Informative title:
The Diagnostic Accuracy of Symmetric Dimethylarginine for Chronic Kidney Disease in Cats and Dogs: A Systematic Review

Short running title:
The Diagnostic Accuracy of SDMA for CKD in Cats and Dogs: A Systematic Review

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Abstract

Background

Chronic kidney disease is common in cats and dogs. Diagnosis previously relied upon creatinine; however, symmetric dimethylarginine (SDMA) may identify CKD earlier. A recent evidence summary questioned the superiority of SDMA in cats. Another study raised concerns over the specificity of SDMA in dogs.

Methods

Electronic databases and grey literature were systematically searched for all relevant studies up to October 2024. Studies were included based on prespecified criteria by two independent reviewers. Studies were assessed for risk of bias and applicability concerns.

Results

Eleven studies were included: five in cats (481 animals) and six in dogs (460 animals). There was marked heterogeneity in design, population, and tests used. Nine studies were at high risk of bias, and nine had high applicability concerns. There was marked variation in sensitivity and specificity. Heterogeneity and risk of bias present precluded meta-analysis. Sources of heterogeneity were explored.

Limitations

Grey literature searching, data extraction, and risk of bias assessment lacked independent duplication.

Conclusion

Significant uncertainty remains regarding the diagnostic accuracy of SDMA in CKD in cats and dogs. Well-designed diagnostic accuracy trials in clinically relevant populations with optimised reference standards and thresholds are needed. The use of SDMA may increase the risk of misdiagnosis and overdiagnosis of CKD.

Introduction

What is CKD?

Chronic kidney disease (CKD) is a common condition, with an estimated overall prevalence of 1.2% in cats(1) and 0.2% in dogs(2) based on electronic health records from a subset of first-opinion practices in the UK.

CKD is defined as the presence of structural or functional abnormalities of one or both kidneys that have been present for more than approximately three months(3). It results from irreversible loss of renal function or structure, which is ultimately progressive(3). Manifestations of CKD include reduced glomerular filtration rate (GFR) leading to elevated blood concentrations of creatinine, reduced renal concentrating ability, persistent proteinuria, and change in renal structure(4). It is important to note that CKD is a broad term, and can occur in the absence of a reduction in GFR.

Diagnostic tests

GFR is directly correlated with functional renal mass. Measuring GFR based on renal or plasma clearance of a filtration marker is considered to provide the most accurate assessment of renal function(5). Renal clearance of the marker inulin is considered the "gold-standard" method of GFR measurement, but plasma clearance methods are more commonly used. Several markers, including radiolabelled markers and the radiographic contrast marker iohexol, have been evaluated for GFR measurement in cats(5) and dogs(6). However, due to the complexities and infrastructure necessary for undertaking these diagnostic methodologies, they are almost exclusively confined to research and referral practice settings.

Diagnosis and staging of CKD in clinical practice is most commonly based on indirect markers of GFR, including serum creatinine levels and, more recently, the biomarker symmetric dimethylarginine (SDMA)(7). These tests are interpreted in the context of the owner's observations, physical examination, other clinicopathological data, imaging findings, and, where indicated, histopathology results. The abnormalities should be persistent without pre- or post-renal causes.

SDMA

SDMA is a chemical produced in all nucleated cells and released into the circulation during proteolysis. Despite a systematic review and meta-analysis of the diagnostic accuracy of SDMA in human medicine(8), the diagnosis of CKD in people continues to be based on serum creatinine(9).

In 2015, a commercial SDMA test for dogs and cats became available as part of a biochemistry panel and as a stand-alone test(10).

After a diagnosis is made, CKD is categorised into one of four stages based on IRIS guidelines(11). These stages are then used to guide treatment decisions and to give prognostic information. Initially, this categorisation was based on serum creatinine concentrations alone; however, in 2015, SDMA was added with the stated benefit of being able to detect kidney disease earlier than previous diagnostic pathways(10). The clinical utility of a diagnostic test that can identify CKD at an earlier stage depends on whether interventions at this stage result in better clinical outcomes(12).

Several studies have reported that SDMA detects a decrease in GFR before creatinine(13) (14, 15) leading narrative reviews to support the use of this test (7, 16). There are, however, recent publications questioning the diagnostic utility of SDMA. A recent knowledge summary concluded that SDMA was not superior to creatinine for assessing GFR in cats with CKD(17). Furthermore, a canine study raised concerns over the low specificity of SDMA in dogs with normal creatinine, with 54% of dogs with an elevated SDMA having a GFR that was not consistent with renal disease(18).

Aim

The aim of this review is to systematically assess the current evidence of the diagnostic accuracy of SDMA in the diagnosis of CKD in cats and dogs to answer the clinical question: "In cats and dogs presenting to veterinary practice with clinical signs or owner-reported observations of naturally occurring CKD, what is the diagnostic accuracy of SDMA compared to any reference test for the diagnosis of CKD?

Methods

This systematic review was performed using methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (v2.0)(19). This review also used the definition of diagnostic accuracy from this handbook, where diagnostic accuracy refers to the comparison between classifications of a condition's presence or absence made by an index test and those determined by a reference standard. Sensitivity and specificity are statistical measures that summarize these comparisons. The PRISMA-DTA statement(20) was used as guidance to ensure complete and transparent reporting of this review.

Protocol

The protocol (Appendix 1) for this systematic review was developed a priori and registered on Open Science Framework on January 30, 2024 (https://osf.io/9gxup/). DOI 10.17605/OSF.IO/9GXUP.

Search strategy

The search strategy (Appendix 2) used a combination of free text and MeSH headings for cats, dogs and SDMA. To maximise the sensitivity of the search strategy, no filters for diagnostic studies were used. VetsRev(21), MEDLINE, CAB abstracts, Zoological Record and Scopus were searched from inception until 30 October 2024. Searches were not limited by publication date, study country or language and methodological filters were not used.

Searching for dissertations, theses, and other grey literature was performed. A Google Scholar search was carried out with screening of the full available results. A further Google search using an incognito browser was also performed, with all results screened(22). Reference scanning of included studies and three recent reviews, (7, 17, 23) and handsearching of 3 journals (24-26) was performed from 2012 to the present.

Forward citation searching was performed on included studies using the "cited by" function within Scopus and Google Scholar. Further snowballing was performed using the "Find Similar" function within the CAB abstracts database for included studies. Searching the trial registry Animal Health Studies Database and OSF.io was also performed, and two key opinion leaders were contacted by email to ask if they knew of any other published, unpublished, or ongoing studies.

Study selection

The results from all searches were combined and exported into reference management software (EndNote 21). Deduplication was performed using a systematic method(27).
Two reviewers (CS and RD) independently screened titles and abstracts against the inclusion and exclusion criteria from the initial search. One reviewer (CS) screened additional studies identified in the updated search in October 2024. Any non-English language texts were translated into English using Google Translate. Authors of abstracts without full-text articles were contacted by email to inquire about the study's status.
Studies were included that reported a measure of diagnostic accuracy as an outcome, and compared the result of an SDMA test, measured by any method, with any relevant reference standard, including but not limited to, any method of GFR measurement, clinical diagnosis of

CKD using indirect markers and longitudinal studies in cats or dogs. Studies which included animals with experimentally induced CKD or Leishmaniasis were excluded.
Diagnostic test accuracy (DTA) studies, comparative DTAs, randomised controlled trials, cohort studies and case-control studies of any quality were included. Conference abstracts with no associated published journal article, case reports, reviews and validation studies were excluded. Full inclusion and exclusion criteria can be found in Appendix 3.

All potentially relevant studies had their full text reviewed. Lists of included and excluded studies were recorded independently by the reviewers. Reasons for excluding studies were recorded and any disagreements resolved by discussion.

Data extraction

Data extraction was performed by one reviewer (CS). Extraction of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values was performed twice on separate days for all studies to mitigate the increased number of data extraction errors found with single data extraction(28). A standardised data extraction template was created in Excel for this purpose. Data extracted is outlined in Appendix 4.

Risk of bias/Reporting Quality

The QUADAS-2 tool(29) was used by one reviewer (CS) to assess the methodological quality of the primary studies. Risk of bias and applicability concerns were judged as high, low or unclear. The author produced written guidance on how to answer each signalling question and how to use these answers to reach a judgment for each domain (30). Results were reported using Cochrane's review manager (RevMan v8.1.1(31)). The quality of reporting of the included studies was assessed by one reviewer (CS) using the STARD toolkit(32).

Data analysis

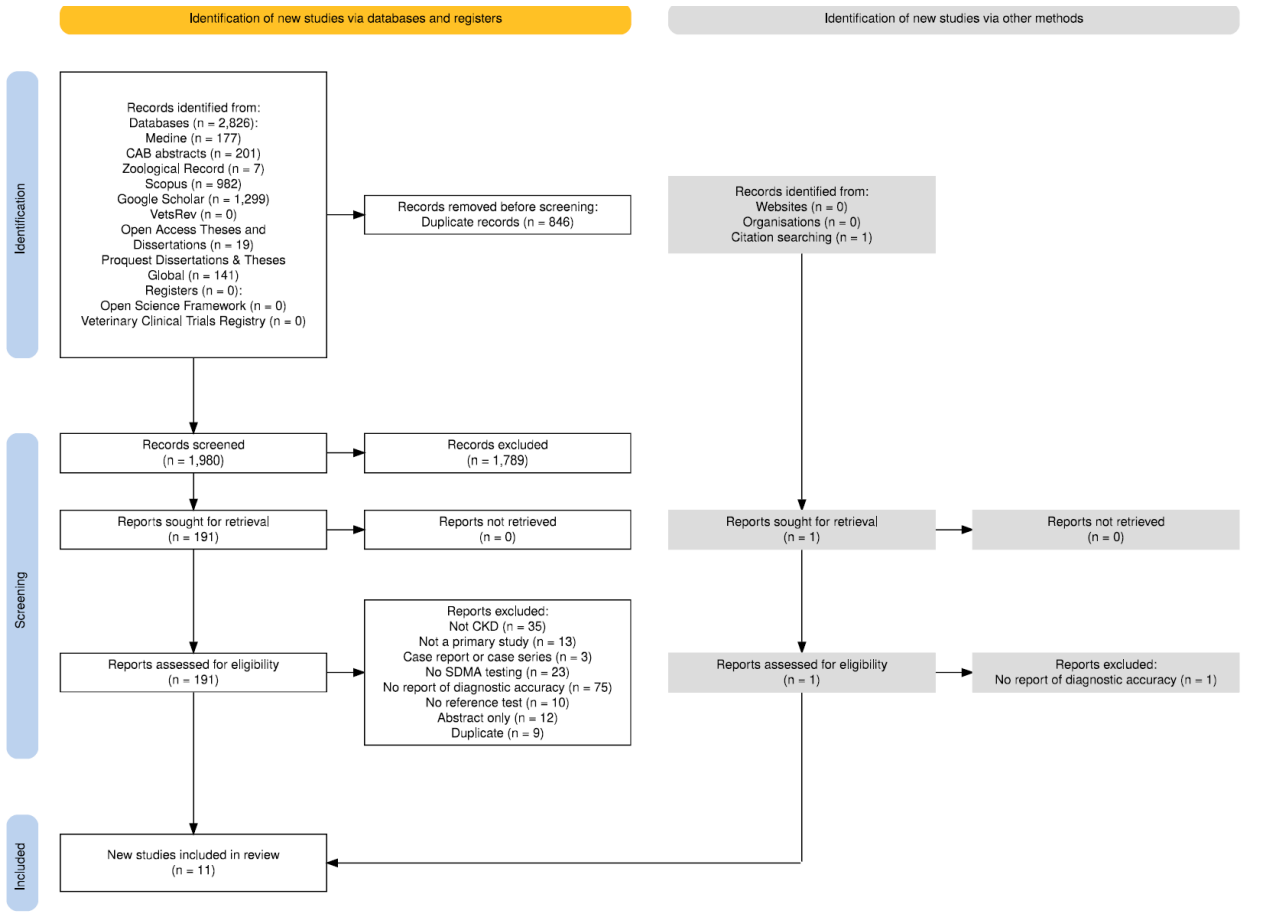
Canine and feline data were analysed separately. The sensitivity and specificity data from all studies were used to construct 2x2 tables using the index test threshold of 14µg/dL if present (or the primarily stated index test threshold) and the primarily stated reference standard threshold. Paired forest plots were created with corresponding 95% confidence intervals. Receiver operating characteristic (ROC) plots of sensitivity and specificity estimates were created to obtain an overview of test accuracy. Due to the small number of studies, marked heterogeneity, and high risk of bias present in many studies, meta-analysis was not appropriate and, therefore, not performed(33).
A formal subgroup analysis was not performed. However, ROC plots of sensitivity and specificity estimates were created and annotated by study design (case-control or cross-sectional/cohort), index test threshold, and reference standard used. Visual inspection of the paired forest and ROC plots was performed to assess heterogeneity between studies and explore potential sources of this heterogeneity.

Results

Search results

Searches identified 2826 studies. Deduplication resulted in the removal of 846 studies. The titles and abstracts of 1980 papers were screened from which 1789 records were excluded. One hundred and ninety-one papers had their full text reviewed for eligibility. Eleven were found to be eligible for inclusion. No eligible studies were found within a grey literature search. No additional studies were found by reference scanning and citation searching of included papers and three recent reviews. One potentially relevant study was found during hand searching. However, this was excluded after a full-text review as there were no reports of diagnostic accuracy. The search process is summarised in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram (Figure 1)(34). The diagram was created using the PRISMA2020 Shiny app. (35)

Figure 1 - PRISMA Diagram



Study description

The key characteristics of the eleven included studies are presented in Table 1, including study design, species, setting, disease prevalence, and population characteristics. There were six canine(18, 36-40) and five feline studies(15, 41-44). Publication dates ranged from 2014 – 2024. All studies were published in English.

Six studies had a case-control design, and five studies were cross-sectional or cohort in design. Studies varied in how patient demographics were described. In studies where information was available, the mean age in cats ranged from 5-14 years old, and the median age in dogs ranged

240 from 5.2–14.1 years old. The severity and prevalence of CKD varied greatly between studies,
241 with the overall prevalence ranging from 13.3-79.6% and the proportion of animals with CKD
242 graded at IRIS stage 2 or above ranging from 0-41.9%. Much of this variation was due to study
243 design and differences in inclusion and exclusion criteria.

244 Table 1. Included studies, study design and setting, and population characteristics

245

Study ID	Study Design	Setting	Number of animals analysed	Disease Prevalence	Age in years: Mean (Range)	Sex	Breeds	Severity of disease (IRIS stage)
Cats								
Brans, 2021	Case-control	University Hospital, Belgium	49	42.9%	Not stated	CKD: 1 EF, 6 NF, 10 NM Healthy: 1 EF, 13 NF, 1 EM, 17 NM	DSH 40; BSH 3; Burmese 2; other 4	Healthy or DM: 32 IRIS II: 11 IRIS III: 6
da Cruz Schaefer, 2023	Cross-sectional/ cohort	University Hospital, Brazil	44	40.9%	Overall: 5.0 (0.6 - 13.0) Healthy: 3.0 (0.6 - 13.0) IRIS I: 4.6 (0.6 - 12.0) IRIS II 8.5 (4.8 - 13.0)	7 EF, 19 NF, 2 EM, 16 NM	All DSH	Healthy: 14 IRIS I: 20 IRIS II: 10
DeMonaco, 2020	Cross-sectional/ cohort	University Hospital, USA	84	15.5%	13 (median) (7 - 19)	42 NF, 42 NM	DSH 66; DLH 7; Ragdoll 3; DMH 2; Maine Coon 2; other 4	All non-azotaemic
Hall, 2014	Case-control	Industry Research Facility, USA	42	50%	CKD: 14.3 (8.0 - 18.5) Healthy: 11.7 (10.2 - 13.1)	CKD: 15 NF, 6 NM Healthy: 12 NF, 9NM	All DSH	Not stated
Peterson, 2018	Cross-sectional/ cohort	Private Referral Hospital, USA	262	16.0%	12 (median) (6-18y)	NF 149, NM 113	DLH/DSH 236; Maine Coon 7; Siamese 6; Norwegian Forest 3; other 10	All non-azotaemic
Dogs								
Guess, 2018	Cross-sectional/ cohort	University Hospital, USA	43	51.2%	8.9 (7.0 - 14.0) at enrolment	Not stated	Mixed breed 11; Cocker Spaniel 4; Labrador Retriever 4; GSD 3; Border Collie 3; other 18	All non-azotaemic
Kim, 2020	Case-control	University Hospital, Korea	49	79.6%	CKD: <5yo 5; 5-10yo 10; >10yo 24 Healthy: all 3yo	5 EF, 20 NF, 11 EM, 13NM	CKD: Shih Tzu 10; Maltese 7; Yorkshire Terrier 6; Miniature Poodle 3; other 13 Healthy: Beagle 10	Healthy: 10 IRIS I: 18; IRIS II: 7 IRIS III: 13; IRIS IV: 1
Kim, 2024	Case-control	University Hospital Korea	117	78.6%	Healthy: 6 (median) Risk 10 (median) CKD I 10.3 (median) CKD II 14.1 (median)	Control: NF 3, NM 7, EM 1 Risk: NF 2, EF 1, NM 11 CKD: NF 29, EF 4, NM 56, EM 3	Small breed (<10kg) breeds not stated	Healthy: 11 Risk of CKD: 14 IRIS stage 1: 43 IRIS stage 2: 33 IRIS stage 3–4: 16
Ko, 2021	Case-control	University Hospital, Korea	41	78%	11 (median) (2–16)	8 EF, 11 NF, 4 EM, 18 NM,	Maltese 7; Shih Tzu 6; Schnauzer 5; Beagle 5; Pekingese 4; Yorkshire Terrier 3; other 11	Healthy: 9 IRIS I: 9; IRIS II: 12 IRIS III: 6; IRIS IV: 5
McKenna, 2020	Cross-sectional/ cohort	University Hospital, UK	113	13.3%	6.2 (median) (0.5 to 15.5)	70 F, 62 M	Labrador 20; WHWT 7; Border Collie 7; Golden retriever 6; SBT 6; Boxer 6; Greyhound 4; Lurcher 4 and other	All non-azotaemic
Pelander, 2019	Case-control	University Hospital, Sweden	97	29.9%	5.2 (median) (IQR 2.5-8.7)	Not stated	Mixed breed 12; Labrador 6; Golden Retriever 6; Boxer 5; Border Collie 4; Other 51	Healthy: 30 Inconclusive: 14 IRIS I: 26; IRIS II: 12 IRIS III: 12 IRIS IV: 3

EF Entire Female, NF Neutered Female, EM Entire Male, NM Neutered Male, DSH Domestic Shorthair, BSH British Shorthair, DM Diabetes Mellitus, DLH Domestic Longhair, DMH Domestic Medium Hair, GSD German Shepherd Dog, WHWT West Highland White Terrier, SBT Staffordshire Bull Terrier

Index test

Information on the index test and reference standard is given in Table 2. SDMA was measured at a reference laboratory in eight studies, six using an immunoassay (18, 39, 41-44) and two using liquid chromatography-mass spectroscopy (15, 40). Two studies measured SDMA using an IDEXX in-clinic immunoassay(37, 45), and in one study, the method of measurement is unclear(38). In eight of the studies, the primary threshold used for SDMA was 14µg/dL(15, 18, 39-44). Two studies used a threshold of 13.5µg/dL and another 11µg/dL(37). Four studies looked at multiple thresholds for SDMA ranging from 10-20µg/dL(18, 41, 42, 44).

Table 2. Included studies, index test, reference standard and thresholds used

Study ID	Index test	Manufacturer	Index threshold (µg/dL) (additional thresholds)	Reference standard	Reference threshold (additional thresholds)
Cats					
Brans, 2021	SDMA - Reference Lab Immunoassay	IDEXX	>14 (>18)	GFR measurement Iohexol	<1.7 mL/min/kg) (<1.2 mL/min/kg))
da Cruz Schaefer, 2023	SDMA - Reference Lab Immunoassay	IDEXX	>14 (>18)	GFR measurement Scintigraphy	<2.5 ml/min/kg
DeMonaco, 2020	SDMA - Reference Lab Immunoassay	IDEXX	>14	Serum Creatinine	>2.3 mg/dL SI: 203.37 µmol/L
Hall, 2014	SDMA - Reference Lab LC-MS	Shimadzu	>14	Composite reference test (creatinine, iohexol clearance or renal imaging)	creatinine >2.1 mg/dL SI: 185.68 µmol/L >30% reduction in iohexol clearance (<1.36 ml/min/kg) Presence of calcium oxalate stones
Peterson, 2018	SDMA - Reference Lab Immunoassay	IDEXX	>14 (>12 & >10)	Serum creatinine	>2.1mg/dL SI: 185.68 µmol/L
Dogs					
Guess, 2018	SDMA - Reference Lab LC-MS	IDEXX	>14	Composite reference test (based on one or more of ultrasound, UPC, iohexol clearance, necropsy)	Ultrasound findings UPC >0.5 >40% reduction in iohexol clearance histological necroscopy findings
Kim, 2020	Unclear	Unclear	>13.5	Clinical classification	Not specified
Ko, 2021	SDMA - In-Clinic Immunoassay	IDEXX	>11	Clinical classification	Not specified
Kim, 2024	SDMA – In-Clinic Immunoassay	IDEXX	>13.5	Clinical classification	Not specified
McKenna, 2020	SDMA - Reference Lab Immunoassay	IDEXX	>14 (>10, >12, >16, >18 & >20)	GFR measurement Iohexol	>40% decrease from the mean (also 30-40, 20-30 and <20%)
Pelander, 2019	SDMA - Reference Lab Immunoassay	IDEXX	>14	GFR measurement Scintigraphy	<30.8 ml/min/l

GFR Glomerular Filtration Rate, LC-MS Liquid Chromatography-Mass Spectroscopy, UPC Urine Protein to Creatinine Ratio,

Reference test

The reference standard used varied widely between studies (Table 2). Four studies used GFR measurement,(18, 39, 41, 42) (two using plasma clearance of iohexol(18, 41) and two using scintigraphy methods(39, 42)). There was variation in thresholds used for the reference standard, with every study using a different value. The variation in GFR measurement methods and thresholds is provided in Table 3.

Three case-control studies used clinical classification of CKD without specified thresholds(37, 38, 45). Two studies used a composite reference test with a proportion of animals receiving iohexol clearance, creatinine measurement, renal imaging, proteinuria measurement and necropsy(15, 40). Two studies used were specifically assessing the diagnostic accuracy of SDMA in "masked CKD", where hyperthyroidism artificially increases GFR, therefore reducing renal biomarkers(46). There was also variability between thresholds in these studies, with one using a creatinine of >2.3mg/dl (203.37 µmol/L)(43) and the other >2.1mg/dL (185.68 µmol/L)(44)

Table 3. Studies using GFR measurement as or as part of the reference standard with threshold information

Study ID	GFR measurement method	Reference threshold	Rationale for threshold
Cat			
Brans, 2021	Iohexol	<1.7mL/min/kg	Borderline GFR threshold from a previous study[75]
da Cruz Schaefer, 2023	Scintigraphy	<2.5ml/min/kg	Gates' method (previous study[76])
Hall, 2014	Iohexol (within composite)	<1.36ml/min/kg	>30% reduction from 1.94mL/min/kg (mean GFR in healthy cats in this study)
Dog			
Guess, 2018	Iohexol (within composite)	<3.29ml/min/kg	>40% reduction from 5.48ml/min/kg (Michigan State University Diagnostic Centre)
McKenna, 2020	Iohexol	<2.16-2.89ml/min/kg	>40% decrease from mean (by bodyweight category) in a previous study [77]
Pelander, 2019	Scintigraphy	<30.8ml/min/l	(predefined cut of at laboratory) Plasma volume method – different units

Excluded studies

Of the 191 full-text reports assessed for eligibility, 180 were excluded (Figure 1). The authors of the twelve abstracts where full text was not available were contacted. Five replied, confirming the reports were abstracts only(47-49), or the data were included in a separate eligible(50) or a non-eligible study(51). Details of excluded studies, their references and the reasons for exclusion are presented in Appendix 5.

Methodological quality of included studies

The QUADAS-2 tool(29) was used to assess the methodological quality of the primary studies. This was reported in diagrammatic form using Cochrane's review manager (RevMan v8.1.1(31)) (Figure 2).

All eleven studies were judged to be at high or unclear risk of bias. Nine studies had at least one domain judged to be at high risk of bias. Flow and timing was the domain most likely to be judged as at high risk of bias, as found in seven studies. A high risk of bias was judged to be present in six studies in the patient selection domain and the reference standard domain. The index test domain had three studies deemed to be at high risk of bias. Three studies were deemed to be at high risk of bias across all four domains.

All studies were judged to have high or unclear applicability concerns. Nine had at least one domain judged to have high concern. Patient selection had high applicability concerns in nine of the studies(15, 18, 37-39, 41, 43-45) and unclear concerns in one(42). There were high concerns in six studies regarding the reference standard and three studies regarding the index test. Three studies had high concerns in all three applicability domains.

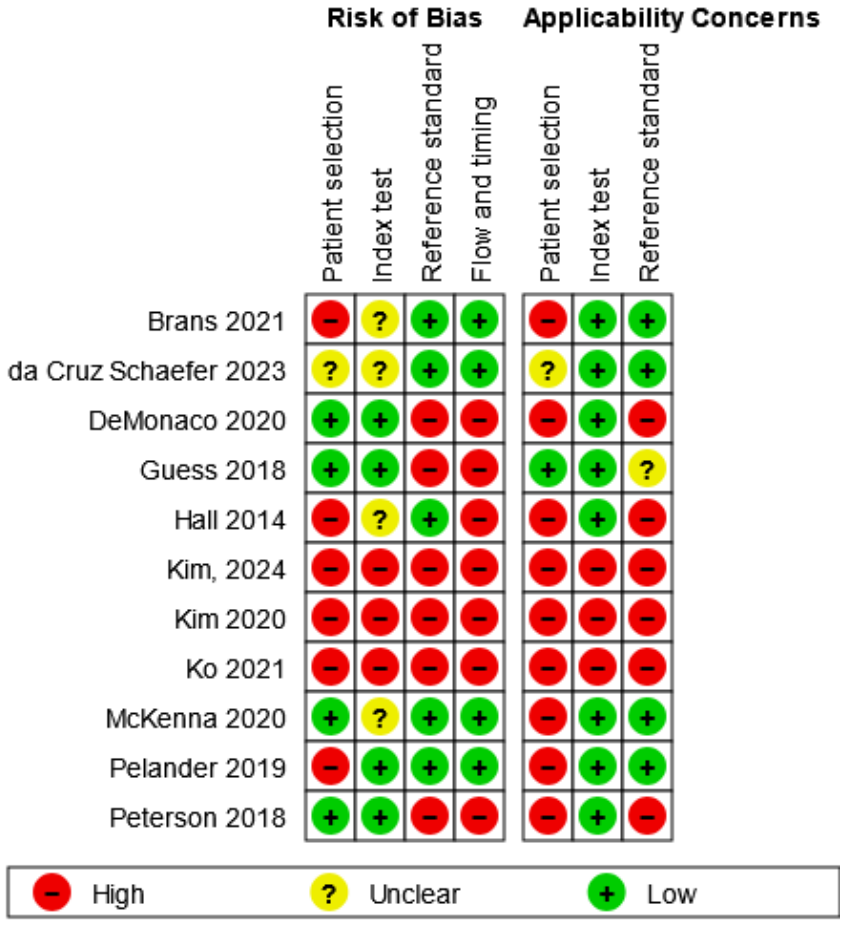


Figure 2a. QUADAS-2 methodological quality summary

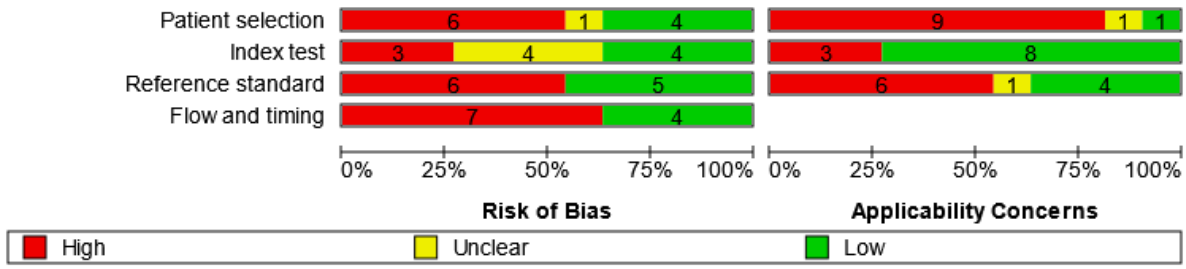


Figure 2b. QUADAS - Methodological quality graph

Patient selection

Seven studies were deemed to have a high or unclear risk of bias in this domain. The main driver of risk was the use of a case-control design in six studies(15, 36-39, 41). This has been shown to result in significant overestimation in diagnostic accuracy(52). Eight studies had high applicability concerns(15, 18, 36-39, 41, 43, 44), mainly due to recruiting previously diagnosed and healthy participants rather than patients with a suspicion of disease.

Index test

Three studies were deemed at high risk of bias in the index test domain(37, 38, 45). These studies did not use a prespecified threshold. The optimal threshold was determined using receiver operating characteristic (ROC) curves. This data-driven selection of thresholds can falsely inflate diagnostic accuracy due to the study's ROC curve fluctuating from the true underlying ROC curve due to chance (53). Blinding of the interpretation of the index test to the results of the reference test was specifically performed in only one study(39). However, the risk of bias due to lack of blinding is lower with this objective numerical test than with tests that require interpretation (30).

There were high applicability concerns due to the index test in three studies(37, 38, 45) due to the use of thresholds that are not clinically utilised.

Reference test

Six studies were deemed to be at high risk of bias due to the reference standard(36-38, 40, 43, 44). The main driver of this judgement was that the reference standard used was unlikely to classify animals with or without CKD correctly. Five studies used serum creatinine, alone or alongside other parameters, without confirmatory GFR measurement(36-38, 43, 44). Creatinine lacks sensitivity in the early stages of reducing renal function and is likely to classify some animals as normal incorrectly. Blinding was purposively performed in only one study(39). As part of a composite reference test, one study (40) performed renal ultrasonography only if there were biochemical abnormalities including in SDMA. As ultrasonography relies on subjective interpretation(54), the lack of blinding could result in increased concordance and therefore improved diagnostic accuracy. Two studies used SDMA as part of the reference standard(38, 45) and were therefore at high risk of incorporation bias(55) and overestimation of diagnostic accuracy.

There were high applicability concerns due to the reference test in six studies(15, 36-38, 43, 44) mainly due to the lack of GFR measurement.

Flow and Timing

Seven studies were deemed to have a high risk of bias due to factors around flow and timing. Two studies had an inappropriately long interval between the index and reference tests(43, 44).

Potential for differential verification bias was present in three case-control studies where the reference standard was not the same in the CKD and non-CKD groups(15, 37, 38).

No studies had issues with patients being missing from the analysis.

Reporting Quality

Reporting issues resulted in unclear risk of bias and applicability concerns in many studies. All eleven studies failed to specifically report whether participants formed a consecutive, random or convenience series. Only one study reported whether those interpreting the results of the index test or reference standard were blinded(39).

In addition to reporting deficits that directly impacted the risk of bias assessments, issues were present in other items within the STARD guidelines(32). No studies reported a sample size calculation. Only two studies showed the cross-tabulation of the index test results by the results of the reference standard(18, 39).

No studies were registered in a trial registry or had full protocols available.

Summary of findings

SDMA diagnostic accuracy was assessed separately in cats and dogs. Figure 3 shows paired forest plots containing the sensitivity, specificity, true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN). The canine forest plots also contain the index test threshold used, as this varied.

There was marked variation, mainly in sensitivity, with this measure in feline studies ranging from 15%(43) to 100%(15). Specificity in feline studies varied from 75%(41) to 98%(44). In canine studies, sensitivity ranged from 36%(40) to 90%(39) and specificity from 52%(18) to 100%(37, 38, 40).

The variation in the population, reference tests used and high risk of bias in most studies precluded the use of meta-analysis. Therefore, no summary values were calculated.

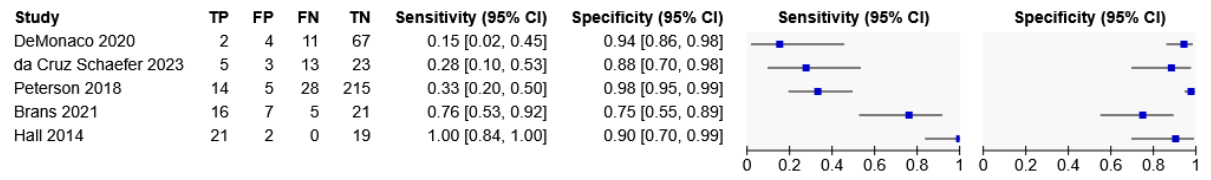


Figure 3a. Feline Studies Forest Plots

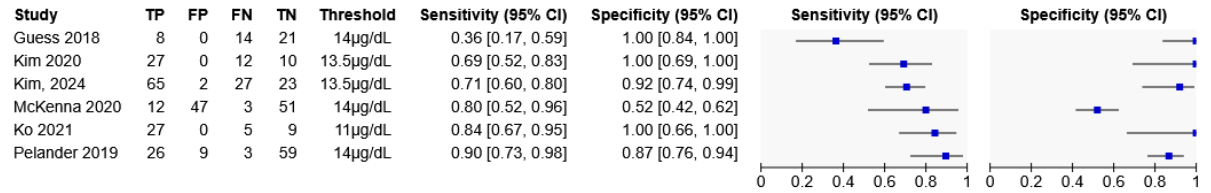


Figure 3b. Canine Studies Forest Plots

Investigation of heterogeneity

The paired results for sensitivity and specificity from the studies were presented in ROC plots. The best diagnostic test would sit in the upper left corner of these plots where both sensitivity and specificity are close to 1. These plots were used to assess the sensitivity and specificity across studies, with different symbols used to facilitate visual subgroup comparisons by patient spectrum, index thresholds, and reference test.

Analysis by patient spectrum

Cats

The sensitivity and specificity of the feline studies with their 95% confidence intervals (CIs) are shown in Figure 4. The cross-sectional studies(42-44) are seen to cluster in the lower left area of the plot. These studies have relatively high specificities (88% - 98%), but lower sensitivities (15% - 33%). This is compared to the case-control studies(15, 41) with specificities of 75% and 90% and much higher sensitivities of 76% and 100%.

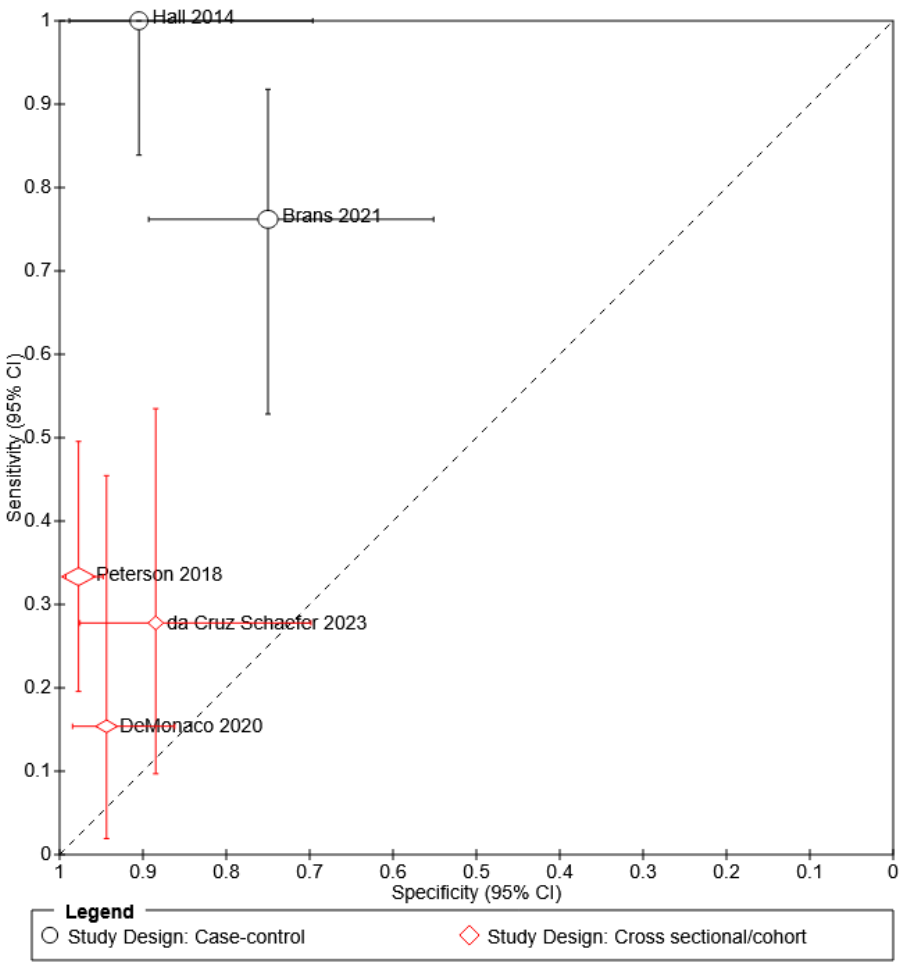


Figure 4. Feline ROC by study design

Dogs

Figure 5 shows the sensitivity and specificity of the canine studies. The case-control studies cluster in the upper left area of the plot with the highest diagnostic odds ratios (DORs). The DOR summarizes the diagnostic accuracy of the index test as a single number that describes how many times higher the odds are of obtaining a test positive result in a diseased rather than a non-diseased individual(19). These studies have relatively high specificities (87 – 100%) and sensitivities (69 – 90%). One cross-sectional/cohort study sits to the lower left of the plot with a specificity of 100% and a lower sensitivity of 36%(40). The other sits higher, within the centre of the plot, with a specificity of only 52% and a sensitivity of 80%.

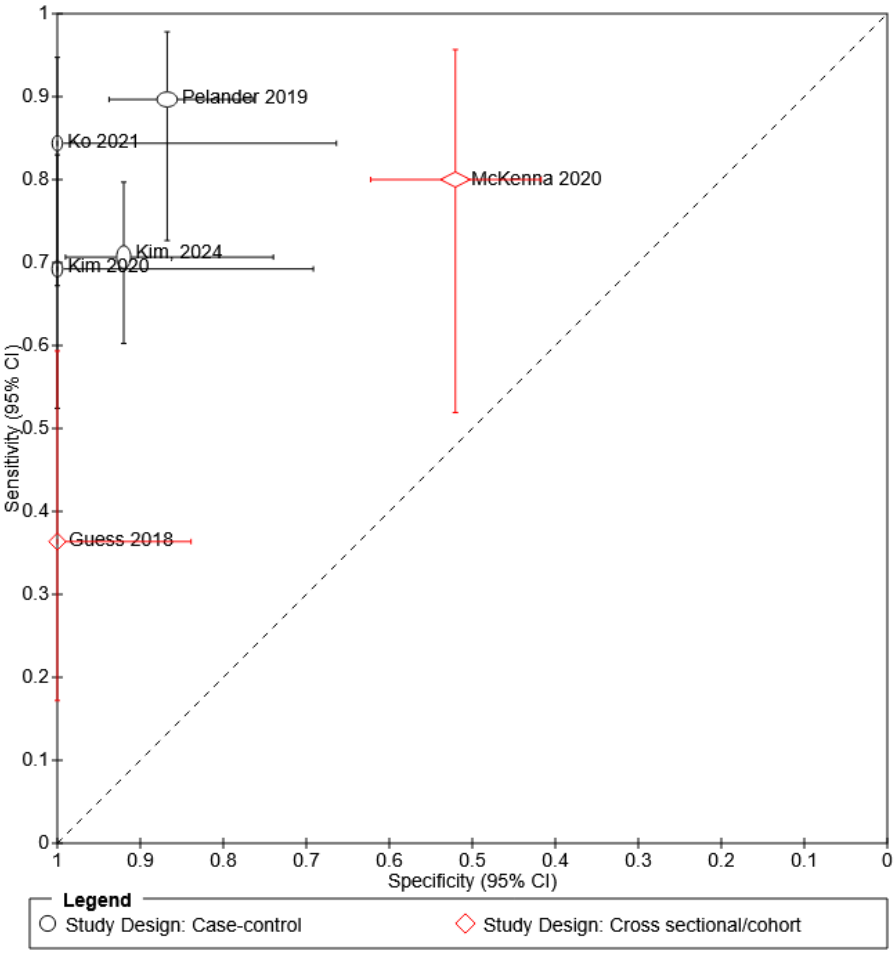


Figure 5. Canine ROC by study design

Analysis by index test

Cats

All feline studies used a reference laboratory to measure SDMA and the manufacturer's upper reference limit of 14 µg/dL as the threshold,(56) therefore heterogeneity due to index test was not explored.

Dogs

Three canine studies used a reference laboratory test to measure SDMA(18, 39, 40), two used a point-of-care test(36, 37), and the method used was unclear in the sixth(38). Figure 6 shows the ROC plot with the thresholds used. The three studies that did not use a threshold of 14 µg/dL had a similar study design and used post-hoc data-driven thresholds to maximise sensitivity and specificity. (36-38).

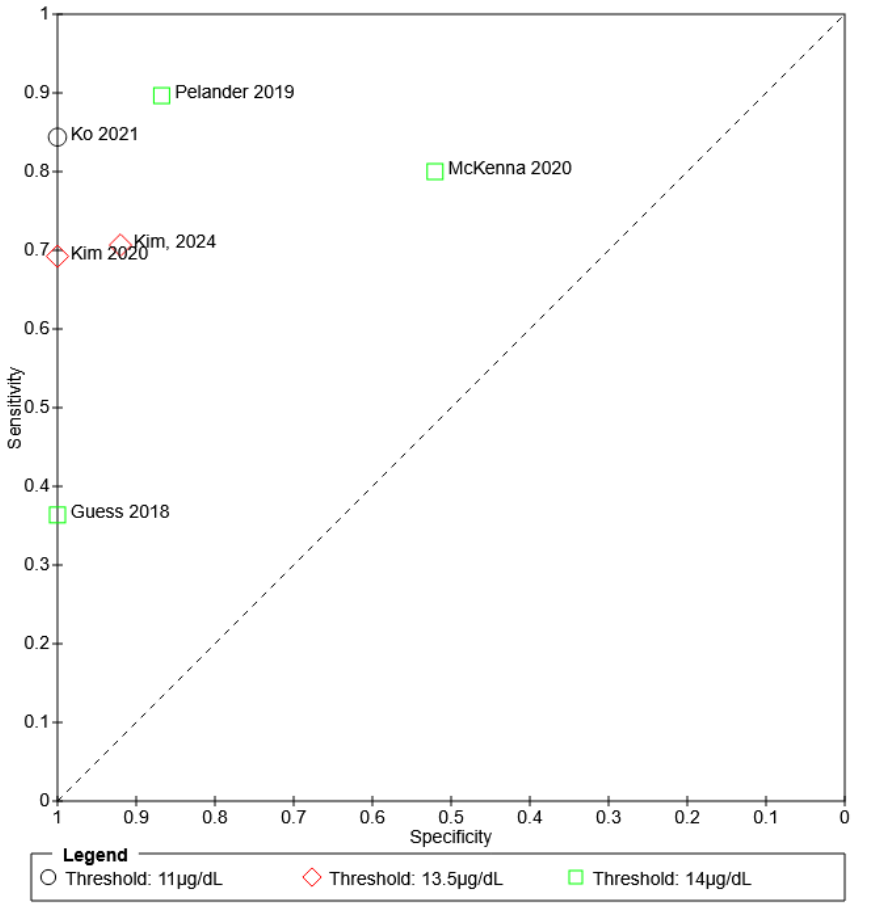


Figure 6. Canine ROC by index threshold

Analysis by reference standard

Feline

Three studies used GFR measurement as a reference standard, either alone(41, 42) or in a composite test(15). Two studies used creatinine 6-8 months post-radioiodine treatment(43, 44) (Figure 7).

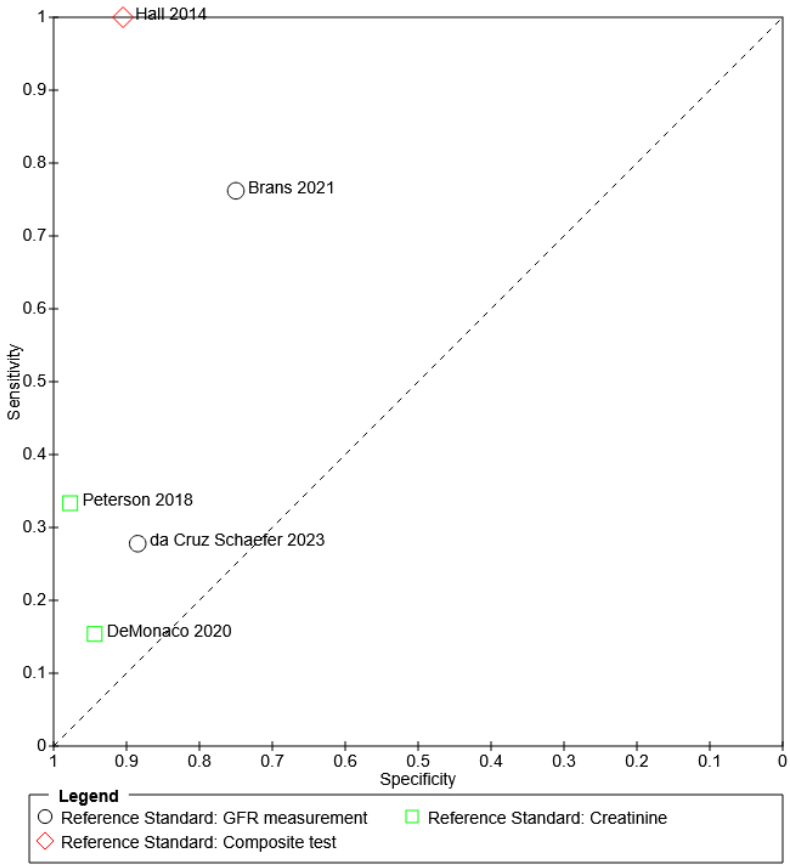


Figure 7. Feline ROC by reference standard

Canine

The two canine studies that used GFR measurement as the reference standard(18, 39) found SDMA to have specificities of 52% and 87%. In the remaining four studies, which used clinical classification(36-38) or a composite reference standard(40)SDMA had higher specificities of 92-100%(Figure 8).

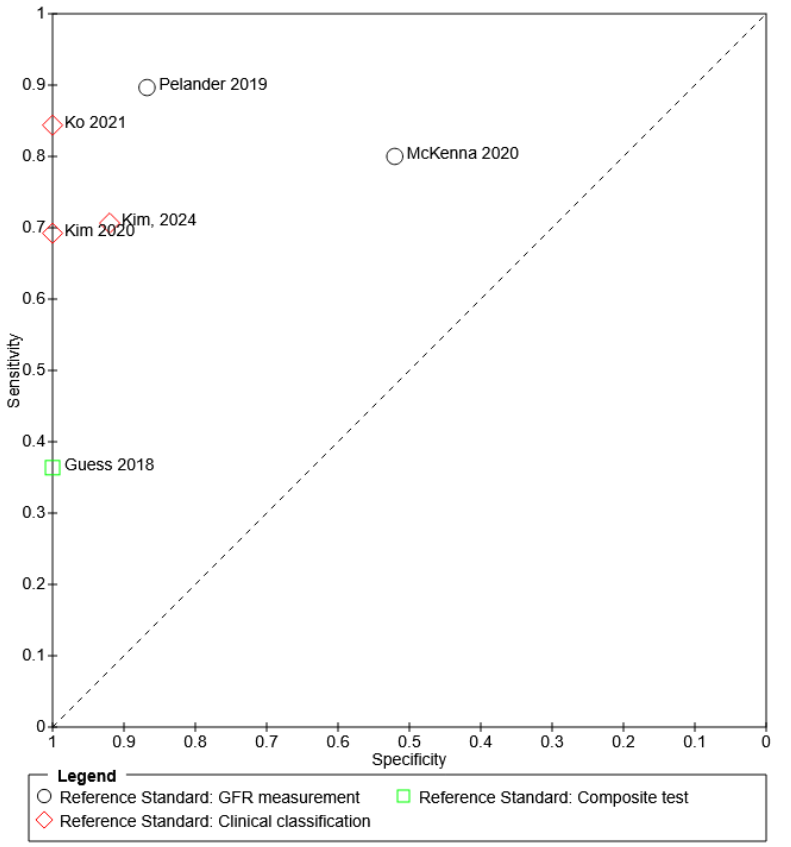


Figure 8. Canine ROC by reference standard

Funding sources

A ROC plot of all included studies grouped by funding sources was created (Figure 9). The only study with perfect sensitivity was industry-funded(15). The other industry-funded study found SDMA to have perfect specificity(40). There are three studies with high specificities (92-100%) that were funded through academia; however, these were the studies with a high risk of bias across all domains. Non-industry-funded studies with an author that had received funding through IDEXX for previous projects have the next highest DORs(39, 44). Other non-industry-funded studies, with or without free SDMA testing provided by IDEXX, had the lowest DORs.

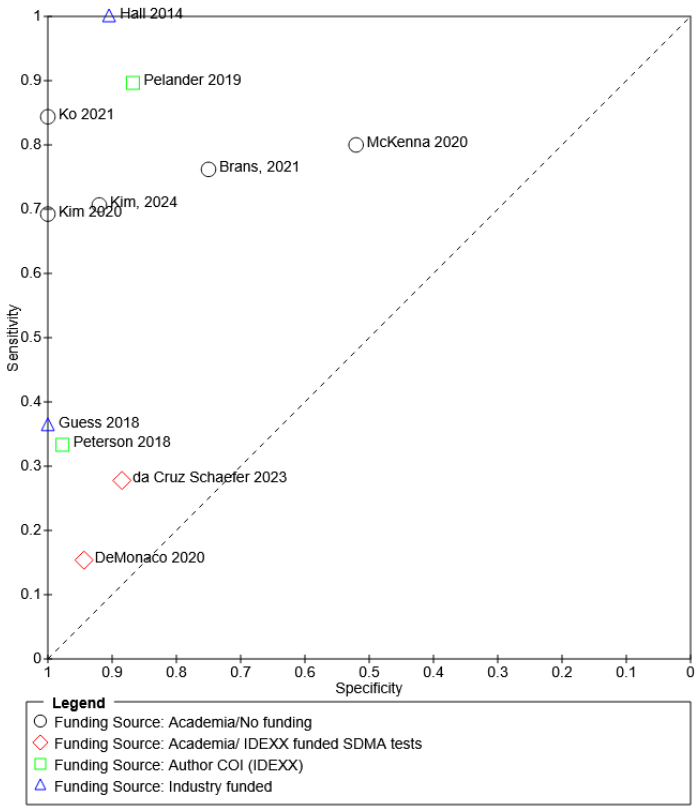


Figure 9. ROC by funding source

Discussion

This review systematically searched and assessed all available evidence on the diagnostic accuracy of SDMA in the diagnosis of CKD in cats and dogs. Eleven relevant studies were included: five in cats, with 481 animals, and 6 in dogs, with 460 animals. This is much lower than the human healthcare systematic review of SDMA, where there were 18 relevant studies involving 2136 individuals(8).

Nine studies had at least one domain judged to be at high risk of bias, and the remaining two had at least one domain judged to be at unclear risk. Three studies were deemed to be at high risk of bias across all four domains. This raises significant concerns about the internal validity of the included studies, as their results may overestimate the accuracy of the test (30). In addition, nine studies had high applicability concerns, all of which had issues in the patient selection domain. This is also highly concerning as the populations analysed are, therefore, different from the animals in which we would use this test(30). These findings should prompt caution when interpreting the results for use in clinical practice.

There are considerable variations in sensitivities and specificities found, likely due to significant differences in study design, population, tests, laboratories, and analysers used, as well as the high risk of bias in most studies. These factors precluded the calculation of summary values for

diagnostic accuracy within this review. The inability to perform meta-analysis highlights the lack of well-designed trials in veterinary medicine intended to answer this research question.

There are limitations to the review. Whilst two reviewers undertook the screening of papers and considered the inclusion and exclusion criteria for this study, only one reviewer searched for grey literature, and performed the data extraction and risk of bias assessments. Ideally, there would have been independent duplication. However, this was not feasible. At all steps, CS, AP, and RD had rigorous discussions around the methodology, studies included and assessment of quality.

To enable further data synthesis, including meta-analysis, further diagnostic accuracy trials are required that have been designed to minimise the risk of bias. Specifically, the use of case-control design should be avoided by consecutive recruitment of a clinically relevant population. Clinically important thresholds of SDMA and GFR measurement should be standardised and used consistently for further research. These changes will reduce research waste and enable more effective consolidation of data, effectively increasing our population size and increasing the precision of our research results.

This review highlights that few studies have been undertaken on which to base clinical decisions. Furthermore, most of these studies are at high risk of bias and do not represent the animals we wish to test in practice. The study with the lowest risk of bias found that, in dogs with normal creatinine, the specificity of SDMA to identify a >40% reduction in GFR was only 52%(18). This raises concerns about the increased likelihood of false positives when SDMA is added to the diagnostic pathway as recommended by current guidelines(11). Despite this, SDMA is already being widely used in first-opinion practice for the diagnosis and staging of CKD in cats and dogs(4, 57).

A low specificity is of more significant concern for SDMA if used for wellness screening, as is currently recommended within support material(10) and international screening guidelines(58). The pre-test probability of CKD in an asymptomatic population will be much lower than that of the population in these studies. This will result in a greater proportion of animals with an elevated SDMA having a normal GFR.

Screening also identifies patients with less severe disease. This increases the risk of overdiagnosis and overtreatment, where a diagnosis is made that ultimately causes more harm than benefit(59). The addition of SDMA to the IRIS guidelines is likely to increase the proportion of dogs and cats in the population labelled as having CKD. These “new patients” will have less severe disease than those that would have been diagnosed with creatinine alone. This may lead to harm if labelling, monitoring and management of these lower-risk patients leads to little or no benefit when compared to the previous diagnostic pathway(59).

Systematic reviews of diagnostic tests are not common in the veterinary literature. In a space where there are limited regulations, it is crucial that the evidence surrounding a diagnostic test is critically evaluated before it enters the care pathway or becomes routine practice. Unless we approach veterinary diagnostic testing in an evidence-based way, we may inadvertently cause harm to our patients due to misdiagnosis and overdiagnosis.

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Legends for Supplementary material

Appendix 1 – Protocol. This protocol was developed a priori and registered on Open Science Framework on January 30, 2024 (https://osf.io/9gxup/). DOI 10.17605/OSF.IO/9GXUP.

Appendix 2 - Search Strategy. Search terms and databases searched during the review.

Appendix 3 - Inclusion and exclusion criteria for study selection

Appendix 4 - Data collected into data extraction form

Appendix 5 - Excluded studies from full text review

Data Availability Statement:
The data that supports the findings of this study are available in the supplementary material of this article.

Author Contribution Statement:

CS and AP conceived and designed the study. CS, AP, RD and JS designed the search strategy. CS performed the searches. CS and RD selected studies for inclusion. CS extracted the data and performed analysis with advice from AP, RD and JS. CS created the Revman plots and wrote the first draft of the manuscript with assistance from AP, RD and JS. All authors contributed critically to manuscript revisions and approved the final manuscript.

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