Symmetrical Dimethylarginine: Evaluating Chronic Kidney Disease in the Era of Multiple Kidney Biomarkers

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KEYWORDS

• Nephrology • Veterinary • Creatinine • SDMA • Glomerular filtration rate

KEY POINTS

- Symmetric dimethylarginine (SDMA) is incorporated into the International Renal Interest Society guidelines for diagnosing, staging, and treating chronic kidney disease (CKD).
- Persistent mild increases in SDMA can be used to diagnose CKD.
- SDMA and creatinine correlate well with each other and with GFR.
- SDMA is affected by fewer nonrenal influences than creatinine.

INTRODUCTION

The diagnosis and management of chronic kidney disease (CKD) is a routine part of the clinical small animal practice. CKD is a common cause of morbidity and mortality in older cats and dogs.[1–3] The prevalence of CKD in cats rises sharply with age, with an estimated prevalence of less than 1% in young cats, 30% to 40% in cats more than 9%, and 60% in geriatric cats.[2,4–6] In dogs, the prevalence of CKD is lower and believed to be less than 1.5% and, similar to cats, is more common in older dogs.[7,8] Diagnosis of CKD is multifactorial involving clinical signs, physical examination, kidney biomarkers, urinalysis, and kidney imaging. The International Renal Interest Society (IRIS) is a globally recognized group of experts that provide education to practitioners around CKD and guidelines to standardize staging and management of cats and dogs with CKD.[9–11] CKD monitoring and management goes beyond renal biomarkers alone to include serum calcium and phosphorus, electrolytes, urine and serum protein, and blood pressure.[10,11]

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CKD stage at diagnosis impacts survival and prognosis for cats and dogs and patients with earlier stages of CKD have longer survival following diagnosis[8,12–14] and recognition at early stages may slow the progression of CKD.[8,15,16] Although recognition of CKD in early stages has the potential to improve the prognosis, it can be difficult due to subtle changes in patients' clinical presentation and kidney biomarkers concentrations. In cats and dogs with IRIS stage 1 and 2 CKD, serum or plasma creatinine (sCr) is often within laboratory reference intervals (RI) and proteinuria, clinical signs, and changes to urine concentrating ability and urine specific gravity (USG) are variable and often absent.[9,17] Symmetric dimethylarginine (SDMA) is often the only kidney biomarker increased above the RI in animals with these early stages of CKD.[9] Single SDMA concentrations can detect smaller declines in glomerular filtration rate (GFR) than traditional kidney biomarkers sCr and blood urea nitrogen (BUN) concentrations.[18–20] Since becoming commercially available SDMA has been explored extensively in acute, chronic, and active kidney disease in cats and dogs, resulting in a large body of literature describing the use of SDMA in diagnosis, treatment, and monitoring of kidney disease in companion animals. Additionally, a recent systematic review and consensus statement of feline CKD treatment trials recommended that SDMA be included in the Core Outcome Set for minimum data collected in those research studies.[21]

Historically, CKD has been thought of as an irreversible, continuously progressive disease process characterized by a linear progression of indirect biomarkers recognizing the regression of GFR. While recent studies still describe CKD as irreversible and progressive, it is often proposed that a series of subtle and clinically impactful active injuries advance the decline in GFR and lead to CKD and CKD-linked sequelae.[22,23] These injuries can lead to nonlinear progression and there can be periods of partial recovery of kidney function between injuries.[24,25] Over the past decade, this changing paradigm and advancements in kidney biomarker availability and improvements in technology have enhanced practitioners' ability to detect more subtle CKD. The addition of SDMA and more frequent inclusion of urine protein to creatinine ratios (UPC) into CKD diagnosis and staging have improved detection and staging of early CKD in the general practice setting. Wide availability of high-quality ultrasound equipment, widespread imaging training, and more robust practice management and medical records software have contributed to improved assessment of patients.[2,26] Electronic medical records software often includes chronologic analyte concentrations and easier visualization of patient trends. There is strong evidence that serial assessment or trending of kidney biomarkers (including SDMA, sCr, USG, and UPC) shortens time to diagnosis and can lead to early intervention and potentially improved outcomes for cats and dogs with CKD.[7,27] Overall, the addition of SDMA, improvements in technology, and updated educational materials and IRIS guidelines have provided clarity around the diagnosis of CKD in early stages and, therefore, provided opportunities to improve outcomes for cats and dogs with CKD.

Discovery and Biochemistry

SDMA was first identified in urine in 1970.[28] SDMA and related asymmetric dimethylarginine (ADMA) are methylated amino acids generated intracellularly during protein turnover.[28,29] Protein arginine methyltransferases (PRMTs) produce SDMA and ADMA precursors through methylation of protein-bound L-arginine residues; SDMA and ADMA are released through protein degradation. Type I PRMTs are primarily responsible for the generation of ADMA and type II PRMTs (primarily PRMT5) generate SDMA. Almost all SDMA undergoes renal excretion[28,30] while only approximately 20% of ADMA is excreted by the kidneys and the rest is metabolized. Increased SDMA was

initially identified in people with advanced kidney disease.[31] A meta-analysis of human patients found significant correlations between SDMA, GFR, and sCr.[32] Studies in cats and dogs have similarly reported a good correlation between SDMA and GFR (Supplemental Tables).[18–20,33–39]

IDENTIFYING DECREASED KIDNEY EXCRETORY FUNCTION

Glomerular Filtration Rate

Measurement of GFR is the recognized gold standard for quantitative assessment of kidney excretory function. However, it is not routinely performed on cats and dogs and is not specifically included in guidelines for diagnosing or staging CKD. Measuring GFR is complicated, time-consuming, requires administration of a suitable filtration marker, and obtaining timed blood samples and/or urine samples.[40] There is no single protocol or methodology for measurement of GFR; rather, there are multiple different protocols, filtration markers, and calculations that can be performed and each yield slightly different results. Methodology can affect the results and can cause substantial differences in measured GFR; published, estimated mean GFR for different methodologies can range from 1.38 to 4.85 mL/min/kg for dogs and 0.85 to 3.05 mL/min/kg for cats (Supplemental Tables).[18–20,33,41–45] Inulin clearance is generally considered the "ideal" method for measuring GFR because inulin is safe and inert, freely filtered through the glomerulus, not bound to any plasma proteins, and neither reabsorbed nor secreted by the renal tubules.[46,47] Nevertheless, inulin clearance is rarely performed because it is not widely available, is technically challenging and requires 24-h collection of all urine produced in a metabolic cage or with urethral catheterization.[47,48] Scintigraphy using radiolabeled markers, including ^{125}I sodium iothalamate, ^{131}I sodium iodohippurate, ^{51}Cr-EDTA, and ^{99}Tc-DTPA can measure either global GFR or GFR of individual kidneys, but requires handling of radioactive waste and animals.

Cr clearance (endogenous or exogenous) techniques to measure GFR are easier to perform in clinical practice. Comparisons of exogenous Cr clearance have generally found a good correlation with inulin clearance in dogs, but results may underestimate GFR.[49–51] Although early studies suggested exogenous Cr clearance with continuous infusion may not be a good indicator of GFR in cats,[52,53] more recent feline studies suggest that bolus creatinine injections may yield a reasonable measurement of GFR.[51,54,55] Creatinine clearance measurements are susceptible to overestimation of creatinine if Jaffe methods are used to measure sCr.[56,57]

Plasma iohexol clearance is also commonly used to measure GFR in cats and dogs. Iohexol is an iodinated contrast agent that is excreted unchanged in urine with a half-life of 74 minutes.[58] Unlike many contrast agents, iohexol is not believed to damage the kidneys.[41] Two stereoisomers, endo- and exo-iohexol, can produce different results[59–61] and the use of exo-iohexol has higher reproducibility.[54,55,62,63] Published protocols use widely varying numbers of plasma samples with different timing to measure iohexol clearance.[41,64,65] These differences in the type of iohexol and protocols should be accounted for when comparing results across published studies. Iohexol clearance has not been compared directly to inulin clearance in cats and dogs; rather, it has primarily been validated through comparison with exogenous Cr clearance.[60,61]

GFR can vary within individuals due to a variety of factors, including hydration, diet, medications, and diurnal variation.[52,66–69] Factors contributing to variation within the population are still poorly defined for cats and dogs. Estimated GFR for human samples is routinely calculated from sCr normalized to body surface area (rather than weight) and corrected for age, sex, and race, but the ideal standardization method(s) for measured GFR across dogs is still under investigation.[41] Body weight is often used

to standardize GFR across dogs of different sizes, but metabolic scaling in very large and small dogs may result in nonlinear relationships between GFR and body weight (Fig. 1).[34,41] Age and sex do not seem to substantially impact GFR in dogs.[41] There have not been thorough investigations of the impact of breed on GFR for either dogs or cats. McKenna et al. (2019) recently published a strategy for estimating the degree of reduction in GFR for dogs with confirmed or suspected CKD by comparing individual GFR to mean GFR of the appropriate body weight category. Only dogs with a clinical indication for measuring GFR were used to generate the mean GFR for the groups. Estimated decreases in GFR greater than 20% identified some dogs without increased sCr that were later diagnosed with CKD or other kidney pathologies.[45] Further evaluation will be needed to understand the applicability of this strategy to a wider population and which normalization technique(s) are best for estimating individual GFR and comparing with the population.

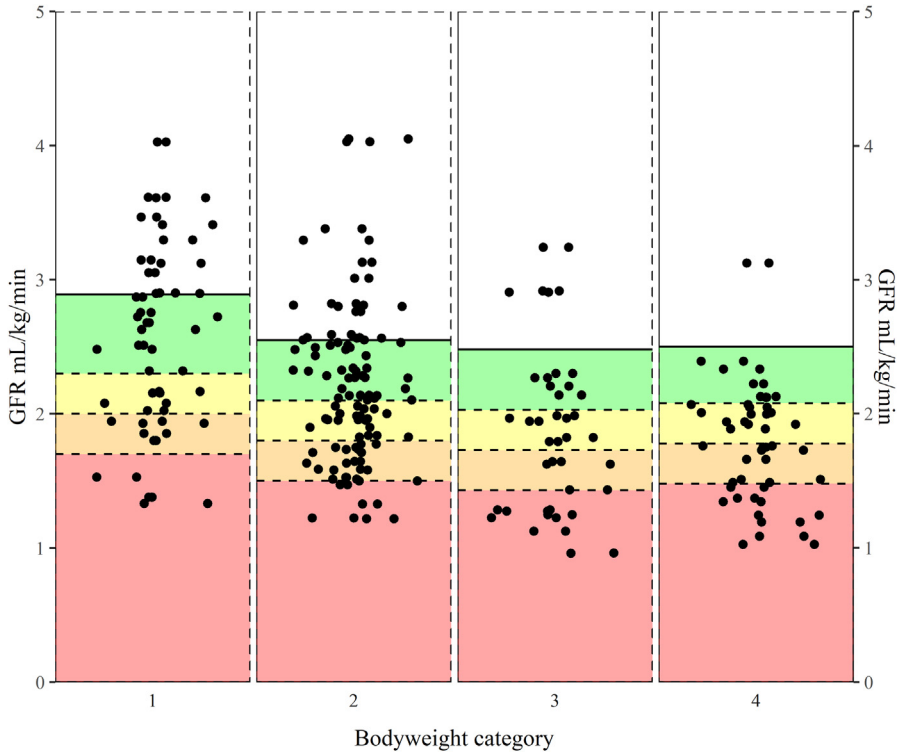

Fig. 1. Canine glomerular filtration rate (GFR) estimation results (mL/kg/min) represented graphically, separated by body weight Categories 1 (1.8–12.4 kg), 2(13.2–25.5 kg), 3 (25.7–31.6 kg), and 4 (32.0–70.3 kg). Each dot represents the GFR result from a patient. The area on each chart with a green background represents a GFR decrease of less than 20% from the mean GFR of the body weight category, the yellow background represents a GFR decrease of $\geq$ 20% but less than 30% from mean GFR, the orange background represents a $\geq$ 30% but less than 40% decrease in GFR from mean GFR, and the red background represents a $\geq$ 40% decrease in GFR from the mean GFR. (Recreated with data from Mckenna and colleagues 2020 https://doi.org/10.1111/jvim.15561).

Relationship of symmetric dimethylarginine and serum creatinine to decreased glomerular filtration rate

SCr and SDMA are the most common surrogate markers for GFR in veterinary medicine. Both sCr and SDMA inversely correlate with GFR, but do not perfectly correlate with each other.[18–20,35,36,45,70] SCr has an exponential relationship with GFR such that at low sCr small changes can represent large changes in GFR, and then at higher sCr, large changes in sCr represent small changes in GFR.[6] SDMA, on the other hand, has a linear relationship with GFR.[33] SDMA increases above the reference interval (RI) with an average of 40% reduction in GFR, while SCr does not increase above the RI until approximately 75% reduction in GFR.[18–20,33,50] Trending of sCr over time can detect smaller changes in GFR with relatively small changes in sCr when sCr remains within the RI; however this approach requires historical baseline data for the individual dog or cat as there can be inter-individual variability in the homeostatic set point for creatinine.

Methodological differences can contribute to analytical variability when comparing results generated using different methodologies. Differences between sCr measured with Jaffe, modified Jaffe, and enzymatic reactions have been described.[71] Less is known about methodologic differences in SDMA. Veterinary research and publications have primarily used IDEXX Laboratories, Inc., proprietary methods to measure SDMA in the Reference Laboratories and on Catalyst analyzers. These methods are highly correlated with liquid chromatography-mass spectrometry, which is the gold standard methodology.[19,20,72,73] Recent research has investigated differences between results generated by IDEXX methodologies,[74–76] and between other commercially available methodologies.[77,78] As expected, differences were found between results from the reference laboratory methodologies and in-house module Catalyst analyzers. While these differences are often expected to be subtle it would be recommended to use the same platform for measurements whereby patient trending of SDMA concentration is clinically indicated. This would extend to exercising consistency in laboratory choice given the variety of methodologies used to measure SDMA in the current commercial market.

Comparisons of different studies around the sensitivity and specificity of sCr and SDMA for specific GFR cutoffs are complicated by differences in GFR measurement, analytical methods, concurrent diseases in the population, patient population selection, and varying GFR cutoffs (Supplemental Tables).[34–37] Most studies have found good sensitivity and specificity for both sCr and SDMA at different GFR cutoffs.[18–20,34–37,70]

Extrarenal contributors to symmetric dimethylarginine and serum creatinine

As a variety of extrarenal factors can impact the serum or plasma concentration of kidney biomarkers, including dehydration and changes in food and water consumption, and production or loss of biomarkers or their precursors, evaluation of kidney function should always include clinical history and physical examination, urinalysis, and relevant imaging findings. Evaluation of the appropriateness of the USG is important for the evaluation of kidney function.[17,21] Dehydration can increase both sCr and SDMA by temporarily decreasing plasma volume and GFR. As sCr correlates positively with muscle mass, it can provide inaccurate estimates of GFR in cats and dogs with muscle loss or heavy muscling.[19,79] Use of the World Small Animal Veterinary Association Global Nutrition Committee muscle condition scoring system (MCS),[80] or other MCS protocols, can help practitioners identify animals with poor muscle condition even if they are overweight or obese.[81,82] Diet is an often overlooked extrarenal contributor to sCr and ingestion of meat (raw or cooked) can cause a transient

postprandial increase in sCr.[12,46] There are fewer known extrarenal influences on SDMA.[20,43,83–85] *In vitro* increases in SDMA production have been found in cells with alanine-glyoxylate aminotransferase 2 variants and in cells with upregulation of PRTM5.[84–86] Increased serum SDMA has been reported in people with a variety of cancers, although the mechanism of these increases remains unclear and could relate to kidney function due to infiltration, paraneoplastic effects, or increased cellular production.[87,88] There seem to be some breed-associated differences in SDMA and sCr concentrations in cats and dogs.[89–92] Greyhounds have higher homeostatic concentrations of both SDMA and sCr.[90,91,93,94] SDMA is higher in Greyhounds of all ages than in non-Greyhound breeds[90,91]; sCr is only increased in adult Greyhounds, likely due to high muscle mass.[93] Boxers appear to have a higher frequency of increased SDMA and/or sCr in puppies through adulthood but whether this is due to increased development of kidney pathology or other mechanisms is unclear.[89,95,96] Birman cats have a higher frequency of increased sCr and SDMA than other cat breeds.[92,97]

Analytical and biological variability of kidney biomarkers

There is inherent variability between measurements of any analyte due to preanalytical, analytical, and biological factors. Preanalytical variability could arise from differences affecting blood collection, storage, shipment, etc. Analytical variability arises from inherent imprecision within an instrument, between instruments, and between methodologies. Biological variability arises within an individual animal or population of animals. A robust quality management program is necessary to minimize preanalytical and analytical variability in samples measured on either reference laboratory or in-clinic analyzers. Although all analyzers need routine quality control and maintenance, there are different recommendations for quality management in reference/academic laboratories and for in-clinic analyzers. There are published recommendations for establishing robust management programs for in-clinic analyzers.[98–100]

Biological variability can occur within an individual (eg, diurnal, seasonal, hormonal, diet, aging, etc.) or between individuals within a population (eg, genetics, environment, age distribution, etc.). Biological variability is presented as the variability within an individual (CV_I) and the variability within the population (CV_G).[101] The index of individuality (IOI) and reference change value (RCV) are common ways to express clinically relevant information about the interaction of biological and analytical variability.

The IOI uses the CV_I, CV_A, and CV_G to provide information about how the amount of variability expected for an individual relates to the amount of variability expected in the population. A low IOI indicates that for a particular individual, the range of repeated measurements around the animal's homeostatic set point would fall within a narrow band of population RI (ie, there is more population variation than within-individual variation) (**Fig. 2**). For analytes with a high IOI, the range of repeated measurements around an animal's homeostatic set point may exceed the width of the population RI (ie, there is more within-individual variation than population variation) (see **Fig. 2**). Although analytes with a higher IOI have a wider range of possible results for a particular "true" value, it does not indicate that results are equally likely across that entire range; most repeated measurements would be clustered around the individual's "true" value. For cats and dogs, sCr has a low IOI and SDMA has a moderate IOI (**Table 1**).[102–106] The IOI also influences how much additional information can be gained by repeating measurements following an unexpectedly increased concentration. Assuming the patient has relatively stable kidney function over the recheck period, a second SDMA concentration is more helpful at identifying the "true" SDMA concentration and identifying false positives than a second sCr is at identifying false positives (see **Fig. 2**).[107]

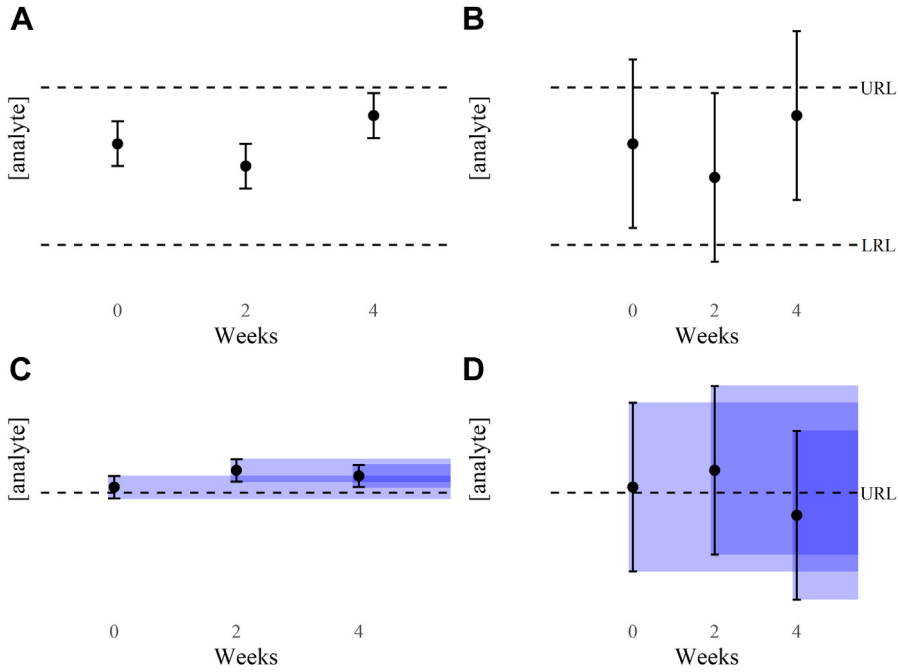

Fig. 2. Relationship of the index of individuality (IOI) to the reference interval (RI). The measured concentration is shown as a dot and the 95% confidence interval (*lines*) shows the range of possible concentrations that could be "true value" associated with this measurement. (*A*,*B*) Show an animal with 3 measurements over time of a hypothetical analyte whereby the concentrations at each measurement fall between the upper reference limit (URL) and lower reference limit (LRL) of the reference interval. If the hypothetical analyte has a low IOI (*A*), all measured concentrations for these "true" values should fall between the URL and LRL. However, if the analyte has a high IOI (*B*), the measured concentrations for the same "true" values could potentially fall above the URL or below the LRL. (*C*,*D*) Assuming stable analyte concentrations in the animal, repeated measurements of analytes can help identify false-positive increases in the analyte concentration and provide additional information about the patient's "true" value. If the analyte has a low IOI (*C*), repeated concentrations should cluster closely and minimal additional information about the likely "true" value is added. For analytes with a high IOI (*D*), more variation in measured concentrations is expected, and the repeated measurements help to narrow the range of likely "true" value.

Additionally, if there is no historical data available for comparison, it is also possible to misinterpret an sCr within the RI as representing "normal" GFR even though it is increased for the individual's homeostatic setpoint.

The RCV uses the CV_I and CV_A to identify the difference needed between 2 concentrations to determine if they are statistically different. Measuring RCV is sometimes recommended to detect a clinically significant change in analyte concentration for analytes with low IOI (<0.6) instead of using population RIs or cut-offs to detect "abnormal" results. However, the putative advantage of using RCV over population RIs to identify patients with significant changes is highly dependent on the IOI and the desired statistical power.[108] The RCV may be helpful for identifying clinically important changes for some analytes, but, similar to clinical decision points, the clinical goals and desired statistical power influence the RCV the study generates. Several

Table 1
Index of individuality (IOI) for symmetric dimethylarginine (SDMA) and serum creatinine (sCr) for cats and dogs

	Index of Individuality (IOI)			
	Dogs		Cats	
Article	SDMA	sCr	SDMA	sCr
Kopke et al,[103] 2018	0.87	0.28	—	—
Hillaert et al,[102] 2021	0.73	—	—	—
Falkenö et al,[104] 2016	—	0.30	—	—
Trumel et al,[105] 2016	—	—	—	0.50
Prieto et al,[106] 2020	—	—	0.91[a]	0.45[a]

[a] Converted from inverse IOI in the original article.

studies have recently calculated RCVs for SDMA and sCr in cats and dogs based on the available biological and analytical variability for those analytes (Supplemental Tables).[75,103,106,109]

Reference intervals and clinical cutoffs

RIs for a given analyte are determined statistically by laboratories to provide a representation of the range of analyte values observed in a characterized, healthy population. In the United States, guidelines for RI generation are set out by Clinical Laboratory Standards Institute[110] and American Society for Veterinary Clinical Pathology.[111] Ideally, a minimum of 120 clinically healthy animals are prospectively selected for the purpose of generating the RI. As prospective selection and large populations are not always feasible or possible, guidelines also contain statistical guidance for smaller sample populations. RIs reflect the reference population and method used to generate that RI, so RIs may vary between laboratories, methodologies, and populations. Statistically, the RI represents the central 95% of the reference population, so 5% of the values from the RI population fall outside of the newly established RI. This indicates that some healthy animals will also have "normal" concentrations that fall outside of the RI and investigation of whether a concentration is "normal" or "abnormal" for the individual may require additional testing. As discussed above, some analytes may benefit more from individual baseline values than population RIs.

Clinical decision points, or cutoffs, serve a fundamentally different purpose from RIs. Cutoffs are intended to separate populations of animals (eg, diagnosis of disease, staging, treatment guidance, etc.) rather than define the range of results expected in a healthy population. Although cutoffs are sometimes referred to as "upper reference limits," that term refers specifically to RIs and should not be used for cutoffs. Therefore, cutoffs can, but do not necessarily, align with RIs; they may overlap with RIs, be clearly distinct from the RI, or be separated by a clinical "gray area" without a clear interpretation. Like RIs, cutoffs reflect the population and population size used to generate the cutoff; they should be applied with caution to broader populations or populations dissimilar to the study population.

Several recent studies have evaluated possible clinical decision limits for SDMA and sCr in cats and dogs. IDEXX Laboratories recommends the same SDMA cutoff of greater than 14 μg/dL for recognizing an average of 40% decrease in GFR for cats and dogs.[18] These cutoffs were generated using colony cats and dogs with and without CKD to understand the relationship between the mean decrease in GFR and the number of subjects identified by an increased SDMA above the RI.[18,19] IRIS uses a similar cutoff

Table 2
Symmetric dimethylarginine and serum creatinine in International Renal Interest Society (IRIS) chronic kidney disease staging guidelines (2019 update)

	Dogs		Cats	
IRIS Stage	SDMA (μg/dL)	sCr (mg/dL)	SDMA (μg/dL)	sCr (mg/dL)
1	< 18	< 1.4	< 18	< 1.6
2	18–35	1.4–2.8	18–25	1.6–2.8
3	36–54	2.9–5.0	26–38	2.9–5.0
4	>54	>5.0	>38	>5.0

of at least 2 SDMA concentrations greater than 14 μg/dL to diagnose CKD and different cutoffs to stage previously diagnosed CKD (Table 2). Two recent publications describing client-owned dogs, and one with client-owned cats, have suggested other SDMA cutoffs to identify cats and dogs with CKD. [34 35] McKenna et al.(2020)[34] proposed clinical cutoffs of 18 μg/dL for SDMA and 1.34 mg/dL for sCr to identify subjects with at least a 40% decrease in GFR in a retrospective study of diagnostic samples submitted by referring veterinarians using a concurrently published method for estimating percentage decreased GFR[455] The population used to develop the estimated GFR included only dogs with diagnostic GFR testing. As the primary reason for clinical GFR measurement is a concern for decreased kidney excretory function, this population may have had decreased GFR compared with a healthy population which may result in lower mean values for healthy dogs and inaccurate estimates of the reduction in GFR for some patients. Pelander and colleagues (2018) prospectively enrolled dogs with a diagnosis or suspicion of stable CKD and a small number of healthy dogs to evaluate the sensitivity and specificity of SDMA, sCr, and cystatin C for identifying GFR less than 30.8 mL/min/L and suggested cutoffs of 16 μg/dL for SDMA and 1.4 mg/dL for sCr for detecting GFR at this level. These suggested cutoffs for dogs are consistent with biomarker concentrations at the border between IRIS stage 1 and 2 CKD but may not be appropriate for identifying many dogs with stage 1 CKD. Brans and colleagues (2021) proposed an SDMA cutoff of 18 μg/dL and an sCr cutoff of 1.76 mg/dL for differentiating between healthy, diabetic, and CKD cats (defined as single sCr > 1.83 mg/dL with USG <1.035) using GFR determined by iohexol. The CKD definition in this study is consistent with IRIS Stage 2 in cats, so the cutoff is not designed to differentiate healthy cats from cats with IRIS Stage 1 CKD. These dog and cat SDMA and sCr cutoffs would primarily identify cats and dogs with IRIS stage 2 and should not be confused with the upper limit of the RI.

Differences in populations, GFR methodologies, and classification of CKD underlie differences in suggested cutoffs. Ideally, further studies to identify if differences between suggested clinical decision points are due to differences in methodology, definitions of CKD, and/or decreased GFR, or populations would be valuable. Clinical decision points should always be evaluated with careful attention to the population and methodologies used to generate them and to the desired clinical goals.

CLINICAL UTILITY OF SYMMETRIC DIMETHYLARGININE

Clinical Presentation of Chronic Kidney Disease

The frequency of abnormal physical examination findings and the severity of clinical signs increase with the severity of CKD. In Stage 1 and Stage 2, clinical signs and

Table 3
Common clinical signs and physical examination findings in cats and dogs with CKD

Clinical Signs	Physical Examination Findings
Polyuria and polydipsia	Palpable kidney abnormalities
Decreased appetite	Evidence of weight loss
Weight loss	Evidence of muscle loss
Lethargy	Dehydration
Bad breath	Pallor
	Oral ulcers
	Hypertensive retinopathy

physical examination findings are often absent, although they become more common or more pronounced with later-stage CKD (Table 3).

Clinical biochemistry and imaging findings are particularly important in assessing kidney health in the early stages of CKD as clinical signs and examination findings are inconsistent. USG often shows adequate or appropriate urine concentration early in the disease when there are more functional nephrons. USG should always be interpreted in the context of the patient's hydration status as a wide range of USGs can be appropriate in well-hydrated healthy cats and dogs (Table 4). Making a diagnosis of CKD based on the IRIS CKD guidelines requires at least one of the specific findings including: increasing sCr or SDMA within the RI, persistently increased SDMA, sCr and/or BUN, inappropriate USG for the hydration status, structural kidney abnormalities identified on imaging, persistent renal proteinuria, or documented renal tubular dysfunction.

Role of Symmetric Dimethylarginine in International Renal Interest Society Guidelines for the Diagnosis and Staging of Chronic Kidney Disease

IRIS was created in 1998 to help veterinary practitioners better understand, diagnose, stage, and treat renal disease in cats and dogs. Once there is a diagnosis of CKD, the IRIS staging guidelines provide a standardized method for assessing severity and recommendations for monitoring and management of CKD. SDMA was provisionally included in the IRIS CKD staging guidelines and fully incorporated in 2019 (see Table 2).[9] For staging, animals should have at least 2 stably increased kidney biomarker concentrations without clinical dehydration.[9] The inclusion of SDMA in the recommendations for diagnosis and staging help identify CKD in animals with minimal to absent clinical signs or physical examination findings, have retained urine concentrating ability, or have sCr within the RI and lack historical data for trending of sCr.[9,18,19] In cases whereby SDMA indicates a higher stage than sCr, the guidelines suggest staging and treating the patient at the higher stage indicated by SDMA.[9] Evaluating SDMA and sCr together, therefore, can provide better clinical information to guide therapeutic recommendations for cats and dogs with CKD, and may be particularly beneficial in animals with muscle loss or poor body condition.[19,43]

Clinical Value of Earlier Identification of Chronic Kidney Disease

CKD is an active process and most cats and dogs experience both recognized and unrecognized active kidney injury events in the course of their disease. It is, therefore, imperative to have a diverse and robust approach to evaluating kidney function. At the time of writing, biomarkers for active kidney injury are a topic of research but

Table 4
Interpretation of urine specific gravity (USG) in evaluating urine concentrating ability adapted from Watson et al,[122] 2015

USG	Classification	Interpretation
>1.030 (dog) >1.035 (cat)	Concentrated	Indicates adequate functioning nephrons (>33% functional nephrons) Suggests potential dehydration in azotemic animals
1.013–1.029 (dog) 1.013–1.034 (cat)	Moderately concentrated	May be appropriate in well-hydrated animals Inappropriate in dehydrated animals Suggests kidney disease in azotemic animals
1.008–1.013	Isosthenuric	Inappropriate in dehydrated animals Substantial kidney disease in azotemic animals
< 1.008	Dilute	May be appropriate in overhydrated animals Suggests retention of urine diluting ability (>33% functional nephrons)

Data from Watson ADJ, Lefebvre HP, Elliot J. Using urine specific gravity. Published 2015. Accessed October 5, 2929. http://www.iris-kidney.com/education/urine_specific_gravity.html.

biomarkers of GFR are still the most available tests for functional kidney injuries.[112] SDMA has made it easier to identify cats and dogs experiencing mild declines in GFR while sCr is within the RI or corroborate animals under suspicion of early disease. Long-term serial evaluation of GFR or surrogate markers can also inform diagnosis and management recommendations for cats and dogs with CKD, though this is still an area with rapid and on-going development.[113–115] Specifically in dogs, using SDMA as part of the parameters to identify CKD is particularly supported in dogs with previous positive tests results for *Borrelia* spp., *Anaplasma* spp., *Ehrlichia* spp., or *Leishmania* spp.[116–118]

Management recommendations for IRIS Stage 1 and Stage 2 CKD focus on discontinuing nephrotoxic medications, preventing dehydration, identifying and treating concurrent diseases, and monitoring and treating hypertension and proteinuria.[10,11] Identification of Stage 1 and Stage 2 CKD may increase the likelihood of finding treatable causes of kidney disease (including pyelonephritis, borreliosis, ehrlichiosis, leishmaniasis, obstructive urolithiasis, or chronic toxicities) and preventing or slowing further kidney damage.[116–118] Even if no treatable underlying conditions are identified, earlier diagnosis and management may slow the rate of progression of CKD and improve the quality and/or quantity of life for affected animals.[15] Prescription renal diets are recommended for cats and dogs with Stage 2 disease and total phosphorus concentrations of ^{3}4.6 mg/dL.[10,11] Preliminary studies have suggested that dietary management may also benefit animals with IRIS Stage 1 CKD and slow age-associated decreases in GFR.[16,119,120] Additional research is needed to identify effective therapies for cats and dogs with Stage 1 and early Stage 2 CKD or identify subsets of cats and dogs that would benefit from therapy.

Behavior of Symmetric Dimethylarginine and Serum Creatinine in Chronic Kidney Disease

Many cats and dogs with CKD have an initial acute kidney injury or small repetitive injuries that contribute to the development of CKD.[24,25,121] In some cases these acute kidney injuries lead to clinical signs and are recognized on biochemistry results, but others likely go undetected. Many cats and dogs go through a “compensatory” stage after initial active injury and biochemical parameters may return to within the RI.[25]

These “normal” parameters may complicate practitioner recognition of the kidney damage that has occurred. This compensatory period can last for several days or many months. When interpreting these fluctuations in renal parameters, it is important to recall that cats and dogs have significant biological variability in GFR and that this biological variability may be more pronounced in animals with disease. Therefore, it is not uncommon to see SDMA or sCr fluctuate around or across the upper reference limit or around clinical decision points before becoming persistently increased.[114,115] This potential for a compensatory period and changes in reported biomarker concentrations due to biological and analytical variation emphasizes the importance of consistent follow-up testing using the same methodology, and of trending kidney biomarkers in animals with suspected or known disease.

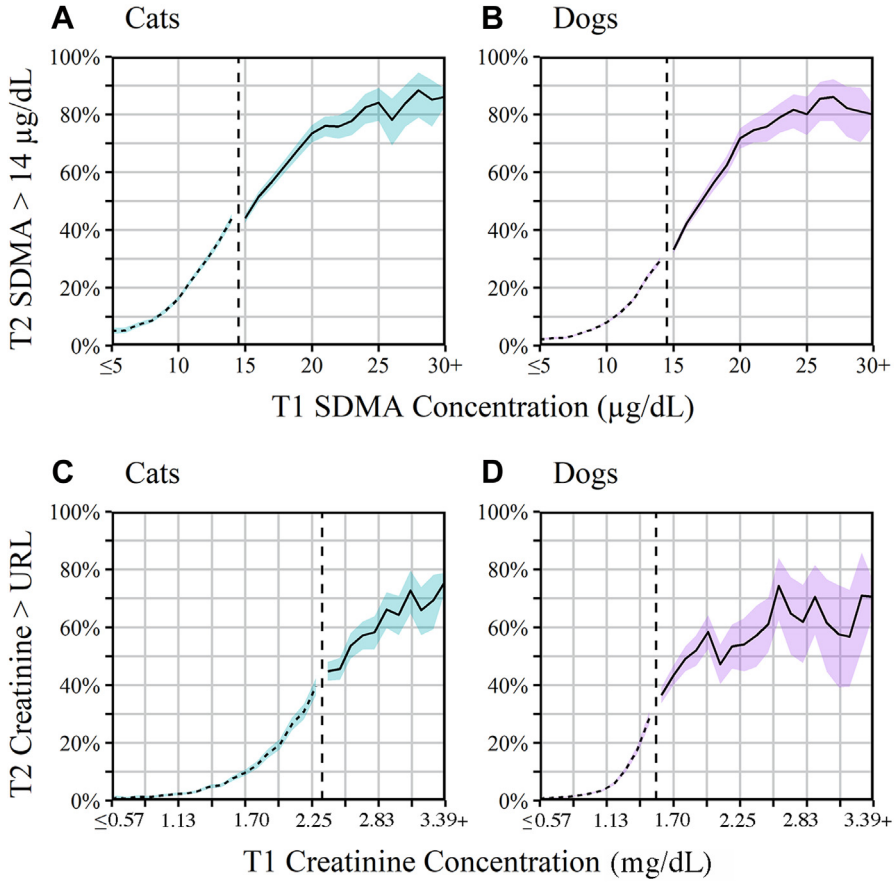

Fig. 3. Probability of an increased kidney biomarker concentration (T2) based on the biomarker concentration from the previous measurement (T1). (*A*, *B*) The probability of an SDMA $\geq$ 14 µg/dL at T2 increased with T1 SDMA concentration. (*C*,*D*) The probability of an sCr above the RI for cats and dogs at T2 increased with the T1 sCr value. A & B are reproduced from Mack and colleagues 2021 (https://doi.org/10.1016/j.tvjl.2021.105732) under a CC-BY copyright agreement. C & D are modified from the figures in Michael and colleagues 2021 (https://doi.org/10.1016/j.tvjl.2021.105729) to show sCr in mg/dL under a CC-BY copyright agreement.

Increased SDMA and sCr are relatively common laboratory findings. A recent study evaluated persistence or probability that the SDMA or sCr remained above the RI at the next measurement, and concordance, or agreement of increased SDMA and sCr, in more than 165,000 dogs and more than 90,000 cats.[114,115] The probabilities of persistently increased SDMA or sCr following an initial increase in SDMA or sCr concentration are shown in **Fig. 3**. Cats and dogs with an initial mild increase in SDMA (defined as 15–19 μg/dL) or any sCr above the species-specific RI had an approximately 50% probability of having persistently increased SDMA or sCr.[114,115] For animals whereby SDMA decreased to within the RI at the next measurement, approximately 50% would be expected to have at least one additional increased SDMA concentration within 12 months.[114] This study suggested that many cats and dogs with mild, persistent SDMA increases would not have increased sCr at the initial increase in SDMA but would develop increased sCr within 2 years.[114] On the other hand, cats and dogs with persistently increased sCr would be expected to already have increased SDMA at the initial increase.[115] There is, therefore, strong evidence that SDMA complements sCr, BUN, and USG in screening animals for early-stage CKD.[18–20,114,115]

SDMA and sCr do not perfectly correlate with each other and different degrees of reduction in GFR result in the biomarker concentration above their respective RIs. In some cases paired SDMA and sCr can seem discrepant, with one result within or below the RI and one above the RI. It is common for SDMA to be mildly increased in cats and dogs with sCr within or below the RI.[9,114] Increased sCr without increased SDMA is less common and occurs in approximately 2% to 4% of cat and dog results (data on file at IDEXX.). In Michael and colleagues (2021), the rate of discrepant results was higher because the cats and dogs with a prior increase in SDMA were excluded from the study, but discrepantly increased sCr usually resolved within 2 years due to an increase in SDMA or reduction in sCr.[115] Although the mechanisms of discrepantly increased sCr are unclear, differences in biomarker handling with individual kidney disease etiologies, extrarenal effects on sCr and/or SDMA, or inter-individual differences in homeostatic set points for these biomarkers are some potential contributors. IRIS staging guidelines indicate that when discrepant biomarkers affect the staging of CKD, animals should be staged and treated in accordance with stable values indicating the higher stage.[5]

SUMMARY

SDMA should be considered a staple surrogate marker of GFR for clinicians diagnosing, staging, and monitoring cats and dogs with CKD. Interpretation of SDMA concentration should be part of the total assessment of kidney function, including sCr, BUN, electrolytes, serum phosphorous and calcium, complete urinalysis, USG, UPC when indicated, complete blood count, and relevant imaging results. Adjunct tests such as infectious disease screening, blood pressure, and imaging should also be considered when clinically indicated to identify underlying diseases. Technological improvements in ultrasound imaging capability and the ability to visualize trends in analyte concentrations over time have also improved clinician's ability to diagnose patients with CKD. In addition to surrogate biomarkers for GFR (eg, SDMA and sCr), research into additional kidney biomarkers for acute kidney injury and for guiding personalized therapy recommendations will likely continue to transform diagnosis and management of CKD in the coming years.

As research into additional kidney biomarkers continues and imaging technology improves, there is a continued opportunity for recognition of patients at risk for

progressive CKD or with early stages of CKD. This provides an opportunity for interventions and management to the slow progression of disease and for research into dietary interventions or targeted therapies for IRIS stage 1 and stage 2 CKD.

CLINICS CARE POINTS

- Optimal evaluation of kidney health would include SDMA alongside traditional kidney function biomarkers, urinalysis, and complete blood count.
- Establishing the nature of the kidney disease, as either acute, chronic, or acute on chronic will allow improved interpretation of SDMA and all kidney biomarkers.
- Inclusion of SDMA in pre-anesthetic, preventive care, and sick patient testing improves interpretation with trended values and individualized patient assessment.
- SDMA is available in multiple methodologies, both reference laboratory and point-of-care, while all measure SDMA given analytical variability it is suggested to trend SDMA on the same methodology for best results.

DISCLOSURE

All authors are employees of IDEXX Laboratories, Inc.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cvsm.2022.01.003. Correlation of symmetric dimethylarginine (SDMA) and serum creatinine (sCr) concentration to glomerular filtration rate (GFR) and methodology for measuring GFR in cats and dogs.

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