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Investigation of symmetric dimethylarginine as a serologic marker for kidney function in striped skunks (*Mephitis mephitis*)

Eun Jung [1,2], Soong-Hee Youn [2], Ki-Yong Shin [2], Hyeon-Joo Shin [2], Joon-Young Yang [2], Yeseul Yang [1,3], Jae-Ha Jung [1,3], Yongbaek Kim [1,4,*]

[1]Laboratory of Veterinary Clinical Pathology, College of Veterinary Medicine, Seoul National University, Seoul 08826, Korea
[2]Everland Animal Hospital, Yongin 17023, Korea
[3]BK21 PLUS Program for Creative Veterinary Science Research, College of Veterinary Medicine, Seoul National University, Seoul 08826, Korea
[4]Research Institute for Veterinary Science, College of Veterinary Medicine, Seoul National University, Seoul 08826, Korea

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***Corresponding author:**
Yongbaek Kim
Laboratory of Veterinary Clinical Pathology, Research Institute for Veterinary Science and College of Veterinary Medicine, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea.
Email: yongbaek@snu.ac.kr
https://orcid.org/0000-0003-1633-9247

ABSTRACT

Importance: Kidney disease is prevalent among veterinary species, including zoo animals; however, investigations into this condition in striped skunks (*Mephitis mephitis*) are scarce. Diagnostic tools for kidney diseases in this species also remain limited.
Objective: This study aimed to assess the utility of symmetric dimethylarginine as a biomarker for kidney disease in captive striped skunks in Korea.
Methods: This retrospective study analysed 11 striped skunks housed at the Everland Zoo between 2017 and 2021. Blood samples were collected during health checks. Kidney function was assessed through blood analysis and diagnostic ultrasound, with necropsies conducted on deceased animals. Symmetric dimethylarginine levels were measured in 27 plasma samples collected from 11 skunks.
Results: Over the study period, seven skunks were diagnosed with kidney disease. Analysis of 27 blood samples revealed a concurrent increase in SDMA levels with concentrations of blood urea nitrogen and blood creatinine. In 3 of the 7 skunks with kidney disease, symmetric dimethylarginine exceeded 14 μg/dL prior to the elevation of blood urea nitrogen and blood creatinine above the upper reference limit.
Conclusions and Relevance: To our knowledge, this is the first study investigating symmetric dimethylarginine in captive striped skunks in Korea. Our findings suggest that symmetric dimethylarginine may serve as an early and consistent biomarker for renal dysfunction in striped skunks. Further studies with larger clinical sample size from striped skunks are needed to validate the clinical utility of blood symmetric dimethylarginine concentration.

Keywords: Biomarkers; striped skunks; kidney diseases

ORCID iDs

Eun Jung
https://orcid.org/0009-0003-5625-1298
Soong-Hee Youn
https://orcid.org/0000-0002-0476-2366
Ki-Yong Shin
https://orcid.org/0009-0002-8996-0632
Hyeon-Joo Shin
https://orcid.org/0009-0009-1194-2718
Joon-Young Yang
https://orcid.org/0009-0003-6042-9570
Yeseul Yang
https://orcid.org/0000-0001-5367-2378
Jae-Ha Jung
https://orcid.org/0000-0002-1115-3745
Yongbaek Kim
https://orcid.org/0000-0003-1633-9247

Author Contributions

Conceptualization: Jung E, Youn SH, Kim Y; Data curation: Jung E; Formal analysis: Jung E; Investigation: Jung E; Methodology: Jung E; Resources: Jung E, Shin KY, Shin HJ, Yang JY, Yang Y, Jung JH; Writing - original draft: Jung E; Writing - review & editing: Jung E, Youn SH, Kim Y.

Conflict of Interest

The authors declare no conflicts of interest.

INTRODUCTION

Renal disease has been described elsewhere in striped skunks (*Mephitis mephitis*) [1]. Renal lesions are diagnosed on postmortem histopathological examination and elevation of renal blood markers has been documented in skunks [1-3]. Notably, a study reported the detection of renal lesions in 74% of skunk kidneys [1], indicating a considerable prevalence of kidney disease within this species.

Blood creatinine (Cr) and blood urea nitrogen (BUN) are commonly utilized biomarkers for assessing renal function in animals including striped skunks [1,3,4]. However, BUN and Cr lack sensitivity for the early detection of renal damage [4]. BUN or Cr remains within the normal reference interval until 75% loss of renal function [5]. Furthermore, BUN production and excretion are not constant and can be influenced by extrarenal factors, such as protein intake and dehydration [5]. Cr levels are also affected by muscle mass, sex, age, and dehydration [4,6]. In animals experiencing continued loss of muscle mass, Cr becomes an unreliable biomarker for estimating the glomerular filtration rate (GFR) [4,6].

Symmetric dimethylarginine (SDMA), a methylated arginine of similar size to Cr, is primarily excreted through the kidneys [4,7]. Several studies have demonstrated a strong correlation between SDMA and GFR in animals [8-10]. SDMA remains unaffected by non-renal factors such as age, weight, and muscle mass [4,6]. Moreover, elevated SDMA levels reflect a decline in GFR before Cr levels deviate from the reference range in dogs and cats, suggesting its potential as an early diagnostic biomarker for renal diseases [4,9-11]. This study aimed to assess the utility of SDMA as a biomarker for kidney disease in striped skunks.

METHODS

This was a retrospective study of striped skunks housed at Everland zoo. Blood samples were collected for clinical purposes, with no additional blood drawn specifically for this study. All striped skunks (n = 11) underwent annual screening or were assessed based on clinical symptoms, such as loss of appetite and decreased vitality, between 2017 and 2021.

Kidney function was determined based on health check-up results, including blood analysis and diagnostic ultrasound. Necropsies were conducted on deceased animals (n = 8), and the kidneys of three animals underwent histological examination at either the College of Veterinary Medicine at Seoul National University (Korea) or IDEXX laboratories (Korea).

Blood was collected from the cephalic vein using physical restraint and a 23-ga needle mounted on a 3-mL syringe. Plasma was separated from the heparinized blood samples and immediately subjected to tests at in-house laboratory. A portion of the plasma sample was transported directly on ice in a cooler to the NEODN BioVet Laboratory (Korea) and/or IDEXX laboratories for the SDMA test. Blood chemistry parameters, including BUN and Cr, were measured using colorimetric methods with an in-house analyzer (Labexchange; Fujifilm Dri-Chem 3500i, Japan), while SDMA levels were determined using a commercially available high-throughput, homogenous immunoassay.

The upper limit of the reference intervals was set at1.0 mg/dL for Cr (range 0.2–1.0 mg/dL) and 42 mg/dL for BUN (range 10–42 mg/dL) based on the International Species Information System (ISIS) 2013: Physiological data reference values [12].

GraphPad Prism 5 (GraphPad Software, USA) was used for statistical analysis. The data were tested for normal distributions using D'Agostino & Pearson omnibus normality test and Shapiro-Wilk normality test. The non-normally distributed data were analyzed using the Spearman Correlation test. A $p < 0.05$ was considered statistically significant.

RESULTS

Of the 11 animals, 8 were males and 3 were females. During the examination, the body condition of the skunk was assessed through body weight and visual inspection. Eleven skunks maintained between 2.0 and 3.7 kg. However, as Skunk 2 and 6 approached the time of death, their weight dropped to less than 2 kg, revealing slight emaciation.

Eight skunks (skunk 1-8) died during the study period, and all 8 underwent necropsy. The mean age (± SD) of 8 deceased skunks was 8 years (± 1.4), with age range of 5 to 10 years. Six skunks (skunk 1-6) died of the kidney disease, while skunk 7 died of round cell tumor and skunk 8 due to hemorrhagic enteritis. Histological examination of the kidneys from three dead skunks revealed membranous glomerulonephritis in one case (skunk 3) and interstitial nephritis in two cases (skunk 1 and 4).

The age at the time of blood collection ranged from 1 to 10 years. Signalment, diagnosis, and test results, including gross and histologic findings (in cases of deceased animals) related to kidney disease of 11 skunks, are summarized in **Table 1**. Following a comprehensive evaluation, which incorporated increased renal parameters in blood tests, clinical symptoms (such as decreased appetite and lethargy), ultrasound examination results, postmortem examination findings (renal lesions), and histopathological analyses, seven skunks were diagnosed with kidney disease (skunk 1–6, 11).

The results for SDMA, Cr, and BUN levels are detailed in **Fig. 1**. The number of samples in which SDMA, Cr, and BUN were all measured among the multiple blood sampling was 27. To compare values obtained from these 27 samples, in skunks diagnosed with kidney disease (n = 7), Cr, BUN, and SDMA levels ranged from 0.2 to 4.96 mg/dL, 20.4 to 236.1 mg/dL, and 5 to 80 μg/dL, respectively. Conversely, in skunks without kidney disease (n = 4), respective ranges were 0.2 to 0.9 mg/dL for Cr, 12.8 to 42.5 mg/dL for BUN, and 6 to 13 μg/dL for SDMA (**Fig. 2**). As SDMA levels increased, there was a corresponding upward trend in the concentrations of BUN and Cr. SDMA values were positively associated with Cr ($r = 0.7969$, $p < 0.0001$) and BUN ($r = 0.7677$, $p < 0.0001$) values. Cr concentration was positively associated with BUN concentration ($r = 0.8192$, $p < 0.0001$) (**Fig. 3**).

DISCUSSION

To our knowledge, this study represents the first attempt to evaluate the potential utility of SDMA as a biomarker for kidney dysfunction in captive striped skunks in Korea.

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Table 1. Signalment, diagnosis and test results relevant to kidney disease in 11 striped skunks (*Mephitis mephitis*)

Name	Sex	Age (yr)[a]	Diagnosis	Increased renal parameters in blood[c]	Ultrasonography	Kidney gross examinations at necropsy	Kidney histologic lesions
Skunk 1	M	8	CKD	BUN, Cr, P	Hyperechoic cortex and medulla of kidney, reduced corticomedullary distinction	Irregular surface, dark brown black discoloration, difficult to distinguish cortex and medulla on the cut surface	Interstitial nephritis
Skunk 2	F	10	CKD	BUN, Cr, P	Hyperechoic cortex and medulla of kidney, reduced corticomedullary distinction	Rough, granular appearing surface	ND
Skunk 3	M	9	CKD	BUN, Cr	ND	Rough, granular appearing surface	Membranous glomerulonephritis
Skunk 4	M	8	CKD	BUN, Cr, P	ND	Rough, granular appearing surface	Severe chronic interstitial nephritis
Skunk 5	M	8	AKI	BUN, Cr, P	Hyperechoic cortex and medulla of kidney, reduced corticomedullary distinction	Pale, white dots on the surface	ND
Skunk 6	M	9	Uremic stomatitis with renal failure	BUN, Cr, P	ND	Pale, multifocal red dots on the surface and medulla	ND
Skunk 7	M	7	-[b]	WNL	ND	NRF	ND
Skunk 8	M	5	-[b]	WNL	ND	NRF	ND
Skunk 9	F	5	-	WNL	NRF	ND	ND
Skunk 10	M	5	-	WNL	ND	ND	ND
Skunk 11	F	4	Hydronephrosis	BUN, Cr	Hyperechoic cortex and medulla of kidney, hydronephrosis	ND	ND

M, male; F, female; CKD, chronic kidney disease; BUN, blood urea nitrogen; Cr, creatinine; P, phosphorus; AKI, acute kidney injury; WNL, within normal limits; NRF, no remarkable findings; ND, not determined.
[a]Age of skunk 1–8 is recorded as age of death. Age of skunk 9–11 is recorded as of 2021.
[b]No diagnosis related to kidney disease.
[c]The upper limit of the reference intervals was considered to be 1.0 mg/dL for Cr (range 0.2–1.0 mg/dL), 42 mg/dL for BUN (range 10–42 mg/dL), and 10.5 mg/dL for P (range 2.7–10.5 mg/dL) based on International Species Information System: *Physiological data reference values* [12].

SDMA, an emerging renal biomarker, has been suggested as an endogenous marker of GFR due to its primary elimination through renal excretion [7,8]. It has been effectively utilized in diagnosing renal dysfunction in dogs and cats [8-10,13]. Furthermore, studies in various wild animal species, including greater flamingos (*Phoenicopterus roseus*), tigers (*Panthera tigris*) and cheetahs (*Acinonyx jubatus*), have indicated SDMA as a promising marker of kidney function [14-16]. While Cr and BUN are commonly employed as renal biomarkers in clinical practice [4,5], our findings demonstrate a strong correlation of SDMA levels with Cr and BUN levels, suggesting the potential utility of SDMA as an additional diagnostic biomarker for kidney disease in striped skunks.

In dogs and cats, the stage of kidney disease is typically determined by the Cr concentration [17,18]. Our study observed a trend of increasing SDMA and Cr levels over time as kidney disease progressed, implying that SDMA concentration may rise with the severity of kidney disease.

The upper limit of the reference range for SDMA is set at 14 μg/dL in healthy dogs and cats [9,11], similar to levels observed in healthy human subjects (6–13.1 μg/dL) [19]. In one study involving horses, over 95% had serum SDMA concentrations below 14 μg/dL, suggesting it could serve as a cut-off value for horses [20]. Similar reference ranges across multiple species indicate that the 14 μg/dL of SDMA could be acceptable to set as the upper limit for skunks. Supporting this notion, the skunks without kidney disease (n = 4) in our study had SDMA concentrations ranging from 6 to 13 μg/dL. However, following the diagnosis of kidney disease, SDMA concentrations exceeded 14 μg/dL in the blood sample of affected skunks (**Fig. 1**). Intriguingly, one sample from skunk 2 diagnosed with kidney disease had an SDMA value of 13 μg/dL, which was possibly attributed to factors such as ongoing treatment for kidney disease, the relatively early disease stage, or fluctuation in results due to inherent nature of the test.

A Skunk 1

Serum chemistry	Reference range	08-Jan-2017[a]	06-Feb-2017	11-Mar-2017[b]	18-Apr-2017	17-May-2017
BUN (mg/dL)	10–42	68.4	100	107.2	111.2	170.8
Cr (mg/dL)	0.2–1.0	1	1.2	1	1.1	2.4
SDMA (μg/dL)	-	-	-	30	-	-
P (mg/dL)	2.7–10.5	7.9	8.7	7	10.3	18

B Skunk 2

Serum chemistry	Reference range	10-Jan-2017	29-Mar-2018[a]	28-May-2018	16-Jun-2018[b]	12-Sep-2018	30-Dec-2018
BUN (mg/dL)	10–42	36.4	46.5	48	36	40	47.5
Cr (mg/dL)	0.2–1.0	0.5	0.7	0.7	0.6	0.6	0.8
SDMA (μg/dL)	-	-	25	-	25	-	-
P (mg/dL)	2.7–10.5	-	3.6	5.3	-	4.9	4.1
		19-Feb-2019	20-May-2019	27-Jun-2019	25-Aug-2019	09-Sep-2019	18-Sep-2019
BUN (mg/dL)	10–42	82.4	49.2	55.1	106.9	116.5	104.9
Cr (mg/dL)	0.2–1.0	1	1.2	0.92	1.56	3.2	2.39
SDMA (μg/dL)	-	13	24	-	-	-	-
P (mg/dL)	2.7–10.5	5.8	4.5	6.6	8.5	13.1	11.9

C Skunk 3

Serum chemistry	Reference range	05-Apr-2017	30-Jun-2017	22-Aug-2017	06-Nov-2017	06-Jan-2018[a]
BUN (mg/dL)	10–42	39.2	56.1	31	41.7	63.2
Cr (mg/dL)	0.2–1.0	0.4	0.6	0.8	0.6	1.2
SDMA (μg/dL)	-	-	12	-	-	36
P (mg/dL)	2.7–10.5	4.1	5.2	5.3	5.1	7.6

D Skunk 4

Serum chemistry	Reference range	17-Nov-2017	10-Jan-2019	16-Apr-2019	06-May-2019	17-Aug-2019[a]
BUN (mg/dL)	10–42	36.6	40.9	48.5	36.1	141.7
Cr (mg/dL)	0.2–1.0	0.3	0.7	0.51	0.6	1.08
SDMA (μg/dL)	-	-	-	20	-	-
P (mg/dL)	2.7–10.5	5	4.5	5	6.1	19

E Skunk 5

Serum chemistry	Reference range	09-Feb-2018	13-Feb-2019	11-Mar-2020	18-Apr-2020	8-May-2020[a]	10-May-2020	12-May-2020
BUN (mg/dL)	10–42	36.4	20.4	41.2	34.9	164	159.4	210.7
Cr (mg/dL)	0.2–1.0	0.3	0.4	0.55	0.4	5.7	4.96	5.33
SDMA (μg/dL)	-	-	7	5	10	-	80	-
P (mg/dL)	2.7–10.5	4.4	4.8	5	4.2	4.2	23.5	23.5

Fig. 1. Serum chemistry results related renal function in 11 striped skunks (*Mephitis mephitis*) between 2017 and 2021. (A)-(K) each corresponds to skunk 1–11. Reference range is based on International Species Information System: *Physiological data reference values* [12].
Skunk 3 and 4 were diagnosed with CKD after death.
BUN, blood urea nitrogen; Cr, creatinine; SDMA, symmetric dimethylarginine; P, phosphorus; CKD, chronic kidney disease.
[a]Date of diagnosis of kidney disease.
[b]Date of diagnosis CKD.

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Several studies have suggested the potential value of SDMA as an early diagnostic biomarker for kidney diseases in animal species other than dogs and cats [4,9-11,14,15]. Elevated SDMA levels reflect a decrease in GFR before Cr levels deviate from the reference range in dogs and cats, suggesting its value as an early diagnostic biomarker for renal diseases [4,9-11]. Three of seven tigers with multiple SDMA measurements exhibited elevated SDMA levels before Cr elevation [15]. Similarly, in cheetahs, a sharp increase in the SDMA levels preceded elevated Cr levels in five of seven animals [14].

F Skunk 6

Serum chemistry	Reference range	07-Mar-2017	09-Feb-2018	09-Feb-2019	25-Dec-2019	25-Apr-2020	14-Jan-2021
BUN (mg/dL)	10–42	15.3	21	43.8	23	24.6	21.7
Cr (mg/dL)	0.2–1.0	0.2	0.5	0.2	0.6	0.45	0.8
SDMA (μg/dL)	-	-	-	7	11	9	-
P (mg/dL)	2.7–10.5	-	-	5.5	4.6	4.2	5.1
		01-Mar-2021	03-May-2021	04-Jun-2021[a]	06-Jun-2021	07-Jun-2021	09-Jun-2021
BUN (mg/dL)	10–42	40.7	72.6	236.1	207.4	133.1	114.6
Cr (mg/dL)	0.2–1.0	0.52	0.78	4.2	5.04	3.85	3.98
SDMA (μg/dL)	-	-	23	61	-	-	-
P (mg/dL)	2.7–10.5	4.4	6.7	20	17.8	12	13.8

G Skunk 7

Serum chemistry	Reference range	22-Jul-2017	17-Jan-2018	03-Jul-2018	26-Feb-2019	27-Jun-2019
BUN (mg/dL)	10–42	31.3	17.8	30.2	35.8	29.9
Cr (mg/dL)	0.2–1.0	0.4	0.2	0.2	0.3	0.4
SDMA (μg/dL)	-	-	11	-	13	-
P (mg/dL)	2.7–10.5	2.9	4.6	-	5.8	4.5

H Skunk 8

Serum chemistry	Reference range	03-Jun-2021	24-Jul-2021	08-Sep-2021
BUN (mg/dL)	10–42	27.4	25.2	32.3
Cr (mg/dL)	0.2–1.0	0.33	0.56	0.3
SDMA (μg/dL)	-	11	-	6
P (mg/dL)	2.7–10.5	5.5	4.6	5

I Skunk 9

Serum chemistry	Reference range	30-Jul-2018	02-Jan-2021	22-Dec-2021
BUN (mg/dL)	10–42	21.2	12.8	38.4
Cr (mg/dL)	0.2–1.0	0.8	0.5	0.42
SDMA (μg/dL)	-	-	9	9
P (mg/dL)	2.7–10.5	3.9	1.5	2.6

J Skunk 10

Serum chemistry	Reference range	10-Apr-2018	04-Sep-2019	18-Oct-2021
BUN (mg/dL)	10–42	25.2	23.3	42.5
Cr (mg/dL)	0.2–1.0	0.4	0.7	0.9
SDMA (μg/dL)	-	-	-	11
P (mg/dL)	2.7–10.5	9.4	8	2.4

K Skunk 11

Serum chemistry	Reference range	03-Aug-2018	04-Sep-2019	25-Nov-2021[a]	07-Dec-2021	16-Dec-2021
BUN (mg/dL)	10–42	19.7	24.1	77.6	86.4	93.6
Cr (mg/dL)	0.2–1.0	0.6	0.4	1.78	1.79	1.6
SDMA (μg/dL)	-	-	-	24	26	28
P (mg/dL)	2.7–10.5	3.6	4.3	5.2	-	6.2

Fig. 1. (Continued) Serum chemistry results related renal function in 11 striped skunks (*Mephitis mephitis*) between 2017 and 2021. (A)-(K) each corresponds to skunk 1–11. Reference range is based on International Species Information System: *Physiological data reference values* [12].
Skunk 3 and 4 were diagnosed with CKD after death.
BUN, blood urea nitrogen; Cr, creatinine; SDMA, symmetric dimethylarginine; P, phosphorus; CKD, chronic kidney disease.
[a]Date of diagnosis of kidney disease.
[b]Date of diagnosis CKD.

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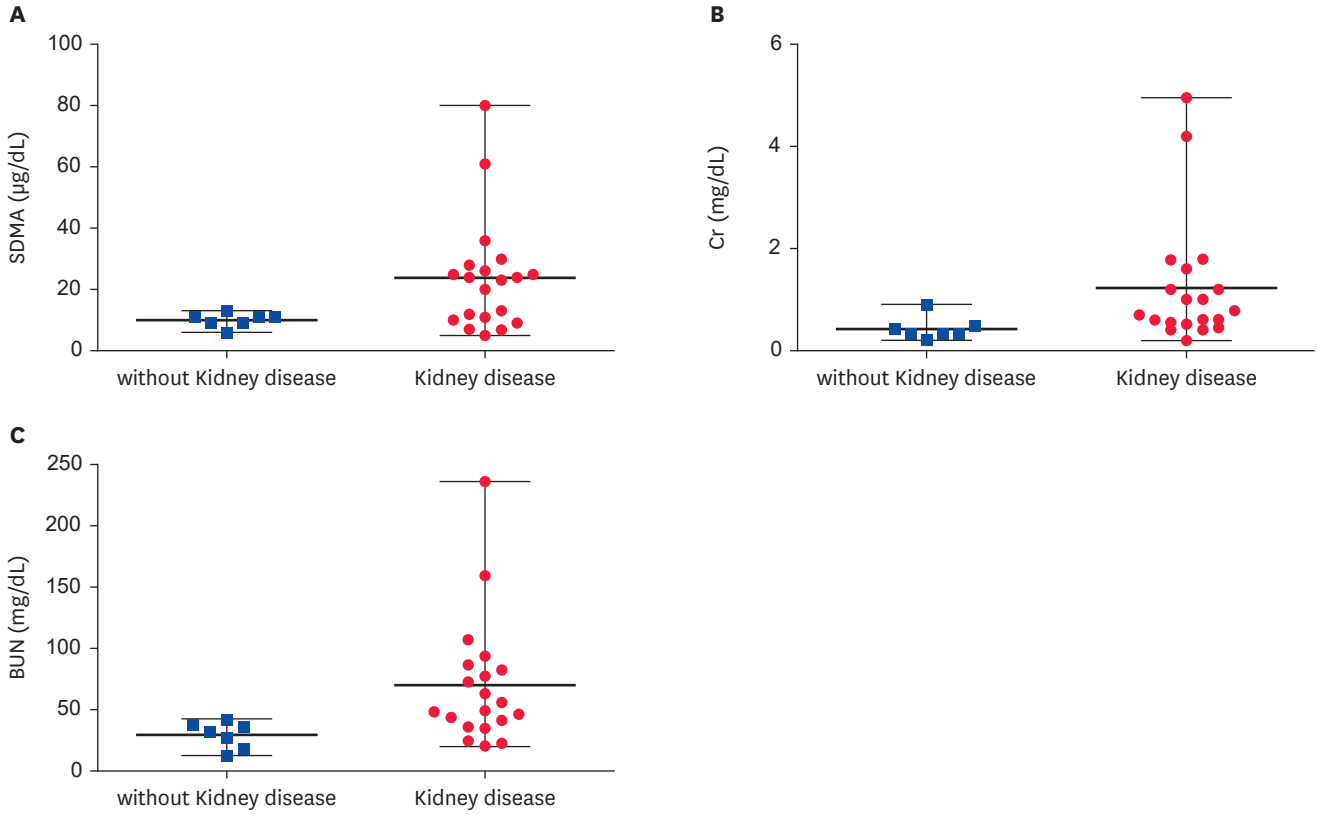

Fig. 2. Comparison (A) SDMA, (B) Cr, and (C) BUN concentrations between skunks with kidney disease and those without kidney disease. Values are from 27 samples in which SDMA, Cr and BUN were all measured. Bars represent mean with range.
SDMA, symmetric dimethylarginine; Cr, creatinine; BUN, blood urea nitrogen.

As no physiological SDMA reference values are available for skunks, it is difficult to determine how far ahead an increase beyond the upper reference limit of SDMA would occur before the increase in Cr and BUN. Nevertheless, SDMA levels first exceeded 14 μg/dL on average 191 days earlier in three skunks (2, 4, and 6; 417 days, 123 days, and 32 days, respectively) before the rise of serum Cr and BUN above the upper reference limit. Although further studies with larger sample sizes are warranted, SDMA could serve as an early biomarker for diagnosing kidney dysfunction in striped skunks.

The body weight range of skunk is 0.75–4 kg [21]. However, there is currently no body condition scoring system available for skunks. Herein, scoring systems for domestic species and weight checks were used to evaluate the skunks' condition. In this study, skunks maintained within 2.0–3.7 kg and their ribs were felt without excessive fat, so the skunks were evaluated to be of normal shape. Before the death, skunk 2 and 6 were slightly emaciated and less than 2.0 kg. SDMA appears to be less affected by extrarenal factors than other markers such as Cr and BUN [6]. Considering the variation in skunk weight range, SDMA would be advantageous for the diagnosis of kidney disease in skunks.

Chronic kidney disease (CKD) occurs in dogs and cats at any age; however, its prevalence increases with age [17,18]. In this study, four of eleven skunks were diagnosed with CKD (**Table 1**). The mean age (± SD) of these four skunks was 8.75 years (± 0.8) (range 8–10 years). Given our study data and the average lifespan of 8 to 10 years in skunks [21],

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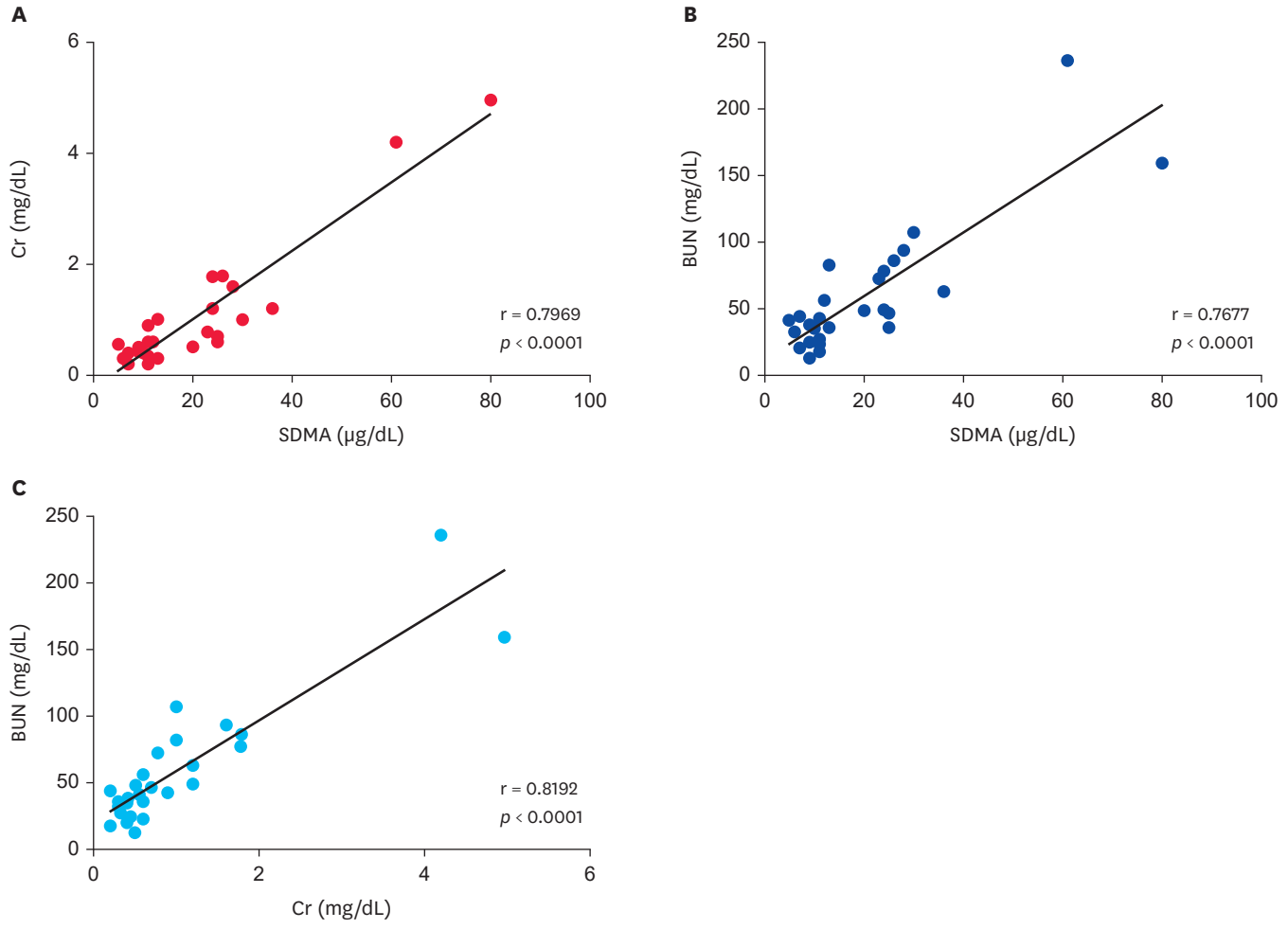

Fig. 3. Spearman correlation analysis. (A) SDMA and Cr (r = 0.7969, $p < 0.0001$), (B) SDMA and BUN (r = 0.7677, $p < 0.0001$), and (C) Cr and BUN (r = 0.8192, $p < 0.0001$) of 11 striped skunks (*Mephitis mephitis*). As SDMA levels increased, there was a concurrent upward trend observed in the concentrations of BUN and Cr. SDMA, symmetric dimethylarginine; Cr, creatinine; BUN, blood urea nitrogen.

further investigations are necessary to delineate the relationship between the CKD and clinicopathological data in elderly skunks.

An SDMA/Cr ratio of > 10 has been reported to have a poor prognosis in dogs and cats with kidney diseases [13]. In this study, five of the seven skunks diagnosed with kidney disease underwent multiple SDMA measurement. Among these five skunks, three (skunk 3, 5, and 6) exhibited a considerable increase in SDMA levels and died within a month. In the case of skunk 3, the SDMA level increased threefold from the previous measurement. Skunk 5 maintained similar SDMA levels (5–10 μg/dL), but the last measured SDMA increased eightfold from the previous value. Similarly, skunk 6 maintained SDMA levels within the range of 7–11 μg/dL, but the value increased 2.6 times from the previous measurement, followed by a 2.7 times increase. Among the other two skunks, Skunk 2 maintained SDMA levels in the range of 24–25 μg/dL but temporarily dropped to 13 μg/dL once, and skunk 11 maintained levels in the range in the 24–28 μg/dL (**Fig. 1**). These findings suggest the potential of assessing the prognosis of kidney disease in skunks based on changes in SDMA levels.

The present study had several limitations. Firstly, the sample size was small, and since normal SDMA, Cr, and BUN reference intervals are lacking in skunks, increases in Cr and BUN levels were determined based on the ISIS. Secondly, due to the retrospective nature of the study, skunks diagnosed with kidney disease received supportive treatment for kidney disease from the time of diagnosis, potentially affecting the blood test results during the study period. Thirdly, non-renal diseases may have an impact on SDMA in skunks. In our study, two animals (skunk 1 and 4) exhibited arrhythmias or cardiac murmurs on auscultation, along with cardiomegaly on radiography which may have influenced the SDMA results [22]. However, heart disease can also lead to a decline in kidney function [23]. Lastly, SDMA was measured using a commercially available high-throughput immunoassay; however, liquid chromatography-mass spectroscopy is considered the most accurate assay for blood SDMA.

In summary, SDMA may enable earlier detection of kidney disease compared to Cr and BUN, potentially aiding in the management of renal dysfunction and leading to improved prognosis in skunks. Further studies with larger sample sizes are warranted to validate the clinical utility of SDMA in captive striped skunks.

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