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Candidate prognostic indicators in cats with histoplasmosis treated with antifungal therapy

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Abstract

Objectives The aim of this study was to retrospectively identify candidate prognostic indicators in cats with histoplasmosis treated with antifungal therapy.

Methods Medical records of cats diagnosed with histoplasmosis were reviewed. Candidate prognostic indicators were assessed for an association with survival to hospital discharge and survival to 1 and 6 months after diagnosis. Potential indicators included easily obtained data at the time of the initial hospital visit derived from cat signalment, historical information, physical examination, laboratory data, form of disease and initial treatment.

Results Approximately 88% of cats survived to discharge, with 77% and 67% surviving to 1 and 6 months, respectively. Clinical variables significantly associated with death at more than one outcome time point included the presence of dyspnea, adventitial lung sounds, fungemia, neurologic disease, neutropenia, lymphopenia, multiple cytopenias (anemia, neutropenia, thrombocytopenia), hyperbilirubinemia and increased creatinine kinase activity. Cats that did not survive were more likely to have received corticosteroids, oxygen supplementation and required hospitalization. In addition, cats that did not survive required significantly longer hospitalization. There was no significant difference between initial antifungal drug and survival.

Conclusions and relevance Potential prognostic indicators were associated with more severe respiratory, hepatic, hematologic or neurologic disease. Prospective investigation concerning clinical indicators of disease severity of these body systems is indicated.

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Introduction

Histoplasma capsulatum, the causative agent of histoplasmosis, is a dimorphic soil-borne fungus found extensively throughout the Midwestern and Southern USA. Histoplasmosis is the second most common systemic mycosis in cats.[1] Disease might be isolated to the respiratory tract or gastrointestinal (GI) tract or be disseminated, involving multiple body systems.[2,3] Definitive diagnosis is most commonly made by identification of the yeast in tissue aspirates, tissue biopsy specimens or bodily fluid. A *Histoplasma* antigen enzyme immunoassay has been shown to be a sensitive test and can help support the diagnosis.[4]

Antifungal treatment options for cats diagnosed with histoplasmosis remain relatively limited and generally consist of triazole-class antifungals with or without the addition of amphotericin B.[5] Itraconazole or fluconazole are considered the treatment of choice, but no prospective studies have compared efficacy of antifungal therapy for cats with histoplasmosis nor provided evidence for when medication beyond azoles should be considered.[3,6,7]

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Published information concerning the outcome of cats treated for histoplasmosis is limited. Excluding one small study that reported 100% survival,[6] two larger retrospective studies reported mortality rates of 33% and 45%, respectively.[3,7] Prognostic indicators have been reported in humans with histoplasmosis. These are used as objective means for the identification of patients at risk for negative outcomes, thus allowing for more targeted treatment.[8] Negative prognostic indicators in humans with histoplasmosis include: older age; dyspnea or respiratory insufficiency or fungemia; prolonged partial thromboplastin time (PTT; >45 s); increased activity of blood lactate dehydrogenase (>2 times the upper reference limit), aspartate aminotransferase (>2.5 times the upper reference limit) and alkaline phosphatase (>2.5 times the upper reference limit); increased blood concentrations of bilirubin (>1.5 mg/dl), urea (>2 or 2.5 times the upper reference limit) and creatinine (>1.5 or 2.1 mg/dl); decreased blood concentration of albumin (<3.5 g/dl); thrombocytopenia (<100,000/µl); and decreased hemoglobin concentration (<8.0 or <9.5 g/dl).[8–10] Identification of prognostic indicators has allowed the Infectious Diseases Society of America and others to publish evidence-based treatment recommendations that are more case-specific in order to guide physicians in determining the best treatment.[11,12]

A recent retrospective study of dogs with histoplasmosis identified several potential negative prognostic indicators of disease severity, including requirement for oxygen therapy, anemia and thrombocytopenia, elevated bilirubin and alkaline phosphatase activity, and hypercalcaemia.[13] To our knowledge, there have been no reported prognostic indicators for cats with histoplasmosis. Clinically relevant objective measures of more severe disease are needed to guide data collection in future studies and ultimately refine appropriate treatment recommendations. The tested hypothesis was that cats with histoplasmosis will have similar prognostic indicators to those already proven in humans and dogs. The purpose of this study was to retrospectively identify candidate prognostic indicators in cats with histoplasmosis.

Materials and methods

Cats

Medical records of cats diagnosed with histoplasmosis at the Veterinary Medial Hospital at Oklahoma State University and the Veterinary Health Center at Kansas State University between the years of 1999 and 2015 were reviewed. Inclusion required the definitive diagnosis of histoplasmosis by detection of *H capsulatum* yeast via cytopathology or histopathology. Exclusion criteria included antifungal treatment of ⩾7 days' duration in the month before presentation to the participating hospital; if complete blood count (CBC) or biochemistry analysis was not available or not performed within 14 days before or 3 days after the diagnosis; if the medical record was incomplete and initial physical examination findings and type of antifungal treatment was not recorded; or if antifungal treatment was not attempted. In addition, cats that were determined to have died of something other than histoplasmosis during the 6 month follow-up period were excluded from the study. If cats had multiple hospital visits owing to relapse or reinfection, only the first visit at which histoplasmosis was diagnosed was considered. Some cats included in the current study have been included in previous publications.[3,4,14]

Candidate prognostic indicators and data extraction

Candidate prognostic indicators were chosen based on being identified as prognostic indicators in humans with histoplasmosis or anecdotally related to disease severity in cats with histoplasmosis. All potential prognostic indicators were considered easily obtainable at or near the time of diagnosis. Data extracted from medical records included signalment (age, weight, sex, breed); presenting clinical signs (duration, weight loss, diarrhea, dyspnea, lameness, neurologic disease); physical examination findings (body temperature; respiratory rate presence of adventitial lung sounds such as crackles or wheezes; joint effusion; lymphadenopathy; abdominal organomegaly; cutaneous lesions; results of neurologic examination); laboratory data (CBC, biochemistry analysis, prothrombin time [PT], PTT); results of thoracic radiographs; method of diagnosis (cytopathology or histopathology), anatomic location where *H capsulatum* was found; initial antifungal treatment (drug, dose, duration); other treatments (need for and duration of hospitalization, oxygen supplementation, dose and duration of concurrent corticosteroid administration); outcome (survival to hospital discharge and 1 and 6 months after diagnosis); and likely cause of death (histoplasmosis related or not).

History and physical examination

If an historical or physical examination finding was not noted in the medical record, then the sign or finding was considered not present. Dyspnea was defined as tachypnea (respiratory rate ⩾40 breaths/min), open-mouth breathing or increased respiratory effort.

Laboratory data

Cats were considered thrombocytopenic if the automated platelet count was below the lower reference limit, and thrombocytopenia with minimal or no clumping was confirmed on blood smear examination. Cats were considered non-thrombocytopenic if the automated platelet count was within the reference interval (RI) or above the upper reference limit, or if the automated platelet count

was low but clumping was present with adequate estimated platelets from blood smear examination. Platelet data were not included if the automated platelet count was below the lower reference limit and a blood smear examination was not available. For the purposes of this study hematocrit was considered equivalent to packed cell volume. Cats were classified as having multiple cytopenias if two or more of the following were present – anemia, neutropenia or thrombocytopenia.

Classification of disease

Cats were categorized into respiratory, GI and disseminated forms of disease, where disseminated included all categories other than disease isolated to the respiratory or GI tract. Respiratory or GI forms of disease required clinical findings of one of these body systems without findings consistent with disease of another body system. Any cat with signs of neurologic disease was placed in a subcategory of disseminated disease and analyzed as a possible prognosticator.

Treatment

Variables included the administration of initial antifungal drug and dose, glucocorticoids and dose, oxygen therapy, and hospitalization and duration. The daily dose of glucocorticoids was reported as the prednisolone dose, or if dexamethasone was administered, this dose was multiplied by seven so that the prednisolone equivalent could be reported.[15] Drug change in the first 30 days and 6 months was considered if the antifungal drug was changed or if an additional antifungal drug was added during the specified time period.

Outcome

Outcome was defined as survival to hospital discharge, 1 month after diagnosis and 6 months after diagnosis. These were determined by reviewing the medical record, contacting the pet owner via telephone or both. Natural death was not differentiated from euthanasia. The cause of death was considered to be disease other than histoplasmosis if an alternative cause was confirmed or due to histoplasmosis if no alternative cause of death was confirmed.

Statistical analysis

Analysis was performed with commercial software (SAS 9.3). Descriptive data were presented as median and interquartile range (IQR). Outcome variables were survival or non-survival to hospital discharge, 1 month after diagnosis and 6 months after diagnosis. Candidate prognostic indicators were compared between survivors and non-survivors for each outcome time point. CBC and biochemistry data were converted to categorical data in relation to the respective laboratory RI (below the lower reference limit, less than half the lower reference limit, above upper reference limit or greater than twice the upper reference limit). A χ^2 test or Fisher's exact test was used to compare categorical variables when all cells were expected to contain >5 values, or at least one cell was expected to contain $\leqslant 5$ values, respectively. Univariate logistic regression was used to compare continuous variables. Statistical significance was set at $P \leqslant 0.05$.

Results

In total, 182 cats were identified as being diagnosed with histoplasmosis. Cats were excluded owing to no *H capsulatum* yeast organisms being found (n = 28), no antifungal treatment (n = 18), no CBC and biochemistry analysis within the appropriate time frame (n = 15), initial antifungal treatment not recorded (n = 10), prior antifungal treatment for >7 days in the month before diagnosis (n = 9) and death as a result of something other than histoplasmosis (n = 1). The cat that died of another cause was confirmed to have lymphoma at necropsy. The 28 cats excluded owing to lack of *H capsulatum* organisms being visualized were diagnosed based on clinical findings and in some cases a positive urine *Histoplasma* antigen enzyme immunoassay. In total, 101 cats met the inclusion criteria and were included in the study.

Outcome

Survival to hospital discharge, 1 month after diagnosis and 6 months after diagnosis was 89/101 (88.1%), 74/96 (77.1%) and 63/94 (67.0%), respectively. One and 6 month outcomes were unknown for five and seven cats, respectively.

Signalment

The median (IQR) age was 6.5 years (4.0–9.0) and the median (IQR) body weight was 3.5 kg (2.8–4.3). There were 49 males and 52 females. Breeds included domestic shorthair (n = 74), domestic longhair (n = 9), Siamese (n = 7), domestic mediumhair (n = 3), Himalayan (n = 3) and one each of Birman, Oriental Shorthair, Tonkinese, Ragdoll and Abyssinian (Tables 1–3).

Clinical signs and examination findings

The median (IQR) duration of clinical signs was 6.0 weeks (3.0–16.0). Weight loss was common (88/101 [87.1%]), followed by dyspnea (58/101 [57.4%]), lameness (16/101 [15.8%]), diarrhea (12/101 [11.9%]) and signs of neurologic disease (4/101 [4.0%]). Median (IQR) body temperature was 102.0°F (101.1–103.0) and the median (IQR) respiratory rate was 46 breaths/min (32–60). Presence of adventitial lungs sounds was the most common abnormal examination finding (37/101 [36.6%]), followed by peripheral lymphadenopathy (34/101 [33.7%]), abdominal organomegaly (27/101 [26.7%]), cutaneous lesions (17/101 [16.8%]) and joint effusion (9/101 [8.9%]). Abnormal neurologic findings

Table 1 Candidate prognostic indicators for survival to hospital discharge in 101 cats with histoplasmosis treated with antifungal therapy

Candidate indicator	Survivors (n = 89)	Non-survivors (n = 12)	*P* value
Clinical findings			
Age (years)	6.1 (5.0)	8.0 (9.0)	0.31
Weight (kg)	3.4 (1.4)	3.5 (1.9)	0.51
Duration of clinical signs (weeks)	7.0 (17.0)	2.5 (5.8)	0.24
Weight loss (% with sign)	87	92	1.0
Diarrhea (% with sign)	12	8	1.0
Dyspnea (% with sign)	53	92	**0.02**
Lameness (% with sign)	18	0	0.21
Adventitial lung sounds (% with finding)	30	83	**<0.001**
Lymphadenopathy (% with finding)	34	33	0.17
Abdominal organomegaly (% with finding)	25	42	0.30
Cutaneous lesions (% with finding)	18	8	0.32
Joint effusion (% with finding)	10	0	0.59
Body temperature (°F)	102.1 (1.9)	101.8 (1.2)	0.27
Respiratory rate (breaths/min)	44 (28)	54 (32)	0.80
Form (% with form)*	74/18/8	83/17/0	0.59
Neurologic disease (% with finding)	3	8	0.40
Fungemia (% with finding)	2	50	**<0.001**
Thrombocytopenia (% with finding)	46	57	0.70
Multiple cytopenias (% with finding)†	21	33	0.46
Treatment			
Initial antifungal treatment (% fluconazole)	44	33	0.55
Fluconazole start dose (mg/kg/day)	14.6 (11.0)	20.3 (5.5)	0.72
Itraconazole start dose (mg/kg/day)	10.0 (1.2)	10.0 (0.6)	0.93
Glucocorticoid treatment (% received)	45	67	**0.05**
Glucocorticoid dose (mg/kg/day)‡	0.75 (0.52)	0.60 (0.8)	0.64
Oxygen supplementation (% required)	21	83	**<0.001**

Values in bold are $P \leqslant 0.05$. Data are median (interquartile range [75th percentile–25th percentile]) or n (%), unless otherwise indicated
*Disseminated/respiratory/gastrointestinal
†Defined as at least two of the following: anemia, neutropenia, thrombocytopenia
‡Prednisolone dose or prednisolone equivalent (dexamethasone dose • 7)

included tremors (n = 3), inappropriate mentation (n = 2), tetraparesis (n = 2), horizontal nystagmus (n = 1), anisocoria (n = 1) and slow pupillary light reflex (n = 1). The cat with neuro-ophthalmic abnormalities had a normal fundic examination. All four cats had multifocal intracranial neuro-localization based on neurologic examination. Clinical signs and physical examination findings that were significantly more common in cats that did not survive at one or more outcome time points were dyspnea, adventitial lung sounds and signs of neurologic disease (Tables 1–3).

Laboratory data

The median (IQR) duration of time from initial diagnosis to when the CBC or biochemical analysis was performed was 0 days (0–1) for each test. The biochemistry analysis and CBC were performed at the referring veterinary hospital in nine and eight cats, respectively. Two cats had CBC data from >2 days before diagnosis at 9 and 11 days, respectively. Four cats had biochemistry analysis data >2 days before diagnosis at 4, 9, 11 and 12 days, respectively. PT and PTT were available for eight cats and thus were not included in the statistical analyses. The median (IQR) PT was 9.9 s (9.4–12.1) and PTT was 14.0 s (8.4–12.7); none of the values fell outside of the laboratory RIs. Laboratory findings associated with decreased survival at one or more outcome time points were neutropenia, lymphopenia, multiple cytopenias, increased creatinine kinase (CK) and hyperbilirubinemia (Tables 4–6).

Thoracic radiography

At the time of diagnosis thoracic radiographs were obtained in 73 cats. A radiology report was not available for five cats. Radiographs were considered normal in 19 cats. Changes consistent with pulmonary histoplasmosis were described as mixed (n = 20), structured interstitial (n = 15), unstructured interstitial (n = 7), mass-like (n = 3), alveolar (n = 2) and focal mineralization (n = 1).

Table 2 Candidate prognostic indicators for survival to 1 month after diagnosis in 96 cats with histoplasmosis treated with antifungal therapy

Candidate indicator	Survivors (n = 74)	Non-survivors (n = 22)	*P* value
Clinical findings			
Age (years)	6.3 (5.0)	8.0 (7.0)	0.36
Weight (kg)	3.5 (1.5)	3.3 (1.4)	0.60
Duration of clinical signs (weeks)	7.0 (17)	3.5 (6.5)	0.42
Weight loss (% with sign)	84	95	0.29
Diarrhea (% with sign)	11	14	1.0
Dyspnea (% with sign)	53	92	**0.01**
Lameness (% with sign)	18	4	0.18
Adventitial lung sounds (% with finding)	32	59	**0.04**
Lymphadenopathy (% with finding)	35	27	0.61
Abdominal organomegaly (% with finding)	22	36	0.17
Cutaneous lesions (% with finding)	16	14	1.0
Joint effusion (% with finding)	9	0	0.35
Body temperature (°F)	102.3 (2.0)	101.7 (1.2)	0.09
Respiratory rate (breaths/min)	44 (28)	48 (36)	0.53
Form (% with form)*	72/19/9	82/18/0	0.31
Neurologic disease (% with finding)	0	14	**0.01**
Fungemia (% with finding)	3	27	**0.001**
Thrombocytopenia (% with finding)	43	52	0.39
Multiple cytopenias (% with finding)†	15	50	**0.001**
Treatment			
Initial antifungal treatment (% fluconazole)	49	27	0.09
Fluconazole start dose (mg/kg/day)	14.3 (11.1)	19.2 (8.9)	0.11
Itraconazole start dose (mg/kg/day)	10.0 (0.75)	9.7 (2.4)	0.21
Glucocorticoid treatment (% did receive)	45	71	**0.05**
Glucocorticoid dose (mg/kg/day)‡	0.80 (0.57)	0.53 (0.28)	0.32
Oxygen supplementation (% did require)	19	68	**<0.001**
Hospitalization (% did require)	50	91	**<0.001**
Hospitalization duration (days)	0.5 (3.0)	3.5 (4.0)	**0.01**

Values in bold are $P \leqslant 0.05$. Data are median (interquartile range [75th percentile–25th percentile]) or n (%), unless otherwise indicated
*Disseminated/respiratory/gastrointestinal
†Defined as at least two of the following: anemia, neutropenia, thrombocytopenia
‡Prednisolone dose or prednisolone equivalent (dexamethasone dose • 7)

Pleural effusion was seen in addition to pulmonary lung disease in five cats. Intrathoracic lymphadenopathy was seen with pulmonary lung disease in three cats and was the only abnormal finding in one cat.

Diagnosis

Histoplasma capsulatum organisms were confirmed in one organ (n = 83) or more than one organ (n = 18) via fine-needle aspirate and cytopathology of lung (n = 18), liver (n = 17), spleen (n = 17), lymph node (n = 17), cutaneous lesion (n = 5), bone (n = 2), oral lesion (n = 2) and one each of eye, kidney and unknown abdominal mass. Additional cytopathologic diagnoses were made on examination of bone marrow aspirate (n = 10), blood smear (n = 8), synovial fluid (n = 4), bronchoalveolar lavage fluid (n = 3), cutaneous impression smear (n = 3), rectal scrape (n = 1) and peritoneal effusion (n = 1). Histopathological diagnoses were made on biopsy of GI tract (n = 5), lymph node (n = 2) and one each of liver, spleen, pancreas, bone and eye. Disseminated disease was the most common (76/101 [75.2%]) followed by respiratory (18/101 [17.8%]) and GI (7/101 [6.9%]). Forty-nine of the cats with disseminated disease had pulmonary involvement (49/76 [64%]). Form of disease was not significantly associated with survival at any outcome time point (Tables 1–3).

Treatment

Itraconazole was the most common antifungal administered (58/101 [57.4%]) followed by fluconazole (43/101 [42.6%]). Two cats received compounded itraconazole and the exact formulation was unknown for two additional cats that received itraconazole. The remainder received a Food and Drug Administration-approved

Table 3 Candidate prognostic indicators for survival to 6 months after diagnosis in 94 cats with histoplasmosis treated with antifungal therapy

Candidate indicator	Survivors (n = 63)	Non-survivors (n = 31)	*P* value
Clinical findings			
Age (years)	7.0 (6.0)	6.0 (6.0)	0.71
Weight (kg)	3.6 (1.6)	3.3 (1.3)	0.82
Duration of clinical signs (weeks)	7.0 (17.0)	4.0 (10.0)	0.41
Weight loss (% with sign)	81	97	**0.05**
Diarrhea (% with sign)	8	19	0.17
Dyspnea (% with sign)	52	71	0.12
Lameness (% with sign)	19	3	**0.05**
Adventitial lung sounds (% with finding)	35	48	0.26
Lymphadenopathy (% with finding)	35	26	0.48
Abdominal organomegaly (% with finding)	22	32	0.32
Cutaneous lesions (% with finding)	16	10	0.53
Joint effusion (% with finding)	9	0	0.17
Body temperature (°F)	102.3 (2.0)	101.8 (1.4)	**0.04**
Respiratory rate (breaths/min)	44 (28)	46 (36)	0.52
Form (% with form)*	71/19/10	77/19/3	0.55
Neurologic disease (% with finding)	0	10	**0.03**
Fungemia (% with finding)	3	19	**0.01**
Thrombocytopenia (% with finding)	43	52	0.58
Multiple cytopenias (% with finding)†	15	39	**0.02**
Treatment			
Initial antifungal treatment (% fluconazole)	49	27	0.09
Fluconazole start dose (mg/kg/day)	14.3 (11.1)	18.9 (9.3)	0.29
Itraconazole start dose (mg/kg/day)	10.0 (0.9)	9.7 (4.8)	**0.04**
Glucocorticoid treatment (% did receive)	44	63	0.12
Glucocorticoid dose (mg/kg/day)‡	0.82 (0.57)	0.59 (0.47)	0.31
Oxygen supplementation (% did require)	19	55	**<0.001**
Hospitalization (% did require)	49	81	**0.003**
Hospitalization duration (days)	0 (3.0)	3.0 (5.0)	**0.01**

Values in bold are $P \leqslant 0.05$. Data are median (interquartile range [75th percentile–25th percentile]) or n (%), unless otherwise indicated
*Disseminated/respiratory/gastrointestinal
†Defined as at least two of the following: anemia, neutropenia, thrombocytopenia
‡Prednisolone dose or prednisolone equivalent (dexamethasone dose • 7)

antifungal drug. Liposomal encapsulated amphotericin B was initially administered with fluconazole or itraconazole (2/101 [2.0%]) in one cat each. The initial dose (IQR) of itraconazole was 10.0 mg/kg/day (9.2–10.3) and the ending dose was 10.3 mg/kg/day (9.7–11.2). The median (IQR) duration of itraconazole therapy was 137 days (6–150). The initial (IQR) dose of fluconazole was 16.2 mg/kg/day (11.0–21.5) and the ending dose was 17.3 mg/kg/day (13.3–22.2). The median (IQR) duration of fluconazole therapy was 171 days (30–193). Cats initially treated with amphotericin B received one and three doses, respectively. The antifungal drug was changed in the first 30 days of treatment in 12/89 cats (13%) and in the first 6 months in 15/78 cats (19%). This included a change from fluconazole to itraconazole in eight cats and itraconazole to fluconazole in seven cats. Liposomal encapsulated amphotericin B was administered to two cats at the time of transition from fluconazole to itraconazole. Initial antifungal drug choice was not significantly associated with survival at any outcome time point (Tables 1–3).

Glucocorticoids were administered to 44/101 (43.6%) cats at a median prednisolone or prednisolone equivalent dose of 0.7 mg/kg/day (IQR 0.5–1.0) for a median (IQR) duration of 14 days (6.8–26.5). Glucocorticoid administration was significantly more common in cats that did not survive to hospital discharge and at 1 month after diagnosis. Oxygen was supplemented to 29/101 (28.7%) cats. Hospitalization was provided to 60/101 (59.4%) cats for a median (IQR) duration of 1 day (0–4). The need for hospitalization or oxygen supplementation was significantly more common in cats that did not survive. In addition hospital duration was significantly longer in cats that did not survive (Tables 1–3).

Table 4 Biochemistry analysis and complete blood count data in relation to survival to hospital discharge in 101 cats with histoplasmosis treated with antifungal therapy

Variable	Survival status	Median (IQR)	<Lower reference limit	⩽Half lower reference limit	>Upper reference limit	⩾Twice upper reference limit
WBC count (10^3/µl)	Yes	9.9 (8.8)	12/89 (13%)	3/89 (3%)	15/89 (17%)	2/89 (2%)
	No	5.9 (8.2)	3/12 (25%)	0/12 (0%)	1/12 (8%)	0/12 (0%)
			P = 0.383	*P* = 1.0	*P* = 0.687	*P* = 1.0
Segmented neutrophil count (10^3/µl)	Yes	6.1 (7.2)	9/89 (10%)	3/89 (3%)	23/89 (26%)	2/89 (2%)
	No	4.6 (6.3)	4/12 (33%)	1/12 (8%)	2/12 (17%)	0/12 (0%)
			***P* = 0.048**	*P* = 0.405	*P* = 0.725	*P* = 1.0
Band neutrophil count (/µl)	Yes	0 (180)	NA	NA	16/89 (18%)	4/89 (4%)
	No	170 (280)	NA	NA	3/12 (25%)	2/12 (17%)
					P = 0.693	*P* = 0.148
Lymphocyte count (10^3/µl)	Yes	2.5 (2.5)	15/89 (17%)	3/89 (3%)	2/89 (2%)	0/89 (0%)
	No	0.9 (1.2)	7/12 (58%)	3/12 (25%)	1/12 (4%)	0/12 (0%)
			***P* = 0.004**	***P* = 0.022**	*P* = 0.322	*P* = 1.0
Eosinophil count (/µl)	Yes	110 (320)	NA	NA	3/88 (3%)	1/88 (1%)
	No	70 (150)	NA	NA	0/12 (0%)	0/12 (0%)
					P = 1.0	*P* = 1.0
Hematocrit (%)	Yes	28 (14)	46/89 (52%)	4/89 (4%)	1/89 (1%)	NA
	No	23 (18)	8/12 (67%)	2/12 (17%)	0/12 (0%)	NA
			P = 0.373	*P* = 0.149	*P* = 1.0	
Albumin (g/dl)	Yes	2.7 (0.7)	34/87 (39%)	0/87 (0%)	NA	NA
	No	2.8 (0.8)	3/12 (25%)	1/12 (8%)		
			P = 0.526	*P* = 0.121		
Globulin (g/dl)	Yes	4.3 (1.2)	NA	NA	14/84 (17%)	NA
	No	4.4 (0.9)			1/12 (8%)	
					P = 0.684	
ALT (IU/l)	Yes	37 (32)	3/87 (3%)	NA	4/87 (5%)	2/87 (2%)
	No	50 (62)	1/12 (8%)		2/12 (17%)	0/12 (0%)
			P = 0.408		*P* = 0.153	*P* = 1.0
ALP (IU/l)	Yes	26 (24)	5/86 (6%)	NA	NA	NA
	No	30 (20)	1/12 (8%)			
			P = 0.553			
Creatinine (mg/dl)	Yes	1.0 (0.4)	12/88 (14%)	0/88 (0%)	4/84 (5%)	NA
	No	0.9 (0.6)	3/12 (25%)	1/12 (8%)	0/12 (0%)	
			P = 0.382	*P* = 0.120	*P* = 1.0	
BUN (mg/dl)	Yes	19 (8)	13/87 (15%)	NA	5/87 (6%)	2/87 (2%)
	No	22 (17)	3/12 (25%)		3/12 (25%)	1/12 (8%)
			P = 0.405		*P* = 0.054	*P* = 0.324
Cholesterol (mg/dl)	Yes	128 (64)	5/75 (7%)	NA	0/75 (0%)	NA
	No	158 (106)	0/12 (0%)		2/12 (17%)	
			P = 1.0		*P* = 0.018	
Creatinine kinase (IU/l)	Yes	185 (202)	3/71 (4%)	NA	3/71 (4%)	0/75 (0%)
	No	375 (926)	0/11 (0%)		4/11 (36%)	2/11 (18%)
			P = 1.0		***P* = 0.005**	***P* = 0.017**
Bilirubin (mg/dl)	Yes	0.2 (0.3)	NA	NA	17/84 (20%)	10/84 (12%)
	No	0.7 (1.5)			8/12 (67%)	4/12 (33%)
					***P* = 0.002**	*P* = 0.071
Total calcium (mg/dl)	Yes	9.2 (1.0%)	7/83 (8%)	NA	1/83 (1%)	NA
	No	9.3 (0.4%)	0/12 (0%)		0/12 (0%)	
			P = 0.590		*P* = 1.0	

Values in bold are $P \leqslant 0.05$
IQR = interquartile range; WBC = white blood cell; NA = not available; ALT = alanine transaminase; ALP = alkaline phosphatase; BUN = blood urea nitrogen

Table 5 Biochemistry analysis and CBC data in relation to survival to 1 month after diagnosis in 96 cats with histoplasmosis treated with antifungal therapy

Variable	Survival status	Median (IQR)	<Lower reference limit	≤Half lower reference limit	>Upper reference limit	≥Twice upper reference limit
WBC count (10^3/µl)	Yes	10.1 (8.3)	9/73 (12%)	1/73 (1%)	11/73 (15%)	1/73 (1%)
	No	5.3 (6.9)	6/22 (27%)	2/22 (9%)	2/22 (9%)	1/22 (5%)
			P = 0.105	*P* = 0.133	*P* = 0.726	*P* = 0.411
Segmented neutrophil count (10^3/µl)	Yes	6.7 (6.3)	5/73 (7%)	2/73 (3%)	19/73 (26%)	1/73 (1%)
	No	3.5 (4.9)	8/22 (36%)	2/20 (10%)	4/22 (18%)	1/21 (5%)
			***P* = 0.001**	*P* = 0.228	*P* = 0.576	*P* = 0.411
Band neutrophil count (/µl)	Yes	0 (160)	NA	NA	12/74 (16%)	3/74 (4%)
	No	120 (200)			5/22 (23%)	2/22 (9%)
					P = 0.529	*P* = 0.322
Lymphocyte count (10^3/µl)	Yes	2.7 (2.4)	12/74 (16%)	3/74 (4%)	1/74 (1%)	NA
	No	1.2 (1.2)	10/21 (48%)	3/21 (14%)	1/21 (5%)	
			***P* = 0.006**	*P* = 0.120	*P* = 0.395	
Eosinophil count (/µl)	Yes	130 (320)	NA	NA	3/72 (4%)	1/72 (1%)
	No	50 (180)			0/22 (0%)	0/22 (0%)
					P = 1.0	*P* = 1.0
Hematocrit (%)	Yes	28 (13)	37/74 (50%)	2/74 (3%)	1/74 (1%)	NA
	No	20 (18)	15/22 (68%)	4/22 (18%)	0/22 (0%)	
			P = 0.151	***P* = 0.024**	*P* = 1.0	
Albumin (g/dl)	Yes	2.8 (0.6)	27/72 (37%)	0/72 (0%)	NA	NA
	No	2.6 (0.8)	7/22 (32%)	1/22 (5%)		
			P = 0.801	*P* = 0.234		
Globulin (g/dl)	Yes	4.3 (1.0)	NA	NA	11/69 (16%)	NA
	No	4.1 (1.0)			2/22 (9%)	
					P = 0.727	
ALT (IU/l)	Yes	38 (31)	2/72 (28%)	NA	3/72 (4%)	1/72 (1%)
	No	–	1/22 (5%)		3/22 (14%)	1/22 (5%)
			P = 0.555		*P* = 0.138	*P* = 0.415
ALP (IU/l)	Yes	26 (25)	4/71 (6%)	NA	3/71 (4%)	NA
	No	29 (19)	1/22 (5%)		0/22 (0%)	
			P = 1.0		*P* = 1.0	
Creatinine (mg/dl)	Yes	1.0 (0.4)	10/73 (14%)	0/73 (0%)	3/73 (4%)	NA
	No	1.0 (0.5)	5/22 (23%)	1/22 (5%)	1/22 (5%)	
			P = 0.327	*P* = 1.0	*P* = 1.0	
BUN (mg/dl)	Yes	19 (9)	12/72 (17%)	NA	4/72 (6%)	1/72 (1%)
	No	22 (9)	3/22 (14%)		4/22 (18%)	2/22 (9%)
			P = 1.0		*P* = 0.083	0.136
Cholesterol (mg/dl)	Yes	123 (62)	5/60 (8%)	NA	0/60 (0%)	NA
	No	139 (95)	0/22 (0%)		2/22 (9%)	
			P = 0.317		*P* = 0.070	
Creatinine kinase (IU/l)	Yes	181 (161)	3/58 (5%)	NA	2/58 (3%)	0/58 (0%)
	No	243 (472)	0/19 (0%)		5/19 (30%)	2/19 (11%)
			P = 0.571		***P* = 0.009**	*P* = 0.059
Bilirubin (mg/dl)	Yes	0.2 (0.2)	NA	NA	12/69 (17%)	8/69 (12%)
	No	0.5 (0.5)			11/22 (50%)	5/22 (23%)
					***P* = 0.004**	*P* = 0.291
Total calcium (mg/dl)	Yes	9.3 (0.9)	4/68 (6%)	NA	1/68 (1%)	NA
	No	9.1 (0.8)	2/22 (9%)		0/22 (0%)	
			P = 0.632		*P* = 1.0	

Values in bold are $P \leq 0.05$
IQR = interquartile range; WBC = white blood cell; NA = not available; ALT = alanine transaminase; ALP = alkaline phosphatase; BUN = blood urea nitrogen

Table 6 Biochemistry analysis and complete blood count data in relation to survival to 6 months after diagnosis in 94 cats with histoplasmosis treated with antifungal therapy

Variable	Survival status	Median (IQR)	<Lower reference limit	≤Half lower reference limit	>Upper reference limit	≥Twice upper reference limit
WBC count (10^3/µl)	Yes	10.1 (7.5)	7/62 (11%)	1/62 (2%)	9/62 (15%)	1/62 (2%)
	No	6.3 (10.7)	3/31 (10%)	2/32 (6%)	3/31 (10%)	1/31 (3%)
			P = 0.132	*P* = 0.257	*P* = 0.745	*P* = 1.0
Segmented neutrophil count (10^3/µl)	Yes	6.7 (6.5)	5/62 (8%)	2/62 (3%)	15/62 (24%)	0/62 (0%)
	No	4.7 (5.6)	8/31 (26%)	2/31 (6%)	7/31 (23%)	2/31 (6%)
			***P* = 0.028**	*P* = 0.598	*P* = 1.0	*P* = 0.109
Band neutrophil count (/µl)	Yes	0 (160)	NA	NA	10/63 (16%)	3/63 (5%)
	No	80 (200)			7/31 (23%)	2/31 (6%)
					P = 0.570	*P* = 1.0
Lymphocyte count (10^3/µl)	Yes	2.8 (2.4)	9/63 (14%)	2/63 (3%)	0/63 (0%)	NA
	No	1.5 (1.5)	13/30 (43%)	4/30 (13%)	2/30 (7%)	
			***P* = 0.004**	*P* = 0.083	*P* = 0.102	
Eosinophil count (/µl)	Yes	140 (340)	NA	NA	3/61 (5%)	1/61 (2%)
	No	0 (200)			0/31 (0%)	0/31 (0%)
					P = 0.548	*P* = 1.0
Hematocrit (%)	Yes	28 (13)	31/63 (49%)	2/63 (3%)	1/63 (2%)	NA
	No	23 (18)	19/31 (61%)	4/31 (13%)	0/22 (0%)	
			P = 0.283	*P* = 0.090	*P* = 1.0	
Albumin (g/dl)	Yes	2.9 (0.6)	20/61 (33%)	0/61 (0%)	NA	NA
	No	2.6 (0.8)	12/31 (39%)	1/31 (3%)		
			P = 0.646	*P* = 0.337		
Globulin (g/dl)	Yes	4.3 (1.1)	NA	NA	9/59 (15%)	NA
	No	4.2 (1.0)			3/31 (10%)	
					P = 0.534	
ALT (IU/l)	Yes	39 (32)	1/62 (2%)	NA	3/62 (5%)	1/62 (1%)
	No	37 (36)	2/31 (6%)		3/31 (10%)	1/31 (3%)
			P = 0.257		*P* = 0.396	*P* = 1.0
ALP (IU/l)	Yes	26 (24)	4/61 (7%)	NA	2/61 (3%)	NA
	No	27 (20)	1/31 (3%)		1/31 (3%)	
			P = 0.660		*P* = 1.0	
Creatinine (mg/dl)	Yes	1.0 (0.5)	8/62 (13%)	0/62 (0%)	2/62 (3%)	NA
	No	0.9 (0.5)	7/31 (23%)	1/31 (3%)	1/31 (3%)	
			P = 0.246	*P* = 0.333	*P* = 1.0	
BUN (mg/dl)	Yes	19 (8)	11/61 (18%)	NA	3/61 (5%)	0/61 (0%)
	No	21 (11)	3/31 (10%)		4/31 (13%)	2/31 (6%)
			P = 0.369		*P* = 0.220	*P* = 0.111
Cholesterol (mg/dl)	Yes	122 (61)	5/50 (10%)	NA	0/50 (0%)	NA
	No	135 (89)	0/31 (0%)		2/31 (6%)	
			P = 0.151		*P* = 0.143	
Creatinine kinase (IU/l)	Yes	183 (159)	3/39 (8%)	NA	2/49 (4%)	0/49 (0%)
	No	243 (454)	0/27 (0%)		5/27 (19%)	2/27 (7%)
			P = 0.548		*P* = 0.090	*P* = 0.123
Bilirubin (mg/dl)	Yes	0.2 (0.2)	NA	NA	7/58 (12%)	5/58 (9%)
	No	0.4 (0.7)			15/31 (48%)	8/31 (26%)
					***P* <0.001**	*P* = 0.055
Total calcium (mg/dl)	Yes	9.3 (1.0)	2/58 (3%)	NA	1/58 (2%)	NA
	No	9.2 (0.9)	4/31 (13%)		0/31 (0%)	
			P = 0.177		*P* = 1.0	

Values in bold are $P \leq 0.05$
IQR = interquartile range; WBC = white blood cell; NA = not available; ALT = alanine transaminase; ALP = alkaline phosphatase; BUN = blood urea nitrogen

Discussion

This study identified multiple potential prognostic indicators in cats with histoplasmosis. In general, these were associated with more severe respiratory, liver, hematologic or neurologic disease. Prognosticators investigated in the current study were obtained at the initial hospital visit and easily obtainable. Both attributes are expected to simplify the use of these variables in future clinical studies.

Findings associated with more severe respiratory disease, such as dyspnea or adventitial lung sounds, were significantly more common in cats that did not survive to hospital discharge and 1 month after diagnosis. These findings are similar to studies in humans with AIDS and histoplasmosis, where respiratory insufficiency or dyspnea is a significant risk factor for death.[9,10] In those studies, respiratory insufficiency was defined as requiring mechanical ventilation and dyspnea was defined as a respiratory rate >20 breaths/min with respiratory distress. Cats that did not survive were also more likely to receive oxygen supplementation, which was due to more severe respiratory disease. In addition, cats that did not survive to 1 month or 6 months were more likely to require hospitalization and the duration of hospitalization was significantly longer. There are many reasons for hospitalization, but one common reason is the need for oxygen supplementation. Irrespective of the specific reason, the need for hospitalization and the duration of hospitalization are expected to be related to the severity of disease. Many cats with disseminated disease had pulmonary involvement. This likely contributed to the lack of a significant association with the form of disease and risk of death.

Signs of neurologic disease were uncommon but were significantly more common in cats that did not survive to 1 month and 6 months after diagnosis. In fact, no cat with signs of neurologic disease survived to 1 month after diagnosis. Similar findings have been reported in humans with histoplasmosis where neurologic manifestations were significantly associated with death before hospital discharge.[10] Further investigation in the treatment of cats with neurologic manifestations of histoplasmosis are warranted.

Finding *H capsulatum* organisms on blood smear (fungemia) was significantly more common in cats that did not survive to all time points. In humans, fungemia has been found to be a negative prognostic indicator for survival to 3 months after diagnosis of histoplasmosis.[16] In humans fungemia is thought to represent more extensive disease.[11] It is likely that fungemia also indicates more extensive disease in cats.

Cats that did not survive to 1 month were more likely to have severe anemia. In humans with histoplasmosis, hemoglobin concentrations <9.5 g/dl and <8.0 g/dl were associated with more severe disease and a risk factor of death before hospital discharge, respectively.[8,10] Anemia in cats with histoplasmosis could be due to hemophagocytosis, hemolysis, GI blood loss, bone marrow involvement or anemia of chronic disease. The fact that neutropenia and the presence of multiple cytopenias were also found to be more common in cats that did not survive suggests that bone marrow involvement is an important prognostic indicator. Bone marrow was not sampled in many cats; thus, the prevalence of bone marrow involvement could not be definitively proven in most cats.

Lymphopenia was significantly more common in cats that did not survive to all outcome time points. CD4+ lymphocyte counts and total white blood cell counts have been included in several studies of prognostic indicators in humans with HIV/AIDS and histoplasmosis.[9,10,16] Results have been mixed. In a case series describing two urban outbreaks of histoplasmosis in humans, lymphopenia was found in over one-third of immunosuppressed individuals. The lymphopenia remained until death or recovered with clinical improvement. That study failed to determine the cause of lymphopenia, but findings suggested that the lymphopenia was a result of the histoplasmosis. It is possible that the lymphopenia, more common in cats that did not survive in the current study, is a result of more severe stress or a direct result of infection.

Serum bilirubin concentration above the upper reference limit was significantly more common in cats that did not survive at all time points. Hyperbilirubinemia (serum bilirubin concentrations >1.5 mg/dl) in humans with histoplasmosis was found to be an indicator of severe disease.[8] In that study severe disease was defined as death due to histoplasmosis, the need for mechanical ventilation, or shock that required treatment with vasopressors. Approximately 50% of cats with serum bilirubin concentrations more than twice the upper reference limit survived to 6 months after diagnosis, suggesting that even these cats can respond to treatment. Proposed causes of higher bilirubin concentrations in cats with histoplasmosis include liver dysfunction due to *H capsulatum* infiltration or hepatic lipidosis, or hemolysis. *H capsulatum* organisms were found by liver cytology in 17 cats and thus liver infiltration and granulomatous hepatitis is likely a contributing factor in many cats, but the absence of hyperbilirubinemia does not rule out liver involvement.

Cats that did not survive to hospital discharge or 1 month after diagnosis more commonly had CK activity above the upper reference limit. This variable has not been included in any published human study of prognostic indicators of histoplasmosis. Lactate dehydrogenase (LDH) has been found to be a negative prognostic indicator in humans.[9] In fact, significantly elevated LDH activity might be a clue to disseminated histoplasmosis

in humans with HIV.[17] Similar to CK activity in cats, LDH activity in humans can be due to muscle damage and can be the result of sepsis, tissue hypoxia, infarction or granulomatous disease.[17] The cause of significantly higher CK activity in cats that did not survive is unknown but might include skeletal muscle hypoxia due to respiratory disease or anemia. Moderate or severe elevations were uncommon, with only two cats having activity more than twice the upper reference limit. The fact that CK was more commonly above the upper reference limit in cats that did not survive at multiple outcome time points, suggests it should be included in future studies of prognostic indicators in cats with histoplasmosis.

This study failed to detect a significant difference in the initial antifungal drug administered between cats that survived and those that did not. This suggests that the ideal antifungal treatment option should be further investigated. Glucocorticoids were commonly administered concurrently with antifungal therapy. The fact that glucocorticoid treatment was significantly more common in cats that did not survive to hospital discharge and at 1 month has two possible explanations. It is possible that glucocorticoids negatively affected treatment outcome. It is also possible that glucocorticoids were more likely to be administered to cats with more severe disease. The latter is considered more likely as corticosteroids are commonly administered to cats with more severe respiratory disease at both participating institutions. Prospective investigation of corticosteroid administration to cats with histoplasmosis is indicated.

This study has several important limitations, most of which are common to retrospective studies, such as lack of standard recording of history and physical examination, standard therapy and follow-up data for every cat. The inclusion criteria were conservative. It is likely that some cats excluded as a result of not finding *H capsulatum* organisms actually had histoplasmosis. Not finding organisms might have been more common in cats with less extensive or less severe disease, in which case this study population would be biased towards more severe disease. With the availability of reliable, non-invasive testing, such as the urine *Histoplasma* antigen enzyme immunoassay (MiraVista Diagnostics), inclusion of cats with appropriate clinical findings and positive antigen testing should be considered in future studies. Owing to the fact that much of the study period preceded the common use of the *Histoplasma* antigen test, this was not considered an inclusion criterion in the current study.

A second limitation includes the fact that multiple laboratories were used for CBC and biochemistry analysis. The RIs from laboratories at the participating hospitals are similar, but even those have changed slightly over the time period for which cases were included. Blood smears were not examined in every cat and thus the prevalence of thrombocytopenia was likely underestimated. This might be a contributing factor to the lack of significant association between thrombocytopenia and death in cats. Thrombocytopenia has been found to be a negative prognostic indicator in humans.[9] The lack of blood smear examination in all cats also likely led to an underestimation of the prevalence of fungemia. Based on the fact that fungemia was significantly associated with death at all time points, blood smear examination should be considered in all cats with histoplasmosis.

A third limitation includes the lack of standard treatment. Cats were excluded if antifungal treatment was not attempted, and in most cases it was not possible to determine the underlying reason precluding treatment. It is likely that some of these cats were not treated owing to more severe disease or financial constraints. If so, data from those cats could have provided valuable information. Future prospective studies should include standardized treatment protocols, ideally with financial incentives to minimize pet owner financial constraints as a confounder.

A final limitation includes the lack of outcome data in a small number of cats. The absence of these data could have altered the ultimate statistical conclusions. Prognostic indicators included in this study were those obtained at the time of diagnosis. This was determined to be the most important time point, as a useful prognostic indicator should allow for early therapeutic intervention in order to improve outcome. It is possible that clinical data obtained at a later time point (1 month recheck) could provide important prognostic information useful to clinical management and ultimately outcome.

Conclusions

Prospective research aimed at identifying prognosticators in cats with histoplasmosis is indicated. This information is expected to help guide treatment and ultimately improve treatment outcome. Future research should be directed towards clinical indicators of more severe respiratory, hepatic, hematologic and neurologic disease.

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