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RESEARCH ARTICLE

Plasma and Urinary Kidney Injury Molecule-1 as Early Biomarkers for the Diagnosis of Stable Chronic Kidney Disease in Dogs

S.J. Yu and J.H. Kim*

Department of Veterinary Internal Medicine, College of Veterinary Medicine, Konkuk University, 120, Neungdong-ro, Gwangjin-gu, Seoul, Republic of Korea.
*Corresponding author: junghyun@konkuk.ac.kr

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ABSTRACT

Early detection of chronic kidney disease (CKD) remains challenging, most likely due to the limited sensitivity of conventional renal biomarkers for identifying subclinical diseases. Kidney injury molecule-1 (KIM-1) is a biomarker for the detection of acute kidney injury; however, its potential role in canine CKD is unclear. This study aimed to evaluate plasma KIM-1 (pKIM-1) and urinary KIM-1-to-creatinine ratio (uKIM-1/uCr) as diagnostic biomarkers for stable CKD in dogs, with or without non-azotemic stages, and assess their correlations with conventional renal biomarkers. Ten healthy control dogs, 14 dogs with non-azotemic stable CKD, and 11 dogs with azotemic stable CKD were prospectively enrolled. Plasma and urinary KIM-1 concentrations were measured using canine-specific ELISA. Conventional renal biomarkers, including blood creatinine, blood urea nitrogen (BUN), symmetric dimethylarginine (SDMA), urine protein-to-creatinine ratio (UPCR), and urine specific gravity (USG) were also analyzed, and the diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis. Results showed that pKIM-1 levels and uKIM-1/uCr ratios were significantly higher in CKD dogs than that in healthy controls ($P<0.05$), regardless of the azotemia status. These markers showed moderate-to-strong positive correlations with conventional renal markers, including creatinine, BUN, SDMA, and the urine protein-to-creatinine ratio. The ROC curve analysis demonstrated precise diagnostic accuracy for stable CKD, including in non-azotemic dogs. In conclusion, plasma and urinary KIM-1 levels are promising biomarkers for the diagnosis of stable CKD in dogs, enabling earlier and more precise detection before azotemia development.

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INTRODUCTION

Chronic kidney disease (CKD) is a common progressive problem in geriatric dogs. However, its exact prevalence is likely to be underestimated because the conventionally used renal biomarkers lack sensitivity for detecting early or subclinical disease stages (Chen *et al.,* 2023). Many dogs with early-stage CKD remain asymptomatic until substantial renal damage has occurred, which has led to CKD being described as a "silent" disease (Bartges, 2012).

Traditionally, markers, such as serum creatinine (CREA), blood urea nitrogen (BUN), urine specific gravity (Hokamp and Nabity, 2016), symmetric dimethylarginine (Wun *et al.,* 2024), and urine protein-to-creatinine ratio (Chen *et al.,* 2023) have been used to evaluate renal function. However, because these biomarkers mainly reflect advanced declines in glomerular filtration rate (GFR), they cannot reliably detect early tubular injury or predict disease progression (Chen *et al.,* 2023; Nabity and Hokamp, 2023; Kim *et al.,* 2024). Delays in CKD diagnosis worsen the prognosis; therefore, novel biomarkers capable of identifying renal tubular damage before the occurrence of substantial functional loss are badly needed (Perini-Perera *et al.,* 2021; Chen *et al.,* 2023; Nabity and Hokamp, 2023).

Kidney injury molecule-1 (KIM-1), a type I transmembrane glycoprotein highly expressed in proximal tubular epithelial cells after toxic or ischemic injury, is a sensitive biomarker for acute kidney injury (AKI) in both human (Griffin *et al.,* 2019; Srisawat and Kellum, 2020; Geng *et al.,* 2021) and veterinary medicine (Lippi *et al.,* 2018; Kuleš *et al.,* 2018; Zheng *et al.,* 2019). Although baseline KIM-1 expression in healthy kidneys is minimal,

it rapidly increases within 24–72h of renal injury (Han *et al.,* 2020; Srisawat and Kellum, 2020). Beyond acute injury, persistent KIM-1 overexpression contributes to tubulo-interstitial inflammation and fibrosis (Tian *et al.,* 2017; Song *et al.,* 2019). Urinary KIM-1 (uKIM-1), urinary KIM-1-to-creatinine ratio (uKIM-1/uCr) and plasma KIM-1 (pKIM-1) have been investigated as biomarkers for chronic renal injury and CKD progression in humans (Fernando *et al.,* 2019; Schulz *et al.,* 2020; Peng *et al.,* 2022).

In veterinary medicine, KIM-1 has mainly been evaluated as a marker of AKI in dogs owing to various etiologies, such as nephrotoxic drug use (Zheng *et al.,* 2019), infectious diseases (Kuleš *et al.,* 2018), and ischemia (Davis *et al.,* 2021; Segev *et al.,* 2024). However, to the best of our knowledge, its role in canine CKD, especially in stable and non-azotemic diseases, has not yet been systematically characterized.

Therefore, this study aimed to evaluate pKIM-1 and uKIM-1/uCr concentrations in healthy dogs and dogs with stable CKD, including non-azotemic stages, and examine their correlations with conventional renal biomarkers. It was hypothesized that both pKIM-1 level and uKIM-1/uCr ratio would be higher in dogs with CKD than in healthy dogs, and that these biomarkers would show significant correlations with conventional renal parameters.

MATERIALS AND METHODS

Study design and animals: A total of 35 client-owned dogs, visiting the Konkuk University Veterinary Medical Teaching Hospital, South Korea during the period from October 2021 to June 2022 were selected for this study. Overall, the study population consisted of 15 males and 20 females, aged 1–18 years, with body weights ranging from 2.23 to 19.5kg. They were brought to the hospital for routine health evaluation or assessment of renal function. The study protocol was duly approved by the Institutional Animal Care and Use Committee (IACUC No. KU21196). These dogs were classified into three groups, healthy controls (n=10), non-azotemic stable CKD (n=14), and azotemic stable CKD (n=11), based on International Renal Interest Society (IRIS) criteria (Lippi *et al.,* 2014).

Stable CKD was defined as a persistent serum creatinine concentration ≥1.4 mg/dL that remained relatively constant without marked fluctuation for at least three months (Lippi *et al.,* 2014). Azotemia was defined as creatinine >1.6 mg/dL (Kim *et al.,* 2019) or BUN >27mg/dL (Nicolle *et al.,* 2007). Chronic kidney disease was confirmed using a combination of blood tests, urinalysis, and ultrasonographic findings (Perondi *et al.,* 2020). Dogs with suspected AKI, urinary tract infection, obstructive uropathy, systemic hypoxia, or recent nephrotoxic exposure were excluded from the study.

Clinical evaluation: Complete physical examination, body condition score, heart and lung auscultation, and systolic arterial pressure (SAP) measurements were performed on each dog. The SAP was measured five times using an oscillometric device (Cardell Insight, Midmark Corp., Versailles, OH, USA), excluding the highest and lowest values and averaging the remainder (Armstrong, 2014). Signalment and clinical histories were recorded through owner interviews. All enrolled dogs underwent a complete clinical examination and were considered clinically stable. None of the dogs showed unsatisfactory results on the clinical evaluation.

Sample collection: Approximately 5mL of jugular venous blood was collected from each dog into lithium-heparin tubes, centrifuged at 2,000×g (≈3,000rpm) for 10min at 4°C, plasma was harvested and stored at −80°C until analysis. Urine was collected by ultrasound-guided cystocentesis, centrifuged at 2,000×g (≈3,000rpm) for 20min at 4°C, the supernatant was collected and stored at −80°C.

Measurement of conventional renal biomarkers: Plasma blood urea nitrogen (BUN), creatinine, and symmetric dimethylarginine (SDMA) levels were measured by using the Catalyst One Analyzer (IDEXX Laboratories, USA). Urinary specific gravity was measured using a refractometer. Urine protein-to-creatinine ratio (UPCR) was calculated based on the urine protein and creatinine concentrations determined after urine centrifugation. Dogs were classified as proteinuric when the urine protein-to-creatinine ratio exceeded 0.5, in accordance with the IRIS guidelines (IRIS, 2019). Additionally, for statistical analysis, UPCR values below the detection limit of the assay were considered as 0. Urine sediments obtained through centrifugation were evaluated under a microscope for the presence of bacteria, casts, crystals, blood cells, and abnormal transitional epithelial cells. Bacterial contamination was suspected when bacteria or pyuria was observed microscopically (Chew *et al.,* 2011). If bacterial presence was suspected, more than 0.5mL of urine samples were transported to a commercial laboratory (Nosvet, South Korea) for urine culture using standard aerobic culture methods on blood and MacConkey agar, incubated at 37°C for 24–48h. Dogs were excluded for further study if urine culture results were positive.

Measurement of KIM-1: The plasma KIM-1 (pKIM-1) and urine KMI-1 (uKIM-1) concentrations were measured using a canine-specific ELISA kit (ab205084, Abcam, UK) according to the manufacturer's instructions. Briefly, the urine was diluted 1:40, and plasma was diluted 1:5 with buffer. The plates were incubated with the samples for 2h, washed, incubated with the detection antibody for 20min, and then with streptavidin-HRP for 20min. After adding the TMB substrate for 10min, the reaction was stopped, and the absorbance was read at 450nm. A standard curve was generated using serially diluted standards provided in the kit, and the KIM-1 concentrations were calculated based on this curve. The uKIM-1 was normalized to urine creatinine to calculate uKIM-1/uCr ratio (Tang *et al.,* 2015).

Statistical analysis: Data were assessed for normality using the Shapiro–Wilk test. As the data were not normally distributed, values are presented as medians with interquartile ranges (IQRs), and non-parametric tests were applied. Kruskal–Wallis test with Bonferroni correction or Mann–Whitney U test was used for group comparisons (Armstrong, 2014). Pearson's correlation coefficients were used to assess the relationships between the markers.

Receiver operating characteristic (ROC) curve analysis using the Youden index method was performed to assess the diagnostic ability of the novel renal biomarkers (pKIM-1 concentration and uKIM-1/uCr ratio) for differentiating dogs with stable CKD and non-azotemic stable CKD from healthy controls, and to determine optimal cut-off values for each biomarker (Unal, 2017). Statistical significance was set at P<0.05.

RESULTS

Study population: Table 1 summarizes the characteristics of the dogs of the three study groups. Dogs of non-azotemic and azotemic groups with stable CKD were significantly older than healthy controls (P<0.05). Similarly, systolic arterial pressure (SAP) was significantly higher in dogs of non-azotemic and azotemic CKD groups than those in the healthy control group (P<0.05). However, there was non-significant difference in body weight among dogs of three groups. In addition to clinical data, the IRIS stage of CKD was considered in the study population. The distribution of IRIS stages among the study groups is presented in Table 1. In the non-azotemic stable CKD group, most dogs (85.71%) were classified as stage II**,** with a few in stage I (14.29%). In the azotemic stable CKD group, the majority were in stage II (72.73%), followed by stage III (18.18%) and stage IV (9.09%).

Table 1: Characteristics of the study population

	Healthy controls	Non-azotemic stable CKD	Azotemic stable CKD
Number of dogs	10	14	11
Sex (male/female)	4/6	7/7	4/7
Body weight (kg)	6.13 (4.29–7.05)	4.79 (3.47–9.75)	3.65 (2.60–6.20)
Age (years)	4 (3.75–4.00)	11 (7.00–13.25)[a]	12 (11.00–16.00)[a]
SAP (mmHg)	120 (120–130)	138.50 (131.75–150.25)[a]	145 (133–150)[a]
IRIS stage (number of dogs)	-	I (2) II (12) III (0) IV (0)	I (0) II (8) III (2) IV (1)

Data are presented as the median (interquartile range). [a] Significant difference (P<0.05) versus healthy group. CKD, chronic kidney disease; IRIS, International Renal Interest Society; SAP, systolic arterial pressure.

Conventional renal biomarkers: Results regarding conventional renal biomarkers are presented in Table 2. Blood urea nitrogen (BUN) and creatinine levels were significantly elevated in the azotemic CKD group than the healthy control and non-azotemic stable CKD groups (P<0.05). However, non-azotemic CKD dogs did not significantly differ from the healthy controls for BUN and creatinine markers. Symmetric dimethylarginine (SDMA) concentrations were significantly higher in both non-azotemic and azotemic CKD dogs than in healthy controls (P<0.05). The UPCR was significantly higher in dogs with azotemic CKD than in controls (P<0.05). Moreover, Urine specific gravity (USG) was significantly lower in both CKD groups than in the healthy dogs (P<0.05). However, there was non-significant difference between the non-azotemic and azotemic CKD groups for SDMA, UPCR, and USG.

KIM-1 concentrations: Both pKIM-1 level (Fig. 1A) and uKIM-1/uCr ratio (Fig. 1B) were significantly higher in CKD dogs than in healthy controls (P<0.01), regardless of azotemia. Median pKIM-1 in non-azotemic CKD was 2.85ng/mL and azotemic CKD it was 3.72ng/mL, versus 1.70ng/mL in healthy dogs (Fig. 1A). Similarly, uKIM-1/uCr ratio was 22.4ng/mg in non-azotemic CKD and 26.0ng/mg in azotemic CKD, compared with 5.76ng/mg in controls (Fig. 1B). However, the differences in pKIM-1 level and uKIM-1/uCr ratio between non-azotemic stable CKD and azotemic stable CKD dogs were statistically non-significant.

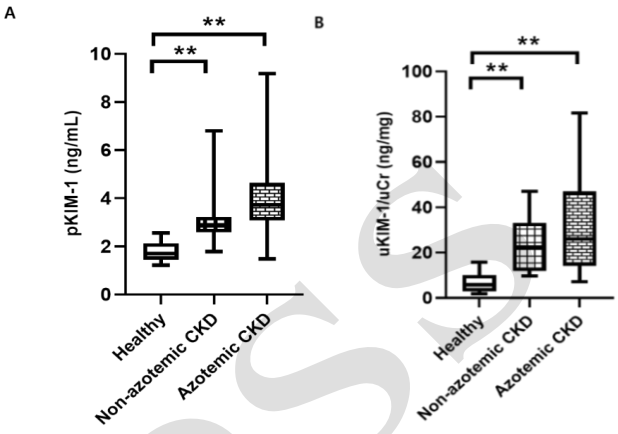

Fig. 1: Comparison of pKIM-1 concentration and uKIM-1/uCr ratio across study groups. (A): Plasma KIM-1 concentrations; (B): Urinary KIM-1-to-creatinine ratios. CKD, chronic kidney disease; pKIM-1, plasma kidney injury molecule-1; uKIM-1/uCr, urinary kidney injury molecule-1-to-creatinine ratio. **Significant difference (P<0.01).

Table 2: Median concentrations of BUN, creatinine, SDMA, UPCR, and USG across study groups

	Healthy controls	Non-azotemic stable CKD	Azotemic stable CKD
BUN (mg/dL)	17.5 (14.5–19)	17.5 (13.0–19.5)	37 (33–50)[a, b]
CREA (mg/dL)	0.8 (0.6–0.9)	1.2 (0.78–1.35)	1.6 (1.3–2.4)[a, b]
SDMA (µg/dL)	8 (7.0–10.25)	21 (19.0–22.5)[a]	29 (20–41)[a]
UPCR	0 (0–0)	0.051 (0–0.563)	0.475 (0.128–3.478)[a]
USG	1.060 (1.050–1.069)	1.017 (1.013–1.036)[a]	1.016 (1.012–1.022)[a]

Data are shown as the median (interquartile range). [a] Significant difference (P<0.05) versus healthy group; [b] Significant difference (P<0.05) versus non-azotemic stable CKD group.

Correlations among conventional renal biomarkers and KIM-1 levels: Correlations among conventional renal biomarkers and KIM-1 levels are shown in Fig. 2. The concentration of pKIM-1 showed a significant (P<0.01) positive correlation with BUN **(**r=0.423; Fig. 2A**),** CREA **(**r=0.773; Fig. 2B**)** and SDMA **(**r=0.770; Fig. 2C**)** levels. Similarly, uKIM-1/uCr showed a significant (P<0.05) positive correlation with BUN **(**r=0.702; Fig. 2D**),** CREA **(**r=0.363; Fig. 2E**)** and SDMA **(**r=0.547; Fig. 2F**)** levels. Furthermore, a moderate positive correlation was also observed between pKIM-1 and uKIM-1/uCr (r=0.529; P<0.05; Fig. 3).

Additionally, pKIM-1 concentration (Fig. 4A) and uKIM-1/uCr ratio (Fig. 4B) were significantly higher in proteinuric dogs than in non-proteinuric dogs (P<0.05). Significant (P<0.05) but negative correlations of pKIM-1 (r=–0.492; Fig. 5A) and uKIM-1/uCr (r=–0.429; Fig. 5B) markers with USG were also observed.

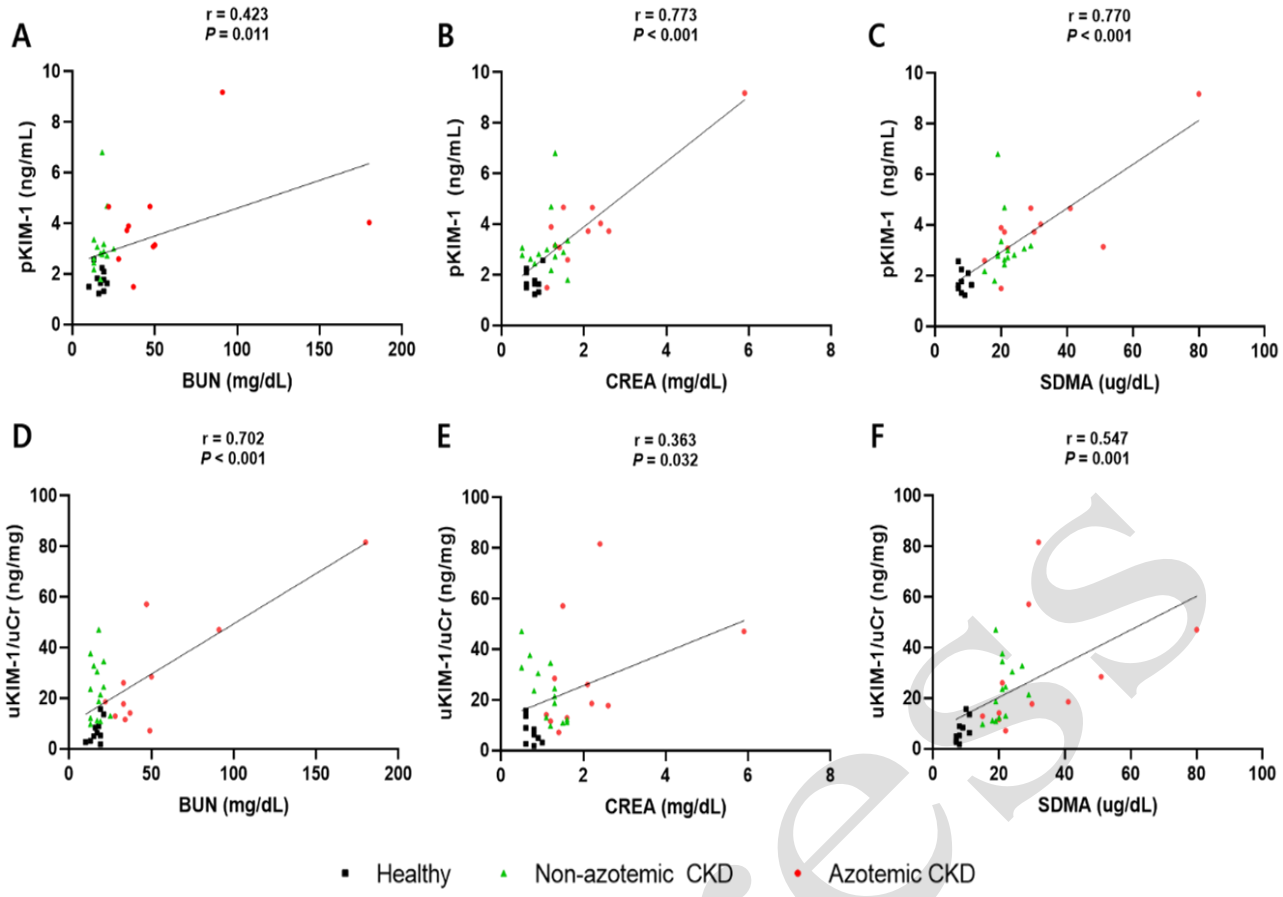

Fig. 2: Correlations of pKIM-1 concentration and uKIM-1/uCr with conventional renal biomarkers in dogs with stable CKD. (A): Relationship between pKIM-1 and BUN; (B): Relationship between pKIM-1 and creatinine; (C): Relationship between pKIM-1 and SDMA; (D): Relationship between uKIM-1/uCr and BUN; (E): Relationship between uKIM-1/uCr ratio and creatinine; (F): Relationship between uKIM-1/uCr and SDMA.

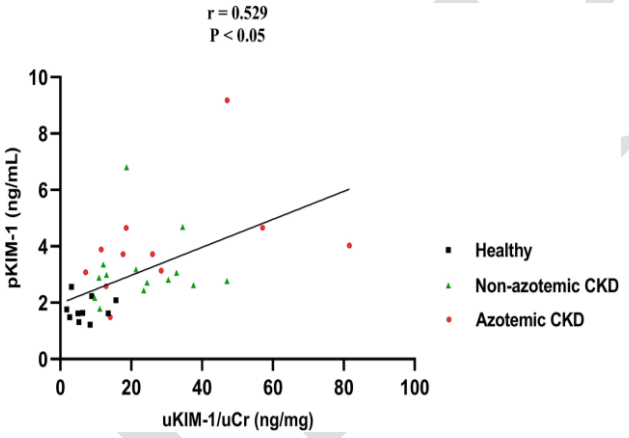

Fig. 3: Correlation between pKIM-1 concentration and uKIM-1/uCr ratio in dogs included in the study.

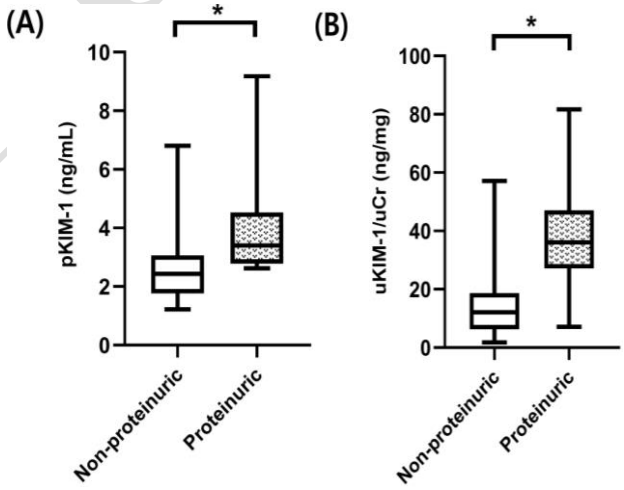

Fig. 4: Comparison of pKIM-1 concentration and uKIM-1/uCr ratio between non-proteinuric and proteinuric dogs. (A): pKIM-1 concentrations in non-proteinuric and proteinuric dogs; (B): uKIM-1/uCr ratio in non-proteinuric and proteinuric dogs. *Significant difference (P<0.05).

Diagnostic accuracy for the prediction of stable CKD: ROC curve analysis demonstrated an excellent discriminatory ability for both pKIM-1 and uKIM-1/uCr in differentiating dogs with stable CKD from healthy controls. The AUC for pKIM-1 was 0.942, with 95% CI of 0.874–1.00 (P<0.01), and a cutoff value of 2.575 ng/mL, showing 84% sensitivity and 100% specificity (Fig. 6A). The AUC for uKIM-1/uCr was 0.932 having 95% CI as 0.844–1.00 (P<0.01), with a cutoff of 9.276 ng/mg, showing 96% sensitivity and 80% specificity (Fig. 6A). Similar results were recorded for non-azotemic stable CKD, with AUCs of 0.950 for pKIM-1 and 0.929 for uKIM-1/uCr, indicating excellent performance even in non-azotemic cases (Fig. 6B). These results indicate excellent diagnostic performance of both biomarkers in differentiating dogs with stable CKD from healthy controls.

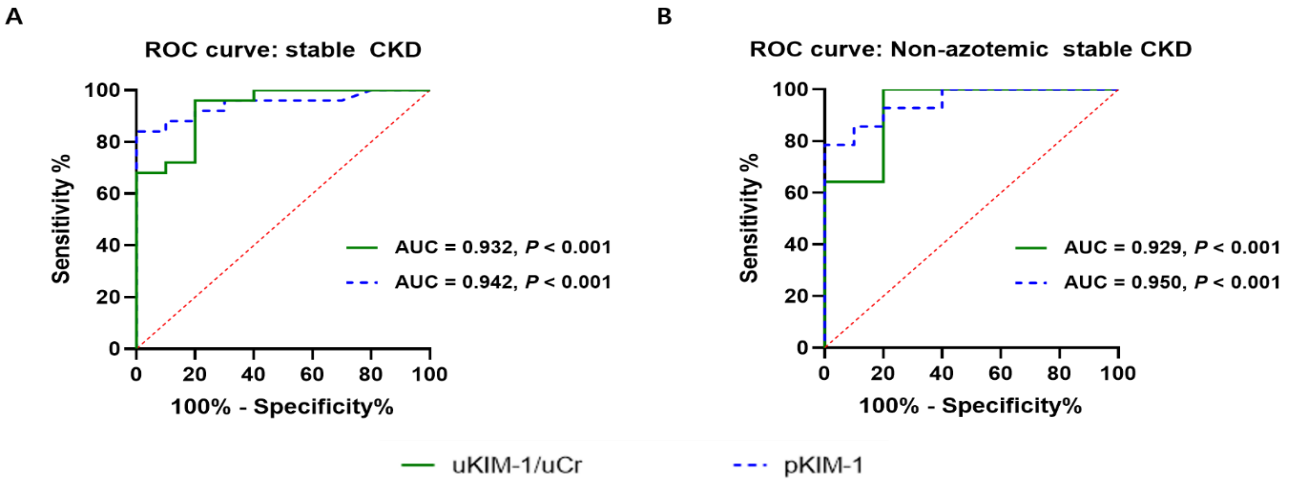

Fig. 6: ROC curves for pKIM-1 and uKIM-1/uCr. (A): ROC curve for distinguishing stable CKD dogs from healthy controls; (B): ROC curve for distinguishing non-azotemic stable CKD dogs from healthy controls. AUC, area under the curve; ROC, receiver operating characteristic; CKD, chronic kidney disease; pKIM-1, plasma kidney injury molecule-1; uKIM-1/uCr, urinary kidney injury molecule-1-to-creatinine ratio.

DISCUSSION

To the best of our knowledge, this is one of the few studies to demonstrate correlations between KIM-1 (both plasma concentrations and urinary creatinine-normalized values) and conventional renal biomarkers in dogs with stable CKD, including both azotemic and non-azotemic stages. Furthermore, ROC-based cutoff values of pKIM-1 and uKIM-1/uCr for the diagnosis of stable CKD in dogs were reported, highlighting their promising clinical potential.

Although the precise pathophysiology of canine CKD is not completely understood, it may involve glomerular hypertension, tubulointerstitial inflammation, and progressive interstitial fibrosis, which ultimately lead to nephron loss and kidney dysfunction (Chen *et al.,* 2023). These processes are consistent with our findings, as both plasma and urinary KIM-1 levels were elevated in dogs with stable CKD, reflecting tubular injury and interstitial fibrosis even in the absence of overt azotemia. KIM-1 is rapidly upregulated in the apical membrane of proximal tubular epithelial cells following injury, where it plays a protective role in the acute phase by facilitating the clearance of apoptotic and necrotic cells (Tian *et al.,* 2017; Beker *et al.,* 2018; Song *et al.,* 2019). However, persistent overexpression of KIM-1 contributes to tubulointerstitial fibrosis and chronic inflammation (Nakagawa *et al.,* 2015). This pathophysiologic pattern parallels our observation that pKIM-1 and uKIM-1/uCr ratio remained increased in stable CKD, suggesting a sustained low-grade tubular injury rather than transient damage. Elevated KIM-1 concentrations in the urine or kidney tissues are known to correlate negatively with renal function and positively with the degree of fibrosis and inflammation (Chen *et al.,* 2023). Similarly, the present study demonstrated significant correlations between both KIM-1 markers and conventional renal parameters such as BUN, creatinine, and USG, supporting their association with reduced renal function. In stable CKD, the normalization of urinary biomarkers, such as KIM-1 to uCr has been validated as a practical and reliable approach (Seo *et al.,* 2022; Chen *et al.,* 2023; Nabity and Hokamp, 2023; Marečáková *et al.,* 2024) and uKIM-1/uCr has been proposed as a sensitive indicator of tubular injury even before detectable changes in GFR (Chen *et al.,* 2023). Consistent with these studies, uKIM-1/uCr in our results effectively differentiated CKD dogs from healthy controls, as confirmed by ROC analysis, further supporting its diagnostic value for early or subclinical disease detection.

Increased pKIM-1 concentrations in dogs with CKD may result from enhanced KIM-1 leakage across damaged tubules and decreased clearance owing to impaired renal excretory function (Sabbisetti *et al.,* 2014; Miao *et al.,* 2017). Unlike urinary markers, pKIM-1 does not require correction for urine concentration or flow rate, thus offering practical advantages (Chen *et al.,* 2023; Nabity and Hokamp, 2023).

In human patients with CKD, pKIM-1 level and uKIM-1/uCr ratio are consistently elevated, with uKIM-1/uCr ratio sometimes being reported higher in chronic kidney injury than in AKI (Chen *et al.,* 2023; Nabity and Hokamp, 2023). Both markers showed moderate-to-strong positive correlations with serum creatinine and BUN, and negative correlations with eGFR (Chen *et al.,* 2023; Nabity and Hokamp, 2023). Moreover, an increase in the levels of these markers is associated with CKD progression and disease staging (Chen *et al.,* 2023; Nabity and Hokamp, 2023). Notably, even in middle-aged humans without overt CKD, elevated pKIM-1 levels have been linked to subsequent deterioration of renal function over time (Schulz *et al.,* 2020). Taken together, pKIM-1 level and uKIM-1/uCr ratio are considered promising practical biomarkers for early CKD detection and progression monitoring in humans (Beker *et al.,* 2018; Fernando *et al.,* 2019; Chen *et al.,* 2023).

In the present study, both pKIM-1 level and uKIM-1/uCr ratio were significantly higher in dogs with stable CKD than those in healthy controls, regardless of azotemia. Although the values tended to be higher in azotemic versus non-azotemic CKD dogs, the difference was not significant. We observed moderate-to-strong positive correlations between these markers and conventional renal indicators, such as BUN, creatinine, and SDMA, suggesting that KIM-1 reflects renal dysfunction in parallel with traditional markers. The moderate negative correlation with USG supports the notion that KIM-1 elevations are associated

with impaired renal concentrating ability. The absence of differences in both pKIM-1 level and uKIM-1/uCr ratio between the azotemic and non-azotemic stable CKD groups may reflect the distribution of disease severity in our sample, which was dominated by IRIS stage II dogs (85.71% in non-azotemic CKD and 72.73% in azotemic CKD), with relatively few advanced cases.

Proteinuria is another critical prognostic factor of canine CKD (Bartges, 2012). Previous studies reported higher uKIM-1/uCr ratio in proteinuric dogs and moderate correlation with UPCR (Medić *et al.,* 2015; Chen *et al.,* 2023). Similar findings have been described in canine AKI, where protein overload contributes to tubular injury and KIM-1 expression (Kuleš *et al.,* 2018). Consistent with these reports, our data showed significantly elevated pKIM-1 level and uKIM-1/uCr ratio in proteinuric dogs with pKIM-1 showing a strong positive correlation with the UPCR results. Importantly, we report for the first time a moderate correlation between pKIM-1 level and uKIM-1/uCr ratio in dogs with stable CKD, consistent with human data, where pKIM-1 can be substituted for urinary measurements with the advantage of not requiring urinary normalization (Sabbisetti *et al.,* 2014).

Previous research on canine AKI has demonstrated good diagnostic utility of uKIM-1/uCr ratio, with AUCs ranging from 0.76 to 0.97 depending on the model (Kuleš *et al.,* 2018; Lippi *et al.,* 2018; Davis *et al.,* 2021). Similarly, pKIM-1 has strong diagnostic value for gentamicin-induced AKI in dogs (AUC 0.954; Zheng *et al.,* 2019). The current study found excellent AUCs for stable CKD diagnosis (0.942 for pKIM-1 and 0.932 for uKIM-1/uCr), as well as for non-azotemic CKD (0.950 and 0.929, respectively), supporting their application in a chronic disease setting. Considering that the majority of dogs in this study were classified as IRIS stage II**,** in which clinical signs associated with CKD are often mild or absent, these markers appear valuable, even for subclinical detection. Compared with traditional biomarkers influenced by extrarenal factors, KIM-1 may offer more specificity for tubular damage, inflammation, and fibrosis.

Additionally, human studies have shown that KIM-1 markers can predict kidney function decline in healthy populations, earlier than changes in creatinine or albuminuria levels (Schulz *et al.,* 2020; Peng *et al.,* 2022; Chen *et al.,* 2023). Similarly, a nephritis rat model showed KIM-1 elevations, while SDMA and creatinine levels remained normal (Coyne *et al.,* 2022; Ryad *et al.,* 2025), implying that KIM-1 could detect early damage before classic markers. In our study, all dogs with CKD had elevated SDMA levels; however, future studies should confirm whether KIM-1 can identify early disease in dogs with normal SDMA (Wun *et al.,* 2024).

The present study has some limitations. First, the sample size was too small to analyze KIM-1 concentrations according to the IRIS stage. Second, as a case-control study, the ability to prospectively measure diagnostic accuracy is limited. Third, although the correlation of KIM-1 with renal dysfunction was presumed to reflect fibrosis and reduced GFR, it could not be confirmed histologically or through measuring GFR. Instead, the GFR was estimated indirectly using serum creatinine and SDMA levels. Future studies should address KIM-1 in relation to direct GFR measurements, IRIS staging, and renal histopathology.

Conclusions: This study demonstrated that pKIM-1 concentrations and uKIM-1/uCr ratio were elevated in dogs with stable CKD, including those without azotemia, and were moderately to strongly correlated with conventional renal biomarkers. Therefore, these markers are promising diagnostic tools for detecting CKD at earlier stages, potentially enabling earlier intervention and improved disease monitoring in canine patients.

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Ethical approval: The animal study protocol was approved by the Institutional Animal Care and Use Committee of Konkuk University, South Korea (approval No. KU 21196). The study was conducted in accordance with the local legislations and institutional requirements. Written informed consent was obtained from the owners of the animals for their participation in this study.

Authors contribution: SJY conceived the idea, designed the study, conducted data analysis and interpretation, and drafted the manuscript. JHK also participated in drafting of the manuscript and critically revised it for important intellectual contents. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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