

Epidemiologic evaluation of canine urate urolithiasis in Thailand: A comparative cross-sectional study between 2016-2023

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Abstract

A comparative cross-sectional study aimed to describe the epidemiological data of canine urate urolithiasis in Thailand by evaluating the change in proportion over the year and identifying risk-associated factors, including age, breed, sex, and neutered status, through comparisons with multiple comparison groups. The urate and non-urate group was dogs whose uroliths were submitted from Thailand to the Minnesota Urolith Center between 2016 and 2023, and the hospital group was dogs that were visited at the Small Animal Hospital, Chulalongkorn University, between 2020 and 2023. Of 6,171 canine urolith submissions, 210 samples (3.4%) were urate-containing uroliths submitted from twenty-eight canine breeds. Twelve breeds were identified as high-risk, and only one breed was recognized as low-risk. The majority of high-risk breeds were medium- to large-breed dogs. Intact male and younger age dogs were found to be at a higher risk of developing urate uroliths, with the mean age $\pm$ standard deviation at diagnosis of 6.07 ± 3.5 years. Based on these findings, a screening program for urate urolithiasis in dogs aged 1-6 years was recommended for these high-risk breeds, particularly in intact male dogs, to achieve clinical benefits through early detection of urate uroliths.

Keywords: Dogs, Epidemiology, Risk factors, Urate urolithiasis

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Introduction

Urate uroliths are reported as the third most common type of uroliths submitted for analysis in dogs (Low *et al.*, 2010; Houston *et al.*, 2017). Dogs suffering from urolithiasis may experience discomfort and pain, which can potentially lead to urinary tract obstruction. The presence of urate uroliths may be associated with significant medical implications as they may be caused by a genetic deficiency in the uric acid transporter or by liver-related conditions, including hepatic portovascular abnormalities (Lulich *et al.*, 2016). Prompt detection of urate uroliths holds therapeutic advantages, such as limiting urolith growth, easing dissolution or removal, decreasing the chance of urinary tract obstruction, and early recognition of other diseases. Hence, comprehension of predisposition is essential for pre-emptive recognition before the onset of clinical manifestations.

Previous studies have identified Dalmatians, English Bulldogs, Miniature Schnauzers, Shih Tzus, Yorkshire Terriers, Pit Bulls, and Russian Black Terriers as breeds with a higher likelihood of developing urate urolithiasis based on an analysis of risk factors between urate uroliths cases and other types of uroliths cases (Bende and Németh, 2004; Houston *et al.*, 2004; Picavet *et al.*, 2007; Kopečný *et al.*, 2021). Furthermore, urate uroliths show a higher prevalence in male dogs compared to females (Roe *et al.*, 2012; Houston *et al.*, 2017; Burggraaf *et al.*, 2021).

In Thailand, one study reported a progressively declining annual prevalence of urate uroliths from 2009 to 2015, accounting for five percent of all urolith types (Hunprasit *et al.*, 2017). However, there has been a research gap in Thailand since 2015 regarding this issue, and there are currently no studies that compare urate urolith cases to other comparison groups, except for non-urate uroliths. This study aims to evaluate the proportion and trend of urate uroliths in Thailand between 2016 and 2023. Additionally, it aims to assess the risk factors of age, breed, sex, and neuter status in relation to the development of urate uroliths. This will be achieved by comparing urate urolith cases with non-urate urolith cases and hospital groups while considering the influence of owner preferences.

Materials and Methods

Urate uroliths case and comparison groups: The records of all canine urolith cases submitted from Thailand for composition analysis to the Minnesota Urolith Center (MUC), University of Minnesota, between 2016 and 2023, will be reviewed and included in this study. Information containing age, breed, sex, neuter status, urolith type, and location of urolith in the urinary tract will be thoroughly collected. The urolith type was classified by its mineral composition when the urolith was composed of a single layer and contained $\geq 70\%$ of a single mineral. Mixed urolith was referred to as a single-layer urolith, which contained $< 70\%$ of any single mineral. A compound urolith was defined as a multiple-layer urolith in which each layer contained $\geq 70\%$ of a single mineral, and minerals were different in each layer (Ulrich *et al.*, 1996). The dogs were categorized into two groups: the urate urolith group and the non-urate urolith group. The urate

urolith-forming group included the dogs in which the urolith was classified as a urate urolith. The non-urate urolith-forming group included the dog, whose urolith was not urate, and was used as a urolith comparison group. Cases presenting with incomplete or missing data will be excluded from the analysis. Furthermore, data about animals, including age, breed, sex, and neuter status of all dogs that were examined at the Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University, between January 1, 2020, and December 31, 2023, will also be tabulated for use as a hospital comparison group.

Statistical analyses: Descriptive statistics will be used to analyze variables, including age, sex, and neuter status. The prevalence of urate urolithiasis will be presented in percentages, and the change in the urate urolith trend over the year will be evaluated by using linear regression analysis. The normality of the age variable will be assessed with the Kolmogorov-Smirnov test. The means and standard deviation of the mean (SD) of each study group will be calculated, and differences between the urate uroliths group and the non-urate urolith group or the hospital comparison group will be compared using a Student's t-test. The age variable will then be categorized, followed by clinical aging stage (Harvey, 2021), into juvenile (under 1 year old), adult (1-6 years old), senior (7-11 years old), and geriatric (above 12 years old). Sex and neuter status will be classified into intact male, neutered male, intact female, and neutered female. The frequency of the data will be calculated and reported as a percentile.

Furthermore, a Generalized linear model with a binomial distribution and a logit link function will be used to examine the potential association between predictor variables, which are breed, age, sex, and neuter status, and the outcome variables, which are the presence of urate uroliths in dogs compared to non-urate uroliths or hospital groups. Wald's tests were used to assess the significance of individual coefficients in the model. The outcome will be reported in terms of odds ratios (ORs) and 95% confidence intervals (95% CIs). The statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). The significance level was set at 0.05

Result

Prevalence: Between 2016 and 2023, a total of 6,674 canine urolith submission samples from Thailand were analyzed by MUC. Of these, 229 samples (3.43%) were classified as urate-containing uroliths, including 8 from the upper urinary tract, 211 from the lower urinary tract, 6 involving both upper and lower urinary tracts, and 14 from an unspecified location. During the same period, 6,445 samples (96.55%) were identified as non-urate uroliths, comprising 220 from the upper urinary tract, 6,003 from the lower urinary tract, 114 from both upper and lower tracts, and 108 from unspecified locations. Following the exclusion of cases with missing data on age, breed, sex, and neuter status, a total of 6,171 samples remained for analysis. These were categorized into 210 samples (3.4%) within the urate-containing urolith group and 5,960 samples

(96.6%) within the non-urate group. The comparison of hospital population consisted of 21,834 dogs that presented to the hospital for various clinical concerns. The annual proportion for urate-containing urolith submission from Thailand was increased over time, but the trend was not statistically significant (P value = 0.54), as illustrated in Figure 1.

Breeds: Urate-containing uroliths were identified in twenty-eight canine breeds, including mixed-breed dogs. The most frequently submitted urate-containing uroliths from Thailand were attributed to Shih Tzu (39; 18.6%), mixed-breed dogs (36; 17.1%), Chihuahua (25; 11.9%), Pug (18; 8.6%), Dalmatian (15; 7.1%), Pomeranian (11; 5.2%), Yorkshire Terrier (10; 4.8%), Pit Bull (10; 4.8%), Poodle (8; 3.8%) and English Bulldog (7; 3.3%) respectively. Other breeds were represented less frequently, with a prevalence of less than 2 percent each. Twelve breeds were classified as being at higher risk for the development of urate-containing uroliths when compared with mixed-breed dogs (Table 1). Pomeranians were the only breed identified as having a significantly lower risk of urate urolith formation compared to mixed-breed dogs, as shown in Table 1.

Age: The mean age of dogs diagnosed with urate uroliths was 6.1 ± 3.6 years, which was significantly younger than that of dogs with non-urate uroliths (7.6 ± 3.4 years, $P < 0.001$). However, there was no statistically significant difference in age when compared to the general hospital canine population (6.6 ± 4.5 years, $P = 0.254$). No significant age difference was observed between male and female dogs within the urate urolith group (6.0 ± 3.7 years and 6.2 ± 2.9 years, $P = 0.59$). When comparing dogs with urate uroliths to those with non-urate uroliths, younger age was significantly associated with increased odds of developing urate-containing uroliths (Table 2). Specifically, dogs under 1 year of age demonstrated the

highest odds (OR, 5.39; 95% CI, 1.73-16.85) for urate urolith formation relative to dogs older than 12 years. Similarly, when compared to the hospital population, younger age remained significantly associated with increased odds of urate urolith development. The greatest risk was observed in the 1-6 year age group (OR, 2.50; 95% CI, 1.50-4.16), as detailed in Table 2.

Sex and neuter status: Urate-containing uroliths were more frequently submitted from male dogs (173; 82.4%) than from female dogs (37; 17.6%). Among male dogs, these uroliths were more commonly identified in intact dogs (136; 78.6%) than in neutered dogs (37; 21.4%). In contrast, submissions from female dogs were approximately equally distributed between intact and neutered dogs (19, 51.4%, and 18, 48.6%, respectively). When comparisons were made between dogs with urate uroliths and those with non-urate uroliths or the hospital population, male sex was associated with significantly increased odds of urate urolith formation (3.45 and 4.53 times greater odds of developing urate uroliths compared to female sex, respectively), as presented in Table 2. Among male dogs with urate uroliths, neuter status was associated with decreased odds of urolith formation, with neutered males exhibiting 0.93 and 0.71 times lower odds of urate urolith development compared to intact males, relative to the non-urate group and the hospital population, respectively (Table 3). In contrast, among female dogs, neuter status was associated with increased odds of urate urolith formation. Specifically, neutered females demonstrated 2.66 and 1.53 times greater odds of developing urate uroliths compared to intact females when evaluated against the non-urate group and the hospital population, respectively (Table 3).

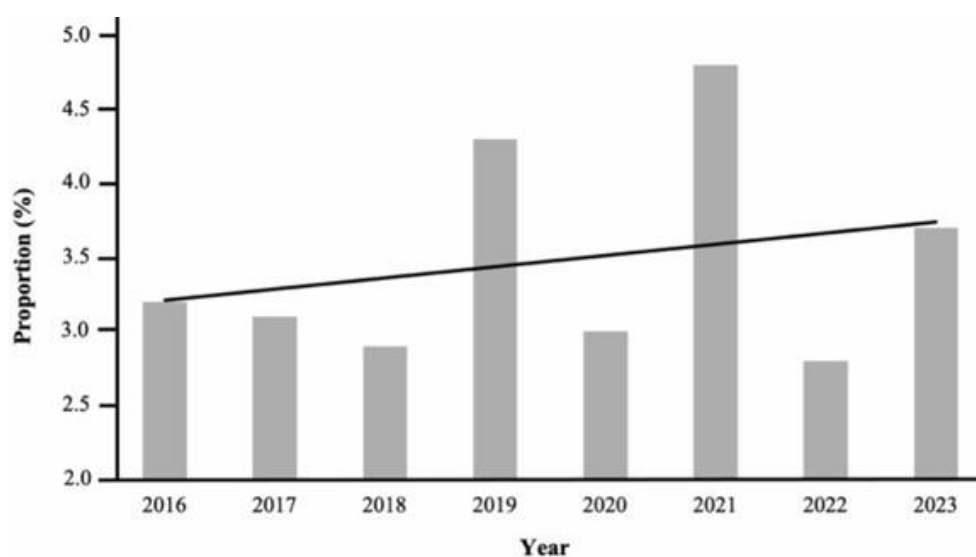


Figure 1 The change in urate-containing urolith trend over the years from 2016 through 2023, presented as a percentage of the proportion between urate-containing uroliths and the overall urolith sample in each year.

Table 1 Odds ratio (OR) and 95% confidence interval (CI) for dog breeds at high risk and low risk of urate uroliths formation compared with non-urate urolith dogs and the hospital population.

Breeds	Urate versus non-urate forming dogs OR (95% CI)	Urate versus hospital group OR (95% CI)
High risk breeds ^a		
Dalmatian	201.25 (44.35-913.24)	187.59 (84.41-416.91)
English Bulldog	5.37 (2.23-12.90)	136.18 (48.10-385.52)
Pit Bull	10.32 (4.63-23.01)	125.06 (52.13-300.04)
American Bulldog	2.82 (0.63-12.59)	58.36 (11.39-298.91)
Spitz	1.85 (0.42-8.06)	23.34 (5.15-105.82)
English Cocker Spaniel	5.37 (0.61-47.13)	12.51 (1.60-97.64)
Pug	2.05 (1.14-3.67)	11.06 (6.20-19.71)
Doberman	8.94 (0.91-88.11)	9.73 (1.26-74.82)
Cocker Spaniel	2.44 (0.55-10.77)	8.75 (2.04-37.59)
Pekingese	1.45 (0.34-6.25)	6.87 (1.61-29.28)
Shih Tzu	0.85 (0.54-1.34)	4.43 (2.81-6.99)
Yorkshire Terrier	1.24 (0.61-2.54)	4.16 (2.05-8.44)
Low risk breeds		
Pomeranian	0.23 (0.12-0.46)	0.17 (0.31-1.22)

^a Only breeds with statistically significant results in at least one comparison group were reported.

Table 2 Number, odds ratio (OR), and 95% confidence interval (CI) for age groups and sex of urate urolith dogs compared with non-urate urolith dogs and hospital population.

Variables	Urate group (n)	Non-urate group (n)	Hospital group (n)	Urate versus non-urate group OR (95% CI)	Urate versus hospital group OR (95% CI)
Age (years)					
< 1	4	36	791	5.39 (1.73- 16.85)	1.11 (0.37-3.29)
1 - 6	119	2,286	10,408	2.53 (1.51-4.23)	2.50 (1.50-4.16)
7 - 11	70	2,814	6,917	1.21 (0.71-2.06)	2.21 (1.30-3.77)
> 12	17	825	3,718	1.00 (Ref)	1.00 (Ref)
Sex					
Male	173	3,430	1,1090	3.45 (2.41-4.94)	4.53 (3.17-6.47)
Female	37	2,531	10,744	1.00 (Ref)	1.00 (Ref)

Table 3 Odds ratio (OR) and 95% confidence interval (CI) for the neuter status of each sex in comparison of urate urolith dogs with non-urate urolith dogs and the hospital population.

Variables	Urate versus non-urate group OR (95% CI)		Urate versus hospital group OR (95% CI)	
	Male	Female	Male	Female
Neuter status				
Neuter	0.93 (0.64 - 1.35)	2.66 (1.39 - 5.09)	0.71 (0.49 - 1.02)	1.52 (0.79 - 2.91)
Intact	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Discussion

Between 2016 and 2023, the overall annual proportion of urate-containing urolith submissions from Thailand increased over time, although the change was not statistically significant. This trend differs from previous studies, which reported a progressively declining annual prevalence of urate uroliths in Thailand between 2009 and 2015 (Hunpravit *et al.*, 2017) and another study that reported no significant change in the proportion of urate-containing uroliths between 2006 and 2018 (Kopecný *et al.*, 2021). The apparent upward trend in the proportion of urate uroliths over time, despite a declining population of breeds with strong predisposing factors such as the Dalmatian (Bende *et al.*, 2015), is hypothesized to have resulted from improved diagnostic accuracy, evolving dietary practices that affect purine intake and urine composition, and increased clinical awareness leading to more frequent testing and submission of urate-containing uroliths. In addition, this may be related to the increased incidence of porto-systemic shunting, which occurred in specific breeds (Caporali *et al.*, 2015).

In the present study, both high-risk and low-risk breeds for urate urolith formation were identified. Twelve canine breeds were classified as high-risk, whereas only the Pomeranian was recognized as low-risk. The high-risk breeds observed in this study were similar to those reported in previous research, which included Dalmatians (Ling and Ruby, 1986; Schaible, 1986; Ling *et al.*, 1998; Bartges *et al.*, 1999; Kopecný *et al.*, 2021), English Bulldogs (Ling *et al.*, 1998; Kopecný *et al.*, 2021), and Pit Bulls (Kopecný *et al.*, 2021). Shih Tzus and Yorkshire Terriers were considered high-risk breeds in the previous studies (Lulich *et al.*, 2013; Houston *et al.*, 2017). However, Shih Tzus and Yorkshire Terriers were high-risk breeds in the hospital group compared to mixed breeds. In the present study, we did not observe any Russian Black Terriers, which were considered to be a high-risk breed in the previous study (Bende and Németh, 2004). The identification of these high-risk breeds is considered clinically significant, as it supports the implementation of targeted monitoring strategies in populations at risk. Therefore, the high-risk breeds identified in the present study may be included in the list of dogs for surveillance of urate urolith development.

Among the high-risk breeds, most were classified as medium to large-sized dogs, except for the Pug, Pekingese, Shih Tzu, and Yorkshire Terrier, which are categorized as small breeds. Dalmatians and English Bulldogs have been reported to have genetic alterations in the autosomal recessive SLC2A9 gene (Donner *et al.*, 2023), which impair the function of the purine metabolism mechanism (Duncan and Curtis, 1971) and uric acid transporter (Bannasch *et al.*, 2008), and some reports have suggested that English Bulldogs may also have a genetic predisposition (McCue *et al.*, 2009). Additionally, due to the multifactorial nature of urolith formation, it is hypothesized that dietary factors may also contribute to an increased risk in these breeds. This is particularly relevant concerning the consumption of raw meat-based diets, which are high in purine content that can increase calculi-promoting substances such as calcium and uric acid (Robertson *et al.*, 1979).

Another mechanism contributing to urate urolith formation involves hepatic dysfunction and portovascular anomalies, which result in decreased hepatic conversion of uric acid to allantoin via hepatic uricase (McCue *et al.*, 2009). Several breeds have been significantly overrepresented in portosystemic shunts, including Yorkshire Terriers (Tobias and Rohrbach, 2003) and Shih Tzus (Hunt, 2004), which were also classified as high-risk breeds for urate-containing urolith formation in the present study.

Younger dogs were found to be at a higher risk of developing urate uroliths compared to older dogs. This finding was consistent with results obtained from comparisons between dogs diagnosed with uroliths and both non-urate urolith dogs and the hospital population. The mean age at diagnosis for urate uroliths was 6.07 ± 3.55 years in this study. The highest odds of urate urolith formation, when compared to non-urate urolith cases, were identified in dogs under 1 year of age, and the highest odds relative to the hospital population were observed in dogs aged 1 to 6 years. These findings are in agreement with previous reports indicating that urate uroliths are predominantly detected in dogs less than 7 years of age (Houston *et al.*, 2004; Hunprasit *et al.*, 2017; Kopecny *et al.*, 2021). Determining the age range associated with an increased risk of urate urolith formation may contribute to the development of targeted ages for screening programs aimed at early detection of urolithiasis in predisposed populations.

Urate uroliths have been more frequently submitted from male dogs than from females, a finding that is consistent with most previous studies (Roe *et al.*, 2012; Houston *et al.*, 2017; Burggraaf *et al.*, 2021), except for one study in which female dogs were found to be predisposed to urate urolith formation (Kopecny *et al.*, 2021). The reason for the higher prevalence of urate uroliths in male dogs remains unclear. However, studies in humans have reported significantly higher levels of uric acid in the blood (Xu *et al.*, 2022) and increased urine concentration of uric acid in males (Ferraro *et al.*, 2023), which may offer a potential explanation.

In addition, studies in humans have demonstrated an association between sex hormones and the formation of urolithiasis, with serum testosterone

levels being correlated with higher urinary uric acid excretion (Shakhssalim *et al.*, 2011). This finding may help explain the results observed in our study regarding neuter status, in which neutered male dogs exhibited a reduced risk of urolith formation compared to intact males. Conversely, the opposite trend observed in female dogs may also be attributable to sex hormone dynamics. In intact female dogs, testosterone is converted into estrogen by aromatase enzymes produced in the gonads (Salavati *et al.*, 2018). This may contribute to the increased risk of urolith formation observed in neutered females compared to intact females in this study.

Our Study had several limitations. As the study was conducted retrospectively, certain data were not available, for example, information regarding dietary factors and results from relevant laboratory tests, which may have contributed to a more comprehensive analysis of urolithiasis risk. Additionally, inaccuracies in data collection and breed identification, as reported by owners, may have occurred, potentially leading to the misclassification of some purebred dogs as mixed-breed dogs, which may underestimate the association between breed and urate urolith formation. Similar concerns may apply to the accuracy of information regarding age, sex, and neuter status, which may bias the true association. Nevertheless, due to the large sample size, it is expected that such errors would have minimal impact on the overall data analysis. In addition, there were 2 comparison groups, in which some breeds were statistically significant in one comparison group but not statistically significant in another group, which may mislead the reader. However, breeds like Shih Tzu and Yorkshire Terriers were likely to form urate urolith in the condition of porto-systemic shunting (Tobias and Rohrbach, 2003; Hunt, 2004).

In conclusion, Dalmatians, English Bulldogs, Pit Bull, American Bulldog, Spitz, English Cocker Spaniel, Pug, Doberman, Cocker Spaniel, Pekingese, Shih Tzu, and Yorkshire Terriers were identified as high-risk breeds for urate urolith formation. The screening program for urate uroliths is therefore recommended in these high-risk breeds, particularly in intact male dogs and may be initiated between 1 and 6 years of age to achieve early detection, which can offer clinical benefits by limiting urolith growth, facilitating dissolution or removal, and reducing the risk of urinary tract obstruction.

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Conflict of interest: The authors declare they have no conflict of interest

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