Original Article

Survival time and factors influencing survival time in cats with arterial thromboembolism in Thailand

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Abstract

This study aimed to report the survival time and to determine factors influencing survival time in cats with arterial thromboembolism (ATE) in Thailand. The medical records of 89 ATE cats presenting from January 2016 to December 2018 at four referral centers in Thailand were reviewed. The median survival time of ATE cats was 31 days (interquartile range 3-59 days). Cats with an age of at least 5 years (7 days; 95% confidence interval (CI) 0-25.961) had a shorter survival time than those with an age <5 years old (136 days; 95% CI 0-643.216) (p=0.021). Persian cats (450 days; 95% CI 0-37.552) had a longer survival time than other breed cats (15 days; 95% CI 0.799-7.201) (p=0.044). The multivariable Cox-regression analysis showed that a higher concentration of alanine aminotransferase (ALT) (p=0.002; Hazard ratios (HR)=1.002), circulating glucose (p=0.031; HR=1.005), and creatinine (p=0.011; HR=1.207) were associated with an increased risk of death. In conclusion, the survival time of cats with ATE in Thailand is reported. Age and breed influence the survival time of cats with ATE. The concentration of ALT, circulating glucose and creatinine is associated with an increased risk of death.

Keywords: factor, feline, survival, thrombus

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Introduction

Arterial thromboembolism (ATE) in cats is a condition that can occur acutely secondary to cardiogenic and non-cardiogenic causes. Previous studies reported the prevalence of cats with ATE was 0.006-0.3% (Buchanan, 1966; Smith *et al*., 2003; Borgeat *et al*., 2014). The prevalence of cardiogenic ATE was greater than that of non-cardiogenic ATE (Smith *et al*., 2003). The major factor of cardiogenic ATE is thrombus formation secondary to blood stasis in the left atrium in cats affected with cardiomyopathy (Smith and Tobias, 2004).

Cats with ATE usually present with signs of distal aortic occlusion or "saddle thrombus" (Smith *et al*., 2003). However, ATE can also occlude any vessels supplying organs throughout the body including forelimbs. The prognosis of cats with ATE is poor. Cats usually die shortly after the development signs of thromboembolism. Some cats may be euthanized upon presentation. Previous studies reported that less than 50% of cats with ATE survived to discharge (Buchanan *et al*., 1966; Laste and Harpster, 1993).

Previous studies reported that several factors influenced survival of cats with ATE including sex, body temperature, and the presence of congestive heart failure. (Smith *et al*., 2003; Borgeat *et al*., 2014; Payne *et al*., 2015; Schoeman *et al*., 1999). To authors' knowledge, there is no report of survival time and factors influenced survival time of cats with ATE in Thailand. The objective of this retrospective study was to report the survival time, and to determine factors influencing survival time in cats with ATE in Thailand.

Materials and Methods

A retrospective study was conducted by searching the paper and electronic medical record databases from four referral centers: Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University; Kesetsart Veterinary Hospital, Faculty of Veterinary Sciences, Kasetsart University; Mahanakorn Animal Teaching Hospital, Faculty of Veterinary Medicine, Mahanakorn University of Technology; and Suvarnachad Animal Hospital, Bangkok, Thailand, from January 2015 to December 2018. Inclusion criteria were cats that had an episode of ATE. The diagnosis of ATE was based on the clinical presentation of limb ATE, including pale or purple pads, cold extremities or poikilothermia, pulselessness, pain and paralysis (Schoeman, 1999). Date of presentation, age, sex, weight, breed, rectal temperature, heart rate, and blood pressure were recorded. Physical findings were noted including the number of limbs and the affected limbs.

Cardiogenic and non-cardiogenic causes were recorded. The type of heart disease was assessed using echocardiography. Echocardiographic examination was performed by experienced sonographers (SDS, TA and TM). The criteria for diagnosing hypertrophic cardiomyopathy (HCM) was an increase in the left ventricular wall thickness of more than 6 mm (Koffas *et al*. 2008). Hypertrophic obstructive cardiomyopathy (HoCM) was defined as an increase in the interventricular wall thickness at the left ventricular outflow tract of more than 6 mm or systolic anterior motion that caused the left ventricular outflow tract velocity to be >2.5 m/sec, as assessed by Doppler echocardiography (Jackson *et al*. 2015). Restrictive cardiomyopathy (RCM) was diagnosed by atrial enlargement, normal ventricular wall thickness, normal or decreased systolic function, and restrictive filling pattern, as assessed by pulsed wave Doppler echocardiography (Fox *et al*. 2014). Cats that could not be categorized into the above-mentioned forms of cardiomyopathy were classified as unclassified cardiomyopathy (UCM). The left atrial size was measured at the last flame before the mitral valve opening in the right parasternal long axis four-chamber view (Schober *et al*. 2007). Evidence of congestive heart failure (CHF) defined as the presence of pulmonary edema or pleural effusion on radiographs was recorded for cats with heart disease.

The recurrence of ATE, survival time and cause of death were obtained by reviewing the hospital records or contacting the cat owners. Enoxaparin (Clexane, Sanofi, France) and Clopidogrel (Plavix, Sanofi, France) dose per day were noted. Data of blood chemistry profiles at presentation including albumin, alanine aminotransferase (ALT), glucose, potassium, creatinine, and blood urea nitrogen (BUN), were also recorded.

Statistical analysis was performed using a commercial statistical program (SPSS 22, IBM, USA). Normality was analyzed by the Komogorov-Smirnov test. Values were reported as medians (interquartile range) for non-normally distributed data and mean ± standard deviation for normally-distributed data. Univariable and multivariable Cox-regression analyses were performed to evaluate the independent effects on survival. Hazard ratios (HR) with 95% confidence intervals (CI) were analyzed. Variables used for univariable Cox-regression analysis included age, weight, heart rate, temperature, vertebral heart score, left atrial size, blood pressure, the concentration of potassium, albumin, ALT, circulating glucose, creatinine, and BUN. An association with a p-value less than 0.05 was then included in the multivariable model. The log-rank test was performed to compare the difference in the survival time between categories. The cut-off value of numerical data was selected from the median of each parameter. Data from cats that were alive at the end of the study were censored. The survival time was presented as a median and 95% CI. A $p<0.05$ was considered statistically significant.

Results

Data from 89 cats with ATE were retrieved. The breeds of cats were: domestic short hair (DSH, 58/65.2%), Persian (24/26.9%), Maine Coon (5/5.6%), Korach (1/1.1%) and Kaomanee (1/1.1%). The median age was 5 years (range 5 months – 16 years). The median weight was 4 kg (range 1.9-7.40 kg). Forty-one cats were males, and forty-eight were females. The descriptive data of cats recruited in the study are summarized in Table 1. All cats underwent echocardiography. Seventy-two cats had heart disease including HCM (48/72; 66.7%), HoCM (8/72; 11.1%), UCM (8/72; 11.1%), RCM (7/72; 9.7%) and heart disease secondary to hyperthyroidism (1/89; 1.4%).

94% of cats (68/72) were newly diagnosed with heart disease. Forty-eight of 89 (53.93%) cats received cardiovascular drugs including angiotensin converting enzyme inhibitor (ACEi) (enalapril/ramipril/ benazepril) (9/89; 10.11%), furosemide (8/89; 8.98%), diltiazem (4/89; 4.49%), ACEi and furosemide (12/13.48%), ACEi, furosemide and pimobendane (10/89; 11.23%), and other combination drugs (15/89; 16.85%). Seventeen (19.1%) cats had no heart disease. The median survival time of all ATE cats was 31 days (interquartile range 3-59 days). The median survival time of ATE cats with and without heart disease was similar (Table 2). Fifty-six of 89 (62.9%) cats died from all causes of mortality, including ATE (47/56; 83.9%), CHF (6/56; 10.7%), euthanasia (2/56; 3.6%) and protein-losing nephropathy (1/56; 1.7%). In terms of affected limbs, 87/89 (97.8%) cats had two limbs, 1/89 (1.1%) cat had three limbs and 1/89 (1.1%) cat had one limb affected by ATE.

The median survival time of male and female cats affected with ATE was not different (Table 2). Persian cats had longer survival times compared to other breed cats. There was no difference between the mean age of Persian cats 3 years (interquartile range 2-8 years) and other breed cats 6 years (interquartile range 4-8 years) (p=0.340). The survival time of cats with and without spontaneous contrast in the left atrium was not different.

Cats affected with ATE with an age of at least 5 years had shorter survival times than those with an age <5 years old. Cats with circulating glucose concentrations ≥152 mg/dL had shorter survival times than those with circulating glucose concentrations <152 mg/dL. Cats with creatinine levels ≥1.6 mg/dL had shorter survival times than those with creatinine levels <1.6 mg/dL (Table 2).

The Cox-regression analysis of cats with ATE is summarized in Table 3. Cats with ATE with an increase in age, a concentration of ALT, circulating glucose, and creatinine at presentation had an increased hazard of death. Through multivariable analysis, only cats with a higher concentration of ALT (p=0.002; HR=1.002), circulating glucose (p=0.031; HR=1.005), and creatinine (p=0.011; HR=1.207) had an increased hazard of death.

Table 1 Descriptive data of all eighty-nine cats with arterial thromboembolism recruited in the study

Parameter	Median	Interquartile range	Number
Age (years)	5	2-8	89
Weight (Kg)	4	3.25-4.80	89
Heart rate (beat/min)	200	180-220	89
Temperature (°C)	99.6	98.5-100.4	73
Vertebral heart score	8.2	7.5-9.0	77
Left atrial size (mm)	16.8	12.3-19.1	89
Blood pressure (mmHg)	126	110-149	76
Potassium (mEq/L)	3.5	2.9-4.2	65
Albumin (g/dL)	2.8	2.6-3.3	65
ALT (U/L)	121	67-230	83
Glucose (mg/dL)	152	108-199	70
Creatinine (mg/dL)	1.6	1.0-2.2	82
BUN (mg/dL)	30.8	22.0-42.2	78

ALT=Alanine aminotransferase; BUN=blood urea nitrogen

Table 2 Different median survival time of cats with arterial thromboembolism with different categories

Parameters	Category	Number	Median (days)	95%CI	p-value
All ATE cats (89)					
Age (years)	<5	46	136	0-643.216	0.021*
	≥5	48	7	0-25.961	
Sex	Male	41	53	0-148.397	0.229
	Female	48	8	0-33.717	
Breeds	Other breeds	65	15	0.799-7.201	0.044*
	Persian	24	450	0-37.552	
Heart disease	With	72	30	0-63.837	0.292
	Without	17	136	0-348.461	
Spontaneous contrast	With	53	30	0-60.783	0.199
	Without	36	53	0-112.664	
ALT (U/L)	<121	42	42	0-159.568	0.701
	≥121	41	23	0-53.609	
Circulating glucose (mg/dL)	<152	35	53	0-366.896	0.040*
	≥152	35	7	4.705-9.265	
Creatinine (mg/dL)	<1.6	41	35	0-516.080	0.025*
	≥1.6	41	31	0-72.067	

*indicate statistical significance at $p<0.05$

ATE= arterial thromboembolism; CI=confidence interval

Table 3 The Cox-regression analysis of eighty-nine cats with arterial thromboembolism (n=89)

Factor	Hazard ratio	95% CI	p-value	Number
Age	1.132	1.047-1.197	0.001*	89
Weight	1.209	0.962-1.519	0.104	89
Heart rate	0.993	0.984-1.003	0.165	89
Temperature	0.879	0.747-1.034	0.120	73
Vertebral heart score	1.112	0.824-1.502	0.488	77
Left atrial size	1.044	0.992-1.099	0.100	89
Blood pressure	0.993	0.824-1.502	0.195	77
Potassium	1.130	0.900-1.419	0.294	65
Albumin	0.857	0.459-1.599	0.647	65
ALT	1.001	1.000-1.002	0.022*	83
Glucose	1.005	1.002-1.010	0.004*	70
Creatinine	1.247	1.093-1.422	0.001*	82
BUN	1.002	0.999-1.018	0.083	78

*indicate statistical significance at $p<0.05$
ALT=Alanine aminotransferase, BUN=blood urea nitrogen, CI=confidence interval

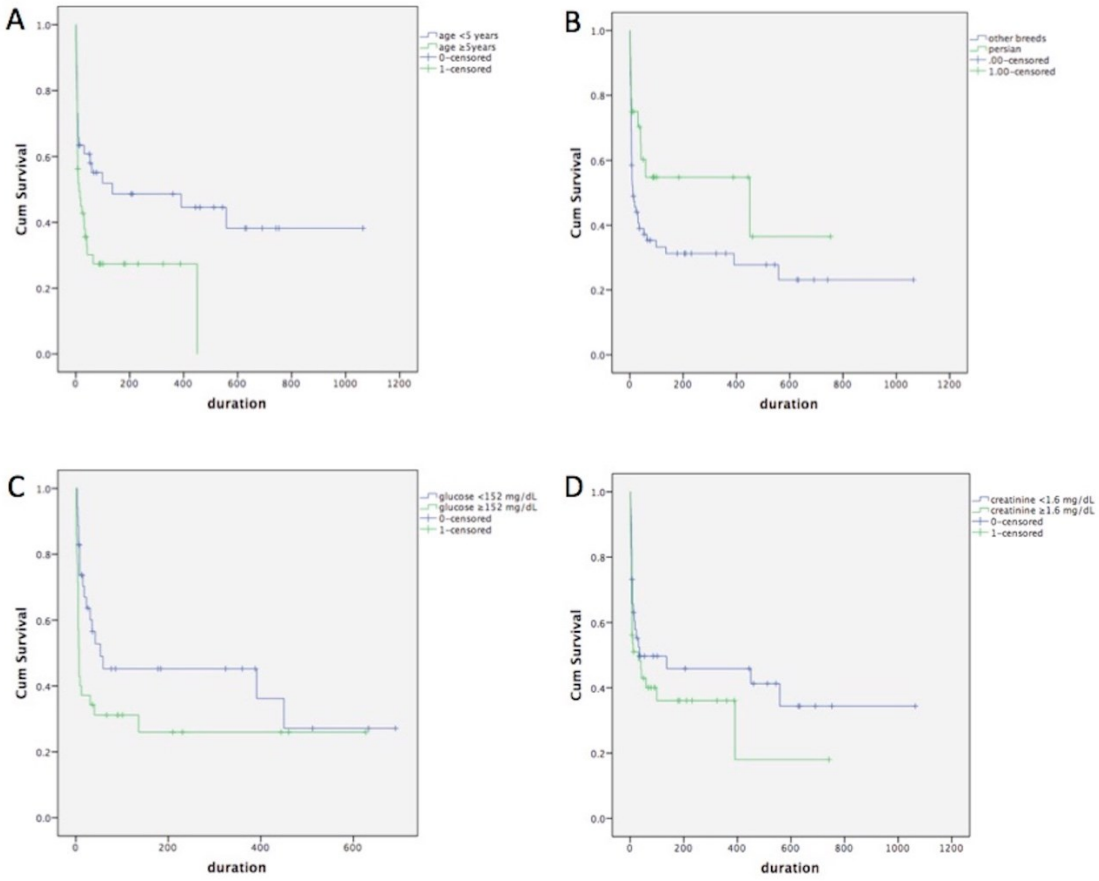

Figure 1 Kaplan-Meier survival curves for showing different median survival time of cats with arterial with different categories including age (A), breeds (B), concentration of circulating glucose (C) and concentration of creatinine (D). The two curves differ significantly at $p<0.05$.

Seventy-nine of 89 (88.8%) cats received enoxaparin and clopidogrel. Ten of 89 (11.2%) cats were treated with only clopidogrel. The average dose of enoxaparin per day was 2.64 ± 0.86 mg/kg (mean ± standard deviation). Forty-three of 79 (54.4%) cats received enoxaparin two times per day and 36/79 (45.6%) cats received enoxaparin three times per day. Four of 79 (4.5%) cats had hematuria after treatment with enoxaparin and clopidogrel. Twenty-seven of 79 (34.2%) cats treated with enoxaparin and clopidogrel were alive. Fourteen of 27 (51.9%) alive cats recovered from ATE and had the ability to walk. Seven of 27 (25.9%) cats were paralyzed for life. Six of 27 cats (22.2%) received amputation. The median recovery time was 6 days (interquartile range 3-14 days). Six out of 10 (60%) cats treated with only clopidogrel died. All alive cats treated with only clopidogrel (4/10;40%) recovered from ATE and had the ability to walk.

Discussion

The present retrospective study shows that cats with ATE had a median survival time of approximately 31 days. Age and breeds were factors that affected the survival of cats with ATE. An increase of ALT,

circulating glucose, and creatinine is associated with an increased risk of death in cats with ATE.

The median age at presentation of cats with ATE in the present study was similar to previous reports (Smith *et al*. 2003; Laste *et al*., 1995). Older cats had an increased risk of death of 1.096. This result suggests that cats develop ATE at a younger age have a better prognosis. The effect of sex on death was not found in cats with ATE in the present study. A previous study found that male cats affected with HCM had an increased risk of ATE death (Payne *et al*. 2015). However, male cats are generally predisposed to HCM. Therefore, the data of sex in HCM cats might be biased and affect the result of the study. Persian cats had the longest survival time compared to other breed cats suggesting a better prognosis in Persian cats affected with ATE. A previous study showed the risk of death increased with a lower temperature (Borgeat *et al*. 2014). The present study did not find the effect of a body temperature on death.

This study showed that an increased concentration of ALT, circulating glucose and creatinine is associated with and increased risk of death in cats affected with ATE. Alanine aminotransferase may increase with liver injury due to emboli occlusion in hepatic vessels or muscle injury secondary to embolism in limb vessels. The concentration of circulating glucose may increase secondary to the induction of stress. Creatinine may increase due to a reduction of the glomerular filtration rate from emboli occlusion to the renal artery. The present study found that eight cats with limb ATE developed acute kidney injury during hospitalization.

The majority of cats with ATE in the present study had heart disease. The survival time of ATE cats with cardiogenic and non-cardiogenic causes was similar. The major type of heart disease of cats in this study was HCM. Although ATE is common in cats affected with HCM (Payne *et al*., 2015), a previous report found that the frequency of ATE among cats with different forms of cardiomyopathy was similar (Hogan *et al*. 2015).

The present study failed to show the association of CHF and death in cats with ATE. This finding was different from the result of a previous study (Smith *et al*., 2003). The presence of spontaneous contrast is associated with increased mortality in humans (Castello *et al*. 1990) and cats (Peck *et al*. 2016). A previous study found that 46% of cats with ATE had concurrent spontaneous contrast in the left atrium. However, the present study failed to show an increased risk of mortality in cats with spontaneous contrast.

A comparison of the survival time between cats treated with clopidogrel alone and clopidogrel and enoxaparin could not be performed due to the limited number of cats that received only clopidogrel. In addition, some cats received cardiovascular drugs that may affect the survival time. 34.2% (27/79) of cats received clopidogrel and enoxaparin survived; half of these cats had the ability to walk. The median recovery time of ATE was approximately 6 days. Recurrent ATE was found in four cats; three of the four cats developed recurrent ATE within 10 days after stopping the use of enoxaparin.

In this study, four cats treated with enoxaparin and clopidogrel developed hematuria that might be a sign of bleeding complications. Hematuria disappeared after stopping the use of enoxaparin in all of these cats. Other complications associated with enoxaparin and clopidogrel such as vomiting, hematemesis and diarrhea, were not observed in this group of cats.

This study has some limitations secondary to its retrospective nature. The data for some parameters were missed, and this missing data may affect the power of the study. This study was conducted in a referral environment that may different from a primary care environment.

In conclusion, the median survival time of cats affected with ATE was approximately 31 days. Age and breeds affect the survival of cats with ATE. Last, some blood chemistry profiles at presentation, such as ALT, circulating glucose and creatinine, are associated with an increased risk of death in cats with ATE.

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