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Serum 25-hydroxyvitamin D concentrations and mortality in dogs with blastomycosis

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ABSTRACT

Blastomycosis is a prominent fungal disease in the United States. Vitamin D status has been found to be altered in critical illness and various infectious diseases. The objectives of this study were to compare serum 25-hydroxyvitamin D (25[OH]D) concentrations in dogs with blastomycosis and healthy controls, to assess the change in serum 25(OH)D concentrations in dogs with blastomycosis after 30 days of treatment, and to determine if baseline serum 25(OH)D concentrations in dogs with blastomycosis were associated with in-hospital, 30-day, or end-of-study mortality.

In this prospective cohort study, 19 dogs newly diagnosed with blastomycosis had serum 25(OH)D concentrations measured with a commercially available validated radioimmunoassay at the time of diagnosis and 30 days after start of treatment. These values were compared to 24 healthy control dogs. Serum 25(OH)D concentrations at the time of diagnosis were lower in dogs with blastomycosis (median, 203 nmol/L; range, 31−590 nmol/L) than in clinically healthy control dogs (259.5 nmol/L, 97−829 nmol/L; $P = 0.01$). Despite clinical improvement, there was no significant change in serum 25(OH)D concentrations from baseline to 30-day follow-up. Dogs with baseline serum 25(OH)D concentrations <180.5 nmol/L had a greater odds of death during hospitalization (odds ratio [OR], 15.0; 95% confidence interval [CI], 1.4–191.3; $P = 0.04$) and at 30 days follow-up (OR, 30.0; 95% CI, 2.5–366.7; $P = 0.006$). These findings highlight the need for further studies evaluating the prognostic value of vitamin D status in dogs with blastomycosis at diagnosis and throughout treatment and remission.

Introduction

Blastomyces dermatitidis is a thermally dimorphic fungus that can infect otherwise healthy dogs in the United States, particularly along the Mississippi and Ohio River Valleys, the Southeast, and around the Great Lakes (Arceneaux et al., 1998; Bromel and Sykes, 2005; Anderson et al., 2014). Blastomycosis incidence in dogs is 1–2% annually in highly endemic areas and risk factors for infection include close proximity to a body of water, exposure to sites of soil disturbance or excavation, young age, male sex, and being a sporting dog or hound breeds (Rudmann et al., 1992; Arceneaux et al., 1998; Chen et al., 2008; Anderson et al., 2014; Shelnutt et al., 2020). Epidemiological studies in humans have identified similar risk factors including proximity to waterways, soil type (i.e., those with increased mercury or decreased copper), increasing patient age, and lower mean annual maximum environmental temperatures (Seitz et al., 2015; Reed et al., 2008).

Vitamin D has been shown in many species to enhance antimicrobial peptide production, leukocyte reactive nitrogen/oxygen species, phagocytic capacity, and modulate exaggerated proinflammatory responses (Chandra et al., 2004; Garcia-Barragan et al., 2018; Jaffey et al., 2018b; Martineau et al., 2007; Motlagh et al., 2015; Rockett et al., 1998; Rodriguez-Lecompte et al., 2016; Tiosano et al., 2013). These immunomodulatory functions highlight the importance of vitamin D to mucosal immunity. Many human studies have documented associations between disease outcome and vitamin D status in varying disease states, although often the exact role of vitamin D in these diseases has not been established. Serum 25-hydroxyvitamin D (25[OH]D) concentrations and genetic polymorphisms in vitamin D handling proteins have been associated with susceptibility to numerous types of respiratory infection in humans, including community-acquired pneumonia, *Mycobacterium tuberculosis*, and blastomycosis (Quraishi et al., 2014; Lee and Song, 2015; Sainsbury et al., 2015). In addition, low serum 25(OH)D

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concentrations have been associated with increased mortality in human patients with community-acquired pneumonia (Kim et al., 2015).

In dogs with blastomycosis, mortality rates can be as high as 40% (Rudmann et al., 1992; Arceneaux et al., 1998; Mazepa et al., 2011; Anderson et al., 2014). Factors associated with poor outcomes in dogs include severe lung involvement, high band neutrophil count, increased lactate concentrations, and number and location of disseminated sites (Legendre et al., 1984, 1996; Crews et al., 2008a,b; O'Brien et al., 2018). A recent study found that dogs with blastomycosis had lower serum 25 (OH)D concentrations than healthy control dogs but did not find an association between serum 25(OH)D concentration and long-term survival (O'Brien et al., 2018). However, it is not known whether baseline serum 25(OH)D concentrations are associated with shorter term mortality in dogs with blastomycosis, or whether serum 25(OH)D concentrations increase with clinical improvement following treatment. These short-term time points are clinically relevant as many dogs that die from blastomycosis do so within the first month of diagnosis (Legendre et al., 1996; Walton et al., 2017).

In order to better understand the potential role of vitamin D in dogs with blastomycosis, our study had three objectives: 1) to compare serum 25(OH)D concentrations in dogs with blastomycosis at the time of diagnosis to concentrations in clinically healthy control dogs, 2) to assess the change in serum 25(OH)D concentrations in dogs with blastomycosis 30-days post-diagnosis, and 3) to determine if baseline serum 25(OH)D concentrations in dogs with blastomycosis were associated with in-hospital, 30-day, or end-of-study mortality.

We hypothesized that serum 25(OH)D concentrations would be lower in dogs with blastomycosis but would increase with clinical improvement following treatment. In addition, we hypothesized that serum 25(OH)D concentrations would be associated with in-hospital, 30-day, and end-of-study mortality.

Material and methods

Animal population

Client-owned dogs presented to the University of Wisconsin Veterinary Care (UWVC), a single veterinarian in Ohio, or two regional specialty hospitals and diagnosed with blastomycosis between April 2018 and February 2020 were eligible for inclusion. Informed written consent was obtained from all clients. This study was approved by the UWVC Animal Care and Use Committee (Protocol #V005682-A02; Initial approval date 16th of November 2016, renewed annually). Exclusion criteria included pregnancy, lactation, presence of total hypercalcemia, or a diagnosis of hypercalcemia of malignancy, hyperparathyroidism, hypoparathyroidism, or chronic kidney disease. Dogs were also excluded if this episode of blastomycosis was a known recurrence or relapse, or if antifungal therapy had been initiated before sample acquisition. A number of clinically healthy dogs was enrolled as a control population. Control dogs had normal physical examinations, no clinical history of chronic illness, and no prescribed medications within 30 days of enrollment other than monthly parasiticides.

The diagnosis of blastomycosis was based on clinical signs plus one or more of the following: a positive serum or urine *Blastomyces* antigen test (MVista Blastomyces Quantitative EIA) (Crews et al., 2008a); a positive culture of *Blastomyces dermatitidis*; intralesional cytologic or histopathologic identification of fungal yeast organisms consistent with *Blastomyces* spp. As Wisconsin is not an endemic region for histoplasmosis, *Blastomyces* antigen positivity is presumed due to blastomycosis and not cross-reaction with *Histoplasma* spp. although travel to histoplasmosis-endemic regions was not screened for in this study.

Data and sample collection

Medical records were reviewed for each dog enrolled. The age, sex and neuter status, weight, breed, and diet were recorded for each dog. Additional clinical information collected, where available, included temperature, heart rate, respiratory rate, clinical signs, documented sites of infection, and radiographic and ultrasonographic imaging findings at the time of initial evaluation, antifungal treatment (type and dosage), concurrent treatment, non-steroidal anti-inflammatory or glucocorticoid administration, oxygen supplementation, and survival to discharge from the hospital discharge and at 30-days post-diagnosis, and cause of death.

Whole blood was collected from control dogs and dogs diagnosed with blastomycosis (prior to antifungal treatment and again 30-days post-diagnosis). Samples were centrifuged to harvest serum within 1 h of collection. Sera were stored at −80 °C for a maximum of 9 months for batch analyses on two separate occasions. 25(OH)D concentrations remain stable in sera stored at −80 °C for many years in humans (Agborsangaya et al., 2010), and is believed to be consistent across species. Samples shipped frozen to Michigan State University Veterinary Diagnostic Laboratory for serum 25(OH)D quantification using a commercially available validated radioimmunoassay. Using this assay, the reference interval for serum 25(OH)D in normal dogs established by this laboratory was 109−423 nmol/L.

Statistical analyses

All statistical analyses were performed using commercially available software (Prism 8).

Data for all continuous variables are reported as median and range. For baseline demographics between case and controls, age was compared using a Mann–Whitney *U* test and neuter status was compared with a Chi-square test. Baseline serum 25(OH)D concentrations were compared between cases and controls using a Mann–Whitney *U* test.

Baseline and 30-day post-diagnosis serum 25(OH)D concentrations were compared using a Wilcoxon matched-pairs signed rank test; dogs that did not survive to 30 days were removed from these analyses. Data from a previously published manuscript (O'Brien et al., 2018), was used to calculate the necessary sample size. In that manuscript, the median serum 25(OH)D for control dogs was 132 nmol/L (range, 81−209 nmol/L) with an estimated standard deviation (range/4) of 32. The median serum 25(OH)D for blastomycosis dogs was 79 nmol/L (range, 33−125 nmol/L) with an estimated standard deviation (range/4) of 23. An a priori sample size calculation for a power of 0.80 and alpha 0.05 indicated that 11 dogs would be needed to detect a 50% increase in serum 25(OH)D concentration (from 79 nmol/L to 118.5 nmol/L) at 30 days post-diagnosis, based on data reported in O'Brien et al. (2018).

Baseline serum 25(OH)D concentrations were compared between survivor and non-survivor cases at hospital discharge, at 30-days post-diagnosis, and at study's end, using Mann–Whitney *U* tests. A receiver operating characteristics (ROC) curve was used to establish an optimal cut-off for serum 25(OH)D concentrations and association with survival to discharge. Survival was compared between dogs with baseline serum 25(OH)D concentrations above or below this threshold using a Fisher's exact test and Baptista-Pike exact confidence interval for the odds ratio (OR). Long-term survival time was counted from the day of blastomycosis diagnosis to either the day of death or cessation of study (15th March 2020). Dogs alive at the end of the study were right-censored as nonevents. Date of death was determined from a combination of medical records and phone communication with owners or referring veterinarian. The level of significance was set at $P < 0.05$.

Results

Animal populations

Nineteen dogs with blastomycosis were enrolled, and no screened dogs were excluded. Twenty-four healthy control dogs were included. Demographic data for cases and controls can be found in Table 1. Details regarding offered food can be found in Supplemental Material. The

Table 1
Demographic data for 19 dogs with blastomycosis and 24 healthy control dogs. Data are expressed as medians and range (minimum-maximum).

	Blastomycosis group	Healthy control group	P
Age (years)	6.0 (0.6–10.0)	5.0 (1.0–9.0)	0.55
Weight (kg)	30.1 (4.5–45.6)	24.0 (2.0–44.0)	0.27
Body condition score	5/9 (3–7/9)	5/9 (4–7/9)	–
Sex/Neuter Status (n)	11 MN, 1 MI, 6 FS, 1 FI	15 MN, 1 MI, 7 FS, 1 FI	0.99
Breeds (n)	Mixed breed (3), Golden retriever (3), Weimaraner (2), Karakachen (1), Cocker spaniel (1), Scottish deerhound (1), Goldendoodle (1), Red heeler (1), papillon (1), Doberman pinscher (1), Labrador retriever (1), Alaskan malamute (1), Miniature dachshund (1), Siberian husky (1)	Mixed breed (6), Greyhound (4), Australian shepherd (2), Cocker spaniel (1), German shepherd dog (1), German shorthair pointer (1), Labrador retriever (1), Siberian husky (1), Pit bull terrier (1), Golden retriever (1), Papillon (1), Catahoula leopard hound (1), Curly-coated retriever (1), English setter (1), Beagle (1)	–

MN, male neutered; MI, male intact; FS, female spayed; FI, female intact; –, Not calculated.

median heart rate, temperature, and respiratory rate at the time of diagnosis was 114 beats/min (range, 72–230 beats/min), 39.3 °C (38.5–39.3 °C), and 42 breaths/min (12–108 breaths/min), respectively. The heart rate, temperature, and respiratory rate were not available for one dog and five dogs were recorded to be panting and thus an ordinal value was not available.

A diagnosis of blastomycosis was most commonly achieved by cytology, either alone ($n = 4$) or in combination with a positive urine *Blastomyces* antigen test ($n = 11$; Fig. 1). Most dogs ($n = 14$; 74%) with blastomycosis had two or more affected sites (Fig. 1).

Thirteen dogs had pulmonary involvement, either alone ($n = 3$) or in combination with one or more additional site ($n = 10$; Fig. 1). The most common clinical signs included tachypnea ($n = 12$; 63%), skin lesions ($n = 11$; 58%), hyporexia ($n = 11$; 58%), and fever ($n = 9$; 47%; Fig. 1).

Serum 25(OH)D concentrations

Dogs with blastomycosis had significantly lower serum 25(OH)D concentrations at diagnosis (median, 203 nmol/L; range, 31–590 nmol/L, $n = 19$) than control dogs (259.5 nmol/L, 97–829 nmol/L, $n = 24$; $P = 0.01$). Within the blastomycosis group three dogs (16%) had serum 25(OH)D concentrations below the reference interval, while one dog (5%) had a serum 25(OH)D concentration above the reference interval. Within the control group one dog (4%) had a serum 25(OH)D concentration below the reference interval, while five dogs (21%) had serum 25(OH)D concentrations above the reference interval.

Eleven of the 19 dogs with blastomycosis were reexamined a median of 30 days after initial diagnosis (range, 27–37 days). All were reported to have improved or resolved clinical signs. The remaining seven dogs were deceased. For 10 of the dogs reexamined, there was an observed median change in serum 25(OH)D concentration from baseline to 30-days post-diagnosis of only 1 nmol/L (range −138 to +44 nmol/L), which was not significant ($P = 0.98$; Fig. 2). Serum was not available from one dog.

Survival analysis

Shortly after the initial diagnosis with blastomycosis, five dogs were euthanized and one dog died, for an in-hospital mortality rate of 32%

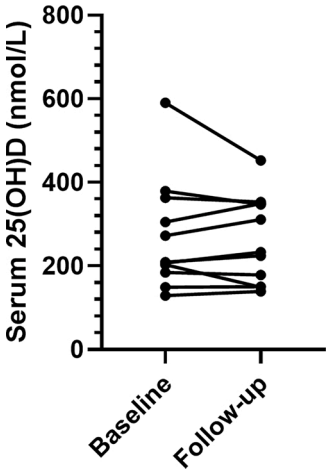

Fig. 2. Serum 25-hydroxyvitamin D (25[OH]D) concentrations in 10 dogs with blastomycosis alive at 30 days post-diagnosis, both at the time of diagnosis (median, 209 nmol/L; range, 129-590 nmol/L) and at treatment follow-up 27 to 37 days into antifungal treatment (median, 233 nmol/L; range, 139–452 nmol/L; $P = 0.98$).

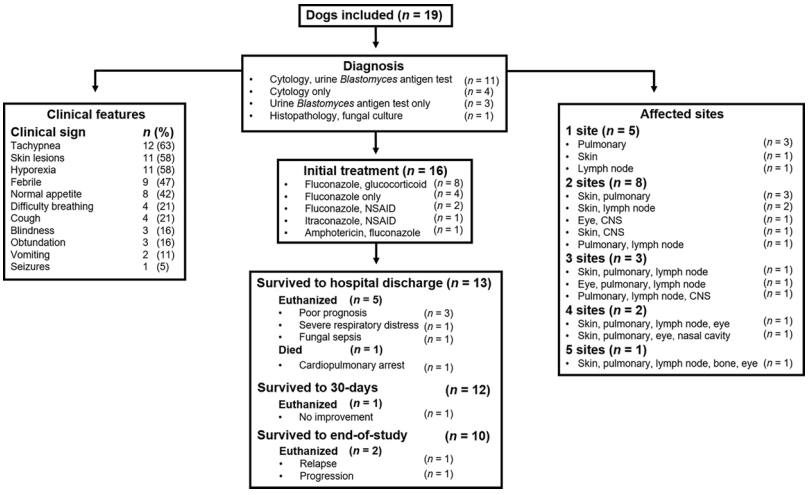

Fig. 1. Flow diagram illustrating method of diagnosis, number and type of affected sites of dissemination, clinical features, initial treatment, and survival (i.e., in-hospital, 30-day after diagnosis, and end-of-study) in 19 dogs with blastomycosis enrolled between April 2018 and February 2020.

(Fig.1). Three of these dogs were euthanized before initiation of antifungal therapy, the remaining 16 dogs had started antifungal therapy. The mortality rate for dogs 30 days after diagnosis was 37% (Fig. 1), as one additional dog was euthanized 18 days after diagnosis due to lack of clinical improvement. That dog's baseline serum 25(OH)D was 77 nmol/L. Ten dogs were alive at the end of the study for an overall mortality rate of 47%, as an additional two dogs were euthanized due to blastomycosis relapse or progression at 43 and 224 days after diagnosis (Fig. 1). Their baseline serum 25(OH)D concentrations were 379 nmol/L and 203 nmol/L, respectively. Survival times ranged from 1 to >696 days (Supplemental Fig. 1). A median survival time for all dogs could not be calculated because more than half of the dogs were alive at the end of the study period. The median follow-up time (from date of diagnosis to death or study end) was 142 days (range, 1–696 days).

Baseline serum 25(OH)D concentrations were significantly lower in dogs that did not survive to hospital discharge (median 147 nmol/L; $n = 6$) compared to survivors (median 208 nmol/L, $n = 13$; $P = 0.025$; Fig. 3). Serum 25(OH)D concentrations were also lower in non-survivors at 30 days (median 145 nmol/L, $n = 7$, vs. 209 nmol/L, $n = 11$; $P = 0.005$), and at study end (median, 149 nmol/L, $n = 9$, vs. 209 nmol/L, $n = 10$; $P = 0.034$; Fig. 3). Baseline serum 25(OH)D concentrations in blastomycosis dogs that survived to reexamination (median, 240.5 nmol/L; range, 129–590 nmol/L; $n = 12$) were not significantly different to those of healthy controls ($P = 0.32$).

Baseline 25(OH)D concentration was not associated with survival to hospital discharge (OR, 1.02; 95% CI, 1.00–1.04; $P = 0.07$) or survival 30-days post-diagnosis (OR, 1.03; 95% CI,1.00–1.06; $P = 0.06$), when interrogated as a continuous variable. However, ROC analysis indicated that a baseline serum 25(OH)D concentration <180.5 nmol/L had a sensitivity of 83.3% and a specificity of 76.9% for mortality prior to discharge, and a sensitivity of 85.7% and a specificity of 83.3% for 30-day mortality (Fig. 4). Dogs with baseline serum 25(OH)D concentrations <180.5 nmol/L had significantly greater odds of death prior to discharge (OR, 15.0; 95% CI, 1.4–191.3; $P = 0.04$) and by 30 days post-diagnosis (OR, 30.0; 95% CI, 2.6–366.7; $P = 0.006$), compared to dogs above this threshold at baseline.

Discussion

Dogs with blastomycosis had significantly lower serum 25(OH)D concentrations at time of diagnosis than healthy control dogs, but serum 25(OH)D concentrations did not significantly change in dogs 30-days post-diagnosis despite clinical improvement. Baseline serum 25(OH)D concentrations were also significantly lower in dogs that did not survive to hospital discharge, to 30 days post-diagnosis, or to the end-of-study follow-up, as compared to those that did. Moreover, a baseline serum 25(OH)D concentration of <180.5 nmol/L was predictive of in-hospital and 30-day mortality.

Serum 25(OH)D concentrations were significantly lower in dogs with blastomycosis than healthy control dogs. These results corroborate our hypothesis and findings from a recent study that found lower serum 25(OH)D concentrations in 22 dogs with blastomycosis compared to healthy control dogs (O'Brien et al., 2018). Lower serum 25(OH)D concentrations have been identified in dogs with various infectious diseases including leishmaniasis (Rodriguez-Cortes et al., 2017), spirocercosis (Rosa et al., 2013), and bacterial sepsis (Jaffey et al., 2018a), compared to healthy control dogs. However, the underlying mechanisms are not clear.

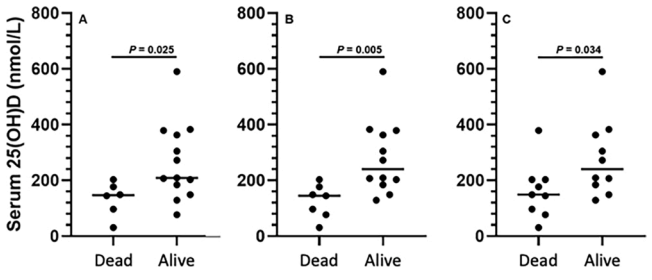

Fig. 3. Scatter plots comparing baseline serum 25-hydroxyvitamin D (25[OH]D) concentrations in dogs with blastomycosis grouped by survival outcomes at (A) hospital discharge, (B) 30-days after diagnosis, and (C) end-of-study. Black horizontal line represents the median. Closed circles represent individual dog data.

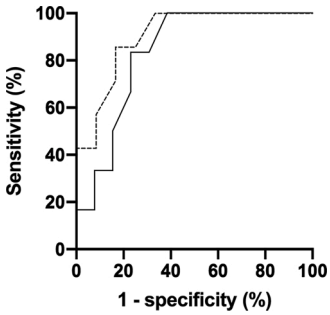

Fig. 4. Receiver operating characteristic curves for serum 25-hydroxyvitamin D (25[OH]D) concentrations <180.5 nmol/L and mortality during hospitalization (solid line) or after 30 days of antifungal treatment (dashed line) in dogs with blastomycosis. Areas under the curve were 0.83 and 0.90, respectively.

Several mechanisms could lead to lower serum 25(OH)D concentrations in dogs with systemic infectious disease. One possibility could be increased renal loss of unbound filtered vitamin D during periods of systemic inflammation, because the majority of vitamin D is bound to the negative acute phase proteins vitamin D binding protein (VDBP) (80–90%) and albumin (10–20%) (Reid et al., 2011; Clements et al., 2020). However, had systemic inflammation at the time of diagnosis been affecting serum 25(OH)D concentrations, then a significant increase in serum 25(OH)D concentrations at the 30-day post-diagnosis time-point, when inflammation was presumably abrogated, would have been expected. However, there was just a median 1 nmol/L increase in serum 25(OH)D concentration that was not significant. A second possible mechanism for lower serum 25(OH)D concentrations is that dogs, unlike humans, are unable to synthesize vitamin D_3 in the skin and as a result are dependent on nutrition to meet their vitamin D needs (Parker et al., 2017). It is plausible that decreased food intake in dogs that are systemically ill with blastomycosis could have contributed to lower serum 25(OH)D concentrations compared to controls. Objective measurement of food intake was not included in this study to further assess this possibility. A final mechanism to consider is decreased intestinal absorption of 25(OH)D due to subclinical gastrointestinal disease. While this is considered unlikely in our population due to lack of clinical signs or clinicopathologic abnormalities, it cannot be definitively ruled out. Ultimately, it remains unclear if lower 25(OH)D concentrations may predispose some dogs to blastomycosis or if the lower concentrations are a consequence of the disease and inflammation.

In humans, some variants in the genes that modulate either serum 25(OH)D concentrations or its cellular availability influence the likelihood of acquiring respiratory infections (Afzal et al., 2014). For example, a polymorphism in VDBP is associated with reduced susceptibility to blastomycosis (Sainsbury et al., 2015). This variant was predicted to be protective because of a decreased affinity of VDBP for 25(OH)D, resulting in enhanced cellular availability. Another study identified polymorphisms in the vitamin D receptor that are associated with altered susceptibility to *M. tuberculosis* (Lee and Song, 2015).

We evaluated the change in serum 25(OH)D in dogs with blastomycosis 30-days after-diagnosis, when all dogs evaluated were clinically improved, but did not detect any overall increase in serum 25(OH)D concentration with treatment. This lack of improvement with initial

treatment was unexpected. One possible explanation is that decreased serum 25(OH)D concentrations were a pre-existing risk factor for development of blastomycosis and thus a change would not be seen with treatment. Alternatively, given that there was no significant difference in serum 25(OH)D concentrations between surviving dogs at 30-days after diagnosis and healthy controls it is also possible that lower 25 (OH)D concentrations in non-survivors serve primarily as a marker of disease severity and not directly related to pathogenesis. Outcome in some dogs, especially those that were euthanased beyond the initial 30-days after-diagnosis recheck may have been serum 25(OH)D independent. The absence of significance could have been biased because dogs that survived to discharge had greater baseline serum 25(OH)D concentrations than dogs that died or were euthanased in-hospital. In addition, it is possible that a more substantial increase in serum 25(OH) D concentration could have been identified if dogs had been followed for a longer period of time after diagnosis, e.g. until their urine *Blastomyces* antigen test became negative. To better assess this, ideally dogs would be followed and serum 25(OH)D reassessed at point of complete clinical remission to determine whether low serum 25(OH)D concentrations were a persistent or dynamic finding.

In this study, baseline serum 25(OH)D concentrations were associated with decreased survival at each follow-up timepoint. Dogs with baseline serum 25(OH)D concentrations <180.5 nmol/L had 15- and 30-times greater odds of in-hospital and 30-day mortality, respectively, although confidence intervals were wide. These results support our hypothesis but are in contrast with the O'Brien et al. (2018) study that did not find an association between serum 25(OH)D concentrations and survival. One potential explanation for these contrasting results is differences in the proportion and distribution of censored data, i.e., no dogs in the current study were lost to follow-up. A unique feature of the survival analyses performed in this study is that we included clinically relevant short-term survival benchmark time-points. In our study population, as in other reports, most dogs (78%; $n = 7/9$) that died or were euthanased as a result of blastomycosis, did so within the first 30 days of diagnosis (Legendre et al., 1996; Walton et al., 2017).

Our study had several limitations, many of which were associated with the small population size. While it would have been ideal to control for potential confounding covariates in this study, our population of 19 dogs precluded our ability to do this. Therefore, it is possible that an unexplored covariate could have affected baseline serum 25(OH)D concentrations as a predictor of survival. These differences in statistical analysis may additionally explain the difference in apparent association between mortality and serum 25(OH)D in the dogs in this study and the O'Brien et al. (2018) study. Additionally, when assessing serum 25(OH) D a standardized diet across all enrolled dogs would have been ideal to limit variation due to individual dietary differences (Sharp et al., 2015). We also lacked objective measures of several variables that may have helped to further assess the significance of our findings such as appetite and disease status at the 30-day reexamination. Finally, as most dogs died or were euthanized within the first two weeks, this precluded more analysis of any association between 25(OH)D and long-term mortality in dogs with blastomycosis. Future studies with larger populations of dogs with blastomycosis that include measurement of total calcium, ionized calcium, parathyroid hormone, and both 25(OH)D and 1,25-dihydroxy-vitamin D are needed to further characterize the role of 25(OH)D in disease pathogenesis.

Conclusions

This study confirms a recent finding that dogs with blastomycosis have lower serum 25(OH)D concentrations compared to healthy control dogs and identified associations between baseline (time of diagnosis) serum 25(OH)D concentrations and survival to hospital discharge, 30 days of treatment, and long-term follow-up. These results provide the rationale for future studies to more comprehensively investigate vitamin D status at point of diagnosis, throughout treatment, and after completion of treatment in larger numbers of dogs with blastomycosis.

Conflict of interest

None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2021.105707.

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