PAPER

Period prevalence and mortality rates associated with hypocholesterolaemia in dogs and cats: 1,375 cases

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Objectives: To determine the period prevalence of hypocholesterolaemia and the associated mortality rates in dogs and cats at a university teaching hospital. The secondary aim was to identify disease processes associated with hypocholesterolaemia.

Materials and Methods: Medical records over a 5-year period were reviewed to determine the severity of hypocholesterolaemia and its associated mortality rate. Medical records of animals with moderate to severe hypocholesterolaemia (<2.59 mmol/L in dogs, <1.81 mmol/L in cats) were analysed further. Animals with hospital-acquired hypocholesterolaemia were identified.

Results: Among 16,977 dogs and 3,788 cats that had at least one cholesterol measurement, the period prevalence of hypocholesterolaemia was 7.0% in dogs and 4.7% in cats. The mortality rate of hypocholesteraemic dogs and cats was 12% in both species which was significantly higher than that of animals with normal serum cholesterol. The degree of hypocholesterolaemia was significantly associated with mortality. Dogs, but not cats, with hospital-acquired hypocholesterolaemia had a higher mortality rate than those presenting with hypocholesterolaemia. Disease of hepatic, gastrointestinal and lymphoreticular systems were most commonly associated with hypocholesterolaemia, and infectious and neoplastic disease were the most commonly associated pathophysiologic processes in both species. Lymphoma was over-represented in dogs with neoplasia.

Clinical Significance: Hypocholesterolaemia is not a frequent abnormality but was associated with mortality in this study and may be a negative prognostic indicator. It is not known if hypocholesterolaemia is simply a marker for disease severity, or if it is has active physiologic effects contributing to poor outcomes.

Journal of Small Animal Practice (2020), 1–7
DOI: 10.1111/jsap.13204

Accepted: 25 June 2020

INTRODUCTION

Anomalous serum cholesterol concentration is generally regarded as an indicator of disease and is included in small animal biochemistry panels, but is not commonly considered a prognostic marker in dogs and cats. Hypocholesterolaemia has been reported to be associated with liver and gastrointestinal disease, hypoadrenocorticism and, more recently, with sepsis and neoplasia in small animals (Patel *et al.* 2005, Moore *et al.* 2006, Little *et al.* 2007, Yilmaz & Senturk 2007, Hardy *et al.* 2018). The incidence of hypocholesterolaemia is unknown in small animals, although its prevalence in some specific disease processes has been reported (Littman *et al.* 2000, Kull *et al.* 2001, Segev *et al.* 2004, Patel *et al.* 2005, Moore *et al.* 2006, Little *et al.* 2007, Thompson *et al.* 2007, Dereszynski *et al.* 2008, Lyles *et al.* 2009, Wakayama *et al.* 2017). Only four veterinary studies have specifically assessed its association with mortality. Hypocholesterolaemia was associated with non-survival in dogs with severe sepsis from parvoviral enteritis and in another study of dogs with sepsis from any cause (Yilmaz & Senturk 2007, Hardy *et al.* 2018). In a third study, dogs hospitalised in the ICU that had hypocholesterolaemia showed increased odds of death (Viall *et al.* 2019). There is only one study to date in cats, which did not show an association between the degree of hypocholesterolaemia and survival (Bowman *et al.* 2019).

In humans, hypocholesterolaemia is associated with critical illness (Gui *et al.* 1996, Gordon *et al.* 2001, Bonville *et al.* 2004), various malignancies (Marini *et al.* 1989, Siemianowicz *et al.* 2000, Tomiki *et al.* 2004, Yavasoglu *et al.* 2008) and sepsis (Dunham *et al.* 2003, Barlage *et al.* 2009), amongst many others. The prevalence of hypocholesterolaemia is reported to be 1.2-6.2% depending on the study population (Oster *et al.* 1981, Lévesque *et al.* 1991, Windler *et al.* 1994). Hypocholesterolaemia has also repeatedly been shown to be a strong and significant prognosticator for mortality and clinical outcome. Mortality has been shown to be 10-fold higher in people with acute kidney injury and among hospitalised people with hypocholesterolaemia (Windler *et al.* 1994, Guimarães *et al.* 2008). People with hypocholesterolaemia were also reported to be more likely to develop multi-organ dysfunction (Gordon *et al.* 2001).

The primary aims of this retrospective study were to report the period prevalence of hypocholesterolaemia and to determine the associated mortality rate in dogs and cats. Secondary aims were to identify the disease processes associated with hypocholesterolaemia and to investigate whether hospital acquired hypocholesterolaemia was associated with increased rates of non-survival in dogs and cats.

MATERIAL AND METHODS

Sample population

Computerized medical records were searched to identify all dogs and cats that had at least 1 cholesterol measurement at the University of California, Davis, William R. Pritchard, Veterinary Medical Teaching Hospital during a 5-year period from September 1, 2011 to August 30, 2016. Serum or plasma cholesterol levels were measured as part of a serum chemistry panel, which were analysed by a diagnostic laboratory biochemical analyser (Chemistry analyzer, Hitachi c501, Roche Diagnostics, Indianapolis, IN, USA).

Reference intervals for canine and feline cholesterol levels were 3.60 to 9.14 mmol/L and 2.31 to 6.68 mmol/L, respectively, during this study period. There are currently no defining guidelines stratifying mild, moderate and severe hypocholesterolaemia in small animals. For the purposes of this study, mild, moderate and severe hypocholesterolaemia were defined for dogs as 2.60 to 3.59 mmol/L, 1.79 to 2.59 mmol/L and ≤1.78 mmol/L, respectively. In cats, mild, moderate and severe hypocholesterolaemia was defined as 1.84 to 2.30 mmol/L, 1.14 to 1.83 mmol/L and ≤ 1.13 mmol/L, respectively. These values of mild, moderate and severe hypocholesterolaemia approximated to 75, 50 and 25% of the lower bound of the reference interval.

Data collection and classification

Patient signalment and clinical information were collated from medical records. Only the first visit for a patient was included if multiple visits occurred in the time period evaluated. If all the cholesterol measurements in the visit were within reference interval, only the first value was recorded. If abnormal cholesterol values or a mixture of abnormal and normal values were recorded, only the first abnormal value was included.

The overall prevalence of hypocholesterolaemia at our institution was determined for all cats and dogs with a cholesterol measurement, which included both hospitalised animals and outpatients. Hypocholesterolaemia was additionally subcategorised as hospital-acquired if the first measured value was normal or high and then subsequently decreased below the reference interval during a single hospitalised visit. Visit outcome was classified as dead (euthanasia and natural death) or alive (survival to discharge) for all animals identified.

The medical records of animals with moderate to severe hypocholesterolaemia were reviewed further to identify the primary disease processes, determined from the available data, primary clinician's clinical diagnosis, histopathology and/or necropsy results. Primary diseases were categorised into organ systems: hepatic, gastrointestinal, lymphoreticular, endocrine, respiratory, haematologic, pancreatic and others. Primary diseases were also categorised into pathophysiologic processes or known aetiologies that were commonly encountered in this study population. Pathophysiologic processes included neoplasia, infectious, trauma, inflammatory/immune-mediated and haemorrhage. Animals could be assigned more than one organ system or pathophysiologic process. Animals with insufficient diagnostics or an unclear diagnosis after investigations were classified as "unknown/unclear diagnosis."

Statistics

The data were assessed for normality with a D'Agostino & Pearson normality test using commercially available software (Graph Pad Prism 7.0 La Jolla, CA, USA). Non-normally distributed data were presented as medians with interquartile ranges (IQR). The proportion of animals that died were compared between groups using a chi-squared test. The relationship between degree of hypocholesterolaemia and outcome was investigated using chi-squared test for trend. A P value of <0.05 was considered significant.

RESULTS

During the study period, 16,977 dogs and 3,788 cats were identified as having a cholesterol value measured on a biochemistry panel at our institution. Hypocholesterolaemia was identified in 1,196 of 16,997 (7.0%) of dogs and 179 of 3,788 (4.7%) of cats. The median (IQR) cholesterol value of hypocholesterolaemic animals was 3.11 mmol/L (2.64 to 3.37 mmol/L) in dogs and 2.03 mmol/L (1.81 to 2.18 mmol/L) in cats. The distribution of cholesterol values above, within, or below the reference interval is shown in Table 1. The lowest cholesterol value measured in a dog was 0.67 and 0.41 mmol/L in a cat.

Table 1. Distribution of cholesterol values from all dogs and cats with a biochemistry panel analysed at a university teaching hospital over a 5-year period

	Dogs n (%) Total n=16,977	Cats n (%) Total n=3,788
Hypocholesterolaemia	1,196 (7.0) Mild: 911 (76.2) Moderate: 242 (20.2) Severe: 43 (3.6)	179 (4.7) Mild: 127 (70.9) Moderate: 48 (26.8) Severe: 4 (2.2)
Normocholesterolaemia	14,394 (84.8)	3,390 (89.5)
Hypercholesterolaemia	1,387 (8.2)	219 (5.8)

Mild, moderate and severe hypocholesterolaemia were defined as 2.60–3.59, 1.79–2.59 and ≤1.78 mmol/L in dogs and 1.84–2.30, 1.14–1.83 and ≤1.13 mmol/L in cats, respectively. Hypercholesterolaemia was defined as >9.14 mmol/L in dogs and >6.68 mmol/L in cats

Among dogs with hypocholesterolaemia, the median age (IQR) was 6.8 years (3.6-9.8 years) and median weight (IQR) was 14.3 kg (5.3-28.7 kg). Mixed breed dogs (284, 23.7%), Labrador retrievers (79, 6.6%), Yorkshire terriers (68, 5.7%) and Chihuahuas (59, 4.9%) were the most commonly represented breeds. Of all dogs presenting to our hospital during this time period, these breeds were identified, respectively, in 84.9, 1.8, 0.2 and 0.9% of visits. There were 515 (43%) spayed females, 67 (6%) intact females, 441 (37%) castrated males and 169 (14%) intact males.

Among cats with hypocholesterolaemia, the median age (IQR) was 6.1 years (2.4-10.3 years) and median weight (IQR) was 4.6 kg (3.6-5.6 kg). Domestic short hair (118, 65.9%), domestic medium hair (20, 11.2%) and domestic long hair (20, 11.2%) cats were most commonly presented. Of all cats presenting to our hospital during this time period, these were identified, respectively, in 22.6, 3.6, and 2.9% visits. There were 73 (41%) spayed females, four (2%) intact females, 84 (47%) castrated males and 15 (8%) intact males.

The mortality rate was 141 of 1,196 (11.8%) of all dogs with hypocholesterolaemia, 580 of 14,394 (4.0%) with normocholesterolaemia and 102 of 1,387 (7.4%) with hypercholesterolemia. The mortality rate of dogs for mild, moderate and severe hypocholesterolaemia was 93 of 911 (10.2%), 37 of 242 (15.3%) and 11 of 43 (25.6%), respectively (Fig 1). There was a significant association with hypocholesterolaemia and non-survival in dogs compared to normocholesterolaemia. The odds of death in dogs with hypocholesterolaemia were 3.2 (95% CI: 2.6-3.9; P <0.001; chi-squared test) times higher than in those with normal serum cholesterol values. There was a significant linear trend towards higher mortality in association with more severe hypocholesterolaemia (P <0.001; chi-squared test for trend) in dogs.

Fifty-five dogs were identified with hospital-acquired hypocholesterolaemia: 39 mild, 11 moderate and 5 severe. Of those, 18 of 55 (32.7%) did not survive, which was a significantly greater mortality rate than that of dogs that presented with a low cholesterol (P<0.001). The mortality rates of mild, moderate and severe hospital-acquired hypocholesterolaemia were 11 of 39 (28.2%), 5 of 11 (45.5%) and 2 of 5 (40%), respectively.

The mortality rate was 21 of 179 (11.7%) of all cats with hypocholesterolaemia, 173 of 3,390 (5.1%) with normocholesterolaemia and 11 of 219 (5.0%) with hypercholesterolaemia.

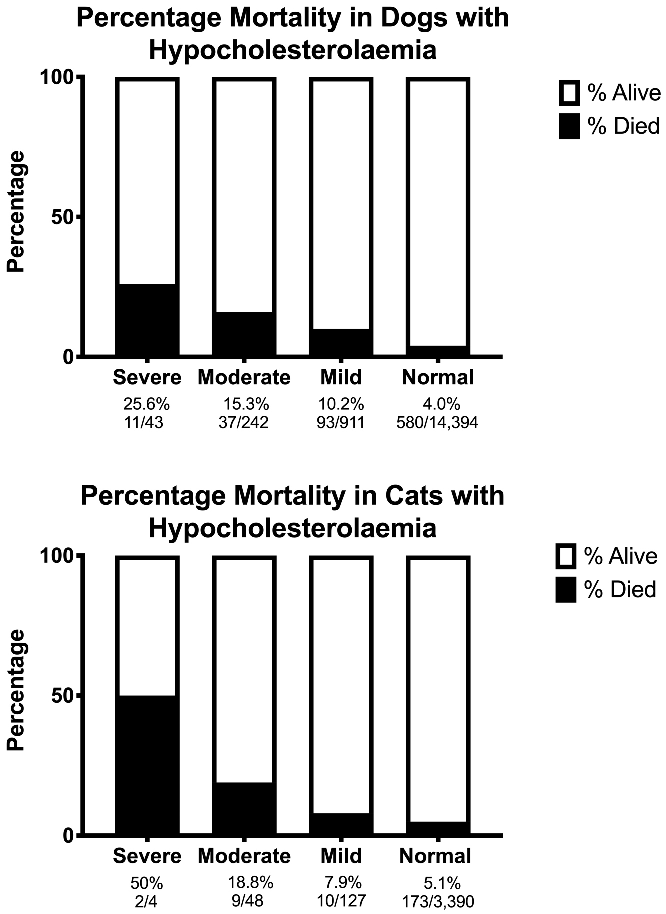

FIG 1. Percentage of non-survivors and number of patients that died/total number in each group of hypocholesterolaemia in dogs and cats. There is a significant linear association between the severity of hypocholesterolaemia and mortality P<0.0001

The mortality rate of cats with mild, moderate and severe hypocholesterolaemia was 10 of 127 (7.9%), 9 of 48 (18.8%) and 2 of 4 (50%), respectively (Fig 1). There was a significant association of hypocholesterolaemia with non-survival in cats compared to those with normal serum cholesterol values. The odds of death in cats with hypocholesterolaemia were 2.5 (95% CI: 1.5-3.9; P <0.001; chi-squared test) times higher than in those with normal serum cholesterol values. There was also a significant linear trend towards higher mortality in cats with more severe hypocholesterolaemia (P <0.001; chi-squared test for trend).

Ten cats were identified with hospital-acquired hypocholesterolaemia: seven mild and three moderate. Of those cats, 2 of 10 (20%) died, which was not significantly different to cats that presented with hypocholesterolaemia (P = 0.62). The mortality rate of mild and moderate feline hospital-acquired hypocholesterolaemia was one of seven (14.2%) and 1 of 3 (33.3%), respectively.

The primary diseases identified in animals with moderate or severe hypocholesterolaemia are summarised in Table 2. In dogs, the most frequent organ systems affected were hepatic (107 of 285; 37.5%), followed by gastrointestinal (89 of 285; 31.2%). In cats, the most commonly affected organ systems were hepatic (9 of 52; 17.3%), gastrointestinal (6 of 52; 11.5%) and lymphoreticular (6 of 52; 11.5%).

Table 2. Primary diseases listed by organ system identified in 285 dogs and 52 cats with moderate to severe hypocholesterolaemia

Primary diseases	Dogs n (%)	Cats n (%)
Hepatic	107 (37.5)	9 (17.3)
Hepatocellular dysfunction	56 (19.6)	5 (9.6)
Congenital hepatic shunts	40 (14.0)	
Acute liver failure	6 (2.1)	
Congenital hepatic disease	5 (1.8)	
Cholestatic disease	3 (1.1)	1 (1.9)
Hepatic lipidosis		4 (7.7)
Gastrointestinal	89 (31.2)	6 (11.5)
Protein losing enteropathy	39 (13.7)	5 (9.6)
Inflammatory bowel disease	26 (9.1)	
Neoplasia	16 (5.6)	1 (1.9)
Lymphangiectasia	9 (3.2)	
Torsions/perforations	8 (2.8)	1 (1.9)
Gastrointestinal haemorrhage	5 (1.8)	
Haemorrhagic gastroenteritis	3 (1.1)	
Lymphoreticular	42 (14.7)	6 (11.5)
Other systems*	30 (10.5)	13 (25.0)
Endocrine (Hypoadrenocorticism)	22 (7.7)	
Respiratory	19 (6.7)	4 (7.7)
Hematologic	10 (3.5)	2 (3.8)
Immune-mediated thrombocytopenia	8 (2.8)	
Immune-mediated haemolytic anaemia	2 (0.7)	
Pancreatic	7 (2.5)	4 (7.7)
Unknown	43 (15.0)	20 (38.5)

Note animals may appear in more than one category
*Other category includes dermatologic, neurologic, musculoskeletal and maxillofacial disease

Table 3. Pathophysiologic process or suspected aetiology associated with hypocholesterolaemia in dogs and cats with moderate to severe hypocholesterolaemia

Pathophysiologic process or suspected aetiology	Dogs n (%)	Cats n (%)
Neoplasia	58 (20.4)	9 (17.3)
Lymphoma	29 (10.2)	3 (5.8)
Hemophagocytic histiocytic sarcoma	8 (2.8)	
Plasma cell tumour	6 (2.1)	1 (1.9)
Hemangiosarcoma	2 (0.7)	
Mast Cell Tumour		1 (1.9)
Others	10 (3.5)	2 (5.8)
Unclassified neoplasia	3 (1.1)	2 (3.8)
Infectious	22 (7.7)	11 (21.2)
Sepsis	17 (6.0)	5 (9.6)
Localized	5 (1.8)	6 (11.5)
Trauma	11 (3.9)	5 (9.6)
Inflammatory/Immune-mediated	44 (15.4)	
Inflammatory bowel disease	26 (9.1)	
Immune mediated thrombocytopenia	8 (2.8)	
Pancreatitis	5 (1.8)	
Systemic inflammation	3 (1.1)	
Immune mediated haemolytic anaemia	2 (0.7)	
Haemorrhage	13 (4.6)	1 (1.9)
Gastrointestinal system	5 (1.8)	
Other systems	8 (2.8)	1 (1.9)

Pathophysiologic processes or suspected aetiology of hypocholesterolaemia in animals with moderate or severe hypocholesterolaemia are shown in Table 3. In dogs, neoplasia (58 of 285; 20.4%) was the most commonly associated process, followed by infectious disease (22 of 285; 7.7%). The most common association in cats was infectious disease (11 of 52; 21.2%), followed by neoplasia (9 of 52; 17.3%).

Sixteen dogs developed moderate or severe hypocholesterolaemia during hospitalisation. Within this group, 11 dogs (68.7%) had sepsis, four of which developed hypocholesterolaemia after being diagnosed with aspiration pneumonia and five after a diagnosis of septic peritonitis. The remaining two dogs with sepsis had pyothorax and *Neorickettsia helminthoeca* parasitism, respectively. In the other dogs with hospital-acquired hypocholesterolaemia, two had trauma, one dog had inflammatory bowel disease with concurrent lymphangiectasia, one had infiltrative sarcoma and one had immune-mediated haemolytic anaemia. Three cats developed moderate hypocholesterolaemia in hospital: one had sepsis, one had haemorrhage and the third cat had hepatic lipidosis with cholestatic disease.

DISCUSSION

In this study of dogs and cats that had a cholesterol measured on a biochemistry panel at our institution, the period prevalence of hypocholesterolaemia was 7.0% in dogs and 4.7% in cats. As far as we know, this is the first report of the prevalence of hypocholesterolaemia in a diverse population of dogs. The period prevalence of feline hypocholesterolaemia in our study differs from the reported prevalence of 0.3-0.4% at other academic institutions (Bowman *et al.* 2019). This is likely explained by different inclusion methods for the study populations. The denominator population for both dogs and cats in our study only included patients that underwent biochemical analysis, rather than the total census of patients presenting to the hospital during the time period. The reported prevalence of hypocholesterolaemia in human medicine ranges between 1.2 and 6.2% (Oster *et al.* 1981, Lévesque *et al.* 1991, Windler *et al.* 1994) and are only focused on hospitalised patients. Our study had a similar prevalence but evaluated a hospital-wide, multi-department population which included outpatients. The period prevalence of hospital-acquired hypocholesterolaemia was 4.6% in dogs and 5.6% in cats, which is lower than the reported value of 9% in older hospitalised human patients who developed hypocholesterolaemia after admission (Noel *et al.* 1991). This lower percentage may be due to variable intervals of chemistry monitoring in our study population.

Hypocholesterolaemia in this study was significantly associated with non-survival and had an inverse linear relationship with mortality. In parallel to our results, a recent study in septic dogs found significantly lower cholesterol values in eight dogs that went into cardiopulmonary arrest despite treatment, compared to 28 dogs that survived to discharge (Hardy *et al.* 2018). Another retrospective study also found that sick dogs in the ICU had increased odds of non-survival with hypocholesterolaemia, with or without hypertriglyceridaemia (Viall *et al.* 2019). This association with mortality has also been previously shown in canine aflatoxin hepatotoxicosis and in dogs with severe sepsis resulting from parvoviral enteritis (Yilmaz & Senturk 2007, Dereszynski *et al.* 2008). Although a retrospective study in 106 cats did not find a relationship between mortality and severity of hypocholesterolaemia alone, it did find that when hypocholesterolaemia and hypoalbuminaemia were evaluated together, the odds ratio of non-survival increased to 15.6 (Bowman *et al.* 2019). The relationship of hypocholesterolaemia with death in humans is well established and a similar linear trend to our study was also demonstrated in three human hospitals (Windler *et al.* 1994, Bonville *et al.* 2004). Hypocholesterolaemia is not only acknowledged to have a strong prognostic significance in human critical illness and acute disease (Gui *et al.* 1996, Gordon *et al.* 2001, Dunham *et al.* 2003, Bonville *et al.* 2004, Barlage *et al.* 2009, Lagrost *et al.* 2014, Yamano *et al.* 2016), but also in chronic disease processes such as chronic kidney disease (Iseki *et al.* 2002, Tsirpanlis *et al.* 2009), neoplasia (Muller *et al.* 1989, Sok *et al.* 2009) and liver cirrhosis (Janičko *et al.* 2013). The findings in our study provide further evidence in veterinary medicine to support cholesterol as a prognostic marker for non-survival in a broad small animal population and not just in critical illness.

The mortality rate among dogs with hospital-acquired hypocholesterolaemia in our study was significantly greater than those that initially presented with a low cholesterol. This sub-group may represent a sicker subset of animals within our population because they were hospitalised. The development of hypocholesterolaemia during hospitalisation suggests progression of the disease process(es) despite therapy, which may explain the higher mortality rate in this population. Multiple studies in humans noted that decrease in serum cholesterol during hospitalisation is associated with non-survival (Noel *et al.* 1991, Dunham *et al.* 2003, Bonville *et al.* 2004). Our study suggests that there is value in including cholesterol as part of trending biochemistries in critical or deteriorating hospitalised patients.

It is not definitively known if hypocholesterolaemia is simply a marker for severity of disease, or if it is has active physiologic effects contributing to poor outcomes. There is emerging data for both theories. Cholesterol may be a marker of the negative acute phase response and the mechanism is likely a combination of reduced synthesis and augmented catabolism (Chiarla *et al.* 2004, 2010, Marik 2006). Several studies have observed inverse correlations between cholesterol and inflammatory factors such as interleukin-6, interleukin-10 and C-reactive protein (Bentz & Magnette 1998, Gordon *et al.* 2001) and parenteral infusions of pro-inflammatory cytokines reduce lipid levels (Spriggs *et al.* 1988, Van Gameren *et al.* 1994). Synthesis of apolipoproteins is hindered in hepatic cell lines exposed to inflammatory cytokines (Ettinger *et al.* 1994).

Direct effects of hypocholesterolaemia on physiologic outcomes are potentially linked to decreased immune function and adrenal failure. Lipoproteins bind to and neutralise lipopolysaccharides and are thought to be part of the innate host immune response (Quezado *et al.* 1995, Harris *et al.* 2000). Thus, patients with hypocholesterolaemia may be predisposed to endotoxaemia and sepsis: the incidence of post-operative septic complications was reported to be 73% among humans with serum cholesterol less than 105 mg/dL, as compared to 35% in patients with higher cholesterol (Leardi *et al.* 2000). Decline in cholesterol levels in non-surviving ventilated trauma patients also coincided with the onset of infection in a different study (Dunham *et al.* 2003). At rest and during periods of physiologic stress, about 80% of the circulating cortisol is derived from plasma cholesterol (Borkowski *et al.* 1967). It is suggested that relative adrenal insufficiency occurs during critical illness, partially due to decreased delivery of substrate in the face of increased demand, because cholesterol is the major precursor for steroid synthesis in the adrenal gland.

In our population, the most frequently affected organ systems for both species were the hepatic and gastrointestinal system, with the lymphoreticular system as the third most common in cats. The most common diseases in both species were hepatocellular dysfunction and non-characterised protein-losing enteropathies. Congenital hepatic disease and hepatic lipidosis were also frequent in dogs and cats, respectively. All cats with lymphoreticular disease had neoplasia. All of these are expected physiologic causes of hypocholesterolaemia in veterinary medicine. There are no specific reports of the prevalence of hypocholesterolaemia in small animals with hepatocellular dysfunction, but approximately 62% of dogs with portosystemic shunts present with hypocholesterolaemia (Center & Magne 1990). Interestingly, in a descriptive study of cats with hepatic lipidosis only two of 60 cats had hypocholesterolaemia (Center *et al.* 1993). A low cholesterol measurement has been observed to occur in 29-85% of dogs with protein-losing enteropathies (Littman *et al.* 2000, Kull *et al.* 2001, Lyles *et al.* 2009). Congruent to our findings, liver disease was the most common disease associated with hypocholesterolaemia among hospitalised human medicine patients and also occurred in 31% of the study group (Oster *et al.* 1981).

Chronic and non-critical illness were the major disease processes in our study population of animals with moderate to severe hypocholesterolaemia, rather than acute disease. Comparing with human medicine, hypocholesterolaemia has been similarly identified in chronic diseases, especially neoplasia (Oster *et al.* 1981, Muller *et al.* 1989, Lévesque *et al.* 1991, Iseki *et al.* 2002, Sok *et al.* 2009, Tsirpanlis *et al.* 2009, Janičko *et al.* 2013). There is also a strong association with acute diseases such as sepsis, multiorgan dysfunction, trauma and post-surgical critical illness (Gui *et al.* 1996, Gordon *et al.* 2001, Dunham *et al.* 2003, Bonville *et al.* 2004, Chiarla *et al.* 2004, 2010, Marik 2006, Lagrost *et al.* 2014, Yamano *et al.* 2016). A possible explanation for the low prevalence of critical illness in our study may be due to our identification of disease process in both moderate and severe hypocholesterolaemia, which allowed for a diverse study population.

Neoplastic and infectious disease were the most common underlying diseases in both species, with a higher prevalence of neoplasia in dogs and a higher prevalence of infectious disease in cats. Studies in hospitalised humans have reported hypocholesterolaemia in association with malignant disease in 19.8-25% (Oster *et al.* 1981, Lévesque *et al.* 1991). This percentage is comparable to both our dog and cat cohorts. Among dogs with neoplasia, lymphoma made up 50% of cases, and 10% of the moderate to severe hypocholesterolaemia group of dogs investigated. This is a new finding, because hypocholesterolaemia in malignancy is anecdotally, and more frequently, linked with canine haemophagocytic histiocytic sarcoma (Moore *et al.* 2006). This neoplasm only occurred in 13.8% of our dogs with neoplasia which may be related to its prevalence in dogs presenting to our hospital rather than the prevalence of hypocholesterolaemia in dogs with this neoplasia. The only other report linking hypocholesterolaemia with lymphoma was a study among cats with nasal and nasopharyngeal lymphoma, with 24% of cats having low cholesterol (Little *et al*. 2007). There is a third study of multiple myeloma in cats that reported a prevalence of 68.7% for hypocholesterolaemia (Patel *et al*. 2005).

Among dogs and cats that had infectious disease, over 40% were considered to have sepsis. In addition, 69% of dogs that had hospital-acquired hypocholesterolaemia were considered to have sepsis in our study. Due to the retrospective nature of patient information, in combination with the limited numbers in this group, our study is only able to provide descriptive data in respect to patients with sepsis, as compared to the extensive range of human studies evaluating the relationship between sepsis and hypocholesterolaemia. Multiple studies have demonstrated significant decreases in total cholesterol, apolipoprotein, high-density and low-density lipoprotein in septic patients, which bear considerable and repeatable prognostication for non-survival and organ dysfunction (Dunham *et al*. 2003, Barlage *et al*. 2009, Biller *et al*. 2014, Lagrost *et al*. 2014, Yamano *et al*. 2016, Cirstea *et al*. 2017).

Strengths of this study include the large population of small animals identified with a cholesterol measurement and the diverse population. Limitations include those inherent to any retrospective study. The primary processes, unless confirmed by necropsy and histopathology, were inferred from the clinical diagnosis or clinical record, which may not equate to a definitive diagnosis. There were also multiple disease processes in most patients and it was not possible to determine which specific process was responsible for the development of hypocholesterolaemia in each individual. We were also not able to ascertain or report the timeline of samples in relation to meals or fasting periods, which can have effects on cholesterol levels. Being an academic institution, our study is also biased towards tertiary referral patients and may not be fully applicable to a general population. Additionally, haemolysis and icterus have the potential to alter the cholesterol measurement and those indices were not analysed.

In conclusion, hypocholesterolaemia is not a frequent abnormality but has a significant and inverse linear association with mortality. Cholesterol may be a useful prognostic marker for mortality, although further studies are needed prospectively to evaluate the extent and physiology of this relationship. Although hypocholesterolaemia is associated with a higher mortality rate than the one observed in animals with normal serum cholesterol, that rate is still only ~12% for both cats and dogs. A similar prognostic marker should be used to enhance intensity of diagnostic effort and therapy for affected animals rather than to allocate them for euthanasia. Moderate to severe hypocholesterolaemia was most commonly identified in animals with hepatic disease, gastrointestinal disease, lymphoreticular disease, infectious disease and neoplasia in our population. Monitoring cholesterol concentrations in animals with these disease processes could be of particular interest.

Conflict of interest

The authors declare no financial or other conflicts of interest.

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