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Association Between Serum Symmetric Dimethylarginine Concentration and Kidney Ultrasonographic Findings in Dogs and Cats: A Multicenter Retrospective Study

Miquel Monroig [1,2,*], Laura Gil-Vicente [2,3], Paula F. Navarro [2], María Rocío Saiz-Álvarez [4,†], Jorge Castro-López [5,‡], Xavier Roura [6], Judit Verdés [7,§], Carla Zamora [1,2,8] and Rebeca Movilla [2,3,‖]

1 Doctoral School, Universidad Católica de Valencia San Vicente Mártir, 46001 Valencia, Spain; carla.zamora@ucv.es
2 Department of Animal Medicine and Surgery, Universidad Católica de Valencia San Vicente Mártir, 46001 Valencia, Spain; laura.gil@ucv.es (L.G.-V.); pf.navarro@ucv.es (P.F.N.)
3 Internal Medicine Department, Hospital Veterinario de Referencia UCV, 46018 Valencia, Spain
4 Internal Medicine Department, AniCura Valencia Sur Hospital Veterinario, 46460 Valencia, Spain; mdr.saiz@ucv.es
5 Internal Medicine Department, Hospital Clínico Veterinario CEU-UCH, 46115 Valencia, Spain
6 Hospital Clínic Veterinari de la Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain
7 Diagnostic Imaging Department, Hospital Clínic Veterinari de la Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain
8 Diagnostic Imaging Department, Hospital Veterinario de Referencia UCV, 46018 Valencia, Spain
* Correspondence: miquel.monroig@ucv.es
† Current address: Department of Animal Medicine and Surgery, Universidad Católica de Valencia San Vicente Mártir and Internal Medicine Department, Hospital Veterinario de Referencia UCV, 46018 Valencia, Spain.
‡ Current address: Internal Medicine Department, AniCura Indautxu Hospital Veterinario, 48950 Bilbao, Spain.
§ Current address: Department of Animal Medicine and Surgery, Universidad Católica de Valencia San Vicente Mártir and Diagnostic Imaging Department, Hospital Veterinario de Referencia UCV, 46018 Valencia, Spain.
‖ Current address: Internal Medicine Department, Puchol Hospital Veterinario, 28050 Madrid, Spain.

Simple Summary

Kidney disease is common in dogs and cats, and veterinarians often combine blood tests with abdominal ultrasound to assess kidney health. A blood marker called symmetric dimethylarginine can help detect reduced kidney function, whereas ultrasound shows changes in kidney structure. However, it is unclear whether higher values of this blood marker are consistently associated with visible kidney changes on ultrasound. This study reviewed clinical records from 190 dogs and 92 cats examined at 4 veterinary hospitals. Both dogs and cats with higher symmetric dimethylarginine concentrations tended to have a greater number of kidney changes on ultrasound. The marker did not clearly identify which animals had at least one abnormality, indicating that it relates more to how much structural change is present than to whether any change is present at all. Together, blood testing and ultrasound may provide complementary information when assessing kidney health in dogs and cats.

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Academic Editor: Massimo Vignoli

Received: 1 November 2026
Revised: 22 November 2026
Accepted: 25 November 2026
Published: 27 November 2026

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Abstract

Symmetric dimethylarginine (SDMA) is a biomarker of kidney function, whereas ultrasonography assesses kidney morphology. This retrospective multicenter study evaluated associations between SDMA and kidney ultrasonographic findings in 190 dogs and 92 cats with SDMA and creatinine measured within 30 days of urinary tract ultrasonography. Within each species, models adjusted for age, sex, and center used logistic regression (Firth-penalized in cats) for the presence of any abnormal ultrasonographic finding (AUS) and Poisson regression for the total number of abnormalities. SDMA was associated with the

number of abnormalities in dogs (incidence rate ratio [IRR] 1.08 per 5 µg/dL; 95% confidence interval [CI] 1.04–1.12; $p < 0.001$) and cats (IRR 1.05; 95% CI 1.01–1.08; $p = 0.004$). Associations with AUS did not reach significance (dogs: odds ratio [OR] 1.27; 95% CI 1.00–1.62; $p = 0.051$; cats: OR 1.83; 95% bootstrap CI 0.99–4.25; $p = 0.057$). In exploratory, multiplicity-adjusted analyses, SDMA was associated with renal pelvic dilation in dogs and with small kidneys and renal cysts in cats. SDMA related more consistently to the number of abnormalities than to individual lesions. SDMA and kidney ultrasonography provide complementary information on kidney function and structure in clinical practice.

Keywords: azotemia; biomarker; canine; feline; kidney; SDMA; ultrasound

1. Introduction

Kidney disease is a common and clinically important disorder in dogs and cats, characterized by structural or functional kidney abnormalities that may progress over time and contribute substantially to morbidity and mortality [1,2]. Accurate assessment of kidney function is essential for early diagnosis, staging, monitoring, and therapeutic decision-making. Although direct measurement of glomerular filtration rate (GFR) remains the most accurate method for evaluating kidney function, it is rarely performed in routine clinical practice because it is time-consuming, technically demanding, and not widely available [3]. Consequently, serum creatinine concentration, urine specific gravity (USG), proteinuria assessment, blood pressure measurement, and diagnostic imaging are commonly used in combination to evaluate kidney disease in small animals [1,2].

Serum creatinine concentration remains one of the most widely used markers of kidney function, but it has important limitations, including its dependence on muscle mass and its relatively low sensitivity for detecting early reductions in GFR [2,4]. Symmetric dimethylarginine (SDMA), a methylated arginine derivative eliminated primarily by the kidneys, has become an established biomarker of kidney function in dogs and cats. Previous studies have shown that serum SDMA concentration correlates with GFR in cats and increases in dogs and cats with naturally occurring chronic kidney disease (CKD) [5–8]. In dogs, SDMA may detect reductions in kidney function earlier than creatinine in some cases [7]. However, SDMA should not be interpreted in isolation, because biological variability, disease stage, analytical factors, and the clinical context influence its interpretation [9–16].

The International Renal Interest Society (IRIS) incorporates SDMA as an adjunctive marker in kidney disease grading and staging alongside serum creatinine concentration, urinalysis, proteinuria, blood pressure, and clinical context [17,18]. Nevertheless, kidney function biomarkers provide limited information regarding kidney morphology. Abdominal ultrasonography is frequently used in dogs and cats with suspected or confirmed kidney disease because it allows assessment of kidney size, shape, parenchymal echogenicity, corticomedullary distinction, renal pelvic dilation (RPD), mineralization, cystic lesions, and other structural abnormalities [19,20]. However, many kidney ultrasonographic findings are non-specific, may be observed in animals with and without azotemia, and do not always correlate closely with kidney function or histopathological severity [19,21,22].

Previous studies have evaluated the relationship between kidney ultrasonographic abnormalities and kidney dysfunction in dogs and cats. In cats, ultrasonographic abnormalities have been reported in both azotemic and non-azotemic individuals, highlighting the limited specificity of individual structural findings for functional impairment [23]. In dogs, kidney ultrasonographic abnormalities have been associated with reduced GFR and have been proposed as complementary information for kidney disease assessment [24,25]. More recently, studies have investigated the relationship between SDMA and quantitative or ad-

vanced ultrasonographic techniques, including kidney elastography, as well as conventional ultrasonographic abnormalities in cats without clinical signs [26,27]; in the latter population, elevated SDMA was associated with selected ultrasonographic abnormalities, although the overall correlation between SDMA and an ultrasonographic score was weak [27]. Despite these advances, the relationship between serum SDMA concentration and a broad range of conventional kidney ultrasonographic findings remains incompletely characterized in heterogeneous clinical populations evaluated under routine practice conditions. It is unclear whether SDMA is associated with the presence of any kidney ultrasonographic abnormality, with specific structural lesions, or with the cumulative number of abnormalities. Clarifying these relationships may help define how functional biomarkers and structural imaging findings should be integrated in the clinical assessment of kidney disease.

This study aimed to evaluate the association between serum SDMA concentration and kidney ultrasonographic findings in dogs and cats evaluated under routine clinical conditions. The working hypothesis was that higher serum SDMA concentration would be associated with the presence and number of kidney ultrasonographic abnormalities in both species.

2. Materials and Methods

2.1. Study Design and Case Selection

This retrospective multicenter observational study included data collected between 2016 and 2024 from 4 referral veterinary hospitals in Spain: AniCura Valencia Sur Hospital Veterinario (Valencia, Spain), Hospital Clínico Veterinario CEU-UCH (Valencia), Hospital Clínic Veterinari de la Universitat Autònoma de Barcelona (Barcelona, Spain), and Hospital Veterinario de Referencia UCV (Valencia).

Medical records and imaging databases were retrospectively searched at each participating center. Animals were evaluated as part of routine diagnostic work-up, preventive health screening, or follow-up of suspected or confirmed kidney or urinary tract disease. Inclusion criteria were (i) dogs or cats evaluated at one of the participating centers between 2016 and 2024; (ii) a complete urinary tract ultrasonographic examination with stored Digital Imaging and Communications in Medicine (DICOM) images available for retrospective review; and (iii) serum SDMA and creatinine concentrations measured within 30 days of ultrasonography. This window reflects routine clinical practice, in which laboratory testing and imaging are frequently performed on different days, and is considerably shorter than the minimum 3-month duration that defines CKD, over which chronic structural kidney lesions are expected to persist [1]. Recorded data included signalment, physical examination findings, SDMA and creatinine concentrations, USG, urine protein-to-creatinine ratio (UPCR), urinary tract ultrasonographic images, and final diagnoses when available. Concurrent diseases, including vector-borne infections, were obtained from the final diagnoses recorded in the medical records; screening for vector-borne pathogens was not performed systematically, and the confirmatory tests on which these diagnoses were based were not available for review. Dogs and cats were analyzed separately, so all estimates refer to associations within each species; differences between species were not formally tested. Animals with a serum creatinine concentration $\geq$ 1.4 mg/dL (dogs) or $\geq$1.6 mg/dL (cats), corresponding to IRIS CKD Stage 2 or higher, were classified as azotemic, and the remainder as non-azotemic [17]. Exclusion criteria were (i) pre-renal azotemia, defined as azotemia with concentrated urine (USG > 1.030 in dogs or >1.035 in cats) [28] in animals without previously diagnosed CKD, and (ii) post-renal azotemia, defined as azotemia with ultrasonographic evidence of urinary tract obstruction or rupture. These animals were excluded because pre-renal and post-renal causes of azotemia may alter serum kidney biomarkers independently of primary renal parenchymal disease, which could confound

their association with ultrasonographic findings. When USG was unavailable, azotemia was classified on the basis of the clinical information documented in the medical records. Because standardized criteria could not be applied in these cases, some misclassification cannot be excluded; its potential influence was assessed in a sensitivity analysis. Renal pelvic dilation (RPD) was recorded as a morphological finding irrespective of its cause and was not, on its own, considered evidence of obstruction.

2.2. Laboratory Analyses

Serum SDMA concentrations were measured with the IDEXX SDMA Test, either at a commercial reference laboratory (IDEXX Laboratories, Barcelona, Spain) or in-clinic on a Catalyst One analyzer (Catalyst SDMA Test; IDEXX Laboratories, Hoofddorp, The Netherlands), or with DLD SDMA ELISA at LABOKLIN GmbH & Co. KG (Bad Kissingen, Germany). Results reported in SI units (LABOKLIN) were converted to µg/dL according to the conversion factor provided by the reporting laboratory to express all results in common units.

Serum SDMA concentrations > 14 µg/dL were considered above the assay reference interval, a limit lower than the 18 µg/dL at which IRIS places animals with CKD in Stage 2 [17,18]. Because only a single measurement was available for each animal and IRIS staging is applicable only after CKD has been diagnosed in a stable patient, no formal IRIS stage was assigned in this study. CKD stage was not used in the inferential analyses. When available, UPCR was used to classify animals as non-proteinuric (<0.2), borderline proteinuric (0.2–0.5 in dogs; 0.2–0.4 in cats), or proteinuric (>0.5 in dogs; >0.4 in cats) according to IRIS criteria [17].

2.3. Ultrasonographic Evaluation

Clinicians affiliated with diagnostic imaging services, including board-certified specialists, residents under specialist supervision, and experienced clinicians with advanced training in diagnostic imaging, performed the ultrasonographic examinations as part of routine clinical evaluation following institutional imaging protocols. Operators were not blinded to clinical data at the time of examination. For this study, a single clinician from the diagnostic imaging service of each center, blinded to SDMA concentrations and to creatinine concentrations, urinalysis results, and clinical diagnoses, retrospectively reviewed the stored DICOM images. Only static images were available for review. Kidney ultrasonographic variables were defined a priori, and image interpretation was based on predefined criteria. Abnormal ultrasonographic findings (AUS) were defined as the presence of any kidney ultrasonographic alteration and included hydronephrosis (HYDRO), hyperechoic renal cortex (HRC), increased corticomedullary differentiation (ICD), irregular renal surface (IRS), large kidney (LK), loss of corticomedullary differentiation (LCMD), loss of kidney structure (LKS), medullary rim sign (MRS), non-obstructive urolithiasis (NOU), perirenal fluid (PF), renal cysts (RC), renal infarcts (RI), renal parenchymal calcification (RCP), RPD (>2 mm in cats; >3 mm in dogs) [20,29], small kidneys (SK), and thickened renal cortex (TRC). The total number of kidney ultrasonographic abnormalities (hereafter, lesion count) was calculated as the sum of the 16 predefined ultrasonographic abnormalities, each recorded as present or absent in every animal of both species; abnormalities not observed in a species contributed zero to its count. All abnormalities contributed equally to the count, irrespective of their individual clinical significance. This exploratory variable summarized the cumulative burden of kidney structural abnormalities and was not intended as a validated ultrasonographic severity score. Variables with a frequency < 5% in the corresponding species were excluded from the analyses of individual ultrasonographic abnormalities but were retained in the total lesion count.

2.4. Statistical Analysis

Normality was assessed using the Shapiro–Wilk test. Age, body weight, and serum SDMA concentration deviated from a normal distribution in both species (all $p \leq 0.02$); these continuous variables are therefore reported as median and interquartile range (IQR). Associations between SDMA concentration and the presence of AUS were evaluated using multivariable logistic regression models. SDMA was analyzed as a continuous variable scaled per 5 µg/dL increase. Covariates were selected a priori based on biological and clinical plausibility as potential confounders (age, sex, and center) and were retained in all multivariable models in both species regardless of statistical significance. The number of covariates was kept low relative to the number of events (12.2 events per variable in the canine logistic model). For cats, penalized logistic regression with Firth's correction was applied to address quasi-complete separation. Odds ratios (OR) from penalized models are reported with profile penalized-likelihood confidence intervals (CI), and the corresponding p-values were derived from penalized likelihood ratio tests. When the penalized profile-likelihood algorithm did not converge for a given coefficient because of quasi-complete separation, this is indicated in the text and a bootstrap percentile interval (1000 replicates) is reported instead. Potential non-linear relationships between SDMA concentration and AUS were explored in dogs using natural cubic spline functions with three degrees of freedom and compared with the linear model using a likelihood ratio test. Because the spline model did not significantly improve model fit, the linear SDMA term was retained. A spline analysis was not performed in cats because sparse outcome cells and quasi-complete separation made an unpenalized spline model unreliable; the continuous linear SDMA term was therefore prespecified in the Firth model.

Associations between SDMA concentration and individual ultrasonographic abnormalities were explored using Firth's penalized logistic regression, with p-values adjusted for multiple testing using the Benjamini–Hochberg false discovery rate procedure. The association between SDMA concentration and the total number of ultrasonographic abnormalities was evaluated using generalized linear models with a Poisson distribution and log link. Overdispersion in Poisson models was assessed using the ratio of residual deviance to degrees of freedom and the regression-based test of Cameron and Trivedi. Negative binomial models were fitted as a sensitivity analysis and compared with Poisson models using the Akaike information criterion (AIC).

Results from logistic regression models are reported as OR with 95% CI, and results from Poisson models are reported as incidence rate ratios (IRR) with 95% CI. Multicollinearity was assessed using variance inflation factors. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC) and the Brier score, reported both as apparent values and after bootstrap correction for optimism (500 resamples in both species). Sensitivity analyses were performed by additionally adjusting the models for body weight and for the analytical provider recorded in the database, and by refitting them after excluding (i) animals with a diagnosis of a vector-borne disease and (ii) azotemic animals with USG above the cut-off used to define pre-renal azotemia or without USG available; in cats, only the Poisson model was refitted, because quasi-complete separation and the small number of cats without AUS precluded reliable estimation of the logistic model in the reduced samples. All statistical analyses were performed using R statistical software (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria), and $p < 0.05$ was considered statistically significant.

3. Results

Of the 300 animals that met the inclusion criteria (196 dogs and 104 cats), 18 were excluded because of suspected pre-renal ($n = 10$; 4 dogs and 6 cats) or post-renal ($n = 8$;

2 dogs and 6 cats) azotemia, and 282 animals (190 dogs and 92 cats) were included in the study (Figure 1).

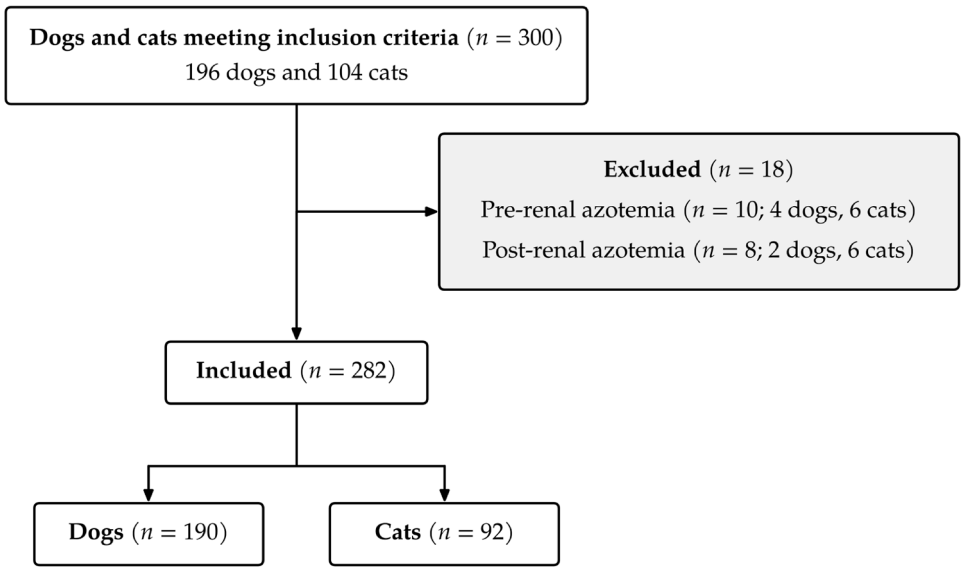

Figure 1. Flow diagram of case selection.

3.1. Dogs

The canine cohort included 190 dogs with a median age of 9.0 years (IQR 6.0–12.0) and a median body weight of 14.85 kg (IQR 7.71–24.22; $n = 160$). The population consisted of 106 females (59 spayed, 47 intact) and 84 males (41 neutered, 43 intact). The most represented breeds were crossbreed dogs (26%), Yorkshire Terrier (12%), and West Highland White Terrier (5%). Forty-nine dogs (26%) were azotemic, and serum SDMA concentration exceeded the assay reference limit of 14 µg/dL in 64 dogs (34%). Median serum SDMA concentration was 12.0 µg/dL (IQR 9.0–16.0). UPCR was available in 113 dogs, of which 30 (27%) were non-proteinuric (UPCR < 0.2), 33 (29%) borderline proteinuric (0.2–0.5), and 50 (44%) proteinuric (>0.5). Final diagnoses were available in 160 dogs (84%); the most frequent concurrent diagnoses were CKD ($n = 49$; 26%), vector-borne diseases ($n = 28$; 15%; leishmaniosis in 27 and ehrlichiosis in 1), gastrointestinal disease ($n = 28$; 15%), adrenal disease ($n = 21$; 11%), and neurological and hepatobiliary disease ($n = 20$ each; 11%) (Supplementary Table S1). AUS were detected in 61.6% of dogs (117/190). The most common findings were LCMD ($n = 67$; 35%) and RCP ($n = 55$; 29%) (Table 1).

In the canine multivariable logistic regression model including SDMA, age, sex, and center, each 5 µg/dL increase in SDMA was associated with a 27% increase in the odds of AUS, although this association did not reach statistical significance (OR 1.27; 95% CI 1.00–1.62; $p = 0.051$). Age showed a comparable borderline association (OR 1.09 per year; 95% CI 1.00–1.18; $p = 0.051$), whereas male sex was not associated with AUS (OR 1.47; 95% CI 0.76–2.83; $p = 0.253$). Abnormal findings were more frequent at one center than at the reference center (OR 2.64; 95% CI 1.18–5.90; $p = 0.018$).

In dogs, spline terms did not improve model fit (likelihood ratio test, $p = 0.113$), and the linear model was retained. Variance inflation factors were below 1.1, indicating no relevant multicollinearity. Model discrimination was moderate, with an apparent AUC of 0.75 (95% CI 0.68–0.82) and an apparent Brier score of 0.20; after bootstrap correction for optimism, the AUC was 0.72 and the Brier score was 0.21.

Table 1. Distribution of kidney ultrasonographic abnormalities in dogs and cats.

Ultrasonographic Finding	Dogs	Cats
LCMD	67 (35%)	43 (47%)
RCP	55 (29%)	25 (27%)
RPD	25 (13%)	26 (28%)
NOU	22 (12%)	13 (14%)
RC	14 (7%)	8 (9%)
IRS	11 (6%)	21 (23%)
HRC	11 (6%)	16 (17%)
LKS	7 (4%)	3 (3%)
MRS	7 (4%)	2 (2%)
SK	6 (3%)	5 (5%)
TRC	3 (2%)	2 (2%)
RI	3 (2%)	14 (15%)
HYDRO	1 (1%)	0 (0%)
PF	1 (1%)	0 (0%)
LK	1 (1%)	9 (10%)
ICD	0 (0%)	1 (1%)

Data are presented as the number of animals (%). LCMD = loss of corticomedullary differentiation; IRS = irregular renal surface; SK = small kidneys; RCP = renal parenchymal calcification; RPD = renal pelvic dilation; RC = renal cysts; RI = renal infarcts; NOU = non-obstructive urolithiasis; HRC = hyperechoic renal cortex; LKS = loss of kidney structure; MRS = medullary rim sign; TRC = thickened renal cortex; HYDRO = hydronephrosis; PF = perirenal fluid; LK = large kidney; ICD = increased corticomedullary differentiation.

Among the 160 dogs with available body weight data, the SDMA estimate was similar before (OR 1.26 per 5 µg/dL; 95% CI 0.97–1.65; $p = 0.086$) and after adjustment for body weight (OR 1.26; 95% CI 0.96–1.66; $p = 0.098$). Body weight remained associated with AUS after adjustment (OR 0.94 per kg; 95% CI 0.90–0.97; $p < 0.001$), and male sex was also associated with AUS in the weight-adjusted model (OR 2.31; 95% CI 1.05–5.12; $p = 0.039$). Additional adjustment for the analytical provider recorded in the database did not materially change the SDMA estimate (OR 1.27; 95% CI 1.00–1.61; $p = 0.050$). The effect of the alternative analytical-provider category could not be meaningfully estimated (OR 1.38; 95% CI 0.15–12.88; $p = 0.775$), because only seven dogs belonged to this category.

In exploratory analyses of individual ultrasonographic abnormalities in dogs, SDMA concentration was associated with RPD after correction for multiple testing (OR 1.25 per 5 µg/dL; 95% CI 1.06–1.53; adjusted $p = 0.047$; 25 affected dogs). Associations with IRS (OR 1.23; 95% CI 0.99–1.47; adjusted $p = 0.165$) and HRC (OR 1.25; 95% CI 0.98–1.64; adjusted $p = 0.165$) were of similar magnitude but did not reach significance after correction, and each was based on 11 affected dogs. No other ultrasonographic abnormality was associated with SDMA (Table 2).

Table 2. Associations between serum SDMA concentration and individual kidney ultrasonographic abnormalities in dogs.

Variable	OR (95% CI)	*p*-Value	Adjusted *p*-Value
LCMD	1.02 (0.87–1.25)	0.856	0.856
RCP	1.07 (0.93–1.27)	0.341	0.398
RPD	1.25 (1.06–1.53)	0.007	0.047
RC	1.13 (0.95–1.40)	0.162	0.284
HRC	1.25 (0.98–1.64)	0.071	0.165
IRS	1.23 (0.99–1.47)	0.061	0.165
NOU	1.11 (0.93–1.31)	0.227	0.318

Odds ratios (OR) represent the change in odds of each ultrasonographic abnormality per 5 µg/dL increase in serum SDMA concentration, estimated by Firth's penalized logistic regression. Confidence intervals (CI) are profile penalized-likelihood intervals and *p*-values were obtained from penalized likelihood ratio tests. Models were adjusted for age, sex, and center. *p*-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure. LCMD = loss of corticomedullary differentiation; IRS = irregular renal surface; RCP = renal parenchymal calcification; RPD = renal pelvic dilation; RC = renal cysts; NOU = non-obstructive urolithiasis; HRC = hyperechoic renal cortex.

In the canine multivariable Poisson regression model including SDMA, age, sex, and center, SDMA concentration was independently associated with the total number of ultrasonographic abnormalities. Each 5 µg/dL increase in SDMA was associated with an 8% increase in the expected number of abnormalities (IRR 1.08; 95% CI 1.04–1.12; $p < 0.001$) (Figure 2a). Age showed a positive but non-significant association (IRR 1.03 per year; 95% CI 0.99–1.07; $p = 0.066$) and sex was not associated with the lesion count (IRR 1.07; 95% CI 0.82–1.39; $p = 0.64$). Mild overdispersion was detected (dispersion 1.17; $p = 0.041$; residual deviance/degrees of freedom = 1.32), but a negative binomial model did not improve fit (AIC: Poisson 550.8 vs. negative binomial 552.2) and yielded almost identical estimates (IRR 1.09; 95% CI 1.04–1.14; $p < 0.001$); the Poisson model was therefore retained.

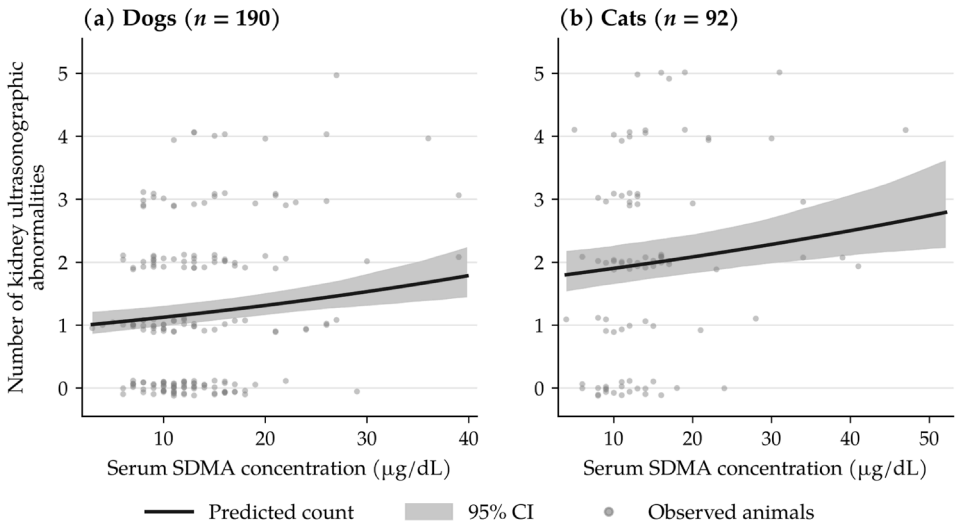

Figure 2. Association between serum SDMA concentration and the total number of kidney ultrasonographic abnormalities in dogs (**a**) and cats (**b**). Lines show predicted counts from the multivariable Poisson models adjusted for age, sex, and center, averaged over the observed covariate distribution; shaded areas are 95% confidence intervals obtained by simulation from the asymptotic distribution of the model coefficients (2000 draws). Points are observed values, vertically jittered to reduce overplotting. Axes are scaled independently for each species; the *x*-axis is truncated at the 97.5th percentile of SDMA (5 dogs and 3 cats with higher concentrations are not shown but were included in all models).

In dogs, excluding the 28 animals with a vector-borne disease did not materially change the association between SDMA and the lesion count (IRR 1.08 per 5 µg/dL; 95% CI 1.03–1.12; $p < 0.001$; $n = 162$) or the presence of AUS (OR 1.25; 95% CI 0.95–1.63; $p = 0.108$). Similarly, after excluding the 9 azotemic dogs with USG above the pre-renal threshold or without USG, the association with the lesion count was unchanged (IRR 1.08; 95% CI 1.03–1.12; $p < 0.001$; $n = 181$) and the estimate for AUS remained similar (OR 1.29; 95% CI 1.00–1.66; $p = 0.046$).

3.2. Cats

The feline cohort included 92 cats with a median age of 9.0 years (IQR 6.0–12.2) and a median body weight of 3.88 kg (IQR 3.16–4.84; $n = 74$). The population consisted of 47 females (39 spayed, 8 intact) and 45 males (42 neutered, 3 intact). The most represented breed was Domestic Shorthair (77%), followed by Persian (9%). Forty-seven cats (51%) were azotemic, and serum SDMA concentration exceeded 14 µg/dL in 34 cats (37%). Median serum SDMA concentration was 13.0 µg/dL (IQR 10.0–16.2). UPCR was available in 45 cats, of which 15 (33%) were non-proteinuric (UPCR < 0.2), 13 (29%) borderline proteinuric (0.2–0.4), and 17 (38%) proteinuric (>0.4). Final diagnoses were available in 87 cats (95%); the most frequent concurrent diagnoses were CKD ($n = 42$; 46%), gastrointestinal disease ($n = 32$; 35%), hepatobiliary disease ($n = 13$; 14%), and hyperthyroidism ($n = 10$; 11%). Leishmaniosis was reported in 3 cats (3%), and 6 cats (7%) had a history of ureteral obstruction, 4 of them with a patent subcutaneous ureteral bypass device (Supplementary Table S1). AUS were detected in 76% of cats (70/92). The most common findings were LCMD ($n = 43$; 47%), RPD ($n = 26$; 28%), RCP ($n = 25$; 27%), IRS ($n = 21$; 23%), HRC ($n = 16$; 17%), and RI ($n = 14$; 15%) (Table 1).

In cats, SDMA concentration was not significantly associated with AUS, although the point estimate was large and of the same direction as in dogs (OR 1.83 per 5 µg/dL; $p = 0.057$). The penalized profile-likelihood algorithm did not converge for this coefficient because of quasi-complete separation; a bootstrap percentile interval was therefore computed (1000 replicates; 95% CI 0.99–4.25); the estimate should be regarded as imprecise rather than as evidence of absence of association: the feline cohort included only 22 animals in the minority outcome class. Age remained associated with AUS after adjustment (OR 1.30 per year; 95% CI 1.12–1.57; $p < 0.001$), and male cats had higher odds of abnormalities than females (OR 7.34; 95% CI 2.13–30.78; $p = 0.001$).

In the feline model, variance inflation factors were below 1.6. Apparent model discrimination was high (AUC 0.90; 95% CI 0.83–0.96) with an apparent Brier score of 0.11; after bootstrap correction for optimism, the AUC was 0.85 and the Brier score was 0.14.

Among the 74 cats with recorded body weight, SDMA was not associated with AUS either before (OR 1.06 per 5 µg/dL; $p = 0.303$) or after adjustment for body weight (OR 1.07; $p = 0.209$). The SDMA estimate was markedly lower than in the full cohort and unstable in this smaller subset, in which the penalized profile-likelihood limits did not converge because of quasi-complete separation. Body weight showed no adjusted association with AUS ($p = 0.326$). In a separate sensitivity analysis, additional adjustment for the analytical provider recorded in the database reduced the SDMA point estimate (OR 1.41; $p = 0.159$). The estimated provider effect was highly imprecise ($p = 0.110$), because only four cats belonged to the alternative analytical-provider category.

In exploratory analyses of individual ultrasonographic abnormalities in cats, SDMA concentration was significantly associated with the presence of SK (OR 1.94; 95% CI 1.24–3.55; adjusted $p = 0.014$) and RC (OR 1.20; 95% CI 1.04–2.44; adjusted $p = 0.027$) after Benjamini–Hochberg correction for multiple testing. No other ultrasonographic variables showed a significant association with SDMA (Table 3). These associations were based on 5 cats with SK and 8 with RC and should therefore be regarded as hypothesis-generating.

In the feline multivariable Poisson regression model including SDMA, age, sex, and center, SDMA concentration was independently associated with the number of ultrasonographic abnormalities. Each 5 µg/dL increase in SDMA was associated with a 5% increase in the expected number of ultrasonographic abnormalities (IRR 1.05; 95% CI 1.01–1.08; $p = 0.004$) (Figure 2b). Age (IRR 1.07 per year; 95% CI 1.03–1.10; $p < 0.001$) and male sex (IRR 1.61; 95% CI 1.18–2.21; $p = 0.003$) also showed adjusted associations with a higher total number of ultrasonographic abnormalities. The residual deviance to degrees of freedom

ratio was 1.38, but the regression-based dispersion test was not significant (dispersion 1.14; $p = 0.188$) and the Poisson model had a lower AIC than the negative binomial alternative (326.1 vs. 327.9); the Poisson model was therefore retained.

Table 3. Associations between serum SDMA concentration and individual kidney ultrasonographic abnormalities in cats.

Variable	OR (95% CI)	*p*-Value	Adjusted *p*-Value
LCMD	1.05 (0.96–1.17)	0.285	0.539
RCP	1.07 (0.91–1.50)	0.300	0.539
RPD	1.03 (0.91–1.13)	0.561	0.623
RC	1.20 (1.04–2.44)	0.005	0.027
HRC	1.09 (0.83–1.50)	0.313	0.539
IRS	1.00 (0.91–1.11)	0.978	0.978
SK	1.94 (1.24–3.55)	0.001	0.014
NOU	1.06 (0.90–1.49)	0.378	0.539
LK	1.07 (0.81–1.65)	0.373	0.539
RI	1.04 (0.82–1.37)	0.500	0.623

Odds ratios (OR) represent the change in odds of each ultrasonographic abnormality per 5 µg/dL increase in serum SDMA concentration, estimated by Firth's penalized logistic regression. Confidence intervals (CI) are profile penalized-likelihood intervals and *p*-values were obtained from penalized likelihood ratio tests. Models were adjusted for age, sex, and center. *p*-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure. LCMD = loss of corticomedullary differentiation; IRS = irregular renal surface; SK = small kidneys; RCP = renal parenchymal calcification; RPD = renal pelvic dilation; RC = renal cysts; RI = renal infarcts; NOU = non-obstructive urolithiasis; HRC = hyperechoic renal cortex; LK = large kidney.

In cats, excluding the 3 animals with leishmaniosis did not change the association between SDMA and the lesion count (IRR 1.05 per 5 µg/dL; 95% CI 1.02–1.08; $p = 0.003$; $n = 89$), nor did excluding the 8 azotemic cats with USG above the pre-renal threshold or without USG (IRR 1.05; 95% CI 1.02–1.08; $p = 0.004$; $n = 84$).

4. Discussion

The main finding of this study was that higher serum SDMA concentrations were independently associated with a greater number of kidney ultrasonographic abnormalities in both dogs and cats. SDMA appeared to relate more consistently to the cumulative burden of structural change than to the presence of any abnormality or of any specific lesion, which suggests that SDMA and conventional kidney ultrasonography provide complementary, but not interchangeable, information in the evaluation of kidney disease.

The contrast between the lesion count and the binary outcome requires cautious interpretation. A dichotomous outcome discards information and has less statistical power than a count, and the binary estimates pointed in the same direction as the count models in both species, so part of the contrast may reflect precision and not biology. The high background prevalence of structural findings probably contributes as well. Kidney ultrasonographic abnormalities were considerably more prevalent in cats than in dogs (76% vs. 62%); feline CKD is characterized by tubulointerstitial inflammation and fibrosis that are already present in early, non-azotemic stages of the disease [30], and ultrasonographic abnormalities are common in cats both with and without azotemia [23]. Such a prevalence reduces the ability of any biomarker to discriminate on a binary basis: many animals have at least one abnormality regardless of SDMA status, whereas increasing SDMA concentrations may still reflect a higher overall burden of kidney structural change. Because species were modeled separately without a formal test of interaction, these results do not constitute evidence of a genuine species difference. An integrated assessment of the number and pattern of abnormalities may be more informative than a dichotomous classification of ultrasonographic

status, in line with the proposal that kidney ultrasonography is most useful as an adjunct for staging CKD in dogs when multiple structural abnormalities are present [25].

In dogs, higher SDMA concentrations showed a borderline association with the presence of at least one kidney ultrasonographic abnormality and were clearly associated with the total number of abnormalities. This supported a relationship between increasing functional impairment and a greater number of ultrasonographic abnormalities, consistent with previous studies showing that SDMA correlates with reduced GFR and increases in dogs with naturally occurring CKD [7,8] and with imaging studies reporting associations between kidney ultrasonographic abnormalities and reduced kidney function in dogs [24,25]. The moderate discriminative performance of the model nevertheless indicated that SDMA alone was not sufficient to predict kidney ultrasonographic status and should be interpreted together with other clinical, laboratory, and imaging findings. Among dogs with available body weight data, the association between SDMA and AUS was weaker than in the full cohort, but the SDMA estimate changed very little after body weight was added to the model fitted in the same subset; the attenuation primarily reflected the reduced analytical sample rather than confounding by body weight. Body weight itself was associated with AUS after adjustment, a finding that requires cautious interpretation because body weight was unavailable in 30 dogs (16%) and may also reflect differences in breed or body size. The potential relationship between body size and kidney ultrasonographic findings deserves specific evaluation in prospective studies.

No single ultrasonographic abnormality appeared to account for the association between SDMA and lesion count. In dogs, RPD was the only individual ultrasonographic abnormality associated with SDMA after correction for multiple comparisons, and this association should be interpreted with caution: RPD may occur in several clinical contexts, including increased urine flow associated with diuresis or fluid therapy, urinary tract disease, pyelonephritis, or obstruction, and may also be observed in dogs and cats without clinically relevant kidney dysfunction; pelvic width alone does not establish obstruction and requires interpretation alongside hydration status, diuresis, and concurrent ultrasonographic findings [20]. The absence of robust independent associations between SDMA and individual ultrasonographic abnormalities is consistent with the view that increasing SDMA relates more to the cumulative presence of multiple structural abnormalities than to any single ultrasonographic finding, although the lesion-specific analyses were based on few events and had limited power.

In cats, SDMA was not independently associated with the presence of AUS, whereas age was. This supports the interpretation that structural kidney changes are frequent in older cats and may not always correspond directly to functional impairment, consistent with the high prevalence of CKD and age-associated kidney lesions reported in cats [30–32]. The high discriminative performance of the feline model should not be attributed to SDMA, because age, sex, and center effects most likely drove it. Male sex was also associated with both feline outcomes, whereas no comparable association was observed in dogs. This finding may reflect indication or referral bias, for example, if male cats were more likely to undergo urinary tract imaging in the participating centers. Alternatively, several ultrasonographic criteria, including kidney size, depend on body size and breed [29,33] and male cats have larger kidneys than females [23]; a genuine sex-related difference in kidney structural change cannot be excluded. Sex was a pre-specified confounder and not a hypothesis, so this finding should be regarded as exploratory.

In the feline cohort, SDMA was also associated with SK and RC after correction for multiple testing. SK are generally compatible with chronic remodeling and loss of renal parenchyma, which makes the association biologically plausible, although kidney size can be influenced by body size, breed, hydration status, and chronicity of disease [29,33]. RC may

be incidental, age-related, breed-associated, or part of CKD, and their clinical significance depends on number, size, distribution, and concurrent kidney abnormalities [29,33]; the association does not imply a direct causal relationship. Both estimates rested on few affected cats and remain hypothesis-generating.

The lesion count is a pragmatic measure of structural burden. Composite ultrasonographic scores proposed in human and veterinary medicine may represent chronic kidney damage better than isolated findings [25,34], but the lesion count used in this study was not a validated scoring system and weighted all abnormalities equally; its association with SDMA should be confirmed in prospective studies using standardized kidney ultrasound scoring systems. Accordingly, the association between SDMA and the lesion count should not be interpreted as evidence of a direct relationship with the severity of kidney damage. Until such scores are validated, the imperfect association between SDMA and ultrasonographic abnormalities supports the complementary use of both diagnostic modalities. SDMA is used as an indirect indicator of GFR [5–8] and is less influenced by lean body mass than creatinine [35], but its diagnostic performance can vary according to species, biological variability, disease stage, persistence of the increase, analytical method, and the reference standard used to define kidney dysfunction [9–14,16,36,37]. The cut-off applied matters as well: the proportion of animals above the 14 µg/dL reference limit reported here would be lower under the 18 µg/dL threshold that IRIS uses for Stage 2, although no regression estimate depends on either cut-off. Kidney ultrasonography provides structural information that cannot be obtained from circulating biomarkers, including kidney size, contour, architecture, corticomedullary distinction, RPD, mineralization, and cystic lesions [20,29,33], yet many ultrasonographic findings have limited specificity and may be influenced by non-renal factors, technical settings, and observer interpretation [15,19,20,22]. SDMA may help identify reduced kidney function, whereas ultrasonography may detect structural abnormalities, chronic remodeling, or concurrent urinary tract changes that influence diagnosis and management.

This study has several limitations. The retrospective design limited control over case selection, over the timing of diagnostic tests, and over the standardization of ultrasonographic acquisition. SDMA measurement and ultrasonography were not always performed on the same day, and a window of up to 30 days was accepted; although kidney structural changes are unlikely to develop substantially over this interval, minor temporal misclassification of functional status cannot be excluded. Both SDMA and creatinine were measured on a single occasion, so persistence and short-term stability of the biomarker concentrations could not be confirmed, and transient increases or biological and analytical variability in SDMA could not be distinguished from persistent reductions in kidney function. Consequently, the study was not designed to provide formal IRIS CKD staging, and its cross-sectional design precludes any assessment of whether changes in SDMA over time parallel the progression or resolution of ultrasonographic abnormalities. Azotemia was classified retrospectively from USG and the clinical history. Urine glucose, sodium, and creatinine, as well as serum AST and ALT activities, were not available and UPCR was missing in part of the population, so the classification could not be confirmed with urinary or biochemical indices [28,38]. Nevertheless, excluding azotemic animals with uncertain classification did not change the main findings. Concurrent diseases were obtained from the final diagnoses recorded in the medical records. Vector-borne infections such as leishmaniosis, which is endemic in Spain [39] and frequently associated with kidney disease in dogs [40], were not screened systematically and the confirmatory tests were not available for review, so subclinical infections may have been missed, although excluding animals with a diagnosed vector-borne disease did not change the main findings.

Ultrasound examinations were performed in different institutions and by different operators, which may have introduced interobserver and technical variability. Each center's images were reviewed by a single clinician, and inter-observer agreement was not assessed; reviewer-related variability may therefore have contributed to the center effects observed in dogs. Although reviewers were blinded to SDMA concentrations and other clinical information, the potential influence of inter-observer variability on the observed associations cannot be excluded. In addition, only static images were available for retrospective review, and subtle changes in echogenicity or corticomedullary differentiation may be more difficult to evaluate on static images than on cine-loop recordings. The multicenter design improves external validity but also increases heterogeneity in equipment, image quality, and clinical populations. SDMA concentrations were likewise obtained from different laboratories and measurement settings, which may have introduced residual analytical variability despite conversion to common units and the use of standardized clinical interpretation thresholds. Commercial SDMA assays also differ in analytical accuracy and precision [37]. Additional adjustment for the analytical provider did not materially change the SDMA estimate in dogs, whereas in cats it reduced the point estimate; in both species, however, the alternative provider included very few animals (seven dogs and four cats), so the influence of the assay could not be reliably assessed. Neither histopathology nor measured GFR was available, so the exact pathological substrate of the ultrasonographic findings could not be determined and neither SDMA nor the imaging findings could be compared with a gold-standard measure of kidney function. The present results should be interpreted as associations observed under routine clinical conditions, and not as evidence that SDMA can predict histopathological kidney damage or that ultrasonography can be used as a surrogate marker of GFR.

These limitations are balanced by several strengths, including the multicenter design, the inclusion of both dogs and cats, a relatively large clinical population, the evaluation of multiple conventional kidney ultrasonographic abnormalities, and the review of stored DICOM images by clinicians blinded to all laboratory results and clinical diagnoses. Together with multivariable, species-specific models that accounted for demographic and center-related effects, these features provide a broad assessment of the relationship between a functional kidney biomarker and structural kidney findings under routine clinical conditions.

5. Conclusions

Higher serum SDMA concentrations were associated with a greater number of kidney ultrasonographic abnormalities in dogs and cats, in models fitted separately for each species. In contrast, SDMA was not consistently associated with individual ultrasonographic lesions, and its association with the presence of any ultrasonographic abnormality did not reach statistical significance in either species. These findings suggest that serum SDMA concentration and kidney ultrasonography provide complementary information on kidney function and structure, respectively, and should not be considered interchangeable diagnostic measures. The observed associations were modest and exploratory and do not support the use of SDMA as a surrogate marker of kidney structural damage. They are compatible with the hypothesis that SDMA tracks the cumulative burden of kidney ultrasonographic abnormalities more closely than the presence of individual lesions, which this study was not designed to test formally. Prospective multicenter studies using standardized ultrasonographic scoring systems and direct measures of kidney function are warranted to confirm these findings.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/vetsci13121291/s1, Table S1: Anonymized dataset of the 190 dogs

and 92 cats included in the study. Data are presented in separate sheets for dogs and cats (one row per animal) and include signalment, serum symmetric dimethylarginine (SDMA), creatinine and urea nitrogen concentrations, urinalysis results, SDMA provider, concurrent diagnoses and kidney ultrasonographic findings. Definitions, units and coding of all variables and abbreviations are provided in the README sheet. Empty cells indicate data not available in the medical record.

Author Contributions: Conceptualization, M.M. and R.M.; methodology, M.M.; software, M.M.; validation, M.M., L.G.-V., P.F.N., M.R.S.-Á., J.C.-L., X.R., J.V., C.Z. and R.M.; formal analysis, M.M.; investigation, M.M.; resources, M.M.; data curation, M.M.; writing—original draft preparation, M.M.; writing—review and editing, M.M., L.G.-V., P.F.N., M.R.S.-Á., J.C.-L., X.R., J.V., C.Z. and R.M.; visualization, M.M., L.G.-V., P.F.N., M.R.S.-Á., J.C.-L., X.R., J.V., C.Z. and R.M.; supervision, R.M.; project administration, M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were not required for this study because it involved the retrospective analysis of existing clinical records and no additional procedures were performed on the animals.

Informed Consent Statement: Written informed consent for the clinical procedures and for the use of the animals' clinical data for research purposes was obtained from the owners as part of routine clinical care.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Acknowledgments: Acknowledgment is extended to AniCura Valencia Sur Hospital Veterinario (Valencia), Hospital Clínico Veterinario CEU-UCH (Valencia), Hospital Clínic Veterinari de la Universitat Autònoma de Barcelona (Barcelona), and Hospital Veterinario de Referencia UCV (Valencia) for their participation and valuable contribution to this study. The authors also thank Universidad Católica de Valencia San Vicente Mártir for supporting the publication of this work.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AIC	Akaike information criterion
AUC	Area under the receiver operating characteristic curve
AUS	Abnormal ultrasonographic findings
CI	Confidence interval
CKD	Chronic kidney disease
DICOM	Digital Imaging and Communications in Medicine
GFR	Glomerular filtration rate
HRC	Hyperechoic renal cortex
HYDRO	Hydronephrosis
ICD	Increased corticomedullary differentiation
IQR	Interquartile range
IRIS	International Renal Interest Society
IRR	Incidence rate ratio
IRS	Irregular renal surface
LCMD	Loss of corticomedullary differentiation
LK	Large kidney
LKS	Loss of kidney structure
MRS	Medullary rim sign
NOU	Non-obstructive urolithiasis
OR	Odds ratio
PF	Perirenal fluid
RC	Renal cysts
RCP	Renal parenchymal calcification
RI	Renal infarcts

RPD	Renal pelvic dilation
SDMA	Symmetric dimethylarginine
SK	Small kidneys
TRC	Thickened renal cortex
UPCR	Urine protein-to-creatinine ratio
USG	Urine specific gravity

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