] While the pathogenesis relating these three diseases remains unclear, the predominant theory is that underlying IBD may predispose cats to cholangitis and pancreatitis as a result of reflux of enteric bacteria into the shared opening of the pancreatic and common bile ducts.[4,12,17] Bacterial infection is more frequently associated with NC than LC, though

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there is speculation that LC may be a progression of NC and, therefore, have a chronic bacterial origin.[4,8] Despite prior speculation, recent evidence does not support a role for bacteria in the etiopathogenesis of LC, but rather suggests an immune-mediated mechanism.[18] The evidence for the association between cholangitis, pancreatitis and IBD does not clearly delineate whether cats had neutrophilic or lymphocytic forms of cholangitis.

The primary goal of this study was to describe a group of cats diagnosed with moderate to severe cholangitis at necropsy and characterize their disease using the WSAVA classification scheme. We aimed to describe the clinical, laboratory, imaging and necropsy findings in a population of non-survivors. We hypothesized that concurrent disease would be common and sought to describe concurrent diseases recognized at necropsy.

Materials and methods

The necropsy database of the Matthew J Ryan Veterinary Hospital of the University of Pennsylvania was searched from January 1986 through June 2008 for cats with liver sections available for review and a final diagnosis including cholangitis, cholangiohepatitis, or hepatitis. Over the 22-year period 5126 feline necropsies were performed. Of those, 67 cases met criteria for inclusion. At the onset of this study, liver sections were reviewed by one board-certified veterinary pathologist (TVW). Cases with moderate or severe cholangitis were included. Severity of inflammation was based on the density of the inflammatory infiltrate, measured by the approximate number of layers of cells within the inflammatory foci (minimal = <2, mild = 1–2, moderate = 3–5, severe = >5). Twenty-three cases were excluded for the following reasons; neoplasia (five), hepatitis without biliary involvement (five), eosinophilic infiltrate (one), marked autolysis (one), embolic hepatitis (one), incomplete medical records (three) and minimal or mild inflammation (seven). The remaining 44 cases were classified into one of the following groups based on the WSAVA standards: acute neutrophilic cholangitis (ANC), chronic neutrophilic cholangitis (CNC), lymphocytic cholangitis (LC) or chronic cholangitis associated with liver fluke infestation (CC). The classification was determined by predominant type of inflammatory cells and degree of bile duct hyperplasia, fibroplasia, and fibrosis.[5] Cases with a predominance of neutrophils with only minimal or mild bile duct hyperplasia, fibroplasia, or fibrosis were classified as ANC. Cases with mixed inflammatory cells, including a component of neutrophilic inflammation, with moderate or severe bile duct hyperplasia, fibroplasia, or fibrosis were classified as CNC. Cases with a predominance of lymphocytes with minimal to no neutrophilic infiltrate were classified as LC. The single case of CC was classified as such based on marked bile duct ectasia, severe diffuse eosinophilic and lymphoplasmacytic inflammation with fibrosis and bile duct hyperplasia.

Medical records were reviewed by a single investigator (JCC) for the following information: signalment, history, physical examination findings, clinicopathology, imaging, and necropsy data. All radiologic studies were performed or reviewed by board-certified radiologists. Tissue samples obtained for histopathology at the time of necropsy were determined by the attending pathologist, based on history, clinical suspicion and/or gross abnormalities. Clinical outcome was recorded as euthanasia, euthanasia in a peri-arrest situation or death. Patients were defined as being euthanased in a peri-arrest situation if they arrested, were successfully resuscitated and subsequently euthanased, if they were non-responsive prior to euthanasia or if they had markedly diminished vital parameters at the time of euthanasia. Cause of death/euthanasia was determined by review of all available information including the necropsy request form, necropsy report and medical record. Cause of death/euthanasia was classified as one of the following: open (unable to determine), predominantly liver, liver and intestine/pancreas, multiple processes or non-liver.

Descriptive data are included for all cats. Due to the small numbers of cats with LC and CC, statistical comparisons were made only between cats with ANC and CNC. For each variable a test for normality based on skewness is combined with another based on kurtosis to deliver an overall test statistic as described by D'Agostino, Belanger and D'Agostino[19] with the empirical correction developed by Royston.[20] Analysis was performed for categorical variables using the χ^2 test. Due to non-normality of data, for continuous variables, the Wilcoxon rank sum test was used. Data are presented as frequencies and percentages for categorical variables and as medians and ranges for continuous variables. Probabilities less than 0.05 were considered statistically significant. All statistical analyses were performed using a commercial software program (SAS version 9.1, SAS Institute, Cary, NC).

Results

The final diagnoses following histopathologic review of all liver sections were as follows: 33 cats with CNC, seven cats with ANC, three cats with LC and one cat with CC. The prevalence of moderate to severe cholangitis was low (0.86% of the necropsy population).

The median age for all cases was 9 years (range 6 weeks–19 years). Cats with ANC were significantly younger than those with CNC (Fig 1). There were 24 castrated males, 19 spayed females and one intact male, with no differences in sex distribution between the ANC and CNC groups. The majority of cats enrolled were domestic shorthair (38/44, 86%).

The most common clinical signs included lethargy (33/44, 75%), vomiting (29/44, 66%), weight loss
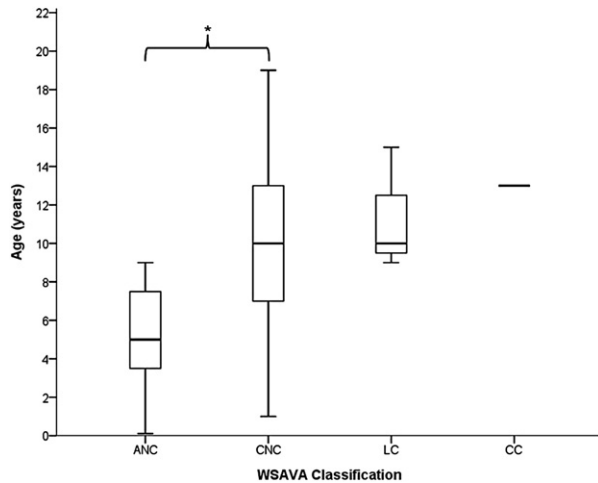
Fig 1. Age distribution of cats with cholangitis. *Significantly different ($P = 0.02$).

(25/43, 58%), and decreased appetite (22/44, 50%). Initial body temperature was recorded in 41 cases; 9/41 (22%) were hyperthermic (>102.5°F), including 1/7 (14.3%) in the ANC group and 8/31 (26%) in the CNC group. Icterus was noted on the initial physical examination in 13/38 cats (34%), including 2/5 (40%) with ANC, 10/30 (33%) with CNC and 1/2 (50%) with LC. Twenty-one percent (8/38) were noted to have hepatomegaly, including 7/31 (23%) in the CNC group and the lone patient with CC. There was no significant difference in the frequency of clinical signs or physical examination findings between the ANC and the CNC groups.

A complete blood count was available in 31 cases. Median white blood cell count was $13.7 \times 10^3/\mu l$ (range $2.24-101.7 \times 10^3/\mu l$; reference interval (RI) $4.04-18.7 \times 10^3/\mu l$). Leukocytosis was present in 39% of cats, including 2/4 (50%) with ANC, 7/23 (30%) with CNC, 2/3 (67%) with LC and 1/1 (100%) with CC. Band neutrophils were seen in approximately one-third of the population. Hematocrit was recorded in 35 patients with a median of 34.2% (range 18–54%; RI 31.7–48%). Anemia was documented in 34% of cases, including 3/7 (43%) with ANC, 7/24 (29%) with CNC, 1/3 (33%) with LC and 1/1 (100%) with CC. A reticulocyte count was only available in four cases (one regenerative, three non-regenerative). No statistical difference in white blood cell count, presence of bands or hematocrit was seen between the ANC and CNC groups.

Serum liver enzyme activity and total bilirubin (TBILI) concentrations were available for the majority of cats (Table 1). Increased activity of alanine transaminase (ALT) was present in only 50% of the population (median 157 U/l, range 12–2685 U/l, RI 33–152 U/l). Similarly, alkaline phosphatase (ALP) activity was increased in 48% of cats (median 83 U/l, range 11–1935 U/l, RI 22–87 U/l). Aspartate transaminase (AST) was the only liver enzyme to show consistently

Table 1. Serum liver enzyme activity and total bilirubin in cats with cholangitis.

Parameter (RI)	ANC			CNC			LC			CC		
	Median	Range	High (n, %)	Median	Range	High (n, %)	Median	Range	High (n, %)	Median	Range	High (n, %)
ALT (33–152 U/l)	117	26–212	2/4 50%	214	12–2685	15/26 58%	66	52–151	0/3 0%	77	77	0/1 0%
AST (1–37 U/l)	100	55–323	3/3 100%	169	37–3181	18/19 95%	80	51–124	3/3 100%	–	–	–
ALP (22–87 U/l)	350	19–1935	2/4 50%	83	11–697	12/25 48%	90	47–112	2/3 67%	68	68	0/1 0%
GGT (5–19 U/l)	5	5–7	0/3 0%	16*	5–41	4/15 27%	6	6–12	0/3 0%	–	–	–
TBILI (0.1–0.8 mg/dl)	4.2	2.7–9.1	4/4 100%	1.4	0.3–24.9	16/25 64%	0.4	0.2–4.8	1/3 33%	0.5	0.5	0/1 0%

*Significantly different from ANC ($P = 0.03$).

increased activity in this population, being increased in all cases except one patient with CNC (median 157 U/l, range 37—3181 U/l, RI 1—37 U/l). The median gamma-glutamyltransferase (GGT) activity was within the RI for all groups (median 11, range 5—41 U/l). Median GGT activity was significantly higher in cats with CNC compared to cats with ANC ($P = 0.03$) (Fig 2); however, there was no statistical difference in the percentage of cats with increased activity of GGT between groups. Twenty-one of 32 cats (66%) were hyperbilirubinemic (median 1.5 mg/dl, range 0.2—24.9 mg/dl, RI 0.1—0.8 mg/dl). Hepatic synthetic parameters were decreased in a small proportion of cats: 3/41 were hypoglycemic, 0/38 had decreased blood urea nitrogen, 4/30 were hypoalbuminemic, and 2/30 were hypocholesterolemic.

A full abdominal ultrasound was performed in 20 cats. In addition, one cat had a focal biliary tract ultrasound and another had a liver and biliary tract ultrasound. Abnormalities of the liver were described in 81% of cats (17/21). The most common abnormalities were an enlarged (10) and hyperechoic liver (nine). The liver was both enlarged and hyperechoic in four cats. Ultrasonographic abnormalities of the biliary tract were reported in 14/22 cases (64%). The most common abnormalities included bile duct distension (10), gallbladder distension (eight), and increased gallbladder sediment (eight). Pancreatic abnormalities were described in 11/21 cases (52%). Most commonly the report described an enlarged pancreas (three) with hypoechoic parenchyma (eight) and surrounding hyperechoic fat (eight). Thirteen of 20 cats (65%) had an abnormality within their gastrointestinal tract. Fluid distension (six) and thickened/irregular wall (six) were reported most frequently. There were no differences in the frequency of ultrasonographic abnormalities between the ANC and CNC groups.

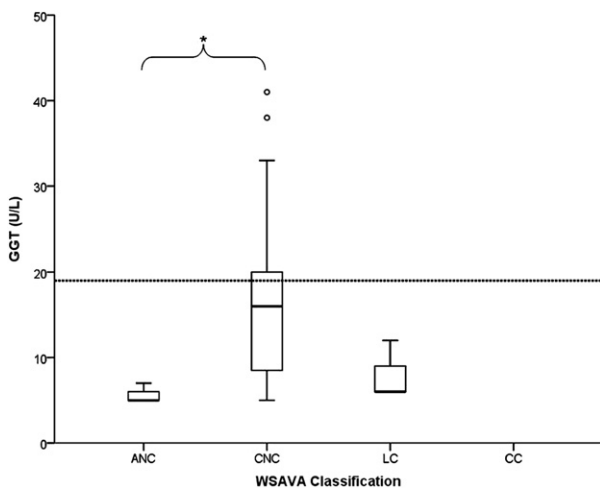While all cats had moderate to severe inflammatory changes on liver histopathology, the severity varied between different histologic sections within the same patient in many cases (Table 2). Concurrent hepatic lipidosis was reported in 14 cases (31.8%) to varying degrees (two mild, one mild-moderate, two moderate, five severe). Five cats (11%), four with CNC and one with LC, had complete or partial bile duct obstruction caused by inflammation (three), choleliths (one) or sarcoma of the common bile duct (one). Pancreatic histopathology results were available in 34 cats (Table 3). Twenty-two of 34 (65%) had evidence of pancreatitis. Pancreatitis was described as acute or subacute in four cats, chronic-active in six cats, chronic in seven cats and not specified in five cats. Pancreatic necrosis was present in five cats. There was no significant difference in biochemical variables (TBILI, ALP, GGT, AST, ALT) and white blood cell count between cats with and without pancreatitis. Histopathology of at least one section of the GI tract was available in 37 cats (Table 3). Seventeen cats (46%) had GI inflammation. Sites of inflammation included small intestine (13, segment not always specified), stomach (nine) and colon (six). Two patients were diagnosed with intestinal lymphoma and one case was questionable for early intestinal lymphoma. All three cats were in the CNC group and had evidence of concurrent GI inflammation. Renal inflammation was common in this population. Thirty of 37 cats evaluated (81%) had some degree of nephritis (Table 3). Inflammation of the liver, pancreas and GI tract concurrently was reported in 10/31 cases (32%) in which histopathology results were available for all three organs (Table 3). Culture results were only available in four cases (one ANC, two CNC, one LC). Hepatic and bile cultures were positive for an Enterococcus species in one cat with LC. At necropsy, hepatic culture was positive for Escherichia coli in one cat with CNC. Results of seven Gram stains were available, two demonstrated bacteria (both confirmed via culture).

Thirty-one cases were euthanased (72%), three cases died (7%), and nine cases were peri-arrest at the time of euthanasia (21%). Outcome information could not be determined in one cat. Four cats (9%), one with ANC and three with CNC, were presumed to have succumbed to disease unrelated to the liver including: sepsis (one), acute renal failure (one), meningoencephalitis (one) and trauma (one). The cat with sepsis was diagnosed with ANC based on histopathologic evidence of neutrophilic inflammation confined

Fig 2. Serum activity of GGT in cats with cholangitis. *Significantly different ($P = 0.03$).

Table 2. Severity of inflammatory infiltrate within the liver specimens of cats with cholangitis.

Severity	ANC (n = 7)	CNC (n = 33)	LC (n = 3)	CC (n = 1)
Mild—moderate	2	3	1	0
Moderate	3	10	1	0
Mild—severe	0	3	0	0
Moderate—severe	1	7	1	0
Severe	1	10	0	1

Table 3. Prevalence of inflammation on histopathology of pancreas, GI tract and kidneys in cats with cholangitis.

Organ	ANC	CNC	LC	CC
Pancreas	3/5 (60%)	15/26 (58%)	2/2 (100%)	1/1 (100%)
GI tract	3/6 (50%)	11/26 (42%)	2/2 (100%)	1/1 (100%)
Kidneys	3/5 (60%)	25/30 (83%)	2/2 (100%)	−
Pancreas + GI tract	1/5 (20%)	6/23 (26%)	2/2 (100%)	1/1 (100%)

to the bile ducts, but it lacked lesions of neutrophilic hepatitis and necrosis often seen secondary to sepsis. In two cats (4.5%), both of the CNC group, the cause of death was classified as open due to insufficient information. Sixteen cats (36%) died of liver disease with concurrent pancreatic and/or gastrointestinal disease, including two with ANC, 12 with CNC, one with LC and one with CC. Fourteen cats (32%) were classified as having died as a direct result of hepatobiliary disease (cholangitis was the lone disease process reported), including three with ANC and 11 with CNC. The remaining eight cats (18%), including one with ANC, five with CNC and one with LC, most likely died as a result of multiple processes including cholangitis. Examples of extra-hepatic diseases included renal disease (four), neurologic disease (two), systemic inflammatory response syndrome (one), pneumonia (one), and congestive heart failure (one).

Discussion

In general, cholangitis was not a common cause of death in cats, as these cases represented less than 1% of the necropsy population during the study period. In this population, CNC was the most common subtype represented and there were surprisingly few cats with LC. A recent retrospective analysis of clinical cases from the same institution, over the same study period, enrolled 10 times as many cats with LC.[7] None of the cats with LC in the current study died solely as a result of their cholangitis. These findings may suggest that cats with NC, rather than LC, are more likely to succumb to their disease. Previous work has suggested that patients with LC rarely present clinically ill and the results of this study support that claim.[4] Cholangitis appeared to contribute to the death of most cats in the study; however, the majority of mortality was associated with concurrent disease. Various reasons were cited for euthanasia; more commonly poor prognosis or lack of clinical response to treatment was reported as the inciting factor, however other cases were euthanased for financial and/or personal concerns.

In contrast to previous studies which have highlighted differences between various forms of cholangitis, there were few differences in clinical findings between cats with ANC and CNC.[4,8,9] The only repeatable difference from previous reports was that of cats with ANC being younger. We also identified a difference in the median GGT activity, which was higher in cats with CNC. While these differences attained statistical significance, it is our opinion that they carry no clinical significance. There is a large degree of overlap between groups in regards to patient age, as seen in the box and whisker plot (Fig 1). Furthermore, the majority of cats had normal activity of GGT, and the median GGT activity in the CNC cats was within the RI. Given the number of cases in the study, it is possible that the lack of significant difference is due to type II error. However, previous data evaluating cats with cholangitis using the WSAVA classification system have shown similar overlap in clinical findings.[7] Direct comparisons between this and previous studies may not be relevant given that we may be comparing different patient populations. The degree of clinical overlap reported here underscores the importance of histopathology in arriving at an accurate diagnosis. Currently, determining the histopathologic subtype cannot dictate an evidence-based treatment protocol or prognosis. However, the authors see merit in utilizing the WSAVA criteria to standardize future research.

Increased serum liver enzyme activity was absent in many cats. This was an unexpected finding given that the population comprises cats with moderate to severe cholangitis. Several sources state that the majority of cats with cholangitis have increased serum liver enzyme activity.[4,9,21] However, in one report only 14% of cats with acute cholangiohepatitis and 55% with chronic cholangiohepatitis had increased ALP activity. Similarly, only 57% of acute cases demonstrated increased ALT activity.[9] The large proportion of cats reported here with normal activity of ALT and/or ALP is difficult to explain, especially given that reported sensitivities of ALT and ALP for feline cholangitis are 80% and 60% respectively.[21] Serum GGT activity was within the RI in the majority of cats. GGT is reportedly more sensitive but less specific than ALP for hepatobiliary disease in cats,[22] however, one report cites only 60% sensitivity for cholangitis.[21] AST was the only hepatic enzyme with consistently increased activity in this population. Although serum AST activity typically parallels serum ALT activity, clinical exceptions have been documented, including cholangitis.[21] In some cats AST is a more sensitive but less specific marker of liver injury compared to ALT.[21] Based on this population, it is possible for cats with significant cholangitis to have normal serum ALT,

ALP and GGT activity. The sensitivity of these serum liver enzymes appears to be low in cats with cholangitis. An alternative explanation for lack of enzyme activity could be due to lack of functional hepatocytes as with end stage liver failure; however, the predominantly normal hepatic synthetic parameters in this population do not support this theory.

An association between feline cholangitis, pancreatitis and IBD has been previously reported.[11] When considering cases in which the pancreas and intestine were evaluated histopathologically, the present study supports that association though no control population was evaluated. The percentage of NC cases with pancreatitis and IBD was similar between the ANC and CNC groups. Although pancreatic and intestinal inflammation was present in all LC and CC cases, the small number of cases precludes us from commenting on the true prevalence in cats with those diseases. However, it is clear that concurrent pancreatitis and IBD occurs in cats with all forms of cholangitis and that some cats with cholangitis do not have pancreatitis or IBD. It is unknown whether a single pathogenesis relating inflammatory disease of these three organs occurs in cats with all forms of cholangitis. Bacterial and immune-mediated etiologies have been proposed for the various forms of cholangitis.[1,4,8,11] Information regarding etiology of, and predisposing factors for, concurrent cholangitis, pancreatitis and IBD could not be determined in this study. Further investigation is required to better understand the etiopathogenesis of this condition.

Many cats in this population demonstrated varying degrees of inflammation in different liver sections. Cholangitis has been described as a diffuse process,[8] therefore, it might be assumed that obtaining a single biopsy is sufficient to obtain a diagnosis. The WSAVA group, however, reported that NC lesions may be diffuse or limited in distribution.[5] The fact that cats in this study demonstrated varying degrees of severity in different liver sections carries important clinical implications when considering liver sampling methods. Samples should be obtained from multiple liver lobes to achieve complete understanding of the disease severity, though specific recommendations regarding number and location of biopsy specimens cannot be made based on our results.

This study has several limitations, mostly inherent in its retrospective and descriptive design. The lack of a control group prevents us from determining the prevalence and contribution to mortality of concurrent disease in cats with cholangitis compared to those without. The small sample size may indicate a low prevalence of mortality associated with feline cholangitis. However, not all cats that die with cholangitis have a necropsy performed. As such, this population may not be a true representation of cats that succumb to cholangitis. Although a single pathologist reviewed the liver histopathology, various pathologists reported the necropsy findings of the remaining organs. Non-hepatic samples were reported over a 22-year period while standards for interpreting biopsies were evolving. Histopathology of extra-hepatic organs was not available for all cases. The majority of the intestinal histopathology was duodenal; however, location was not always specified. Although IBD is considered a diffuse process, recently it was shown that inflammation may be confined to one area in dogs.[23] It would stand to reason that this may also be true in feline patients. Incomplete sampling of all GI segments may underestimate the prevalence of IBD in this population. Within the confines of these limitations, we have described a population of cats with moderate to severe cholangitis identified at necropsy and classified those cases according to the guidelines of the WSAVA Liver Standardization Group. Using this classification system, NC is a more common cause of mortality than other forms of cholangitis, clinical findings are similar and concurrent disease is common in these cats.

Acknowledgments

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