## **ORIGINAL ARTICLE**

# Measurement of the tibial plateau angle of normal small-breed dogs and the application of the tibial plateau angle in cranial cruciate ligament rupture

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#### **ABSTRACT**

**Objective:** In Korea, small dogs are more common than large breeds. This study was performed to measure the influence of body weight, sex, breed, age, and cranial cruciate ligament rupture (RCCL) on the tibial plateau angle (TPA) in small-breed dogs.

**Materials and methods:** A total of 274 dogs (221 normal dogs and 53 RCCL dogs) were selected for this study based on medical records. The TPA was measured from stifle joint radiographs. The dogs were divided according to body weight, sex (male and female; normal and neutered), age, breed, and RCCL, and the TPAs of the dogs were compared.

**Results:** In general, the TPAs of male dogs were significantly (p < 0.05) higher than those of female dogs, and those of healthy neutered dogs were higher than those of healthy intact dogs. The TPA had a tendency to increase along with the animal's age but was not significantly different among the four age groups. In general, the TPA of RCCL dogs was  $27.12^{\circ} \pm 0.62^{\circ}$ , which was significantly higher (p < 0.001) than that of normal dogs ( $20.21^{\circ} \pm 0.32^{\circ}$ ), indicating that an increased TPA is associated with a higher risk for RCCL. Similar results were also observed among dogs with similar body weights, breeds, and ages for male and female RCCL dogs.

**Conclusion:** This study suggested that the sex and neutering status of dogs could affect the TPA. This study also confirmed the use of TPA in the veterinary clinic as a possible indicator of RCCL, as the TPA is higher in RCCL dogs than in normal dogs.

#### **ARTICLE HISTORY**

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#### **KEYWORDS**

Tibial plateau angle; body weight; sex; age; breeds; neutering; cranial cruciate rupture.



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#### Introduction

Cranial tibial thrust (CTT) is a force produced by tibial compression during movement that is directed cranially and is neutralized by the cranial cruciate ligament (CCL) [1]. Due to its load bearing characteristics, the CCL is very prone to torsion, injury, or rupture [2]. Therefore, CCL rupture (RCCL) is a common cause of osteoarthritis, degenerative stifle joint illness, and hind limb lameness disorder in dogs.

The tibial plateau angle (TPA) plays an important role in force distribution during walking, as it has a strong relationship with the amount of CTT produced during axial tibial loading [1]. The TPA is characterized as the angle between a line tangential to the central articular surface or intersecting

the cranial and caudal landmarks of the medial tibial plateau and a line perpendicular to the mechanical long axis of the tibia, which is measured from a standard lateral radiographic image of the tibia [3]. The proximal tibia, especially caudal angulation of the proximal tibia, results in an abnormally high TPA and is associated with canine RCCL. Read et al. [4] first described TPA and its association with CCL injury. It was reported that dogs with a TPA of 22.6° or greater are prone to the occurrence of RCCL [5]. Interestingly, TPA may vary by breed due to skeletal conformation. In addition, radiographic positioning may lead to relative variation in the anatomic TPA. The normal range of TPA in normal dogs is important to determine the cause and severity of stifle joint disorders.

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There have been a few reports regarding TPA measurement in normal dogs, and these reports have revealed contrasting findings, such as the TPA of normal dogs being 18.1° [6],  $23.5^{\circ}$  [7], and  $25.0^{\circ}$  [8]. These contrasting outcomes might have occurred because the breed, body weight, age, and other factors that may influence the TPA may not have been considered. Nonetheless, most of the reports of TPA are from large breed dogs, but the most common dog breeds owned by South Koreans are small-breed dogs [9-11]. Therefore, it is important to examine the TPA of small breed dogs. Sex, age, neutering status, and body weight were also risk factors for RCCL [12]. We hypothesized that these risk factors might also affect the TPA. Therefore, the objective of this study was to measure the TPA value by considering the breed, body weight, age, and other factors in small-breed dogs and to determine the relationship of TPA with RCCL.

## **Materials and Methods**

# Ethical approval

Normal and RCCL-diagnosed dogs were selected according to the medical records of three domestic veterinary hospitals: Royal Animal Medical Center, Royal Dog and Cat Medical Center, and Seoul Animal Medical Center. The ethics committee of Royal Animal Medical Center approved this study, and the approval number was 19-KE-001 (01 Jan 2019).

#### Case selection

Records from all three institutions, from January 2017 to October 2019, were reviewed by searching for cases in which stifle joint radiographs were taken for normal dogs brought for a health screening test or dogs diagnosed as RCCLs. The diagnosis of RCCL was performed according to clinical history, clinical signs (lameness), clinical examination (sit test and cranial drawer sign test), and analysis of radiographic images and direct observation of injured CCL during surgery. The TPA was measured by a diagnostic image specialist and surgeons. A total of 22 varieties of normal dogs (n = 221) (Table 1) and 15 varieties of RCCL-diagnosed dogs (n = 53) (Table 2) were included in this study. The breed, number, sex, and neutering status of dogs were also displayed.

# Radiographic technique

The dogs were positioned in lateral recumbency, and mediolateral radiographs (Titan 2,000 COMED Medical Systems CO.

**Table 1.** Breeds, number, sex, and neutering status of normal dogs (n = 221).

	<b>Breed Varieties</b>	Total number	Total Male	Castrated male	Non-castrated male	Total Female	Spayed Female	Non-spayed Female
1	Maltese	45	30	9	21	15	7	8
2	Poodle	44	27	26	1	17	8	9
3	Pomeranian	25	12	12	0	13	8	5
4	Yorkshire terrier	14	8	4	4	6	4	2
5	Shetland Sheepdog	14	9	4	5	5	2	3
6	Mix dog	12	3	2	1	9	5	4
7	Chihuahua	12	4	2	2	8	0	8
8	Bichon Frise	8	7	5	2	1	0	1
9	Schnauzer	7	3	3	0	4	4	0
10	Dachshund	6	6	4	2	0	0	0
11	Spitz	6	2	2	0	4	2	2
12	Shitzu	5	1	1	0	4	4	0
13	Pekingese	4	2	2	0	2	0	2
14	Cocker Spaniel	4	2	2	0	2	0	2
15	Border Collie	3	2	2	0	1	0	1
16	White Terrier	2	2	0	2	0	0	0
17	Frown dog	2	2	2	0	0	0	0
18	Chinese crested dog	2	2	2	0	0	0	0
19	Boston terrier	2	2	2	0	0	0	0
20	Minipin	2	0	0	0	2	0	2
21	Jindo dog	1	0	0	0	1	0	1
22	beagle	1	1	1	0	0	0	0
	Total	221	127	87	40	94	44	50

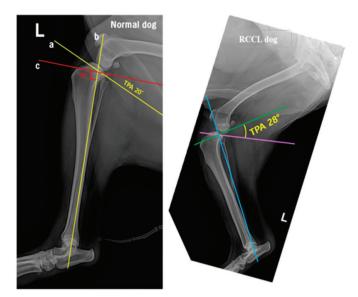
**Table 2.** Breeds, number, sex, and neutering status of RCCL dogs (n = 53).

	Breed Varieties	Total number	Total Male	Castrated male	Non-castrated male	Total Female	Spayed Female	Non-spayed Female
1	Cocker Spaniel	8	4	4	0	4	4	0
2	Maltese	8	7	6	1	1	0	1
3	Mix dog	7	7	6	1	0	0	0
4	Yorkshire terrier	6	2	1	1	4	3	1
5	poodle	6	3	3	0	3	2	1
6	Welshcock	5	5	5	0	0	0	0
7	Bichon Frise	12	2	2	0	1	1	0
8	White Terrier	3	2	2	0	0	0	0
9	Golden Retriever	2	1	1	0	1	1	0
10	Jack Russell Terrier	2	0	0	0	1	1	0
11	Mini pin	1	1	1	0	0	0	0
12	Chihuahua	1	0	0	0	1	1	0
13	Shitzu	1	1	1	0	0	0	0
14	beagle	1	1	1	0	0	0	0
15	Spitz	1	0	0	0	1	0	1
	Total	53	36	33	3	17	13	4

Ltd., Seoul, Korea) were performed with the tarsus and stifle at 90° flexion with the limb parallel to the digital image-capturing device. The X-ray beam was centered over the proximal tibial diaphysis and was collimated to include the tarsus. entire tibia, and distal third of the femur. Superimposition of the femoral condyles and talar trochlea was performed to achieve correct rotational alignment [13]. Caudocranial radiographs were taken with the dog in sternal recumbency, and the limb extended caudally, parallel to the digital image-capturing device. The X-ray beam was centered over the proximal tibia and was collimated, similar to the mediolateral radiographs. The correct rotational alignment was achieved by superimposing the fabellae on the femoral condyles with the medial aspect of the calcaneus aligned with the distal intermediate ridge of the tibia [14]. When there was a discrepancy in rotational alignment, preference was given to superimpose the fabellae on the femoral condyle.

# Measurement of TPA

A single examiner who was unaware of the signalment of the dogs measured each limb for the TPA (Fig. 1). The TPAs were measured as described previously [15,16]. The cranial tibial plateau landmark was detected first as the proximal aspect of the cranial extent of the medial tibial plateau. Then, the caudal landmark was detected as the caudal extent of the medial tibial plateau. To determine the tibial plateau slope, a first line was drawn from the cranial extent to the caudal extents of the tibial plateau (line a). Then, a second line was drawn that started from the center of the intercondylar eminences and ended at the center of the talus (line b). Line b is the long axis of the tibia on the sagittal plane. A third line



**Figure 1.** Measurement of TPA from the radiographic representation of tibial plateau angle in normal and RCCL dog. A line connecting the cranial and caudal extents of the tibial plateau was drawn to determine the tibial plateau slope (line a). A second line was drawn from the center of the intercondylar eminences to the center of the talus (line b). Line b is the long axis of the tibia on the sagittal plane. A third line (line c) was drawn perpendicular to the tibial long axis at the intersection of the lines a and b. The TPA was measured as the angle between the lines a and c.

(line c) was drawn at the intersection of the lines a and b, perpendicular to the tibial long axis. The TPA was calculated as the angle between the lines a and c. Finally, the mean of triplicate measures was used for statistical analysis (Fig. 1).

## Statistical analysis

The data are presented as the mean ± SEM, and statistical analysis was performed by follow-up paired sample *t*-test and Bonferroni post hoc test following one-way analysis of variance (ANOVA) between and among groups using Prism 5.03 (Graph Pad Software Inc., San Diego, CA).

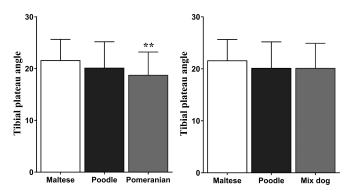
#### **Results and Discussion**

## Influence of sex on TPA

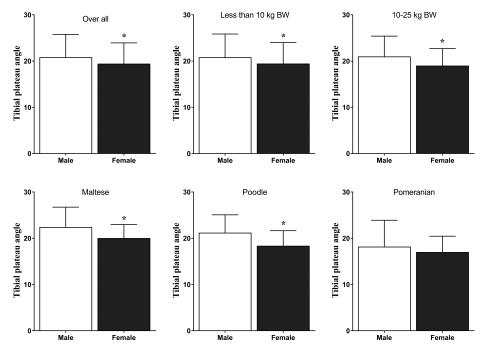
The effects of sex on TPA were measured in this study. For this purpose, we evaluated the body weight and breed of normal dogs. In all cases, the TPA of males was higher than that of females. In general, the TPA of male dogs ( $20.76^{\circ} \pm 0.44^{\circ}$ ) was significantly (p < 0.05) higher than that of female dogs ( $19.45^{\circ} \pm 0.46^{\circ}$ ) (Fig. 2). When we compared the TPA of male and female dogs with similar body weights, it was also found that male dogs' TPA was significantly higher than that of female dogs. Likewise, the TPA of male dogs in the 10-25 kg BW group was significantly higher (p < 0.05) than that of female dogs. Similar results were also found when we divided the dogs according to breed (Fig. 3).

This study found a significant difference in TPA between male and female dogs. Conversely, one study reported that the medial TPA of female dogs was significantly higher than that of male dogs, but there was no difference in lateral TPA between males and females [17]. The limitation of this study

is that large and medium breeds were included without considering body weight and breed specificity. Our study was conducted with only small breed dogs. However, Kim et al. [18] found that there was no remarkable difference in TPA between males and females. Therefore, we cautiously evaluated other risk factors. We divided the male and female dogs according to body weight, age, and breed, but interestingly, in each case, it was found that the TPAs of the male dogs were significantly higher than those of female dogs. The actual cause remains unknown: why are male TPAs higher than female TPAs in small-breed dogs? Therefore, a comparative study of TPA-related components [1,19–21], such



**Figure 3.** Influence of breeds on tibial plateau angle in normal dogs. The data are reported as the mean  $\pm$  SEM. \*\*p < 0.01, Bonferroni post hoc test following one-way ANOVA versus Maltese group.



**Figure 2.** Influence of gender on tibial plateau angle in normal dogs. The data are reported as the mean  $\pm$  SEM. \*p < 0.05, analyzed by follow-up paired sample t-test male group versus female group.

as the femur, tibial plate, intercondylar notches, ligaments, and muscles of stifle joints, between male and female small-breed dogs, is required to elucidate the underlying factors.

## Influence of dog neutering on TPA

The TPA was compared between intact and neutered dogs from different angles. The TPA of neutered dogs was higher than that of intact dogs. For further confirmation, we divided the dogs according to sex. We found that the TPA of castrated males was significantly higher than that of normal healthy intact males. Similarly, the TPA of spayed females was significantly higher (p < 0.05) than that of normal healthy intact females (Table 3).

The effect of neutering on the TPA was evaluated by breeds and sex for further confirmation. The TPA of castrated male Maltese dogs was significantly higher (p < 0.05) than that of intact male Maltese dogs. Similarly, the TPAs of all neutered male dogs were higher than those of the corresponding intact males (Table 4). Additionally, the TPA of spayed female Poodle dogs was significantly higher (p < 0.001) than that of intact female Poodles dogs. Similarly, the TPAs of all spayed female dogs were higher than those of the corresponding intact females (Table 5). Similarly, the TPA of spayed females was significantly higher than that of intact females. Consistently, one study showed that among all dogs, there were higher TPAs in healthy spayed females and healthy castrated males than in healthy intact dogs [3]. Furthermore, we divided the dogs according to the time of neutering, and we found that the TPAs of dogs that were neutered after 6 months were significantly lower than those of dogs that were neutered prior to 6 months of age (Table 3). This study was also supported by a previous study that reported that neutering prior to 6 months of age could predispose dogs to excessive TPAs [22].

Dogs that are neutered before puberty are known to form long limbs, light bone structures, and narrow chests and skulls and have delayed growth plate closure due to the absence of gonadal hormones [20,21]. This abnormal growth causes a large change in body proportions and length of the legs and results in abnormal angles/TPA in the stifle and consequently increases the TPA and risk for RCCL. Neutered dogs and female dogs had higher occurrences of RCCL than intact dogs [23]. In addition, high TPA was suggested as a risk factor for RCCL [6]. Our study strongly recommended that the increased TPA in neutered dogs may act as a predisposing factor for RCCL, and we suggest that early neutering is a risk factor for the development of RCCL as a result of increased TPA in small breed dogs.

## Influence of breed on TPA

A total of 22 varieties of small-breed dogs in the normal dog group and 15 varieties of dogs in the RCCL group were selected in this study (Table 6). We also found some differences in the TPA depending on breed. There

Table 3. Neutering dependence TPA of clinically healthy dogs.

Status of animal	TPA
Intact	19.56 ± 0.57
Neutered	20.56 ± 0.39
Intact male	20.53 ± 0.81
Castrated male	22.51 ± 0.37*
Intact female	18.84 ± 0.63
Spayed female	20.85 ± 0.55*
Neutered before 6 months overall	22.64 ± 0.43
Neutered after 6 months overall	21.35 ± 0.46*
Neutered before 6 months male	23.12 ± 0.47
Neutered after 6 months male	21.86 ± 0.58*
Neutered after 6 months female	21.44 ± 0.90
Neutered after 6 months female	20.34 ± 0.92

The data are reported as the mean  $\pm$  SEM. \*p < 0.05, analyzed by follow-up paired sample t-test.

**Table 4.** Neutering dependence TPA of breed specific clinically healthy male dogs.

	Breeds (No of intact male and castrated male dogs)	TPA of intact male	TPA of castrated male
1	Maltese (9 and 21)	20.85 ± 1.12	24.05 ± 0.85*
2	Yorkshire Terrier (4 and 4)	23.99 ± 2.60	25.59 ± 1.68
3	Shetland Sheepdog (4 and 5)	20.34 ± 2.23	20.94 ± 1.53
4	Bichon Frise (2 and 5)	21.70 ± 0.98	23.06 ± 1.27
5	Chihuahua (2 and 2)	15.29 ± 1.45	22.43 ± 2.13
6	Dachshunds (2 and 4)	16.26 ± 0.82	17.01 ± 1.03
7	Poodle (1 and 26)	23.09	22.49 ± 0.62
8	Mix dog (1 and 2)	16.42	26.58 ± 2.58

The data are reported as the mean  $\pm$  SEM. \* p < 0.05, analyzed by follow-up paired sample t-test TPA of intact male versus TPA of castrated male group.

**Table 5.** Neutering dependence TPA of breed specific clinically healthy female dogs.

	Breeds (No of intact female and spayed female dogs)	TPA of intact female	TPA of spayed female
1	Poddle (9 and 8)	14.42 ± 1.78	21.86 ± 1.92**
2	Maltese (8 and 7)	19.92 ± 0.89	20.90 ± 1.16
3	Pomeranian (5 and 8)	17.52 ± 1.56	20.97 ± 1.14
4	Shetland Sheepdog (2 and 3)	17.24 ± 3.60	22.61 ± 1.40
5	Yorkshire Terrier (2 and 4)	18.64 ± 0.38	19.65 ± 1.26
6	Mix dog (4 and 5)	20.59 ± 2.25	21.69 ± 1.13

The data are reported as the mean  $\pm$  SEM. \*\* p < 0.01, analyzed by follow-up paired sample t-test TPA of intact female versus TPA of spayed female group.

was a significant difference (p < 0.01) between Maltese and Pomeranians. However, when we compared the TPA of mixed dogs ( $20.72^{\circ} \pm 1.44^{\circ}$ ), we did not find any

**Table 6.** Influence of breed on tibial plateau angle in normal dogs and RCCL dogs.

	Normal dogs				RCCL		
	Breed varieties	Total number	TPA		Breed varieties	Total number	TPA
1	Maltese	45	21.63 ± 0.60°	1	Cocker spaniel	8	28.50 ± 0.61°
2	Poodle	44	19.94 ± 0.79°	2	Maltese	8	28.43 ± 0.82°
3	Pomeranian	25	18.79 ± 0.88°	3	Mix dog	7	28.03 ± 0.30°
4	Yorkshire terrier	14	22.80 ± 1.23°	4	Yorkshire terrier	6	25.57 ± 0.43°
5	Shetland sheepdog	14	19.88 ± 1.09°	5	poodle	6	26.50 ± 0.54°
6	Mix dog	12	20.72 ± 1.44°	6	Welshcock	5	25.83 ± 0.18°
7	Chihuahua	12	21.09 ± 0.99°	7	Bichon Frise	3	29.34 ± 0.78°
8	Bichon Frise	8	22.86 ± 0.83°	8	White terrier	2	29.34 ± 0.78°
9	Schnauzer	7	21.82 ± 1.35°	9	Golden retriever	2	18.76 ± 0.73°
10	Dachshund	6	19.42 ± 1.79°	10	Jack Russell terrier	1	28°
11	Spitz	6	18.86 ± 1.71°	11	Mini pin	1	25°
12	Shitzu	5	20.12 ± 1.35°	12	Chihuahua	1	33°
13	Pekingese	4	22.23 ± 1.47°	13	Shitzu	1	29.99°
14	Cocarspaniel	4	19.01 ± 2.52°	14	beagle	1	21.79°
15	Border collie	3	19.21 ± 2.66°	15	spitz	1	20.21°
16	White terrier	2	20.02 ± 3.11°				
17	Frown dog	2	20.52 ± 3.11°				
18	Chinese crested dog	2	21.98 ± 1.19°				
19	Boston terrier	2	17.61 ± 1.68°				
20	Minipin	2	15.89 ± 1.01°				
21	Jindo dog	1	21.84°				
22	beagle	1	24.95°				

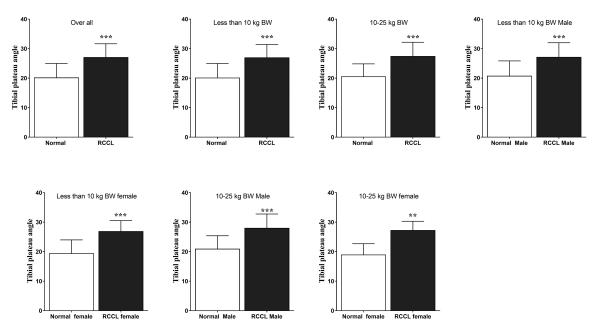
significant differences among the three groups (Fig. 4). Likewise, a study comparing TPA among large-breed dogs with RCCL corrected with tibial-plateau-leveling osteotomy (TPLO) revealed that German shepherd, Rottweilers, Boxers and Labrador retriever breed had mean TPAs of 28.2°, 26.2°, 25.9°, and 25.9°, respectively [24]. Therefore, it can be demonstrated that TPA may vary depending on breed because of postural differences among breeds or individuals, and the standing angle of the stifle may vary.

# Influence of cranial cruciate rupture on TPA

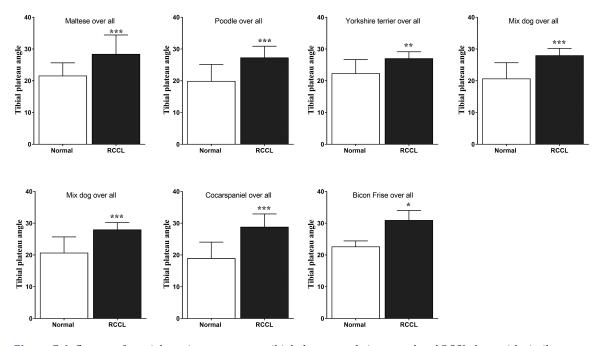
Interestingly, it was found that the TPA of RCCL dogs was significantly higher than that of the dogs in the normal group. Overall, the TPA of RCCL dogs was 27.12  $\pm$  0.62°, which was significantly higher (p < 0.001) than that of normal dogs ( $20.21^{\circ} \pm 0.32^{\circ}$ ). The TPA of RCCL dogs in the less than 10 kg bodyweight group ( $27.02^{\circ} \pm 0.60^{\circ}$ ) was significantly higher (p < 0.001) than that of normal dogs ( $20.16^{\circ} \pm 0.34^{\circ}$ ). Likewise, the TPA of RCCL dogs in the 10-25 kg BW group ( $27.49^{\circ} \pm 0.64^{\circ}$ ) was significantly higher (p < 0.001) was significantly higher (p < 0.00

0.001) than that of female dogs (20.60°  $\pm$  0.98°). Similar results were also reflected when males and females of the RCCL group were compared with the males and females of the normal dog groups. The TPAs of male (27.20°  $\pm$  1.05°) and female (28.08°  $\pm$  1.25°) dogs with RCCL in the less than 10 kg BW group were significantly higher (p < 0.001) than those of male (20.81°  $\pm$  0.50°) and female (20.99°  $\pm$  1.04°) normal dogs (Fig. 4). Likewise, the TPAs of Maltese (22.42°  $\pm$  0.80°), Poodle (21.22°  $\pm$  0.76°), Yorkshire terrier, mixed, Cocker spaniel, and Bichon Frise dogs were higher (p < 0.001) than those of similar breeds in the normal group (Fig. 5).

In this study, the TPA comparison of 221 normal and 53 RCCL dogs of the same breed was performed. It was found that the TPA significantly increased in RCCL dogs compared to that in normal healthy dogs, even after considering body weight, sex, age, and breed. The CTT is directly proportional to the TPA [1,25,26]. Therefore, a higher TPA increases cranial tibial thrust and consequently increases the risk of RCCL. Thus, the TPA can be used as an indicator and predictor for early diagnosis of RCCL.



**Figure 4.** Influence of cranial cruciate rupture on tibial plateau angle in normal and RCCL dogs with similar body weight. The data are reported as the mean  $\pm$  SEM. \*\*\*p < 0.001, analyzed by follow-up paired sample t-test male group versus female group.

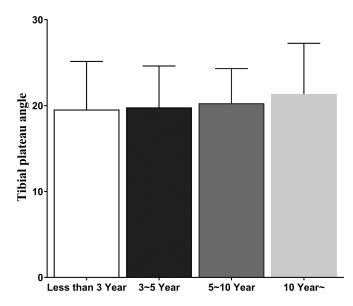


**Figure 5.** Influence of cranial cruciate rupture on tibial plateau angle in normal and RCCL dogs with similar breeds. The data are reported as the mean  $\pm$  SEM. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, analyzed by follow-up paired sample t-test male group versus female group.

# Influence of age on TPA

In this study, an increasing tendency was observed in TPA as animal age increased, but there were no significant differences in TPAs among age groups. The TPAs of dogs

younger than 3 years, 3-5 years, 5-10 years, and 10 years were  $19.47^{\circ} \pm 0.85^{\circ}$ ,  $19.79^{\circ} \pm 71^{\circ}$ ,  $20.27^{\circ} \pm 41^{\circ}$ , and  $21.34^{\circ} \pm 0.90^{\circ}$ , respectively (Fig. 6). This result may partially support the theory proposed by Read et al. [4] who explained that the compression of the caudal site of the proximal



**Figure 6.** Influence of age on tibial plateaeu angle in normal dogs. The data are reported as the mean ± SEM. Analyzed by Bonferroni post hoc test following one-way ANOVA versus Maltese group. Increasing tendency of TPA was found but not any significant differences.

tibial plate triggers premature closure localized to the caudal, proximal tibia. This closure may eventually cause an excessive tibial plateau angle at an early age and, subsequently, an excessive CTT and RCCL [4].

# Limitation

The dogs included in this study were owner-owned dogs, so it was not possible to compare anatomical structures (femur, tibial plate, intercondylar notches, ligaments, and muscles of stifle joints). In addition, having an equal number of animals in each group was not possible, as it was not an experimental study. One by one, image diagnostic specialists analyzed the radiographic images.

#### **Conclusion**

The present study demonstrated that the TPAs of RCCL dogs were significantly higher than those of normal dogs when dogs with similar body weights, ages, and breeds were compared. Therefore, increased TPA can be considered a good indicator and early diagnostic factor for RCCL in dogs. Thus, the TPA should be added as a new item in the panel (weight, body temperature, respiratory rate, heart rate, blood test, urinalysis, chest radiation, abdominal radiation test, etc.) as a predictive factor for the RCCL early diagnosis test. In addition, neutering dogs predispose them to RCCL by increasing TPA.

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#### **Conflict of interests**

The authors declare no conflicts of interests.

#### **Authors' contribution**

Beom-Seok Seo, In Seong Jeong, Md. Mahbubur Rahman and Nam Soo Kim conceived, designed the study, analyzed the data, and wrote the article. Beom-Seok Seo, In Seong Jeong, Min Ju Kim, Zhenglin Piao, and Sehoon Kim participated in clinical and health skinning tests of dogs and collected the data. In Seong Jeong and Nam Soo Kim finalized the article. All the authors read the final version and approved for publication of the data.

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