

Retrospective study of the relative frequency of feline hepatobiliary disease in New Zealand based on 10 years of hepatic biopsy samples

Thomas Fluen ,¹ Michael Hardcastle,² Helen L Smith,³ Robyn N A Gear⁴

To cite: Fluen T, Hardcastle M, Smith HL, *et al.* Retrospective study of the relative frequency of feline hepatobiliary disease in New Zealand based on 10 years of hepatic biopsy samples. *Veterinary Record Open* 2019;**6**:e000367. doi:10.1136/vetreco-2019-000367

Received 16 July 2019

Revised 27 August 2019

Accepted 23 September 2019

ABSTRACT

Aims To retrospectively determine the relative frequency of feline hepatobiliary diseases from biopsy specimens submitted to a single laboratory across a 10-year period and to establish whether age, sex or breed associations exist.

Methods Histopathological data from 154 liver biopsies of New Zealand cats sampled between 2008 and 2018 were analysed. The samples were allocated to primary, secondary and tertiary disease categories using criteria established by the World Small Animal Veterinary Association. Breed associations were derived using ORs and 95% CIs. Gender and age associations were also evaluated.

Results The most frequently diagnosed hepatobiliary diseases were lymphocytic cholangitis (20 per cent), hepatitis (16.9 per cent), reversible hepatocellular injury (16.4 per cent), neutrophilic cholangitis (9.7 per cent), haematopoietic neoplasia (9.7 per cent), hepatocellular neoplasia (5.6 per cent) and cholangiocellular neoplasia (4.1 per cent). Burmese cats were found to be at significantly increased risk of both biliary and parenchymal diseases and Birman cats to be at significantly increased risk of parenchymal disease. Domestic longhair cats were at significantly increased risk of hepatobiliary neoplasia. Birman cats were at significantly increased risk of hepatitis while domestic shorthair cats were at significantly decreased risk of neutrophilic cholangitis, reversible hepatocellular injury and hepatitis.

Conclusions This study is the first retrospective examination of the relative frequency of hepatobiliary disease in biopsy specimens from New Zealand cats. Some breeds were associated with specific histopathology.

INTRODUCTION

Infectious and inflammatory hepatobiliary diseases are common causes of morbidity and mortality in feline patients.¹ Sterile inflammatory liver diseases are more common in feline patients than primary infectious hepatobiliary conditions,^{1 2} but there can be overlap; advanced diagnostics are often needed to secure a definitive diagnosis and therefore appropriate treatment. Bacterial infection is only reported in around 15 per cent of cats with hepatobiliary disease and

is more commonly associated with neutrophilic cholangitis/cholangiohepatitis.¹ Feline hepatic lipidosis has historically been considered the most common feline hepatobiliary disease.³ In the last decade, however, emerging descriptive studies of feline hepatobiliary disease outside of North America have begun to call into question whether the prevalence of feline hepatic lipidosis is consistent across geographically disparate populations of cats.^{4 5} Having accurate pretest prevalence data is important for appropriate use and interpretation of all diagnostic tests, including those of the hepatobiliary system.

The histopathological frequency of feline hepatobiliary disease was initially reported in 1996 in a cohort of cats in North America³ and more recently the frequency has been reported in Japan and the UK.^{4 5} Similar studies of feline hepatobiliary disease in Australasia are lacking. Anecdotally, a diagnosis of hepatic lipidosis in cats is relatively uncommon in New Zealand compared with North America.³ Gagne *et al*³ published a study of hepatobiliary disease in 175 North American cats where 49 per cent of the liver biopsies were consistent with hepatic lipidosis. A more recent study in Japan found neutrophilic cholangiohepatitis/cholangitis to account for 28.1 per cent of all feline liver biopsies.⁵ Similarly, a UK study found biliary disorders to be the most frequent morphological diagnosis with neutrophilic cholangitis representing 20.5 per cent of feline hepatic biopsy samples.⁴ Given the geographical differences already documented in these studies it seems prudent to investigate the distribution of feline hepatobiliary disease in New Zealand. There is also a paucity of descriptive studies reporting feline breed and age predispositions to hepatobiliary disease.

The World Small Animal Veterinary Association (WSAVA) has provided guidelines



© British Veterinary Association 2019. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

¹Internal Medicine, Veterinary Internal Medicine Specialists, Auckland, New Zealand

²Anatomical Pathology, Gribbles Veterinary Pathology New Zealand, Auckland, New Zealand

³PRIMER-e (Quest Research), Massey University, Auckland, New Zealand

⁴Unitec Institute of Technology, Auckland, New Zealand

Correspondence to

Dr Thomas Fluen; tommy.fluen@vsg.co.nz

for the categorisation of canine and feline hepatobiliary disease and recognises four morphological groups of disease: vascular, biliary, parenchymal and neoplastic.⁶ Although these guidelines provide an objective basis for allocation of histopathological findings into disease categories, their application by pathologists remains inherently subjective. There may also be inconsistency in the adherence to these criteria by pathologists over time and across different laboratories.

The aim of this retrospective study was to determine the histopathological frequency of feline hepatobiliary diseases from a large sample of hepatic biopsies from New Zealand cats and to establish whether age, sex or breed associations exist.

MATERIALS AND METHODS

Histopathological data from feline liver biopsies submitted to IDEXX Laboratories/New Zealand Veterinary Pathology from various primary care and referral centres throughout New Zealand between July 2008 and July 2018 were retrieved using a keyword search. The keywords used included: liver and 'hepat%', the 'hepat%' allowing the search to pick up any word beginning with 'hepat-' (hepatitis, hepatopathy, hepatocellular, and so on). Details recorded included breed, age,

sex, gross and histopathological descriptions, diagnosis and any additional comments made by the pathologist. The samples were read by board-certified veterinary anatomical pathologists. All reports were reviewed by one board-certified veterinary anatomical pathologist (MH), and where the final diagnosis was not consistent with the current WSAVA guidelines, these guidelines were retrospectively applied to the histopathological description. Samples were excluded if there was no definitive histopathological diagnosis or if there was no evidence of significant hepatic pathology. If more than one diagnosis was made on a given liver sample, each separate diagnosis was included in the analysis. Each diagnosis was assigned to one of 24 categories according to the WSAVA histopathological criteria for feline hepatobiliary diseases which were nested under the four primary disease categories of vascular, biliary, parenchymal and neoplastic disorders. The WSAVA guidelines for hepatobiliary disease in dogs and cats do not allocate tertiary groupings to every secondary histopathological category, and in our data set not every submission was categorised to a tertiary level even when such criteria were available; the tertiary categories were therefore not used for analysis (table 1).

Demographic information of the New Zealand cat population was derived from the New Zealand

Table 1 Histopathological categorisation hierarchy for feline and canine hepatobiliary diseases according to the WSAVA criteria

Primary category						
Vascular		Biliary	Parenchymal		Neoplastic	
Secondary and tertiary categories*						
Impaired hepatic perfusion	<i>Peliosis hepatis, atrophy, ischaemic necrosis</i>	Biliary cystic disease	Reversible hepatocellular injury	<i>Cloudy swelling, steroid induced, lipidosis</i>	Hepatocellular neoplasia	<i>Hyperplasia, adenoma, carcinoma</i>
Congenital portosystemic shunt		Biliary atresia	Amyloidosis		Cholangiocellular neoplasia	<i>Adenoma, carcinoma</i>
Outflow disorders		Neutrophilic cholangitis	Apoptosis/necrosis		Carcinoid	
Disorders of portal hypertension	<i>Portal vein obstruction, PHPV, AV fistula</i>	Lymphocytic cholangitis	Hepatitis	<i>Acute Chronic Reactive</i>	Hepatoblastoma	
		Destructive cholangitis	Abscess/granuloma		Primary vascular/mesenchymal neoplasia	
		Chronic cholangitis due to fluke infestation	Metabolic storage disease		Haematopoietic neoplasia	<i>Lymphoma, other</i>
		Cholestasis			Metastatic neoplasia	

*Tertiary categories are in italics where applicable.

AV, arteriovenous; PHPV, primary hypoplasia of the portal vein; WSAVA, World Small Animal Veterinary Association.

companion animal register which includes breed, age and gender information for all cats that had microchips registered between 2008 and 2018. There were a total of 358 989 cats suitable for inclusion in the data from 61 specified breeds. These data were used as a control population against which to estimate breed prevalence and sex distribution in the New Zealand cat population, in order to interrogate the possibility of breed and sex associations with specific hepatobiliary diseases in our sample population.

The proportion of diagnoses in each of the WSAVA categories and in each primary disease category was determined for the study population. The distribution of diagnoses among breeds was calculated at two different levels of diagnostic aggregation: the four primary disease categories and the 24 WSAVA secondary categories.

An OR was calculated for each breed in the sample population as well as each primary and secondary disease category. The OR was defined as the ratio of 'the odds of a cat of a specified breed having the disease' to 'the odds of a cat from any other breed having the disease'. This is equivalent to the ratio of 'the number of diseased cats of a given breed' to 'the number of diseased cats from all other breeds' divided by the ratio of 'the number of cats of the same given breed' to 'the number of cats from all other breeds'. A CI of the OR was calculated using Wald's method⁷ and statistical significance was determined using the chi-squared test, except when the number of

diagnoses was fewer than 5, when Fisher's exact test was used. A breed association was deemed significant if the OR CI did not include one, with 5 per cent significance threshold.

An association between gender and disease (primary and secondary categories) was investigated with a chi-squared test. An association among age and diagnostic category was investigated with analysis of variance and pairwise testing using Tukey's multiple comparison test. All statistical analyses were carried out using the statistical package R (R Core Team 2019, V.3.6.0).

RESULTS

A total of 316 histopathology submissions were identified using the initial search criteria. Of this total, 101 submissions were not of hepatic tissue, leaving 215 submissions that contained histopathological data for liver tissue. Twenty-four submissions were excluded as non-diagnostic and 37 were considered to have no hepatic pathology. Of the remaining 154 submissions, 33 had evidence of two primary liver diseases and four had evidence of three primary liver diseases leaving 117 with a single histopathological diagnosis. This generated a total of 195 histopathological diagnoses available for evaluation. Table 2 summarises the distribution of histopathological diagnosis in this population of cats.

Table 2 Overall distribution of feline hepatobiliary diseases

Diagnosis	Cases (n)	Percentage of total cases (%)	Percentage of cases within category (%)
Biliary	68	34.9	100
Lymphocytic cholangitis	39	20.0	57
Neutrophilic cholangitis	19	9.7	28
Biliary cystic disease	5	2.6	7
Cholestasis	5	2.6	7
Parenchymal	65	33.3	100
Hepatitis	33	16.9	51
Reversible hepatocellular injury	32	16.4	49
Neoplastic	46	23.6	100
Haematopoietic neoplasia	19	9.7	41
Hepatocellular neoplasia	11	5.6	24
Cholangiocellular neoplasia	8	4.1	17
Metastatic neoplasia	6	3.1	13
Neoplasia*	1	0.5	2
Carcinoid	1	0.5	2
Vascular	16	8.2	100
Impaired hepatic perfusion	15	7.7	94
cPSS	1	0.5	6
Total	195	100.0	100

*Neoplasia confirmed, but further identification not possible.
cPSS, congenital portosystemic shunt.

The most common biliary disease was lymphocytic cholangitis with 39 cases accounting for 57 per cent of biliary cases and 20 per cent of submissions overall. Neutrophilic cholangitis was the second most common biliary disease with 19 cases, representing 9.7 per cent of all submissions. Parenchymal disease was evenly distributed into hepatitis with 33 cases and reversible hepatocellular injury with 32 cases, making up 16.9 and 16.4 per cent, respectively, of all cases. No cases of chronic hepatitis were recorded. Not all cases of reversible hepatocellular injury were further categorised to the specific type of injury (cloudy swelling, glycogen storage, lipidosis), but 15 cases of hepatic lipidosis were specifically reported, representing 7.6 per cent of all submissions. Haematopoietic neoplasia was the most common neoplastic disease with 19 cases (41 per cent of neoplastic cases) and 9.7 per cent of cases overall. The majority were lymphoma with 16 cases, but two cases of mast cell tumour and a single case of plasma cell tumour were also diagnosed. Of the cholangiocellular tumours, five were reported as adenoma and three as carcinoma. Two of the hepatocellular tumours were diagnosed as adenoma, five as carcinoma and four as hyperplasia. The vascular category comprised the fewest submissions with 15 cases of impaired hepatic perfusion and only a single case of congenital portosystemic shunt.

Breed distributions

Sixty-eight per cent of the control population were domestic shorthair (DSH) cats with 246,459 registered individuals. The most common purebred cats in the control population were the ragdoll with 10,768 registered individuals, Burmese cats with 10,647 registered individuals and Birman cats with 6754 registered individuals comprising 3, 3 and 1.9 per cent of registered cats, respectively. Given the low numbers of purebred cats in our data set, breed associations were first investigated in

the four primary histopathological categories (biliary, parenchymal, neoplastic and vascular), and only breeds with at least five cases were included (table 3).

DSH cats were at decreased risk of biliary and parenchymal diseases, with Burmese cats at increased risk of biliary and parenchymal diseases and Birman cats at increased risk of parenchymal disease. Domestic longhair cats were at increased risk of neoplasia. Breed associations were then investigated in the five most frequent secondary histopathological categories for all breeds with at least two cases (table 4).

Lymphocytic cholangitis was the most common diagnosis with Burmese and Siamese cats at increased risk. Hepatitis was the next most common diagnosis with Birman and Burmese cats shown to be at increased risk, whereas DSH cats were at reduced risk. The third most common diagnosis was reversible hepatocellular injury where DSH cats were at reduced risk. The fourth most common diagnosis was neutrophilic cholangitis; DSH cats were again at a reduced risk while Persian cats and Sphynx were at an increased risk. The fifth most common diagnosis was haematopoietic neoplasia; no breed associations were identified.

Age and sex

The ages of cats in each primary diagnosis group differed significantly ($P<0.001$) as seen in table 5.

Cats with a primary diagnosis of neoplasia were significantly older (median of 13 years) than cats with a parenchymal or vascular primary diagnosis ($P=0.003$ and $P=0.004$, respectively). Males and females were equally represented in each diagnostic category (table 5) and there was no significant difference in gender count across either primary diagnoses or secondary diagnoses ($P=0.351$ and $P=0.786$, respectively). Small numbers

Table 3 Breed associations* according to primary hepatobiliary disease classification

Category	Breed	Cases (n)	In registry (n)	OR	95% CI	P value
Biliary	DSH†	39	246,459	0.44	0.27 to 0.72	<0.001
	DLH	7	22,693	1.54	0.7 to 3.36	0.278
	Burmese‡	6	10,647	2.87	1.24 to 6.64	0.01
Parenchymal	DSH†	27	246,459	0.26	0.16 to 0.43	<0.001
	Burmese†	7	10,647	3.7	1.69 to 8.1	<0.001
	Birman†	7	6754	5.9	2.69 to 12.93	<0.001
	DLH	5	22,693	1.15	0.46 to 2.87	0.759
	DMH	5	30,576	0.83	0.34 to 2.08	0.697
Neoplastic	DSH	31	246,459	0.58	0.3 to 1.08	0.081
	DLH‡	7	22,693	2.31	1.04 to 5.18	0.035
Vascular	DSH	10	246,459	0.48	0.18 to 1.33	0.152

*For breeds with ≥ 5 cases.

†Statistically significant with $P<0.001$.

‡Statistically significant with $P<0.05$.

§Statistically significant with $P<0.01$.

DLH, domestic longhair; DMH, domestic medium hair; DSH, domestic shorthair.

Table 4 Breed associations* according to secondary hepatobiliary disease classification

Diagnosis	Breed	Cases (n)	In registry (n)	OR	95% CI	P value
Lymphocytic cholangitis	DSH	26	246,459	0.60	0.31 to 1.17	0.131
	Burmeset†	4	10,647	3.33	1.18 to 9.37	0.04
	DLH	4	22,693	1.5	0.53 to 4.22	0.354
	Siameset‡	2	2502	6.88	1.66 to 28.56	0.037
Hepatitis	DSH‡	10	246,459	0.16	0.07 to 0.33	<0.001
	Birman†	5	6754	8.7	3.36 to 22.53	<0.001
	Burmeset†	4	10,647	4.2	1.48 to 11.98	0.02
	DLH	3	22,693	1.38	0.42 to 4.52	0.487
	DMH	3	30,576	0.99	0.3 to 3.27	1
	Ragdoll	2	10,768	71.37	17.01 to 299.55	0.286
Reversible hepatocellular injury	DSH§	17	246,459	0.35	0.18 to 0.7	0.002
	Burmeset	3	10,647	3.03	0.92 to 9.96	0.088
	BSH	2	145	5.22	1.25 to 21.85	0.062
	DMH	2	30,576	0.64	0.15 to 2.57	0.765
	Birman	2	6754	0.64	0.15 to 2.67	0.144
	DLH	2	22,693	3.12	0.75 to 13.06	1
Neutrophilic cholangitis	DSH‡	9	246,459	0.17	0.07 to 0.43	<0.001
	DLH	2	22,693	1.41	0.32 to 6.08	0.655
	Persiant†	2	3890	8.77	2.03 to 37.99	0.026
	Sphynx‡	2	276	126.04	28.98 to 548.16	<0.001
Haematopoietic neoplasia	DSH	13	246,459	0.51	0.19 to 1.33	0.158
	DLH	3	22,693	2.32	0.68 to 7.98	0.165

*For breeds with ≥2 cases.

†Statistically significant with $P < 0.05$.

‡Statistically significant with $P < 0.001$.

BSH, British shorthair; DLH, domestic longhair; DMH, domestic medium hair; DSH, domestic shorthair.

Table 5 Age and gender summary of feline hepatobiliary diseases

	Age (years)						Gender
	Min	Q1	Mean	Median	Q3	Max	F:M:U
Biliary	0.25	6	9.66	10	13	19	31:35:2
Biliary cystic disease	6.00	14	14.80	17	18	19	2:3:0
Cholestasis	9.00	9	9.8	10	10	11	4:1:0
Lymphocytic cholangitis	3.00	8	9.97	10	13	17	17:21:1
Neutrophilic cholangitis	0.25	5	7.54	7	10	14	8:10:1
Parenchymal	0.27	4.5	8.66	10	13	16	35:29:1
Hepatitis	0.27	2.75	8.20	9.5	13	16	18:15:0
Reversible hepatocellular injury	0.50	7	9.13	10	13	16	17:14:1
Neoplastic	3.00	10	11.73	13	14	18	22:24:0
Carcinoid	11.00	11	11.00	11	11	11	0:1:0
Cholangiocellular neoplasia	5.00	10.5	11.38	12	14.25	15	4:4:0
Haematopoietic neoplasia	4.00	10	12.17	13	15.75	18	10:9:0
Hepatocellular neoplasia	5.00	10.5	11.55	13	13.5	17	4:7:0
Metastatic neoplasia	3.00	13.25	12.33	14	14.75	15	3:3:0
Neoplasia*	6.00	6	6.00	6	6	6	1:0:0
Vascular	0.25	1.5	7.14	7	12	15	4:10:2
cPSS	1.00	1	1.00	1	1	1	0:1:0
Impaired hepatic perfusion	0.25	2.75	7.58	8	12	15	4:9:2
Grand total	0.25	6	9.62	10	13	19	92:98:5

*Neoplasia confirmed, but further identification not possible.

cPSS, congenital portosystemic shunt; F, Female entire and neutered cats; M, Male entire and neutered cats; Q1, first quartile; Q3, third quartile; U, Unknown gender status.

precluded the analysis of age and gender distributions between breeds.

DISCUSSION

This is the first study to describe the frequency of hepatobiliary diseases in New Zealand cats based on histopathological submissions. Biliary and parenchymal disorders were the most common primary histopathological classifications in this study population with lymphocytic cholangitis being the most common diagnosis overall. Although reversible hepatocellular injury was reported in a number of cases, hepatic lipidosis was only reported in a minority of individuals. These results are similar to the findings in a population of UK cats where biliary and parenchymal disorders made up the majority of submissions.⁴ However, in the UK population of cats, neutrophilic cholangitis was the most frequent hepatobiliary disease comprising 20.5 per cent of all cases whereas lymphocytic cholangitis only comprised 6.8 per cent.⁴ Hirose *et al*⁵ reported neutrophilic cholangiohepatitis as the most common non-proliferative liver disease in a Japanese population of cats.

Haematopoietic neoplasia was the most common hepatic neoplasm in this study population of cats. Hepatocellular tumours were the most common primary hepatic neoplasm followed by cholangiocellular tumours. This

result is similar to what was found by Bayton *et al*⁴, but is in contrast to earlier reports of feline primary hepatic neoplasia where cholangiocellular tumours were the most commonly reported primary hepatic neoplasm.^{8–10}

Within the cholangiocellular tumours, adenomas were more common in this population of cats than carcinoma, similar to what was found by Bayton *et al*.⁴ Within the hepatocellular tumours, carcinoma was more common than adenoma, again similar to the results of a previous study⁴ and in contrast to the preceding literature which reports hepatocellular adenoma to be more common than hepatocellular carcinoma in cats.¹⁰

A broad evaluation of sex and age did not reveal any significant sex predilections, but cats diagnosed with neoplasia were significantly older than cats with parenchymal or vascular diseases. This is not surprising given the incidence of neoplasia generally increases as a function of age due to the longer exposure to external carcinogens, prolonged influence of inflammatory diseases and cumulative mutations necessary for the development of cancer.¹¹

When breed analysis was performed across the four primary hepatobiliary disease categories for breeds with at least five cases, this study found Burmese cats to be at significantly increased risk of both biliary and parenchymal diseases and Birman cats to be at significantly

increased risk of parenchymal disease. These results are similar to those identified by a UK study where Burmese cats were found to be at increased risk of neutrophilic cholangitis and reactive hepatitis and Birman cats were at increased risk of reactive hepatitis.⁴ DSH cats were at a significantly decreased risk of biliary and parenchymal diseases which again aligns with data from a UK population of cats.⁴

The subsequent breed analysis across the secondary hepatobiliary disease categories for breeds with at least two cases identified a number of statistically significant breed associations in Burmese, Birman, DSH, Persian, Siamese and Sphynx cats. However, with the exception of the DSH and Birman cats, these breed associations were based on less than five cases per breed. Despite the statistical significance achieved in this analysis the biological significance of breed associations based on so few cases is tenuous. As these breed associations are similar to those reported in other descriptive studies they warrant further investigation.

Birman cats were found to be at significantly increased risk of hepatitis which is similar to a UK study where Birman cats were at significantly increased risk of reactive hepatitis.⁴ In the present study it was not always reported by the pathologist whether a diagnosis of hepatitis was acute, chronic or reactive, thus they were grouped under the secondary diagnostic category of *hepatitis*. This was primarily due to the inconsistent application of the WSAVA criteria, in particular to the description and subsequent tertiary categorisation of hepatitis. However, it is important to note there was not a single diagnosis of chronic hepatitis in this population of cats similar to reports from the UK (2.4 per cent) and Japan (6.3 per cent), where this was an infrequent diagnosis.^{4,5} DSH cats were at significantly decreased risk of neutrophilic cholangitis, reversible hepatocellular injury and hepatitis. Again, this was similar to a UK study where DSH cats were at decreased risk of neutrophilic cholangitis, reactive hepatitis and reversible hepatocellular injury.⁴

Early descriptions of neutrophilic cholangitis/cholangiohepatitis reported it as a syndrome of aged cats,¹² whereas lymphocytic cholangitis was typically found in younger cats,¹³ a similar pattern was observed by Hirose *et al.*⁵ Other studies found the opposite distribution, and described lymphocytic cholangitis as a disease of older cats, and neutrophilic cholangitis as one of middle-aged and younger cats.¹⁴ The current study, similar to Bayton *et al.*⁴ study, found cats with neutrophilic cholangitis to be younger than those with lymphocytic cholangitis and this warrants further investigation. One confounding factor in this and other studies is the failure to distinguish between acute and chronic neutrophilic cholangitis which Callahan Clark *et al.*¹ described as having significantly different ages of onset. Thus, depending on the population of cats being sampled, and the existence of age-related comorbidities that may preclude liver biopsy, the older cats with chronic neutrophilic cholangitis may not be fairly represented in some studies.

The low prevalence of hepatic lipidosis reported in the UK (3.2 per cent) and Japan (4.4 per cent) compared with that reported in North America (49.9 per cent) has been suggested to be due to breed, dietary or other environmental differences; however, the underlying pathophysiology of the disease remains incompletely understood.³⁻⁵ Recent literatures investigating body condition of domestic cats have found similar rates of feline obesity in New Zealand, France, UK and North America of 2.6–7.8 per cent, suggesting that obesity prevalence alone is not driving the increased frequency of hepatic lipidosis in North American cats.¹⁴⁻¹⁷ This is in contrast to Japanese cats, where a recent descriptive study reported 42 per cent of domestic cats in Japan to be obese.¹⁸ However, the cats in these studies may not accurately represent the populations of cats in the hepatic histopathological surveys either geographically or temporally. Also, it is not possible to distinguish between primary and secondary hepatic lipidosis histopathologically, and as the latter is not as closely associated with obesity, consideration of the body condition of the sampled population may not be relevant.

Triaditis is a syndrome of inflammatory disease in cats affecting three principal organ systems: the gastrointestinal tract, the hepatobiliary system and the pancreas.¹⁹ A recent review has explored the causative relationship between inflammatory bowel disease (IBD) and the development of cholangitis, suggesting intestinal inflammation is the primary disease process which through various mechanisms leads to the development of both lymphocytic and neutrophilic cholangitis.¹⁹ Purebred cats have been suggested to be at increased risk of IBD.^{20,21} If the prevalence of IBD is significantly higher in cats with cholangiohepatitis,²² the breed associations seen in hepatobiliary disease in New Zealand and the UK may be significantly influenced by breeds with concurrent predispositions to IBD. Breed associations should be further investigated with studies integrating biopsy data from the liver and gastrointestinal tract of a wide cross section of cat breeds.

The limitations of this study include the small sample size and limited representation of each breed, meaning some breed associations may have been missed. In particular, the use of OR may not allow for the identification of decreased risk in individuals which are infrequently represented in a given population sample. The derivation of breed associations according to secondary hepatobiliary disease classifications identified a number of breeds as being at significantly increased risk of particular hepatobiliary diseases; however, these ORs were based on very small numbers of cats. The identification of disease risk based on such a small sample size should prompt further research into these potential breed associations rather than making conclusions about disease prevalence. The control population of cats is taken from the New Zealand Companion Animal Registry and this large sample of cats is the best available approximation of the overall feline breed distributions in New Zealand, but

may not necessarily represent the distribution of breeds from which the histopathology samples were taken and from the New Zealand cat population as a whole. The argument may be that purebred cats are disproportionately microchipped and registered compared with the domestic breeds, possibly due to a perception of 'increased' value of these animals. However, one may consider the same factors that influence the over-representation of purebred cats in microchip registries are influencing their presentation to veterinarians for invasive and costly interventions, hence the bias may be applied similarly to both populations of cats. Not all histopathological samples were allocated a hepatobiliary disease category according to the WSAVA guidelines. Where this was the case, a disease category was applied retrospectively to the histopathological description in accordance with the WSAVA guidelines. This process was conducted by a board-certified anatomical pathologist (MH). Given the retrospective nature of the study, further clinicopathological information about each case, which would be of particular relevance to helping identify variables that may confound the breed associations, was not available.

This study adds to the developing literature describing the frequency of feline hepatobiliary disease and reveals both similarities and differences between geographically disparate populations of cats which may be important for efficient diagnostic evaluation of cats with clinical signs of hepatobiliary disease. This study has contributed to the growing evidence of breed associations for feline hepatobiliary diseases as well as identifying a number of breeds worthy of further investigation.

Acknowledgements The authors acknowledge the contribution of IDEXX Laboratories and, in particular, Dr Susan Piripi who provided the data. Dr Geoff Orbell of Gribbles Veterinary helped with evaluation of the pathological reports. The authors also thank Nygillhuw Morris from the New Zealand Companion Animal Registry for his time and effort in generating a control population of cats for this study.

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Thomas Fluen <http://orcid.org/0000-0003-4008-4731>

REFERENCES

- Callahan Clark JE, Haddad JL, Brown DC, *et al.* Feline cholangitis: a necropsy study of 44 cats (1986-2008). *J Feline Med Surg* 2011;13:570-6.
- Gagne JM, Armstrong PJ, Weiss DJ, *et al.* Clinical features of inflammatory liver disease in cats: 41 cases (1983-1993). *J Am Vet Med Assoc* 1999;214:513-6.
- Gagne JM, Weiss DJ, Armstrong PJ. Histopathologic evaluation of feline inflammatory liver disease. *Vet Pathol* 1996;33:521-6.
- Bayton WA, Westgarth C, Scase T, *et al.* Histopathological frequency of feline hepatobiliary disease in the UK. *J Small Anim Pract* 2018;59:404-10.
- Hirose N, Uchida K, Kanemoto H, *et al.* A retrospective histopathological survey on canine and feline liver diseases at the University of Tokyo between 2006 and 2012. *J Vet Med Sci* 2014;76:1015-20.
- Rothuizen J, Bunch SE, Charles JA. *WSAVA standards for clinical and histological diagnosis of canine and feline liver disease: Elsevier Health Sciences*, 2006.
- Wald A. Tests of statistical hypotheses concerning several parameters when the number of observations is large. *Trans Am Math Soc* 1943;54:426-82.
- Lawrence HJ, Erb HN, Harvey HJAY. Nonlymphomatous hepatobiliary masses in cats: 41 cases (1972 to 1991). *Vet Surgery* 1994;23:365-8.
- Patnaik AK. A morphologic and immunocytochemical study of hepatic neoplasms in cats. *Vet Pathol* 1992;29:405-15.
- van Sprundel RGHM, van den Ingh TSGAM, Guscetti F, *et al.* Classification of primary hepatic tumours in the cat. *Vet J* 2014;202:255-66.
- Campisi J. Cancer and ageing: rival demons? *Nat Rev Cancer* 2003;3:339-49.
- Hirsch VM, Doige CE. Suppurative cholangitis in cats. *J Am Vet Med Assoc* 1983;182:1223-6.
- Lucke VM, Davies JD. Progressive lymphocytic cholangitis in the cat. *J Small Animal Practice* 1984;25:249-60.
- Colliard L, Paragon B-M, Lemuet B, *et al.* Prevalence and risk factors of obesity in an urban population of healthy cats. *J Feline Med Surg* 2009;11:135-40.
- Gates MC, Zito S, Harvey LC, *et al.* Assessing obesity in adult dogs and cats presenting for routine vaccination appointments in the North island of new Zealand using electronic medical records data. *N Z Vet J* 2019;1-19.
- Lund EM, Armstrong PJ, Kirk CA, *et al.* Prevalence and risk factors for obesity in adult cats from private us veterinary practices. *Int J App Res Vet Med* 2005;3:88-96.
- O'Neill DG, Church DB, McGreevy PD, *et al.* Prevalence of disorders recorded in cats attending primary-care veterinary practices in England. *Vet J* 2014;202:286-91.
- Mori N, Iwasaki E, Okada Y, *et al.* Overall prevalence of feline overweight/obesity in Japan as determined from a cross-sectional sample pool of healthy veterinary clinic-visiting cats in Japan. *Turk J Vet Anim Sci* 2016;40:304-12.
- Simpson KW. Pancreatitis and triaditis in cats: causes and treatment. *J Small Anim Pract* 2015;56:40-9.
- German AJ. Small Intestine - inflammation. In: Washabau RJ, Day M, eds. *Canine and feline gastroenterology*. Missouri: Saunders, 2013: 669-78.
- Guilford W. Idiopathic inflammatory bowel diseases. In: Guilford W, ed. *Strombeck's Small Animal Gastroenterology*. 3rd ed. Philadelphia: WB Saunders, 1996: 451-86.
- Weiss DJ, Gagne JM, Armstrong PJ. Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis, and nephritis in cats. *J Am Vet Med Assoc* 1996;209:1114-6.