Kafkas Universitesi Veteriner Fakultesi Dergisi
ISSN: 1300-6045 e-ISSN: 1309-2251
Journal Home-Page: http://vetdergikafkas.org

Kafkas Univ Vet Fak Derg
28 (1): 143-147, 2022
DOI: 10.9775/kvfd.2021.26490

SHORT COMMUNICATION

Is There an Association Between Breed, Age, and Sex with High and Low Serum Creatinine Levels in Dogs? - From the Analysis of Electronic Medical Record Data

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Article ID: KVFD-2021-26490 Received: 05.09.2021 Accepted: 19.12.2021 Published Online: 06.01.2022

Abstract

Medical record data were analyzed for serum creatinine level in dogs to determine useful associations between the data. Differences in sex, age, and breed were analyzed using Fisher's exact test, and multiple factors such as sex were analyzed by contingency table analysis. Of the 3347 dogs that were tested for serum creatinine level, 243 dogs had creatinine over 1.4 mg/dL more than once. The overall rate of renal dysfunction in all breeds was 7.3%, but the rate for cavalier King Charles Spaniels was 14.1% (P<0.05), and for Shetland Sheepdogs it was also 14.1% (P<0.05), both significantly higher than the overall rate.

Keywords: *Creatinine, Dog, Electronic chart, Predisposing factor, Renal dysfunction*

Köpeklerde Yüksek ve Düşük Serum Kreatinin Düzeyleri İle Irk, Yaş ve Cinsiyet Arasında Bir İlişki Var mı? - Elektronik Tıbbi Kayıt Veri Analizi

Öz

Veriler arası ilişkilerin saptanması amacıyla köpeklerde serum kreatinin seviyeleri yönünden tıbbi kayıt verileri analiz edildi. Cinsiyet, yaş ve ırk farklılıkları Fisher'in kesinlik testi ile ve cinsiyet gibi çoklu faktörler kontenjans tablosu ile analiz edildi. Test edilen 3347 köpekten 243'ünde serum kreatinin düzeyleri birden fazla kez 1.4 mg/dL'nin üzerinde saptandı. Tüm ırklarda böbrek fonksiyon bozukluğuna ait genel oran %7.3 iken, Cavalier King Charles Spaniels köpeklerde bu oran %14.1 (P<0.05) ve Shetland Çoban Köpeklerinde %14.1 (P<0.05) saptandı ve her iki ırkta da bu oran genel ortalamaya göre önemli ölçüde daha yüksekti.

Anahtar sözcükler: *Kreatinin, Köpek, Elektronik tablo, Predispozan faktör, Böbrek fonksiyon bozukluğu*

INTRODUCTION

The use of medical data obtained by searching electronic medical records and diagnostic images is a rapidly developing field. In human medicine, this method is being used in many different areas, for example, to improve diagnostic accuracy by amassing test data from multiple hospitals [1], to investigate prognostic predictors [2], and in the development of new drugs [3]. Efforts to make use of electronic data on companion animals in clinical practice lag behind those of human medicine. The VetCompass Animal Surveillance Project was launched in the UK

How to cite this article?

Uemura A, Hamabe L, Tanaka R, Tanaka N, Takizawa T, Iwasaki T: Is there an association between breed, age, and sex with high and low serum creatinine levels in dogs? - From the analysis of electronic medical record data. *Kafkas Univ Vet Fak Derg,* 29 (1): 143-147, 2022.
DOI: 10.9775/kvfd.2021.26490

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in 2007 [4], and VetCompass Australia was developed in Australia in collaboration with the UK in 2013 [5]. In both countries, the collection of the medical record data held by individual veterinarians has been contributed to the development of companion animal medicine through knowledge obtained from massive amounts of data that go far beyond individual experience. O'Neill et al.[6] analyzed the electronic medical records of more than 100.000 dogs and reported risk factors for chronic kidney disease (CKD) in dogs among their findings.

In veterinary medicine, the digitization of diagnostic imaging has contributed to the gradual expansion of the use of electronic medical records in secondary veterinary medical institutions and others, and data on matters such as the status of use of anticancer agents are beginning to be published [7]. However, the use of electronic data in most veterinary clinics remains a work in progress, and platforms for the various types of data have yet to be developed. Particularly in cities, there is a tendency for people to keep small dogs. The analysis of electronic medical records from the breeds of dogs commonly kept in cities help to verify risk factors for diseases from a new perspective. In particular, CKD in dogs is a condition commonly encountered by clinicians and obtaining information about CKD in small dog breeds that make up the majority of dogs in cities would contribute to prevent its progress. Stage classification of CKD is mainly based on the patient's serum creatinine (CRE) level [8]. In this study, several years' worth of test data aggregated from the electronic medical record system of a secondary veterinary medical institution was analyzed, and informative associations between different data was investigated, focusing particularly on serum CRE levels, which is important for the classification of CKD stages in dogs.

Material and Methods

Clinical Test Values

We obtained data on blood biochemistry test results (FUJI DRI-CHEM, 7000VZ; FUJIFILM Medical Co., Ltd., Tokyo, Japan), dog breeds, date of birth, medical record number, and testing dates linked to the Anicom Receptor customer management system (Anicom Pafe, Inc., Tokyo, Japan) used by the Animal Medical Center of Tokyo University of Agriculture and Technology, and analyzed the records of 3347 dogs for which CRE test results were available. Data that were outside the measurement range of the test device were excluded.

Observation Period

June 2008 to November 2016 (duration of 8 years and 6 months).

Age and Sex Categories

Dogs aged ≥7.5 years were defined as senior dogs [7], those aged ≥6 months but <7.5 years as adult dogs [9], and those aged <6 months as young dogs. Sex was classified into entire male, neutered male, entire female, and spayed female.

Analysis Software

Statistical Analysis System (SAS) software (SAS Institute Japan Ltd., Tokyo, Japan) was used for analysis. Differences in sex, age, and breed of dog were analyzed using Fisher's exact test, and multiple factors such as age and sex were analyzed by contingency table analysis.

Methods of Analysis

To analyze differences between breeds of dog, the numbers of dogs in each breed were tallied, and the proportions of dogs with renal dysfunction for each breed were calculated. Breeds that included more than 50 dogs were categorized as its own breed, and breeds that were represented by less than 50 dogs were grouped together as "other breeds". The proportions of dogs with renal dysfunction in each breed of dogs were compared with the analysis population excluding these breeds.

Classification of CRE Levels Used in This Study

In reference to the IRIS CKD risk staging [6,7], patients who had serum CRE ≥1.4 mg/dL, the lower limit of CKD stage 2, on ≥2 occasions were classified as the "high CRE group" and the rest were classified as the "low CRE group".

Results

Of the 3347 dogs that were tested for CRE, 243 dogs were classified into high CRE group. By sex, 16.5% were male, 29.7% neutered male, 33.8% female, and 28.2% spayed female, with no sex recorded in 1.8%, and the rate of high CRE group was highest in spayed females ($P<0.01$) *(Table 1)*. By age, 20.0% were young dogs, 33.0% adult dogs, and 60.6% senior dogs. There were significant differences between each age group in the rate of high CRE group, which was most common in senior dogs ($P<0.0001$) *(Table 2)*.

The overall rate of high CRE group in all breeds was 7.3%, but the rate for Cavalier King Charles Spaniels and Shetland Sheepdogs were both 14.1% ($P<0.05$), significantly higher than the overall rate. Conversely, the rate among Dachshunds was 3.4% ($P<0.01$) and those for Poodles ($P<0.05$) and Yorkshire terriers ($P<0.01$) were both 0.7%, all significantly lower than the overall rate *(Table 3)*.

Discussion

Examples of the use of big data in veterinary medicine include a report of mean life expectancy from cremation data of 12039 animals [10], a report of cause of death and mean life expectancy from data of 299555 dogs enrolled in voluntary health insurance [11], and another study using

Table 1. *Effect of sex on high CRE group*

Sex	Study Group (a)		High CRE Group (b)		(b/a)	P Value §
Male	1.133	33.8%	76	31.3%	6.9%	0.7877
Neutered male	550	16.5%	38	15.6%	6.8%	0.6098
Female	993	29.7%	68	28.0%	6.7%	0.3989
Spayed female	609	18.2%	60	24.7%	9.9%	< 0.01
No sex recorded	62	1.9%	1	0.4%	7.3%	0.1301
Total	3.347	100%	243	100%	7.3%	

§ Fisher's exact test
Male was compared with the entire analysis population excluding dogs of entire Male, and Neutered male with the entire analysis population excluding dogs of Neutered male. The comparative controls for entire Male and Neutered male were therefore different

Table 2. *Effect of age on high CRE group. Number of dogs for which CRE test results were available, and with CRE levels within the measurement range*

Age	Study Group (a)		High CRE group (b)		(b/a)	P Value §
Young	213	6.4%	3	1.2%	1.4%	0.0001
Adult	1.105	33.0%	42	17.3%	3.8%	< 0.0001
Senior	2.030	60.6%	198	81.5%	9.8%	< 0.0001
Total	3.347	100%	243	100%	7.3%	

§ Fisher's exact test

Table 3. *Proportions of dogs with high CRE group among breeds represented by at least 50 dogs. It shows the rates of high CRE group in breeds represented by at least 50 dogs within the study population (dogs for which CRE test results were available)*

Breed	Study Group (a)	High CRE Group (b)	(b/a)	P Value §
American Cocker Spaniel	72	3	4.2%	0.4846
Cavalier King Charles Spaniel	64	9	14.1%	< 0.05
Welsh Corgi *	137	16	11.7%	0.0612
Golden Retriever	86	7	8.1%	0.6743
Shih Tzu	190	11	5.8%	0.5625
Shetland Sheepdog	78	11	14.1%	< 0.05
Dachshund	471	16	3.4%	< -0.001
Chihuahua	217	19	8.8%	0.3460
Pug	59	2	3.4%	0.3184
Papillon	91	11	12.1%	0.0959
Beagle	62	5	8.1%	0.8046
French Bulldog	69	4	5.9%	0.8159
Poodle	257	10	3.9%	< -0.05
Pomeranian	104	3	2.9%	0.0844
Maltese	96	4	4.2%	0.3171
Miniature Schnauzer	96	10	10.4%	0.2246
Yorkshire Terrier	142	1	0.7%	< -0.001
Labrador Retriever	131	14	10.7%	0.1194
Mixed Breed	217	21	9.7%	0.1278
Shiba Dog	173	16	9.2%	0.2842
Other**	537	50	9.3%	0.0457
Total	3.347	243	7.3%	

§ Fisher's exact test
** Welsh Corgi: Pembroke Welsh Corgi, Cardigan Welsh Corgi*
*** Including dog breeds of less than 50 dogs*

the same health insurance enrollment data to investigate the prevalence of disease of 18 diagnostic categories [11]. Although such studies are valuable analyses of big data from veterinary medicine, unlike analyses of veterinary medical data such as test results, their results are not immediately applicable to the diagnosis and treatment of patients in clinical practice.

Previous studies have reported that some breeds of dog are genetically susceptible to glomerular disease, a known cause of renal dysfunction. However, because most of these studies have focused on large breeds [12], with almost no studies addressing the breeds and sex at higher risk in small dog breeds that account for the majority of those kept in cities, they have not been particularly useful for clinicians in inner-city area. In this study, we used the hospital electronic customer management system of a secondary veterinary medical institution in the metropolitan district of Tokyo that treats approximately 1.000 new patients per year as a database covering a period of 8 years and 6 months, enabling us to conduct an analysis covering mainly senior small dogs. Since various factors are involved in the rise and fall of CRE level, it is not appropriate to immediately suspect CKD from the elevation. In addition, in recent years, symmetric dimethylarginine (SDMA) has been found to be an index of decreased renal function that appears prior to the elevation of CRE [13]. However, SDMA is difficult to test in the hospital, so it is outsourced to an external laboratory and is not a routine test. It is necessary for clinical veterinarians to be informed of the high and low CRE levels that can be tested in the hospital during routine blood tests, and it is important that this trend is clarified.

CRE levels have been reported to increase with age [8], and our results in this study were consistent with this finding. CKD is a kidney disease that is characterized by structural renal damage with symptoms persisting for at least 3 months [8], and in a study of related factors, O'Neill et al.[6] found no significant difference between males and females. In the present study, sex was classified into entire male, neutered male, entire female, and spayed female, and the rate was significantly higher CRE levels in spayed females than in the other sexes. It is difficult to imagine that spayed females would show high CRE levels for other reasons such as muscle mass, which tends to increase CRE. We were unable to derive a clear answer to this question from the results in the present study, and further investigation is required.

With respect to the significant differences between different breeds of dog, Shelties have been reported to be at increased genetic risk of glomerular disease [12], and this may be related to the high proportion of Shelties with high CRE group seen in this study. The high rate of high CRE seen in Cavalier King Charles Spaniels has also been reported in a British study [6]. This may be connected to the fact that this breed is at high risk of mitral insufficiency [7]. Poodles have also been reported to be susceptible to glomerular disease [12], although the relevance of this to the significantly lower CRE levels in our study is unclear. A diet with restricted protein and phosphate content in stage 1 is also reportedly effective in slowing IRIS stage progression [14]. Incorporating these preventive measures into the health management of spayed female dogs and those breeds with significantly high CRE levels in this study while they are still healthy may lead to the early detection of CKD and to slowing of its progress.

In the present study, the dogs were grouped according to their serum CRE levels, and the related factors were analyzed using electronic medical records as a database. The results suggested that there were differences in the proportion of dogs with high and low CRE levels depending on gender and breed. Although CRE levels are considered to be one of the useful indicators of renal function, comprehensive data such as urinalysis, imaging tests, and blood pressure measurements are necessary for the diagnosis of CKD. A limitation of the database used in our animal hospital is that it is incapable of reflecting data that are managed in analog form, such as in paper medical records, or that are not linked to the customer management system. As a system, it is expected that all medical records will be comprehensively digitized so that the results of further data analysis can be utilized in clinical practice.

It is now common for medical data to be put to clinical use in human medicine, and in companion animal medicine this process is also underway in the UK and Australia. Efforts by individual veterinarians are insufficient to make valuable data widely available for clinical use. Backup from the hardware perspective will also be essential, for example, by enabling the generation of electronic medical records from voice data.

Because the institution where this study was performed is a secondary veterinary medical institution, the study subjects had been referred by their local veterinarians. Not only were all the study subjects were proved difficult to diagnose or treat by the local veterinarians, but the institution was located in the metropolitan district of Tokyo. It is thus unlikely that the study population of this study perfectly reflected the status of pet ownership in Japan as a whole. Nevertheless, the data from secondary veterinary care facilities in the Tokyo metropolitan area, where many small dogs are located, were analyzed over a period of 8 years and 6 months. As a result, it is significant that some parameters related to high and low CRE values, one of the important indexes for health management, were clarified.

In the present study, the factors associated with high CRE levels were advanced age, spayed female, and a number of different breeds. Although the development of frameworks of cooperation between universities and animal hospitals is a major issue in terms of both hardware and organizational issues, the present study is highly significant, we successfully identified findings from electronic medical records data that will be useful in clinical practice.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author (R Tanaka) on reasonable request.

Acknowledgements

The authors are grateful to the laboratory colleagues for providing expertise and advice necessary to conduct this study.

Funding Support

One of the authors (Noriko Tanaka) has received funding from Meiji Seika Pharma (Tokyo, Japan) for the data analysis in this study. However, the funders were not involved in any part of this study, including the methods, results, discussion, writing, or editing.

Competing Interests

The authors declared that there is no conflict of interest.

Authors' Contributions

AU reviewed all the data and wrote a full chapter of the paper. LH is a native speaker of British English and edited the full text. RT participated as a representative of the Animal Medical Center of TUAT, assessing validity from overall clinical laboratory values and overseeing from the clinician's perspective. NT was responsible for planning, determining work algorithms, selecting categories, deciding on data handling, and overseeing data handling and analysis from a data analysis perspective. TT assessed the feasibility of handling test results and was responsible for analysis and statistical method selection decisions and statistics. TI was responsible for the Animal Medical Center of TUAT at the start of the study.

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