

Research Article

Prevalence of Systemic Hypertension in Dogs and Plasma Cystatin C as a Biomarker for Target Organ Damage Risk Assessment

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Doi : [10.5281/zenodo.18095560](https://doi.org/10.5281/zenodo.18095560)

This article is derived from the first author's thesis project, which was supported by the Scientific Research Projects Coordination Unit of Aydın Adnan Menderes University under project number VTF-20019.

Abstract

This study aimed to determine the prevalence of systemic hypertension and the associated risk of target organ damage in dogs, while evaluating plasma cystatin C levels as a potential biomarker for early renal damage detection. A total of 93 dogs presented to the Small Animal Clinic, Faculty of Veterinary Medicine, Aydın Adnan Menderes University were included. Blood pressure measurements were performed using a non-invasive oscillometric device (petMAP Graphic II), and dogs were classified according to the American College of Veterinary Internal Medicine guidelines. Of the dogs evaluated, 61% were hypertensive, with 18% classified as prehypertensive, 23% as hypertensive, and 19% as severely hypertensive based on target organ damage risk. Plasma cystatin C levels were significantly higher in hypertensive dogs compared to normotensive dogs ($p<0.01$). Furthermore, cystatin C levels were notably elevated in the prehypertensive ($p<0.05$) and severely hypertensive ($p<0.001$) groups compared to the normotensive group. These results highlight systemic hypertension as a significant health concern in dogs and suggest that plasma cystatin C may serve as a reliable biomarker for early renal damage detection associated with hypertension. However, further studies with larger sample sizes and long-term monitoring are required to validate these findings.

Keywords: cystatin C, dogs, hypertension, target organ damage

Introduction

Systemic hypertension is a chronic condition prevalent in both humans and animals, often leading to significant target organ damage if left untreated (Brown et al., 2007; Acierno et al., 2018). Prolonged elevation of blood pressure beyond normal limits can result in severe health complications, affecting vital organs such as the heart, kidneys, eyes, and brain (Stepien et al., 2003). In veterinary medicine, diagnosing and managing systemic hypertension pose challenges, as the disease often remains asymptomatic until advanced stages, when irreversible damage may have already occurred (Acierno et al., 2018). Hypertension is broadly categorized into primary

(essential) hypertension and secondary hypertension. While the precise etiology of primary hypertension remains unclear, genetic predisposition and environmental factors are believed to play key roles (Mooney et al., 2017). In contrast, secondary hypertension typically arises from identifiable underlying causes, including renal diseases, endocrine disorders, and the use of certain pharmacological agents (Acierno et al., 2018).

Accurate blood pressure measurement is essential for diagnosing and monitoring hypertension in dogs. Non-invasive measurement techniques, widely favored in clinical settings, are considered reliable tools for

assessing target organ damage risk (Haberman et al., 2004; Stepień et al., 2003). However, relying solely on blood pressure values may not provide a complete picture of the pathological impacts of hypertension, highlighting the need for additional biomarkers to assess early organ damage (Brown et al., 2007).

In recent years, the use of biomarkers for the early detection of target organ damage associated with hypertension has gained significant attention. Among these, cystatin C has emerged as a reliable indicator for assessing glomerular filtration rate (GFR) and detecting early renal damage in hypertensive dogs. Studies have shown that serum cystatin C possesses greater sensitivity and specificity for diagnosing chronic kidney disease (CKD) compared to traditional markers like creatinine (Ko et al., 2021). Furthermore, cystatin C has demonstrated superior prognostic value in predicting mortality and cardiovascular morbidity in hypertensive populations, outperforming creatinine in clinical relevance (Carretero et al., 2018). Additionally, urinary cystatin C has shown promise as an early biomarker for detecting kidney disease and organ damage in dogs with hypertension (Sivasakthi et al., 2018). Its association with early kidney injury in critically ill dogs further emphasizes its utility in intensive care settings for monitoring renal function and identifying acute kidney injury (AKI) (Paes-Leme et al., 2021).

This study aimed to evaluate the prevalence of systemic hypertension in dogs and to assess the effectiveness of plasma cystatin C levels as a biomarker for hypertension-related target organ damage. The findings are expected to contribute to the early diagnosis and management of hypertension in dogs, facilitating the development of appropriate therapeutic strategies to improve clinical outcomes.

Materials and Methods

This study was approved by the Aydın Adnan Menderes University Animal Experiments Local Ethics Committee (Approval No: 64583101/2019/086, dated 28.08.2019). Written informed consent was obtained from the owners of all participating dogs prior to their inclusion in the study. A total of 93 dogs of varying breeds, ages, and genders, presented to the Small Animal Clinic, Department of Internal Medicine, Faculty of Veterinary Medicine, Aydın Adnan Menderes University, for examination or treatment between January 2020 and April 2021, were enrolled in the study.

Detailed anamnesis data were collected for each dog included in the study, encompassing information such as breed, age, gender, body weight, diet, medical and surgical history, current medications, antiparasitic treatments, and vaccination status. Clinical examination findings, including body temperature, heart and respiratory rates, skin elasticity, mucous membrane appearance, capillary refill time, heart auscultation results, and stress levels, were meticulously recorded. Additionally, complete blood count and serum biochemical analyses were performed, and radiological and echocardiographic findings were documented.

Dogs previously diagnosed with acute or chronic cardiac/renal failure, those on medications affecting blood pressure, those displaying stress-induced variations during measurements, or dogs for which reliable data could not be obtained through oscillometric blood pressure measurements were excluded from the study (Acierno et al., 2018).

The included dogs were classified based on the 2018 American College of Veterinary Internal Medicine (ACVIM) hypertension guidelines (Acierno et al., 2018). In the first classification, a systolic blood pressure (SBP) threshold of 140 mmHg was used, and dogs were categorized into normotensive and hypertensive groups. In the second classification, considering the risk of target organ damage, dogs were divided into four subgroups: normotensive, prehypertensive, hypertensive, and severely hypertensive.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate measurements were performed non-invasively using appropriately sized cuffs placed on the tail, front, and hind legs with an oscillometric device (petMAP Graphic II, Ramsey Medical, USA) (Vachon et al., 2014; Gloria et al., 2015). For each dog, a minimum of six repeated measurements were taken, and the average value was calculated to determine systemic blood pressure. To ensure measurement accuracy, dogs were kept calm, and proper attention was given to selecting cuff sizes appropriate to limb circumference and ensuring correct cuff placement. Additionally, arterial pulsation graphs were monitored throughout the measurement process, and

emphasis was placed on obtaining a clear and accurate oscillometric curve.

Blood samples were collected from the Vena cephalica antebrachii of each dog in a single 8 mL dose using heparinized tubes. The samples were then centrifuged at 3000 rpm for 15 minutes (Hettich, Germany) to separate the plasma portion and subsequently stored at -20 °C until analysis. Cystatin C levels were measured using a dog-specific ELISA kit (Canine Cystatin C ELISA Kit, Abbkine, China). The analysis was conducted following the manufacturer's protocol, and the results were evaluated with a microplate reader. Urea and creatinine levels were analyzed using commercial test kits (Randox, USA) with an autoanalyzer (RX Monaco, Randox, USA) via the colorimetric method.

Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., USA). Data from normotensive and systemic hypertensive dog groups were compared using the Mann-Whitney U test. Data categorized based on target organ damage risk were analyzed using the Kruskal-Wallis test, followed by paired comparison methods for multiple group comparisons. The relationship between plasma cystatin C concentration and other parameters was evaluated using the Pearson correlation test. In all statistical analyses, a p-value of <0.05 was considered statistically significant.

Results

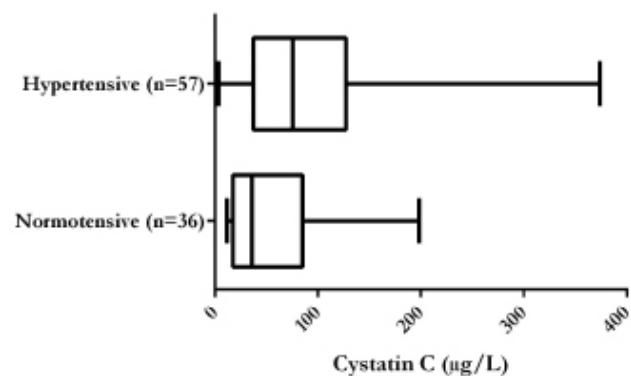
In this study, a total of 164 dogs presented to the Aydın Adnan Menderes University Faculty of Veterinary Medicine Research and Practice Hospital, Internal Medicine Small Animal Clinic for health check-ups, vaccinations, examinations, and treatments were initially evaluated. Following anamnesis and clinical examination, dogs with a history of diseases or medications that could affect the study data, those exhibiting significant stress reactions during blood pressure measurements, dogs for which artifact-free measurements could not be obtained in at least six repetitions, or those lacking an appropriate oscillometric curve were excluded from the study. Ultimately, 93 dogs meeting the study criteria were included, their data were systematically recorded, and detailed analyses were conducted.

The breed distribution of the 93 dogs included in the study was as follows: Mixed breed (n=41), Golden Retriever (n=6), Terrier (n=6), German Shepherd Dog (n=5), English Cocker Spaniel (n=4), Dobermann (n=4), Kangal (n=3), Staffordshire Bull

Terrier (n=3), Poodle (n=3), Pomeranian (n=3), Beagle (n=2), French Bulldog (n=2), Pointer (n=2), Pekingese (n=2), Weimaraner (n=2), Miniature Pinscher (n=2), Siberian Husky (n=1), Labrador Retriever (n=1), and Rottweiler (n=1). Of the included dogs, 32% (n=30) were clinically healthy with no laboratory abnormalities and were presented for routine vaccination and antiparasitic treatments. The remaining 68% (n=63) were brought to the clinic with various complaints, including weakness and loss of appetite.

In the evaluation, it was found that the systolic blood pressure (SBP) average exceeded 140 mmHg in 57 out of 93 dogs (61%), and these dogs were classified as hypertensive. Comparative analyses were conducted between normotensive and hypertensive dogs, focusing on age, gender, body weight, body temperature, heart and respiratory rates, systolic/diastolic/mean arterial blood pressure values, and plasma cystatin C, urea, and creatinine concentrations. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) values were found to be significantly higher in dogs with systemic hypertension compared to normotensive dogs ($p<0.001$). Additionally, plasma cystatin C concentration was significantly elevated in hypertensive dogs compared to normotensive dogs ($p<0.01$). However, no significant differences were observed between the two groups regarding plasma urea and creatinine concentrations ($p>0.05$). The comparative results of plasma cystatin C concentrations are summarized in Figure 1.

Figure 1. Plasma Cystatin C Concentrations in Systemic Hypertensive (SBP >140 mmHg) and Normotensive Dogs



Based on systolic blood pressure values and the risk of target organ damage, dogs were classified into four subgroups: normotensive (n=36), prehypertensive (n=17), hypertensive (n=22), and severely hypertensive (n=18). Comparative analyses were performed across these groups, evaluating age, gender, body weight, body temperature, heart and respiratory rates, systolic/diastolic/mean arterial blood pressure values, and plasma cystatin C, urea, and creatinine concentrations.

Significant differences were observed between the groups regarding systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and plasma cystatin C concentrations ($p<0.05$). Plasma cystatin C concentrations were significantly higher in the prehypertensive group ($p<0.05$) and the severely hypertensive group ($p<0.001$) compared to the normotensive group. Although cystatin C levels were elevated in the hypertensive group compared to the normotensive group, this difference did not reach statistical significance.

In addition, plasma urea concentrations were significantly lower in the prehypertensive group compared to both the normotensive and severely hypertensive groups ($p<0.01$). No significant differences were detected for other parameters among the groups. The distribution of plasma cystatin C concentrations according to target organ damage risk levels is shown in Table 1.

Correlation analyses revealed a moderate positive correlation ($r=0.495$) between plasma cystatin C concentration and body temperature in normotensive dogs, while a moderate negative correlation ($r=-0.387$) was observed with respiratory rate. No significant correlations were detected in systemically hypertensive dogs. When analyzed based on target organ damage risk levels, a moderate positive correlation ($r=0.673$) was found between plasma cystatin C concentration and age in the prehypertensive group. Additionally, a moderate positive correlation ($r=0.492$) was identified between plasma cystatin C concentration and heart rate in the hypertensive group.

Table 1. Demographic, Clinical, and Laboratory Findings of Dogs Classified by Target Organ Damage Risk Level

	Normotensive (SBP<140 mmHg; n=36)	Prehypertensive (SBP 140-159 mmHg; n=17)	Hypertensive (SBP 160-179 mmHg; n=22)	Severely hy- pertensive (SBP>180 mmHg; n=18)	P
Age	3,5 ± 2,9	3,9 ± 3,4	3 ± 2	5,6 ± 4,2	0,200
Gender (female/ male)	20/16	10/7	11/11	8/10	
Body weight (kg)	22 ± 13	15,2 ± 7,71	21,5 ± 9,5	17,6 ± 8,1	0,120
T (°C)	38,4 ± 0,4	38,6 ± 0,5	38,5 ± 0,3	38,6 ± 0,5	0,292
P (beats/min)	112 ± 13	110 ± 13	104 ± 18	119 ± 24	0,186
R (breath/min)	43 ± 13	46 ± 10	46 ± 13	49 ± 13	0,136
SBP (mmHg)	122 ± 10	148 ± 5	168 ± 4	194 ± 10	0,000
DBP (mmHg)	90 ± 14	93 ± 15	112 ± 13	113 ± 12	0,000
MAP (mmHg)	101 ± 11	112 ± 11	131 ± 9	140 ± 8	0,000
Cystatin C (µg/L)	52 ± 50a	89 ± 68b	64 ± 49ab	114 ± 81bc	0,008
Urea (mg/dL)	48 ± 16a	37 ± 16b	50 ± 26ab	89 ± 131a	0,039
Creatinine (mg/dL)	1,04 ± 0,2	1,06 ± 0,33	1,09 ± 0,37	2,0 ± 2,31	0,147

Discussion

In recent years, significant progress has been made in the diagnosis and management of hypertension in cats and dogs, yet current knowledge remains insufficient (Acierno et al., 2018). The widespread adoption of non-invasive blood pressure measurement devices in veterinary clinics has made identifying hypertension risk factors in feline and canine populations across various disease groups more accessible. However, blood pressure measurements are known to be susceptible to physiological fluctuations, and non-invasive devices may not provide results as precise as invasive measurements, which are considered the gold standard (Vachon et al., 2014; Gloria et al., 2015). Despite these limitations, non-invasive devices remain clinically valuable for identifying patients at risk of target organ damage (Acierno et al., 2018). Additionally, it has been emphasized that biomarkers are essential for distinguishing between transient or situational hypertension and pathological hypertension (Syme et al., 2020). This study aimed to measure systemic blood pressure in dogs using non-invasive methods, determine the prevalence of hypertension, and evaluate plasma cystatin C levels as a potential indicator of hypertension-related target organ damage. Hypertension was detected in 61% of the 93 dogs evaluated in this study, highlighting systemic hypertension as a significant health concern in dogs.

Studies investigating the epidemiology of hypertension in dogs remain limited in the veterinary literature compared to the extensive, large-scale studies conducted in humans (Mahmood et al., 2014; Kotchen et al., 2011). Over the years, threshold values for defining hypertension in dogs have been revised and updated. In the 2007 and 2018 guidelines published by the American College of Veterinary Internal Medicine (ACVIM), the normotension threshold was set at 140 mmHg (Brown et al., 2007; Acierno et al., 2018). It is reported that the prevalence of systemic hypertension can reach 100% in diseases associated with secondary hypertension, such as acute or chronic renal failure, hyperadrenocorticism, and diabetes mellitus (Acierno et al., 2018). However, this study did not focus on the etiology of hypertension in detail but rather analyzed the dogs' blood pressure values and biomarker levels. According to the findings, 18% of the dogs were

classified as prehypertensive, 23% as hypertensive, and 19% as severely hypertensive. These results suggest that hypertension and its associated target organ damage risk represent a considerable health issue within the canine population.

The effect of age and sex on blood pressure remains a controversial topic in the veterinary literature. While some studies report a positive correlation between age and blood pressure, suggesting that blood pressure tends to increase with age (Bodey and Michell, 1996; Bright and Dentino, 2002), others have failed to confirm this relationship (Mishina, 1997; Remillard, 1991; Meurs, 2000). Similarly, findings regarding the effect of sex on blood pressure are contradictory. Some studies suggest that male dogs have higher blood pressure values than females (Mishina, 1997; Bodey and Michell, 1996; Bright and Dentino, 2002), while others report no significant difference between sexes (Surman, 2012). In this study, age and sex were not found to have a statistically significant effect on blood pressure among dogs classified based on hypertension status and target organ damage risk. This observation aligns with findings from some previous studies (Mishina, 1997; Remillard, 1991; Surman, 2012). However, it is important to note that most of these studies were conducted on small sample sizes, and the absence of large-scale studies involving thousands of subjects, as seen in human medicine, remains a limitation in veterinary research.

The effect of breed on blood pressure has also been addressed in previous studies. It has been reported that hunting dogs, particularly Greyhounds, exhibit higher blood pressure levels and a higher prevalence of hypertension (Bright and Dentino, 2002). Conversely, certain breeds, such as Irish Wolfhounds, are noted to have relatively lower blood pressure values (Bright and Dentino, 2002). In this study, the breed information of each dog was recorded, but statistical analysis could not be performed due to an insufficient sample size for individual breeds. This limitation highlights the need for larger-scale studies that include sufficient representation of specific breeds to better understand the relationship between breed and blood pressure variability in dogs.

Accurate and reliable blood pressure measurement is essential for determining normotension and diagnosing hypertension in dogs. Although arterial

catheterization is considered the gold standard for blood pressure measurement, its use in routine clinical practice is limited due to the risk of complications and the need for specialized equipment (Acierno et al., 2018). In clinical settings, non-invasive oscillometric devices are preferred for their ability to provide quick and reliable measurements (Shih et al., 2010; Tebaldi et al., 2012; Da Silva et al., 2013; Vachon et al., 2014; Lyberg et al., 2021). The petMAP Graphic II device used in this study offered advantages such as arterial pulsation graph tracking, contributing to the acquisition of accurate and consistent measurement results.

It is well established that hypertension can cause target organ damage, primarily affecting the kidneys, eyes, brain, heart, and blood vessels (Acierno et al., 2018). While glomerular filtration rate (GFR) is considered the gold standard for evaluating renal function, routine clinical practice often relies on serum creatinine and urea levels. However, these parameters can be influenced by factors such as muscle mass, nutritional status, and body weight (Feeman et al., 2003; Parker and Freeman, 2011). In contrast, cystatin C has emerged as a more sensitive biomarker for assessing glomerular filtration rate (Laterza et al., 2002; Peralta et al., 2011). In human medicine, cystatin C is widely used for the early diagnosis of chronic kidney disease (CKD) and serves as a prognostic indicator of renal function (Hari et al., 2014; Wu et al., 2010). Its advantages over traditional markers highlight its potential for early detection of kidney damage in dogs with systemic hypertension.

In this study, plasma cystatin C concentration was found to be significantly higher in dogs with systemic hypertension compared to normotensive dogs ($p < 0.01$). Furthermore, when dogs were classified based on the risk of target organ damage, cystatin C levels were significantly elevated in the prehypertensive group ($p < 0.05$) and the severely hypertensive group ($p < 0.001$). These findings suggest that cystatin C may serve as an important biomarker for the early detection of hypertension-related kidney damage (Prats et al., 2010; Salgado et al., 2012; Zhao et al., 2020). However, the limited sample size and the single-time blood sampling approach in this study highlight the need for larger-scale studies with long-term follow-up to validate and expand upon these results.

Conclusion

This study reveals a high prevalence of systemic

hypertension in dogs and highlights plasma cystatin C as a promising biomarker for the early detection of hypertension-related renal damage. Elevated cystatin C levels, particularly in prehypertensive and severely hypertensive groups, suggest its clinical value in assessing target organ damage risk. While non-invasive blood pressure measurement remains essential, integrating cystatin C evaluation could improve early diagnosis and management. Larger-scale, long-term studies are needed to confirm these findings and enhance their clinical applicability.

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