ORIGINAL ARTICLE

Hypoalbuminaemia and its association with disease and clinical outcomes in cats

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Objectives: To report the incidence of feline hypoalbuminaemia and characterise the distribution of presenting disease categories and pathoaetiologies of hypoalbuminaemia in cats. The secondary aim was to evaluate the relationship between hypoalbuminaemia and clinical outcomes.

Materials and Methods: Medical records of cats with hypoalbuminaemia (<28.0 g/L, reference interval: 28.0 to 39.0 g/L) presenting to a veterinary teaching hospital over 5 years were retrospectively reviewed. The severity of hypoalbuminaemia was further stratified into mild (24.0 to 27.9 g/L), moderate (20.0 to 23.9 g/L) and severe (≤19.9 g/L) groups. The median albumin and severity groups were compared between the determined disease categories, pathoaetiologies and clinical outcomes.

Results: The incidence of hypoalbuminaemia was 32.7% (533/1632). Gastrointestinal disease was the most common disease category associated with hypoalbuminaemia [154/533 (28.9%)], of which, 49.4% (76/154) of cats had gastrointestinal neoplasia. Neoplastic [159/533 (29.8%)] and inflammatory conditions [158/533 (29.6%)] were common pathoaetiologies noted. Statistically significant differences in the serum albumin between individual disease and pathoaetiological categories were found. Cats with moderate to severe hypoalbuminaemia had a statistically significantly longer hospitalisation period, cost of treatment and increased odds of death (odds ratio 2.4, 95% confidence interval: 1.3 to 4.6 and odds ratio 3.2, 95% confidence interval: 1.5 to 6.6, respectively).

Clinical Significance: The incidence of feline hypoalbuminaemia in our study surpasses previous canine reports. Our findings support albumin as a negative acute phase protein in cats, with hypoalbuminaemia frequently associated with inflammatory disease. Hypoalbuminaemia also features prominently in cats with gastrointestinal neoplasia, indicating careful appraisal of the presence of protein-losing enteropathy is required in these cases. Finally, albumin is found to be a prognostic indicator in this study.

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INTRODUCTION

Albumin is the most abundant serum protein, constituting 35% to 50% of plasma protein in dogs and cats and is measured routinely in veterinary clinical practice. Albumin is produced exclusively by hepatocytes and accounts for around 75% of plasma oncotic pressure. It is a vital transporter of endogenous (e.g., hormones) and exogenous molecules (e.g., drugs) and is a prominent negative acute phase protein (Cerón et al., 2005). Hypoalbuminaemia is a common finding in sick animals and

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has been implicated in impaired wound healing, elevated risk of surgical site dehiscence and increased patient morbidity and mortality (Mazzaferro & Edwards, 2020). Severe hypoalbuminaemia decreases plasma oncotic pressure, resulting in extravascular fluid accumulation (Côté et al., 2017).

In dogs, hypoalbuminaemia is associated with a variety of diseases (Assawarachan et al., 2023; Molina et al., 2023) and the pathogenic mechanisms have been described (Côté et al., 2017). Like humans, several studies have highlighted albumin as a reliable prognostic indicator in canine medicine. Most renowned is albumin's role as a negative prognostic indicator in canine chronic enteropathies (Allenspach et al., 2007; Craven et al., 2004), but other presentations including critically ill animals, pancreatitis, and protein-losing nephropathies (PLN) have also been published (Gori et al., 2020; Klosterman et al., 2011). Albumin's prognostic role in dogs has led it to be incorporated into scoring systems including the Canine Chronic Enteropathy Clinical Activity Index (CCECAI) (Craven et al., 2004), modified Glasgow Prognostic Score (mGPS) for various tumours (Hu et al., 2019) and the Acute Patient Physical and Laboratory Evaluation (APPLE) score (Hayes et al., 2010).

In contrast, there is a lack of studies investigating the clinical significance of hypoalbuminaemia in cats. Testament to this is the unsubstantiated role of albumin as a negative acute phase protein in cats (Paltrinieri, 2008). Feline hypoalbuminaemia has been identified in specific conditions such as hepatic lipidosis (Kuzi et al., 2017) and high-grade alimentary lymphoma (Lingard et al., 2009). Rarely have studies postulated the prognostic value of hypoalbuminaemia in feline disease (Jergens et al., 2010; Kruse et al., 2010; Lee et al., 2012).

Despite the established importance of hypoalbuminaemia in morbidity and mortality in dogs, there is a paucity of literature pertaining to the prevalence, aetiology, pathogenesis and prognostic implications of hypoalbuminaemia in cats. This is particularly striking when one considers the high protein requirements of cats as obligate carnivores. Interestingly, the clinical impression is that severe hypoalbuminaemia and its consequences are less common in cats, with most research on hypoalbuminaemia treatment focusing on dogs (Allenspach, 2015; Mazzaferro & Edwards, 2020). There is little evidence, however, to support such claims and robust characterisation of feline hypoalbuminaemia is required.

The following databases (Pubmed, Science Direct and Web of Science) have been searched with the following keywords "feline," "cat," "hypoalbuminaemia" and "albumin" on November 1, 2023. The Textbook of Veterinary Internal Medicine by Côté et al. has also been consulted. No other reports describing the prevalence of hypoalbuminaemia in cats have been found. These searches have not revealed any reports characterising disease categories or pathoaetiology relating to feline hypoalbuminaemia.

As such, the primary aim of this study was to assess the incidence of feline hypoalbuminaemia and characterise the distribution of presenting disease categories and pathoaetiologies of hypoalbuminaemia in cats that were presented to a veterinary teaching hospital. The secondary aim was to assess the relationship between serum albumin and the categories of disease and pathoaetiology of hypoalbuminaemia. The final aim was to evaluate the relationship between hypoalbuminaemia and clinical outcomes.

MATERIAL AND METHODS

Sample population

Retrospective data were collected by searching the electronic medical records (Provet) for cats with hypoalbuminaemia, defined as albumin <28.0 g/L (reference interval: 28.0 to 39.0 g/L) that presented to the Hospital for Small Animals, Royal (Dick) School of Veterinary Studies between January 1, 2018 and January 31, 2023. Only cats with hypoalbuminaemia confirmed by our on-site reference laboratory, using the AU480 biochemical analysers were included. For cats with multiple biochemical analyses performed, only the first visit with a low serum albumin concentration was included. Once cases were identified, information such as patient signalment, weight, body condition score, appetite and hydration status were documented. Medical records were manually reviewed for further details on pertinent history, clinical examination findings, comorbidities, diagnostic test results, final diagnoses and follow-up data. Other pertinent haematological and biochemical analytes measured at the same time point as albumin were also recorded. Cases were examined for short-term survival which was defined as survival to discharge.

Biochemical analysis

Albumin and other biochemical analyte measurements were conducted by the AU480 biochemistry analyser (Beckman Coulter, High Wycombe, Buckinghamshire, UK). Bromocresol green assay was used for the measurement of albumin. Hospital protocol mandates that samples be collected in plain non-gel clot activator tubes and delivered to the lab promptly for analysis. Then, samples are centrifuged within 30 minutes and serum is harvested. Serum samples that were on hold were kept refrigerated under 3°C to minimise artefacts. Quality control assessments were conducted every day to ensure international laboratory standards were met.

Data classification

Stratification of albumin severity

There is currently no consensus in feline medicine regarding the classification of the severity of hypoalbuminaemia. For this study, mild, moderate and severe hypoalbuminaemia measured by the biochemical analyser was defined as 24.0 to 27.9 g/L, 20.0 to 23.9 g/L and ≤19.9 g/L, respectively, modified from the classification system used in human medicine (Akirov et al., 2017).

Disease process categorisation

The cases were categorised according to the main body system affected based on a recently published paper on hypocholesterolaemia in cats (Bowman et al., 2019). Categories in this study included the following: cardiac, dermatological, gastrointestinal, hepatobiliary, haematological, urogenital and respiratory. Additional categories: endocrine, musculoskeletal, neurological and ophthalmological diseases were introduced based on the pertinence of these disease processes upon review of the database and to minimise inappropriate categorisation influencing results.

Pathoaetiology categorisation

The primary pathoaetiologies were determined based on the presumed or definitive diagnoses and were categorised as anomalous, degenerative, infectious, inflammatory, idiopathic, metabolic, neoplastic, traumatic, toxic and vascular. Cases were categorised as idiopathic if differentials were excluded by the primary clinician notes and corroborated by authors KF and GW.

Statistical analysis

The data distribution was assessed using the Shapiro–Wilk test. The Kruskal-Wallis rank sum test with Bonferroni for post-hoc Dunn's pairwise test was used for median comparisons between three or more independent groups. The correlation between the two variables was examined with Spearman's correlation coefficient. Logistic regression analysis was used to determine the effects of age (continuous variable), pathoaetiology (categorical variable) and serum albumin (continuous or categorical variable) on the outcome. All the statistical analyses were performed using the statistical language R (R Foundation for Statistical Computing, Vienna, Austria). A P value <0.05 was considered significant for all tests.

RESULTS

Signalment

A total of 1645 cats had serum albumin measured within the 5 years, where 546 cats were found to have hypoalbuminaemia. Thirteen cases within the hypoalbuminaemia population were excluded from the study as they were healthy at the time of presentation and no further tests were performed. The incidence of hypoalbuminaemia in the population of cats that were presented to the teaching hospital within the study period was 32.7% (533/1632). The median age of the cats was 10 years old (range: 4 months to 19 years old). There were 272 neutered males (51.0%), 208 neutered females (39.0%), 31 entire males (5.8%) and 22 entire females (4.1%). Domestic short-haired cats were the predominant breed in this population [343/533 (64.4%)]. Other common breeds include Ragdolls [38/533 (7.1%)], Maine coons [24/533 (4.5%)] and British Short Hairs [20/533 (3.8%)]. Details of breed distributions are shown in Fig 1.

Severity of hypoalbuminaemia

Mild hypoalbuminaemia was documented most frequently in our study population [337/533 (63.2%)]. There were 125 cases with moderate hypoalbuminaemia (23.4%) and 71 cases with severe hypoalbuminaemia (13.3%).

Disease categories

Gastrointestinal causes were the most frequently identified disease process, accounting for 28.9% (154/533) of the feline population with hypoalbuminaemia. Respiratory and hepatobiliary conditions were diagnosed in 16.1% (86/533) and 13.9% (74/533) of cats, respectively.

The distribution of disease categories when assessed in the context of the severity of hypoalbuminaemia is described in Table 1. In comparison, an increased proportion of cats diagnosed with gastrointestinal [77/154 (50.0%)] and respiratory conditions [36/86 (41.8%)] had a moderate or severe hypoalbuminaemia of less than 24.0 g/L. Of the gastrointestinal diseases diagnosed, neoplasia was over-represented [76/154 (49.4%)] and alimentary lymphoma was the most prevalent diagnosis [36/76 (47.4%)]. Other less common aetiologies include inflammatory [58/154 (37.7%)] and infectious diseases [15/154 (9.7%)]. Gastrointestinal neoplasia was also the prevailing aetiology when analysing gastrointestinal disease with moderate or severe hypoalbuminaemia [39/77 (50.6%)].

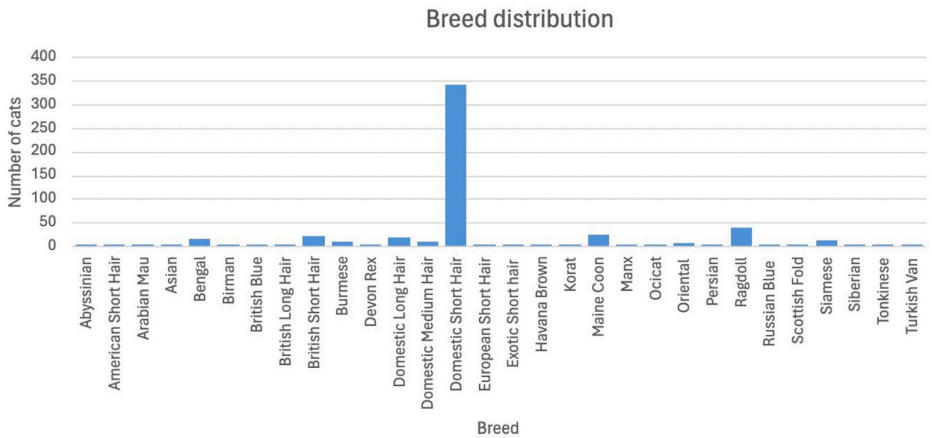

FIG 1. Breed distribution of cats presented with hypoalbuminaemia.

Table 1. Disease categories associated with the severity of hypoalbuminaemia

Disease categories	Mild, *n* (%)	Moderate, *n* (%)	Severe, *n* (%)	Total number of cases in disease categories
Cardiac	23 (82.1)	2 (7.1)	3 (10.7)	28
Dermatological	10 (83.3)	1 (8.3)	1 (8.3)	12
Endocrine	38 (84.4)	6 (13.3)	1 (2.2)	45
Gastrointestinal	77 (50.0)	51 (33.1)	26 (16.9)	154
Haematological	12 (63.1)	5 (26.3)	2 (10.5)	19
Hepatobiliary	46 (62.2)	16 (21.6)	12 (16.2)	74
Musculoskeletal	21 (87.5)	2 (8.3)	1 (4.2)	24
Neurological	8 (57.1)	5 (35.7)	1 (7.1)	14
Ophthalmological	8 (80.0)	2 (20.0)	0 (0.0)	10
Respiratory	50 (58.1)	21 (24.4)	15 (17.4)	86
Urogenital	44 (65.7)	14 (20.9)	9 (13.4)	67
Total number of cats in hypoalbuminaemia categories	337	125	71	533

Mild hypoalbuminaemia was defined as a serum albumin concentration of 24.0 to 27.9 g/L. Moderate and severe hypoalbuminaemia were defined as a serum albumin concentration of 20.0 to 23.9 g/L and ≤19.9 g/L, respectively

The albumin concentration in each disease process category is depicted in Fig 2. There was an overall statistically significant difference ($P < 0.001$) in albumin concentrations amongst the diagnostic categories. The median albumin concentration in the gastrointestinal group (24.1 g/L, range 14.8 to 27.9 g/L) was significantly lower ($P < 0.001$) than the endocrine group (26.9 g/L, range 21.6 to 27.9 g/L). The same was noted with the hepatobiliary (25.5 g/L, range 17.2 to 27.9 g/L) and endocrine groups, where the serum albumin is significantly lower in the former ($P = 0.009$). Similarly, cats diagnosed with respiratory (24.9 g/L, range 13.4 to 27.9 g/L) and urogenital disease (25.6 g/L, range 11.7 to 27.9 g/L) were also found to have significantly lower albumin compared to cases with endocrinopathies ($P = 0.001$ and $P = 0.017$, respectively). Of the 45 endocrine cases, 84.4% of cats were diagnosed with hyperthyroidism (38/45).

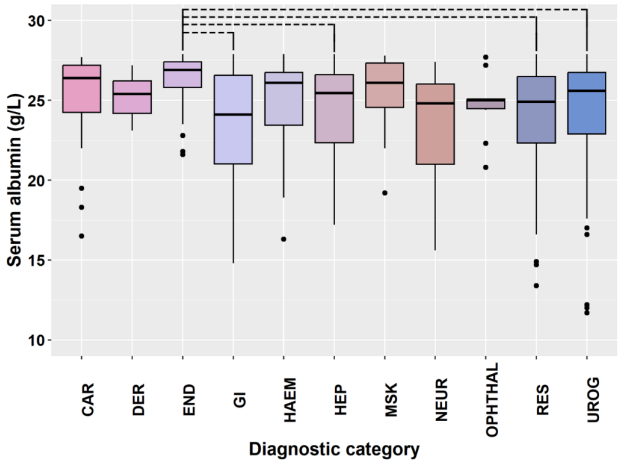

FIG 2. Serum albumin concentrations by diagnostic categories. The solid bars represent the interquartile range from the 25th to the 75th percentile. The bold horizontal bar in the middle marks the median. The dots represent the outliers. CAR Cardiac disease, DER Dermatological disease, END Endocrine disease, GI Gastrointestinal disease, HAEM Haematological disease, HEP Hepatobiliary disease, MSK Musculoskeletal disease, NEUR Neurological disease, OPHTHAL Ophthalmological disease, RES Respiratory disease, UROG Urogenital disease.

Pathoaetiology categories

Within the hypoalbuminaemic population, the three most diagnosed pathoaetiologies were neoplastic diseases [159/533 (29.8%)], inflammatory conditions [158/533 (29.6%)] and infectious diseases [94/533 (17.6%)].

The pathoaetiological diagnosis across the albumin categories is detailed in Table 2. With the exception of infectious disease, mild hypoalbuminaemia was the most common across the pathoaetiological categories. Of the infectious diseases, FIP accounted for 28.7% of cases (27/94). Other common diagnoses include pyothorax [11/94 (11.7%)] and bronchopneumonia [9/94 (9.6%)]. When assessing specific diseases within the inflammatory group, chronic enteropathy (CE) was the top diagnosis [21/158 (13.3%)]. Cholangiohepatitis [15/158 (9.5%)], pancreatitis [13/158 (8.2%)] and dental diseases [13/158 (8.2%)] were other common inflammatory conditions.

An overall statistically significant difference ($P < 0.001$) was observed in the serum albumin concentrations between different pathoaetiology groups. The albumin concentration of pathoaetiology categories is depicted in Fig 3. The median albumin concentration was significantly lower in the infectious disease category (22.8 g/L, range 13.4 to 27.6 g/L) as compared to the inflammatory disease group (25.6 g/L, range 11.7 to 27.9 g/L, $P < 0.001$), metabolic (26.9 g/L, range 12.0 to 27.9 g/L, $P < 0.001$), neoplastic (25.0 g/L, range 16.3 to 27.9 g/L, $P < 0.001$) or anomalous conditions (26.6 g/L, range 16.5 to 27.9 g/L, $P < 0.001$). The median albumin concentration in cases with metabolic diseases (26.9 g/L, range 12.0 to 27.9 g/L) was also significantly higher compared to neoplastic (25.0 g/L, range 16.3 to 27.9 g/L, $P = 0.001$) and inflammatory conditions (25.6 g/L, range 11.7 to 27.9 g/L, $P = 0.006$).

Prognosis

Of all cats that were presented to the hospital with hypoalbuminaemia, 461 cats (86.5%) survived to discharge. Hyperthyroid cats boarding for radioiodine I131 treatment were excluded when analysing the duration of hospitalisation. The median duration of hospitalisation overall was 2 days (range 0 to 14 days). The duration of hospitalisation in each hypoalbuminaemia category is detailed in Fig 4. There was a statistical difference ($P < 0.001$)

Table 2. Pathoaetiological categories associated with the severity of hypoalbuminaemia

Pathoaetiological categories	Mild, *n* (%)	Moderate, *n* (%)	Severe, *n* (%)	Total number of cases in pathoaetiological categories
Anomalous	23 (76.7)	4 (17.4)	3 (10.0)	30
Degenerative	6 (85.7)	0 (0)	1 (14.3)	7
Idiopathic	6 (66.7)	3 (33.3)	0 (0.0)	9
Infectious	34 (36.2)	37 (39.4)	23 (24.5)	94
Inflammatory	103 (65.2)	30 (51.7)	25 (15.8)	158
Metabolic	45 (84.9)	6 (11.3)	2 (3.8)	53
Neoplastic	103 (64.8)	41 (25.8)	15 (9.4)	159
Toxic	4 (80.0)	1 (20.0)	0 (0.0)	5
Traumatic	11 (68.8)	3 (18.8)	2 (12.5)	16
Vascular	2 (100.0)	0 (0.0)	0 (0.0)	2
Total number of cats in hypoalbuminaemia categories	337	125	71	533

Mild hypoalbuminaemia was defined as a serum albumin concentration of 24.0 to 27.9 g/L. Moderate and severe hypoalbuminaemia were defined as a serum albumin concentration of 20.0 to 23.9 g/L and ≤19.9 g/L, respectively

when comparing the duration of hospitalisation in respective hypoalbuminaemia groups. Cats with mild hypoalbuminaemia were hospitalised for a significantly shorter period compared to cats with moderate ($P < 0.001$) and severe hypoalbuminaemia ($P < 0.001$). There was also a statistically significant, weak negative correlation between the serum albumin and the duration of hospitalisation (rho = –0.211, $P < 0.001$).

Cost

The average cost of referral within the hypoalbuminaemic population was £2047.0 (range £66 to 19,241.5). When assessing the cost of treatment, there was a significant difference ($P < 0.001$) in the cost of referral between the albumin groups. The cost of referral in mild hypoalbuminaemic cases was significantly less than in moderate ($P = 0.002$) or severe cases ($P < 0.001$). Similarly, there was also a statistically significant, weak negative correlation between serum albumin and costs (rho = –0.251, $P < 0.001$). Details of the costs in the three albumin categories are described in Fig 5.

Modelling the relationship and the effects of age, pathoaetiology and serum albumin concentration on the outcome

We limited the fitting of the model to pathoaetiology groups with more than 20 cases. Therefore, the groups of degenerative, idiopathic, toxic, traumatic and vascular diseases were excluded from this model. All variables had a statistically significant contribution to predicting the outcome (Table 3) and a small relationship between grouping and prediction was found (Nagelkerke $R^2 = 0.17$). The overall prediction of survival was 86.2% (95% confidence interval: 82.9% to 89.2%). Based on the statistical analysis, each additional increase of 1 g/L in albumin is associated with a 13.1% increase in the odds of survival in the cat. An 8.6% decrease in the odds of death was noted for each additional increase of 1 year in cats' age. When using anomalous diseases as the reference category, cats with infectious diseases have an 81.9% increase in odds of survival. Similarly, cats with inflammatory and metabolic conditions have an 88.1% and 95.3% increase in odds of survival, respectively, when compared with anomalous diseases.

A predictive model using the severity of hypoalbuminaemia categories with the same variables was also created to assess the effects on outcome (Table 4). Similarly, all variables tested contributed to the disease outcome and there was a small relationship between hypoalbuminaemia groups and prediction (Nagelkerke $R^2 = 0.17$). The overall prediction of survival was 86.4% (95% confidence interval: 83.1% to 89.3%). Moderate hypoalbuminaemia was associated with greater odds of death compared to mild hypoalbuminaemia (odds ratio 2.4, 95% confidence interval: 1.3 to 4.6). The odds of death increase further with severe hypoalbuminaemia when compared to mild cases (odds ratio 3.2, 95% confidence interval: 1.5 to 6.6).

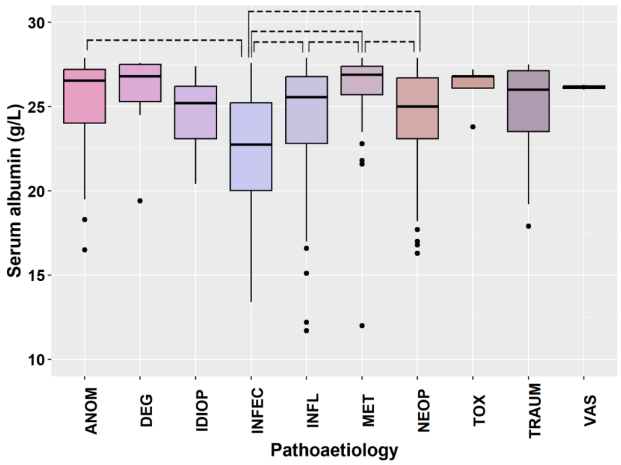

FIG 3. Serum albumin concentrations by pathoaetiological categories. The solid bars represent the interquartile range from the 25th to the 75th percentile. The bold horizontal bar in the middle marks the median. The dots represent the outliers. ANOM Anomalous disease; DEG Degenerative disease; IDIOP Idiopathic disease; INFEC Infectious disease; INFL Inflammatory disease; MET Metabolic disease; NEOP Neoplastic disease; TOX Toxic disease; TRAUM Traumatic disease; VAS Vascular disease.

DISCUSSION

Hypoalbuminaemia was found to have an incidence of 32.7% in the feline population that were presented to a veterinary teaching hospital. This surpasses the reported incidence of

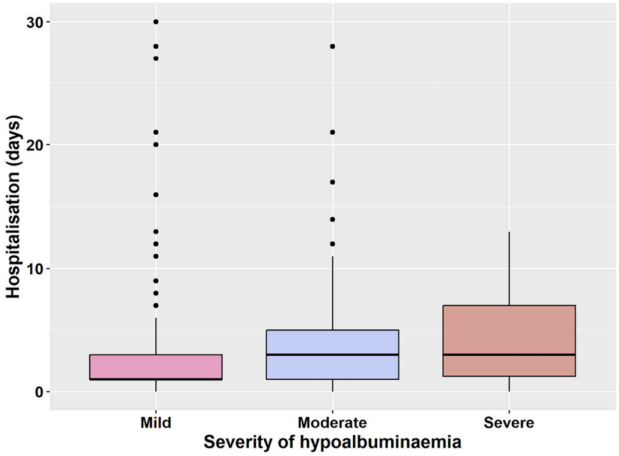

FIG 4. Duration of hospitalisation by severity of hypoalbuminaemia. The solid bars represent the interquartile range from the 25th to the 75th percentile. The bold horizontal bar in the middle marks the median. The dots represent the outliers.

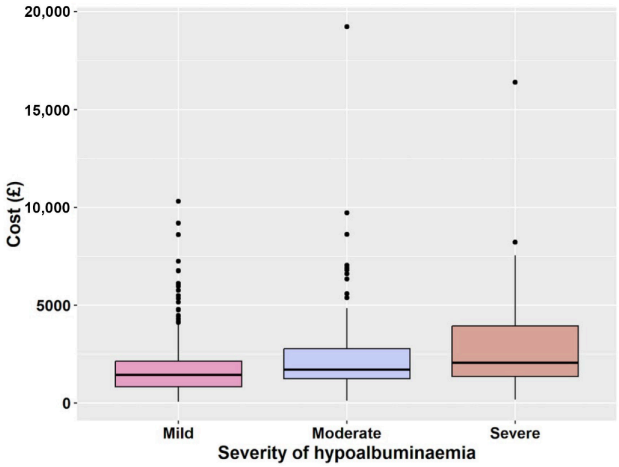

FIG 5. Cost of treatment by severity of hypoalbuminaemia. The solid bars represent the interquartile range from the 25th to the 75th percentile. The bold horizontal bar in the middle marks the median. The dots represent the outliers.

hypoalbuminaemia in the canine population, which was reported to range from 9.8% to 25.2% (Côté et al., 2017). This finding was unexpected and contradicts the long-standing dogma that feline hypoalbuminaemia is uncommon.

In keeping with historic papers, our data found that hypoalbuminaemia is commonly associated with inflammation [158/533 (29.6%)], and provides evidence to support albumin as a negative acute phase protein in cats (Cerón et al., 2005; Paltrinieri, 2008). In our study, the three most common inflammatory conditions were CE [21/158 (13.3%)], cholangiohepatitis [15/158 (9.5%)] and pancreatitis [13/158 (8.2%)]. Interestingly, this cluster of individual diseases could represent cats suffering from triaditis. Concurrent triaditis has been reported in 50% to 56% and 32% to 50% of cats with pancreatitis and cholangiohepatitis, respectively (Simpson, 2015).

Table 3. Logistic regression analysis for the variables associated with the outcome of hypoalbuminaemic cats that were presented in a veterinary teaching hospital between 2018 and 2023

Variable	Odds ratio	95% Confidence interval	*p* value
Albumin concentration	0.869	0.801 to 0.943	<0.001
Age	0.914	0.854 to 0.976	0.008
Infectious disease	0.181	0.063 to 0.518	0.001
Inflammatory disease	0.119	0.042 to 0.331	<0.001
Metabolic disease	0.047	0.003 to 0.280	0.005

Serum albumin concentration was included as one of the independent variables

Table 4. Logistic regression analysis for the variables associated with the outcome of hypoalbuminaemic cats that were presented in a veterinary teaching hospital between 2018 and 2023

Variable	Odds ratio	95% Confidence interval	*p* value
Moderate hypoalbuminaemia	2.414	1.255 to 4.645	0.008
Marked hypoalbuminaemia	3.164	1.486 to 6.645	0.002
Age	0.912	0.852 to 0.974	0.007
Infectious disease	0.178	0.061 to 0.510	0.001
Inflammatory disease	0.118	0.042 to 0.326	<0.001
Metabolic disease	0.046	0.002 to 0.270	0.005

The severity of hypoalbuminaemia categories was included as one of the independent variables

In addition, these cats can often be asymptomatic, with evidence of pancreatitis found in up to 45% of apparently healthy cats undergoing necropsy (Forman et al., 2021). As such, it is important to note that whilst cats have been allocated to a disease category, concurrent subclinical inflammatory diseases could also contribute to hypoalbuminaemia. Similarly, the 13 healthy hypoalbuminaemic cats excluded from this study could have subclinical disease, but the retrospective nature of this study precludes in-depth assessment.

Notably, infectious diseases have significantly decreased serum albumin concentration when compared with other categories. Almost two-thirds of the cases were associated with moderate to severe hypoalbuminaemia. In humans, hypoalbuminaemia is associated with the severity of infectious disease, presumably associated with the degree of inflammation and its role as a negative phase protein (Wiedermann, 2021). Of the infectious diseases, FIP was most commonly diagnosed and accounted for 30.1% of cases in our study (28/93). Feline Infectious Peritonitis is a multisystemic disease that can result in severe systemic inflammation (Kipar et al., 2005). Whilst vasculitis and third spacing likely contribute to hypoalbuminaemia in FIP, severe hyperglobulinaemia is also theorised to induce a hepatic-mediated compensatory hypoalbuminaemia to maintain oncotic pressure (Côté et al., 2017; Hoey et al., 2020). The overrepresentation of this population of FIP cats may account for the lower albumin level within the infectious category.

Gastrointestinal disease was the most common diagnostic category associated with hypoalbuminaemia in our study

[154/533 (28.9%)]. This finding suggests that the prevalence of hypoalbuminaemia associated with gastrointestinal diseases in cats may be higher than previously reported in published studies on gastroenteropathy (5% to 24%) (Allenspach, 2015). However, the reported prevalence of hypoalbuminaemia in feline gastroenteropathy is variable across the literature. Recently, the American College of Veterinary Internal Medicine (ACVIM) consensus statement described a prevalence of up to 100% in feline CE (Marsilio et al., 2023). Another study has also reported a prevalence of hypoalbuminaemia to be near 100% in severe immunosuppressive-responsive CE, whereas cats with food-responsive CE rarely have low serum albumin (Bandara et al., 2022). Our findings, when paired with previous reports prompt revaluation of the true prevalence of hypoalbuminaemia in feline gastrointestinal conditions.

When analysing the pathoaetiology within the gastrointestinal category, neoplasia accounted for 49.4% of the cases and alimentary lymphoma was the most diagnosed [36/76 (47.4%)]. Studies have shown that up to 50% to 75% of high-grade alimentary lymphoma cases in cats have associated hypoalbuminaemia (Lingard et al., 2009). Research has also been done on feline faecal α1-proteinase inhibitor (α(1)-PI), a marker for protein-losing enteropathies (PLE). It has shown a significantly increased concentration in cats with gastrointestinal neoplasia compared to the healthy control group (Burke et al., 2013). Although histological grading of alimentary lymphoma is beyond the scope of this study, the high proportion of alimentary lymphoma would have contributed to the high prevalence of hypoalbuminaemia in gastrointestinal conditions. Despite albumin not being a component of the Feline Chronic Enteropathy Activity Index (FCEAI), our findings suggest that hypoalbuminaemia is an important feature in alimentary neoplasia and PLE could be clinically significant in this population (Jergens et al., 2010).

Eighty-four percent of cats diagnosed with endocrine disease had mild hypoalbuminaemia in our study. Thirty-eight out of the 45 endocrine cases (84.4%) were diagnosed with hyperthyroidism. This phenomenon is mentioned in a major veterinary internal medicine textbook (Côté et al., 2017). However, hypoalbuminaemia is rarely reported in feline endocrinopathy reviews (Bugbee et al., 2023; Gunn-Moore, 2005). Interestingly, in human hyperthyroidism, hypoalbuminaemia is common, with up to 73% of patients affected (Bartels, 1938). Experimental administration of thyroid hormones in humans has also resulted in a decrease in the biological half-life of albumin and elevated catabolism of protein (Blomstedt & Liljedahl, 1967). We speculate that mild hypoalbuminaemia in hyperthyroid cats could be associated with increased albumin catabolism, though the effects of comorbidities could not be ruled out. Care with interpreting concurrent mild hypoalbuminaemia in hyperthyroid cats is needed until euthyroidism is achieved.

The number of cardiac diseases with mild hypoalbuminaemia was unexpected. With the exception of infectious endocarditis, hypoalbuminaemia is not a commonly reported finding in cardiac disease (Gavazza et al., 2021). Many theories have been postulated regarding the mechanism of hypoalbuminaemia in humans suffering from cardiac disease, including systemic inflammation and third spacing associated with subclinical interstitial oedema (Arques, 2020). Although canine studies identified an association between C-reactive protein concentrations and the severity of congestive heart failure (CHF), supporting the theory of acute phase response, there is currently no consensus on a single prevailing mechanism (Cunningham et al., 2012). Measurements of inflammatory markers such as alpha-1 acid glycoprotein (AGP) were not available in most cardiac cases of our population. Based on the literature search, association between hypoalbuminaemia and feline cardiac diseases have not been reported. Further studies investigating the relationship between albumin and cardiac diseases are warranted.

The severity of hypoalbuminaemia was prognostic in this study. Specifically, severe and moderate hypoalbuminaemia were associated with 141.4% and 216.4% odds of mortality, respectively, when compared to mild hypoalbuminaemia. Other feline studies have found that hypoalbuminaemia was associated with mortality in acute kidney injury and panleukopenia (Kruse et al., 2010; Lee et al., 2012). These findings support the use of albumin in estimating prognosis in cats and the potential to incorporate serum albumin into feline prognostic models. It is worth noting that since the FIP cases within our study period presented before the widespread use of Remdesivir, preventable deaths incurred in this population (Sorrell et al., 2022). This subset of cats may influence our findings.

Within our cohort, the odds of a cat dying decreased with age. Although counterintuitive, this is due to the over-representation of hyperthyroid cats in the senior population and severe infectious diseases such as FIP diagnosed in juveniles.

There are several limitations in this study owing to its retrospective nature. Misclassification may have occurred in cases with multiple morbidities where the definitive diagnosis was unclear and co-morbidities may be misinterpreted as the aetiology. However, these conclusions were made in collaboration by multiple authors, and were uniform across all cases, reducing the impact when comparing within the study population. In addition, due to the nature of referral medicine, some cases were lost to follow-up and long-term prognosis is difficult to assess. Although the severity of hypoalbuminaemia is deemed prognostic, a control group with normoalbuminaemia would allow better statistical evaluation. Confounding factors such as dehydration at the time of blood sampling may also influence serum albumin levels. However, this will likely result in cases being missed or overestimation of albumin concentrations and is less significant when discussing the severity of hypoalbuminaemia in the study. Future prospective studies may consider using serum albumin data following fluid therapy to eliminate the impact of dehydration. Moreover, it is challenging to gauge the effect of subclinical co-morbidities on hypoalbuminaemia. For example, concurrent pancreatitis is known to worsen serum albumin in feline chronic gastrointestinal disease (Bailey et al., 2010). Although cases were thoroughly appraised, subclinical chronic inflammatory diseases cannot be excluded. Medication histories

were also not consistently recorded. Glucocorticoids have been noted to increase circulating albumin at immunosuppressive doses, suspected to be associated with increased hepatic synthesis and haemoconcentration due to polyuria (Lowe et al., 2008). In addition, the diet, muscle condition and duration of anorexia were not quantified and reliably documented in the records. A historic study in dogs detected a drop in serum albumin concentration following starvation of more than 3 weeks (Pointer et al., 2013). A recent study suggested that feline protein requirement has been historically underestimated in nitrogen balance studies (Laflamme & Hannah, 2013). This further demonstrates the high protein requirement in cats and the impact of nutrition on their serum albumin may be more clinically significant than previously noted.

In conclusion, the incidence of feline hypoalbuminaemia in our study was higher than previous canine reports. This study provides evidence supporting albumin as a negative acute phase protein in cats. Gastrointestinal diseases were most frequently associated with hypoalbuminaemia within the study population, with gastrointestinal neoplasia the main pathoaetiology. Careful appraisal of the clinical significance of hypoalbuminaemia and the presence of PLE is required in cats with alimentary neoplasia. Mild hypoalbuminaemia in cats with cardiac disease and hyperthyroidism also warrants further investigation. The severity of hypoalbuminaemia is found to be a prognostic indicator in this study and suggests serum albumin has a role in feline prognostic scores.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Author contributions

K. Y. M. Fong: Data curation (lead); formal analysis (supporting); investigation (lead); methodology (lead); project administration (lead); writing – original draft (lead); writing – review and editing (lead). **I. L. Oikonomidis:** Formal analysis (lead); writing – review and editing (supporting). **D. Leong:** Data curation (supporting). **G. Lo:** Data curation (supporting). **J. Heal:** Data curation (supporting). **G. Woods:** Conceptualization (lead); data curation (supporting); investigation (supporting); methodology (supporting); project administration (supporting); supervision (lead); writing – review and editing (lead).

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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