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A THESIS FOR THE DEGREE OF MASTER

A Retrospective Study of the Correlation between Inorganic Phosphorus Levels and Survival Time in Dogs with Chronic Kidney Disease

개 만성 신부전 환자에서
인수치와 생존기간과의
연관성에 대한 후향적 연구

2018년 12월

서울대학교 대학원

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Abstract

A Retrospective Study of the Correlation between Inorganic Phosphorus Levels and Survival Time in Dogs with Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common disease in dogs. Multivariable analysis using inorganic phosphorus (IP) levels showed to be associated with mortality in humans, dogs, and cats with CKD. In CKD, glomerular filtration rate is reduced, thus inhibiting IP excretion. Because of reduced IP excretion, hyperphosphatemia is one of the most common issues identified in dogs with CKD. However, whether sole effect of IP levels to survival rate in dogs with CKD has not been studied.

One-hundred-six dogs, diagnosed with CKD between 2012 and 2013, were included in this study. Examination of medical records identified 95 dogs that met the inclusion criteria for this study. Eligible dogs were divided into two groups: a hyperphosphatemia group and a normophosphatemia group (normal IP range: 1.3–6.3 mg/dL). Clinical signalments, clinicopathological values, and survival times were collected from the medical records. Decision tree analysis was performed to subdivide the hyperphosphatemia group. Kaplan-Meier survival curves against elevation of IP levels were evaluated. Dogs with normophosphatemia had a significantly increased survival time compared to those with hyperphosphatemia (HR, 8.361; 95% CI, 5.040-13.87; $P < .001$). If the first elevated IP level was 11.5 mg/dL or more, the mean survival time was 14 days.

This study suggest that hyperphosphatemia at the time of diagnosis was significantly associated with a shorter survival time in dogs with CKD and the first elevated IP level alone in patients with CKD is considered a predictive factor.

Key words: canine; hyperphosphatemia; renal disease; predictive factors

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Abbreviations

ACVIM — American College of Veterinary Internal Medicine

AKI— acute kidney injury

BCS—body condition score

BUN—blood urea nitrogen

CI— confidence interval

CKD—chronic kidney disease

CPE— cardiogenic pulmonary edema

CVHD— chronic valvular heart disease

GFR—glomerular filtration rate

IP— inorganic phosphorus

IRIS—International Renal Interest Society

PTH— parathyroid hormone

UPC—urine protein creatinine ratio

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1. Introduction

Chronic kidney disease (CKD) is a disorder characterized by at least 3 months of kidney damage, a reduction of more than 50% of the glomerular filtration rate (GFR), and irreversible lesions in the kidney, in which the renal function is not restored when the pre-renal/post-renal factor is corrected (Finco DR et al., Lees GE, 2004, 1991, Polzin DJ, 2011).

Inorganic phosphorus (IP) is a valuable constituent mineral of the body and IP levels are one of the factors affecting mortality in humans, dogs, and cats with CKD (Geddes et al., 2013, Polzin, 2013). In human medicine, a previous study showed that patients with IP levels of 6.6 to 7.8 mg/dL had a 13% higher mortality risk, and those with levels of 7.9 to 16.9 mg/dL had a 34% higher mortality risk than patients with IP levels in the reference range of 4.6 to 5.5 mg/dL (Block et al., 1998). In addition, a 1 mg/dL (.323 mmol/L) increase in IP levels has been associated with a 23% increased risk of mortality (Kestenbaum et al., 2005). IP levels are controlled by the parathyroid hormone (PTH), which is involved in the reabsorption and excretion of IP in the kidneys (Geddes et al., 2013). In CKD, GFR is reduced, thus inhibiting the excretion of IP (Kestenbaum et al., 2005).

Hyperphosphatemia is associated with increased mortality and various clinical symptoms, such as anorexia, weight loss, vomiting, and convulsions (Brown et al., 1991, Finco et al., 1992). In addition, abnormal calcium and PTH concentrations in the blood result in secondary renal hyperparathyroidism, which not only induces soft tissue calcification, coronary calcification, and cardiovascular disease (Geddes et al., 2013), but also electrolyte abnormalities and metabolic acidosis. Other clinical signs of CKD include anemia, hypertension, and arthritis, as well as major complications such as dehydration, gastrointestinal hemorrhage, metabolic acidosis, anemia, and electrolyte abnormalities (Polzin, 2011).

A significant relationship between mortality and the product of calcium × phosphate in humans and dogs with CKD has been confirmed in previous studies (Block et al., 1998, Lippi et al., 2014). In addition, a significant correlation between mortality and serum phosphorus has been identified in studies of humans (Kestenbaum et al., 2005) and cats (Barber et al., 1998, King et al., 2007). There was also a study demonstrating that IP concentration is the only clinicopathologic factor that predicts survival in cats (Boyd et al., 2008). However, sole effect of IP levels to survival rate in dogs with CKD has not been studied. This is the first study to suggest that IP levels alone have a significant correlation with survival time in dogs with CKD.

This study aimed to determine the correlation between serum IP levels and survival time in dogs with CKD and to evaluate the sole effect of elevated serum IP levels as a predictive factor in dogs with CKD.

2. Material and Methods

2.1. Case selection

The medical records of dogs diagnosed with CKD between January 2012 and December 2013 were retrospectively reviewed. CKD was diagnosed based on medical history, clinical signs, physical examination, urinalysis, blood testing, radiologic examination, and ultrasonography results (hyperechoic renal cortex, corticomedullary attenuation). The dogs were classified according to the International Renal Interest Society (IRIS) staging scheme (International Renal Interest Society, 2018) as follows: stage 2, serum creatinine 1.4-2.0 mg/dL; stage 3, serum creatinine 2.1-5.0 mg/dL; and stage 4, serum creatinine >5.0 mg/dL. Furthermore, the dogs were allotted to one of three groups according to body condition score (BCS) (Laflamme D, 1997[)] as follows: underweight (BCS 1-3), ideal weight (BCS 4-5), and overweight (BCS 6-9). Dogs were excluded from this study if their death was not due to CKD, but from other causes, such as tumor, chronic heart failure, or euthanasia.

2.2. Study design

To monitor renal function after diagnosis of CKD, the dogs' levels of blood urea nitrogen (BUN), creatinine, calcium, and IP were evaluated every 2 to 4 weeks. Dogs that had IP levels evaluated at least two times were selected for this study. Eligible dogs were then divided into two groups, a hyperphosphatemia group and a normophosphatemia group at any point during the follow up they developed hyperphosphatemia, using a value of 1.3–6.3 mg/dL for the normal range of IP. The use of a phosphate binder, along with type and dose, in the hyperphosphatemia group was recorded. Dogs that died of other causes were excluded to maintain data consistency.

The survival time in the normophosphatemia group was determined as the period of time from when the dog was first diagnosed with CKD to the day of death. In the hyperphosphatemia group, the period of time from when the IP levels were first elevated above the reference range to the day of death was defined as the survival time.

2.3. Statistical analysis

All statistical results were analyzed by a SPSS statistical package (version 23). Normality test was performed by Shapiro-Wilk test. The population features of the two groups, based on elevation of IP levels, were compared by an independent sample t-test. Correlation between elevation of IP levels, BUN, creatinine, and mortality was analyzed by a Cox Proportional Hazard model. The relationship among BUN, creatinine, IP, calcium, and albumin was confirmed by a regression analysis. To divide the compartment of the hyperphosphatemia group, a decision tree was used. The survival time of the two groups based on elevation of IP levels and the three groups based on BCS was compared by using the Kaplan-Meier method (log-rank test). A statistical significance was defined as $P \leq .05$. All data are represented as the mean ±standard deviation (SD).

3. Results

3.1. Demographic data

From January 2012 to December 2013, a total of 106 dogs were diagnosed with CKD. Three of these dogs were excluded due to the use of different blood testing equipment. Eight of the dogs were excluded due to death from causes other than CKD; four died or were euthanized due to end stage cancer; and four died from cardiogenic pulmonary edema. The remaining 95 dogs in this study included 70 dogs with hyperphosphatemia and 25 dogs with normophosphatemia. The signalments of the dogs are summarized in Table 1. In the normophosphatemia group (n=25), 10 dogs were male (4 intact, 6 neutered), and 15 dogs were female (7 intact, 8 spayed). In the hyperphosphatemia group (n=70), 34 dogs were male (11 intact, 23 neutered), and 36 dogs were female (14 intact, 22 spayed). The most common breeds were Yorkshire Terrier (23%, n = 22), Shih Tzu (22%, n = 21), Maltese (19%, n = 18), Miniature Schnauzer (9%, n = 9), and Mixed breed (8%, n = 8). The study also included four Cocker Spaniels, four Poodles, two Japanese Chins, one Dachshund, one Scottish Terrier, one

Pomeranian, and one Pointer. At the time of diagnosis, the dogs' ages ranged from 6 to 17 years (11.737 ± 3.285), body weights ranged from 0.9 to 22.6 kg (4.758 ± 2.789), and BCS ranged from 2 to 7 (4.368 ± 1.238). There were no statistically significant differences in sex, age, body weight, and BCS between the two groups.

3.2. Relationship between BUN, Creatinine, IP, Calcium, Albumin, and BCS

A significant correlation between BUN, creatinine, and IP was confirmed by regression analysis, as shown in Table 2. However, there was no significant relationship between these factors and calcium and albumin. There was also no significant difference in survival time among the three groups based on BCS (P = .580).

3.3. The Types and Dosage of Phosphate Binders

The use of phosphate binders and the types of binders used are

summarized in Table 3. Dogs with normophosphatemia were not administered phosphate binders. In the hyperphosphatemia group, 67 dogs were administered phosphate binders. The remaining three dogs were not given phosphate binders, due to the owners' financial constraints. The phosphate binders used were aluminum hydroxide (90–135 mg/kg/day with meal), Chitosan and calcium carbonate (22.2 mg/kg with food), Lanthanum carbonate (12.5–25 mg/kg/day with meal), and Sevelamer hydrochloride (99 – 160 mg/kg/day with food).

3.4. Risk of Mortality According to IP Levels

The results of Cox proportional hazard model analysis comparing survival time to BUN, creatinine, IP levels respectively are shown in Table 4. All of the factors had a significant impact on survival time, especially elevation of IP levels. A decision tree analysis was used to compartmentalize the survival times in the hyperphosphatemia group, and the results are shown in Figure 1. When the IP level was greater than 11.05 mg/dL, the survival time was 14 days, and the survival time increased significantly to 194 days when the IP level was less than 6.65 mg/dL. Kaplan-Meier survival curves of the two groups, based on elevation of IP

levels in the dogs, are shown in Figure 2. The curves were significantly different between the two groups, and dogs in the hyperphosphatemia group had a higher mortality than those in the normophosphatemia group (HR, 8.361; 95% CI, 5.040-13.87; $P < .001$).

4. Discussion

The results of this study suggest that there is a significant correlation between IP levels and survival time in dogs with CKD, as the survival time in the hyperphosphatemia group was significantly lower than that in the normophosphatemia group. When the IP levels increased above 11.5 mg/dL, the mean survival time was less than 14 days, and the mean survival time was 194 days if the IP levels were less than 6.65 mg/dL.

Phosphate binders are routinely used for human patients with CKD to manage hyperphosphatemia and reduce the risk of morbidity and mortality (Habbous et al., 2018). However, no significant reduction in mortality has been shown from the use of certain phosphate binders, despite the decrease in IP levels in patients with hyperphosphatemia (Navaneethan et al., 2011). Similar results were obtained in this study, despite the use of adequate phosphate binders to lower IP levels in dogs with hyperphosphatemia. These results demonstrate that the first elevated value of IP in dogs with CKD is an important predictor of survival time.

In addition to IP levels, BUN and creatinine levels showed a significant correlation with the survival time of dogs with CKD in this study. These results are well known in previous studies in dogs (Boyd et al., 2008, King

et al., 2007, O'neill et al., 2013, Parker et al., 2011). Furthermore, the serum calcium levels of dogs with CKD had no significant relation to the survival time in this study, and similar results have been reported in studies on CKD in cats (Boyd et al., 2008, King et al., 2007). Also in this study, there was no significant correlation between serum albumin levels and survival time. This is in contrast to studies of humans and dogs with CKD and cats with acute kidney injury (AKI), in which a significant reduction in survival time was observed as serum albumin levels decreased (Don et al., 2004, Parker et al., 2011. Worwag et al., 2008). These results are considered to be due to an insufficient number of patients, because the serum albumin levels are not included in the regular blood tests of dogs with CKD.

Previous studies have suggested a close association between BCS and survival time in dogs and cats with CKD, with an increase in survival time as BCS increases (Bartlett et al., 2010, Parker et al., 2011). However, there was no significant correlation between BCS and the survival time in dogs in this study. These results are likely due to the fact that a number of dogs in this study were concentrated into the ideal weight BCS category. Furthermore, the BCS might have been incorrectly classified because the measurer was not constant. In other studies, certain breeds, including Cocker Spaniels, are dominant among dogs with CKD (O'neill et al., 2013); however, in this study, small breeds, such as Yorkshire Terriers, were

dominant. Such results indicate the preference for specific small breeds of dogs in South Korea.

There were several limitations in this retrospective study. The first was the small number of dogs included. In particular, the number of dogs in the normophosphatemia group was smaller than that in the hyperphosphatemia group, which limits the reliability of the significance of the relationship between the two groups. Furthermore, a phosphate-restricted diet is effective in reducing the mortality of CKD in dogs and cats (Bartlett et al., 2010, Jacob et al., 2002, Kidder et al., 2009, Nicolle et al., 2007). Proteinuria is also well known as an important indicator of CKD(Hokamp, Kovarsky and Nabity et al., 2016, Jacob et al., 2005, King et al., 2007, Syme et al., 2006). Because of the retrospective nature of this study, the enforcement of a phosphate-restricted diet and the proteinuria of the dogs were not evaluated. Further investigation is needed on the correlation between these factors and survival time with elevation of IP levels. Therefore, prospective studies would be useful to investigate these factors and their relationships with IP levels.

In conclusion, the first elevated IP level in patients with CKD may be an important factor in evaluating prognosis.

Table 1. Demographic characteristics of the study population

	Normophosphatemia	Hyperphosphatemia
Number (95)	25	70
Age (years)	11.3 ± 3.4	11.9 ± 3.3
Sex	M(10), F(15)	M(34), F(36)
BW (kg)	4.5 ± 1.8	4.9 ± 3.1
BCS (9-pt)	4.4 ± 1.1	4.3 ± 1.3
BP (mmHg)	144.8 ± 20.3	147.2 ± 30.4
Breeds		
Yorkshire Terrier	3	19
Shih-Tzu	10	11
Maltese	4	14
Miniature Schnauzer	1	8
Mixed breed	2	6
Cocker Spaniel		4
Poodle	2	2
Miniature Pinscher	1	2
Japanese Chin	1	1
Dachshund		1
Scottish Terrier		1
Pomeranian	1	
Pointer		1

All data are presented with the mean value (±SD).

BW, body weight; BCS, body condition score; BP, blood pressure; M, male; F, female

Table 2. The regression analysis for the association among BUN, c reatinine, IP, serum calcium, and albumin in dogs with chronic ki dney disease

	BUN			Crea			IP		
	E	SE	*P*	E	SE	*P*	E	SE	*P*
BUN	-	-	-	**0.034**	**0.003**	**<0.001**	**0.089**	**0.008**	**<0.001**
Crea	**15.842**	**1.504**	**<0.001**	-	-	-	**2.068**	**0.149**	**<0.001**
IP	**6.317**	**0.572**	**<0.001**	**0.323**	**0.023**	**<0.001**	-	-	-
Ca	0.1754	0.336	0.952	-0.044	0.134	0.743	-0.556	0.336	0.101
Alb	12.24	0.730	0.233	0.225	0.312	0.474	-1.022	0.730	0.167

Values depicted in bold were significantly associated in the regression analysis.

E, Estimate; SE, Standard Error; *P*, P-value; BUN, Blood Urea Nitrogen; Crea, Creatinine; IP, Inorganic phosphorus; Ca, Serum Calcium; Alb, Albumin.

Table 3. The type of phosphate binder used in the hyperphosphatemia group

Phosphate binder	N (%)
Aluminum hydroxide	53 (75.71%)
Chitosan	3 (4.29%)
Lanthanum carbonate	1 (1.43%)
Sevelamer hydrochloride	1 (1.43%)

Table 4. Hazard ratios calculated using Cox proportional hazard model (multivariate model)

	HR	SE	Z-value	P-value
IP elevation	2.073	0.365	5.67	<0.001
Blood urea nitrogen	0.016	0.002	6.94	<0.001
Creatinine	0.285	0.048	5.95	<0.001

HR, Hazard Ratio; SE, Standard Error; IP, Inorganic Phosphorus.

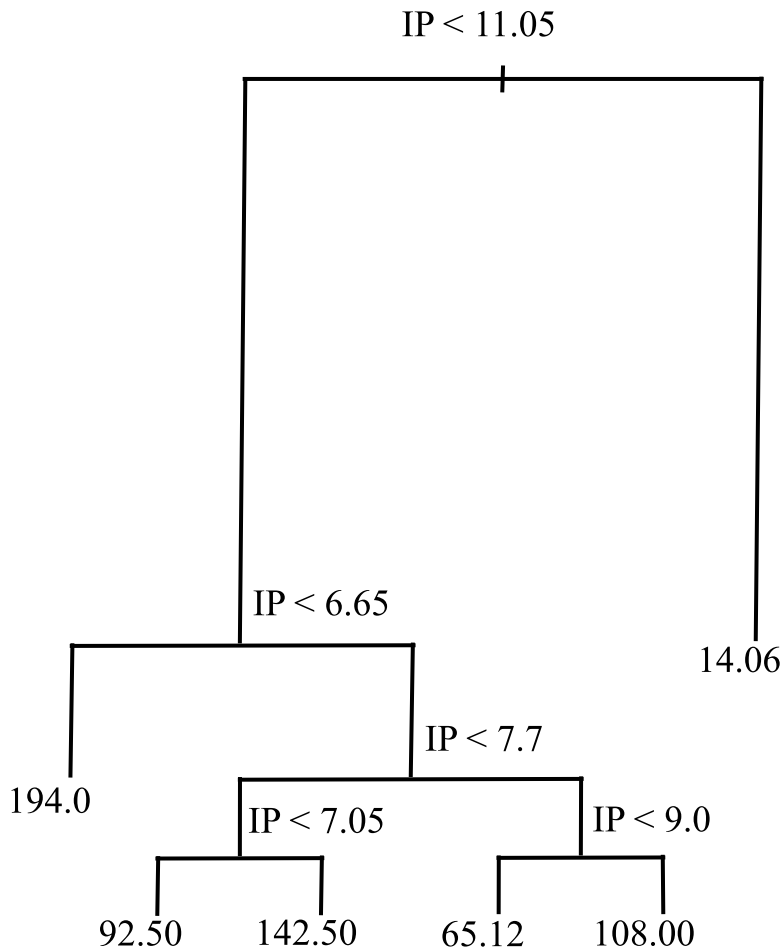

Figure 1. Decision tree analysis to divide the compartments of the hyperphosphatemia group. I f IP is > 11.05 mg/dL, the survival period is 2 weeks. Of the data below 11.0 5 mg/dL, the significant compartment is less than 6.65 mg/dL.

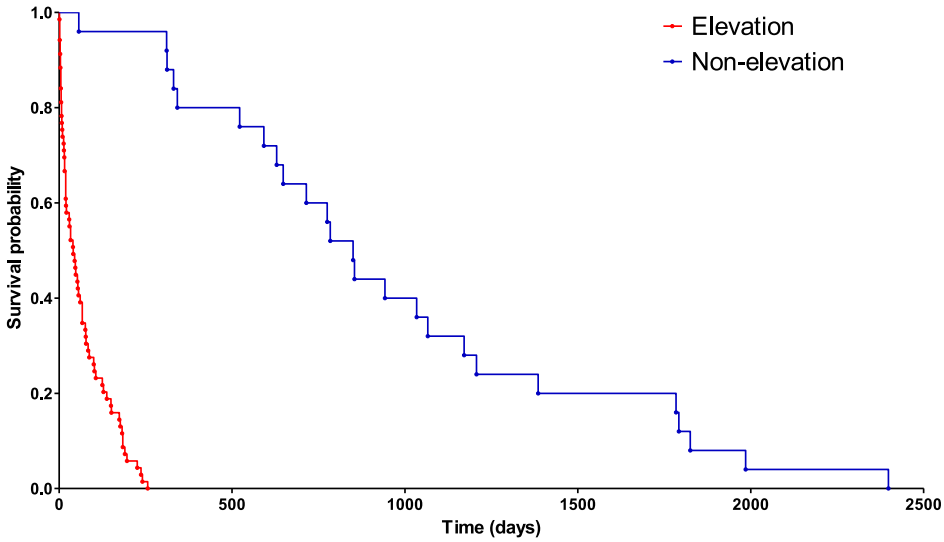

Figure 2. Kaplan-Meier survival curve of dogs with CKD, based on elevation of IP levels. Survival time was from first the elevation of IP levels to death in the hyperphosphatemia group and from the first diagnosis of CKD to death in the normophosphatemia group. Dogs with hyperphosphatemia had a higher mortality than those with normophosphatemia (HR, 8.361; 95% CI, 5.040-13.87; $P < 0.001$). All cases were represented by dots.

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국문 초록

개 만성 신부전 환자에서 인수치와 생존기간의 연관성에 대한 후향적 연구

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전 빈 원

만성 신부전(CKD)은 개에서 흔한 질병이다. 혈청 인 수치를 이용한 다변량 분석은 만성신부전을 가진 사람, 개, 고양이의 사망률과 관련이 있는 것으로 나타났다. CKD시, 사구체 여과율이 감소되어 인의 배출이 억제된다. 인의 분비가 감소하기 때문에 고인산혈증은 CKD가 있는 개에서 확인 된 가장 일반적인 문제 중 하나이다. 본 연구는 개 CKD 환자에서 인 수치 단독으로 생존

기간의 관계에 대한 후향적 연구이다. 2012년부터 2013년까지 서울대학교 동물병원에서 CKD로 진단되어 치료받고 있으며, 이 연구의 기준에 맞는 95 마리의 개를 본 연구에 포함시켰다. 모든 환자들은 최소 3개월 이상, 3번 이상의 혈액검사, 영상검사와 뇨검사를 통해 관리된 환자만 선정되었다. 해당 환자들은 정상인산혈증군, 고인산혈증군의 두 군으로 분류되었다. 의사결정나무 분석은 고인산혈증 그룹을 세분화하기 위해 수행되었다. 인 수치 상승에 대한 Kaplan-Meier 생존 곡선을 평가했다. 정상인산혈증을 가진 개는 고인산혈증 개에 비해 생존 기간이 유의하게 길었다. 처음으로 증가 된 인 수치가 11.5 mg / dL 이상인 경우 평균 생존 기간은 14 일로 확인되었다. 이러한 결과들은 관리를 받고 있는 개 CKD 환자에서 주기적인 검사 시 고인산혈증이 확인될 경우 환자의 생존기간 단축과 유의한 상관 관계가 있음을 시사하며, 처음으로 증가된 인 수치의 정도가 단독으로 CKD 환자의 임상적 예후인자로 간주될 수 있는 것으로 생각된다.

주요어: 개; 고인산혈증; 신장 질환; 예후인자

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