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Diagnostic accuracy of tests based on radiologic measurements of dogs and cats: a systematic review

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Abstract

A systematic review of diagnostic tests based on radiologic measurements of structures in dogs and cats was done in order to reach generalizable conclusions about the value of making such measurements. Literature search was done using the ISI Web of Knowledge^{SM} for studies in the subject category *Veterinary sciences*. Studies were eligible for inclusion that employed length, angle, area or volume measurements from radiographic, ultrasonographic, CT or MR images of dogs or cats as a diagnostic test for a naturally-occurring condition, compared the results of imaging with a reference standard, included at least 10 subjects, and sufficient data that a 2x2 table of results could be constructed. Quality of studies was assessed using the QUADAS-2 tool. Twenty-six studies were found describing 40 tests that satisfied the inclusion criteria. Tests were radiographic in 22 (55%) instances and ultrasonographic in 18 (45%). Quality of studies was generally low, with a risk of bias in patient selection in 92% studies, performance of the index test in 73% studies, and patient flow in 42% studies. Median (range) number of subjects was 64 (20-305), sensitivity was 77% (38-99%), specificity was 82% (50-99%), positive likelihood ratio was 4.1 (1-103), and negative likelihood ratio was 0.29 (0.01-1). Two studies that compared accuracy of radiographic measurements to subjective image interpretation alone found no difference. Evidence is weak that radiologic measurements of structures in dogs and cats are useful for diagnosis, hence measurements should not be emphasized as a basis for diagnosis in either teaching or clinical imaging reports.

Introduction

"When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind." William Thomson, quoted by Keats and Sistrom.[1]

"A radiologist with a ruler is a radiologist in trouble," Ben Felson.[2]

These quotations illustrate two different opinions about the use of measurements, albeit for different purposes. William Thomson, a mathematician and engineer[3] is recognized for his work in thermodynamics, including determining −273.15C to be the value of absolute zero.[*] He considered accurate measurement to be essential for physical science research. Ben Felson, a clinical radiologist[4], is recognized for his remarkable understanding of thoracic radiographs and his innovative teaching.[†] His quote reflects an emphasis on subjective judgment of shadows as a means of diagnosis – basically, if you don't know the diagnosis after looking carefully at the radiographs, making a measurement is unlikely to help you.

Regardless of this point of view, radiographic anatomy textbooks[1,5] include numerous examples of documented methods of measurement, and studies describing measurement of structures in diagnostic images are published frequently. For example, of 52 original investigations published in *Veterinary Radiology & Ultrasound* in 2013, 18 (35%) were primarily about use of measurements. Measurement of organs and structures is done frequently to supplement the descriptive part of an imaging report, to help identify an abnormality, such as a foreign object, or to describe the severity of a condition, such as an angular limb deformity. In animals having repeated imaging, comparison with previous

[*] Ennobled in 1892 as Lord Kelvin. Absolute temperatures are stated in units of Kelvin in his honor.

[†] Among other things, he first elucidated the silhouette sign.

measurements provides objective evidence of the progression of disease or the effect of treatment.[6] Radiologic measurements may also be used as the basis for diagnosis, and it is that application that is the focus of the present study. The term radiologic is used here to embrace all the diagnostic imaging modalities commonly applied to clinical veterinary patients.

It is uncertain what proportion of veterinary radiologists routinely use and/or teach use of radiologic measurements as the basis for diagnosis. Anecdotal evidence suggests that certain methods of radiologic measurement, such as the vertebral heart scale[7], are used routinely in many practices, but conversely some teachers discourage use of the vertebral heart scale. Anecdotal evidence also suggests there is a demand from primary care veterinarians for the results of measurements to be included routinely in imaging reports produced by Board-certified radiologists based on a belief that such results are important for diagnosis. Students, primary care veterinarians, and radiologists may benefit from more information about the diagnostic value of making measurements of structures in radiologic images, hence a systematic review of the literature is indicated.

Systematic reviews attempt to collect and appraise all the empirical evidence applicable to a given research question.[8-10] The primary purpose of systematic reviews is to facilitate healthcare decision-making by clinicians, administrators and policy makers by providing high-level evidence of benefit, risks and harms associated with healthcare.[10] Systematic reviews of diagnostic test accuracy are done to estimate test performance, to evaluate the methodological quality of primary studies, and to explain variations in findings between studies .[8-13] When primary studies are relatively homogeneous, synthesis across studies may be done to produce summary measures of diagnostic accuracy.[8,11]

The aim of the present study was to systematically review studies reporting diagnostic accuracy of tests based on radiologic measurements of dogs and cats in order to reach generalizable conclusions about the value of making such measurements.

Methods

Conduct of this review followed guidelines in the PRISMA Statement.[10]

Search

The search for published studies about diagnostic accuracy of radiologic measurements was done on 25th June 2013 using the ISI Web of Knowledge[SM] (Thomson Reuters) for all years represented in the database. The search was refined to those studies in the research domain *Science technology* and in the subject category *Veterinary sciences*. Three initial search criteria were used: 1, within the title, the search terms were veterinary or canine or feline or equine or dog or cat or horse; 2, also within the title, the search terms were imaging or ultraso* or sono* or echo* or radiograph* or x-ray or CT or MR or magnetic resonance or computed tomograph*; 3, within topic, the search terms measure* or size or thick* or quanti* or diagnos*. Quotations were not used to allow for lemmatization and no language restrictions were applied. As a means of assessing the completeness of the search, 6 papers about radiologic measurement studies published in non-imaging veterinary journals in the period 1987-2000, and already held on file by the authors, were used as sentinels, i.e. failure of the search to retrieve these papers would indicate that it was incomplete. Reference lists of papers reviewed in full were also searched for additional applicable studies. Retrieved articles were imported into a citation database (Endnote 9.0, Thomson Corporation, San Francisco, CA 94105).

Studies eligible for inclusion were those that employed length, angle, area or volume measurements from radiographic, ultrasonographic, computed tomographic (CT) or magnetic resonance (MR) images of dogs or cats as a diagnostic test for a naturally-occurring condition; compared results of imaging with a reference standard; included at least 10 animals as subjects; and included sufficient data that a 2x2 table of results could be constructed. The titles of all studies retrieved by initial search were reviewed independently by both investigators to identify studies about use of imaging to examine dogs or cats or horses. Studies of normal animals and studies with horses as subjects were noted for possible future use, but were excluded from the review. Retained studies that had cats or dogs as subjects were reviewed by abstract, and studies retained on the basis of the abstract were reviewed in full. At each stage of the review process, investigators compared their results and resolved differences by discussion.

Quality assessment

Methodological quality of studies that satisfied the inclusion criteria was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool.[14] Quality was assessed on the basis of studies rather than individual tests because tests within a study used the same methods, which allowed the presentation of results to be simplified. No modifications to the signaling questions included in this tool[14] were considered necessary. Each investigator reviewed independently the methods sections of papers describing studies that satisfied the inclusion criteria with respect to 4 key domains (patient selection, the index test, the reference standard, and patient flow and timing), and answered relevant signaling questions according to QUADAS-2 methodology. For each domain, the risk of bias was recorded as low, high or unclear. Risk of bias was considered low if all signaling questions in a domain were answered ‘yes’; if any signaling question was answered ‘no’, the potential for bias was judged on the basis of the specific methodology used and characteristics of the target condition. The unclear category was used when insufficient data were reported to permit a judgment. Investigators compared their results and resolved any differences by discussion. Similarly, for each domain, concern about applicability of retrieved studies to the present review was judged to be low, high or unclear.

Measures of accuracy

For each study that satisfied the inclusion criteria, study design, use of retrospective or prospective data collection, total number of subjects, and the numbers of true positives, true negatives, false positives and false negatives were recorded. Each investigator reviewed independently the results sections of papers to extract these data, compared their results and resolved any differences by repeat review. The results of any study with zero false positives or false negatives were modified by adding 0.5 subjects into each cell of the 2x2 table.[9] This procedure (Haldane correction) was necessary in order to calculate likelihood ratios for these studies. Sensitivity, specificity, positive (PLR) and negative (NLR) likelihood ratios, and their respective binomial 95% confidence intervals (95% CI) were calculated using the stats calculator available online at the Center for Evidence-based Medicine, University of Toronto (http://ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc). The prevalence of diseased subjects in each study was also calculated.

Sensitivity and specificity estimates from all studies that satisfied the inclusion criteria were included in a summary receiver-operating characteristic (sROC) plot using Review Manager 5.2 (Cochrane Collaboration http://tech.cochrane.org/revman/download). Paired forest plots of sensitivity and specificity were also created for visual assessment of study heterogeneity.

Results

Search

Initial literature search found 4,264 papers, which were reduced to 244 on the basis of title, to 43 of the basis of abstract, and to 26 by detailed review[15-40] (figure 1). All sentinel papers were retrieved by the search. Papers were published in the period 1986-2012 in 10 different journals with 8 (31%) papers in *Journal of Veterinary Internal Medicine*, 5 (19%) in *Veterinary Radiology & Ultrasound*, 3 (12%) in *Journal of the American Veterinary Medical Association*, 3 (12%) in the *Veterinary Record*, 2 (8%) in *Journal of Small Animal Practice*, and one paper in each of 5 other journals.

Of the 26 papers retrieved describing studies that satisfied the inclusion criteria, 8 reported multiple index tests for a total of 40 analyzable tests. Tests were radiographic in 22 (55%) instances (including one CT test) (Table 1) and ultrasonographic in 18 (45%) (Table 2). No eligible MR studies were retrieved by the search. Study design was case-control in 36 (90%) instances and cross-sectional in 4 (10%). Data collection was retrospective in 26 (65%) studies, prospective in 6 (15%), and unclear in 8 (20%). The median (range) number of subjects was 64 (20-305). Tests applied to canine conditions in 29 (73%) instances, feline conditions in 9 (23%), and both dogs and cats in the remaining 2 (4%).

Quality assessment

Results of quality assessment of the radiographic tests and ultrasonographic tests are summarized in tables 3 and 4, respectively. Overall, risk of bias in patient selection was considered high in 24 (92%) studies mainly because case-control study design was not avoided in 23 (89%) studies, and patients were not collected in randomized or consecutive order in 17 (65%) studies. Healthy subjects were included in the control group used for calculation of test accuracy in 14 (54%) studies. Risk of bias in performance of the index test was considered high in 19 (73%) studies primarily because the cut-off point was applied retrospectively in 22 (85%) studies. Risk of bias in performance of the reference standard was considered high in 3 (12%) studies. The reference standard was not considered likely to correctly classify all patients in 2 (8%) studies. Risk of bias arising from patient flow and/or timing of procedures was considered high in 11 (42%) studies primarily because not all patients were subjected to the same reference standard in 17 (65%) studies. Description of study methods was incomplete in many instances. For example, insufficient data were provided to conclude that the index test was interpreted without knowledge of the results of the reference standard in 12 (46%) studies or that the reference standard was interpreted without knowledge of the results of the index test in 11 (42%) studies. Concern about the applicability of retrieved studies to the present review was considered low in all instances.

Measures of accuracy

Overall, the median (range) sensitivity was 77% (38-99%), specificity was 82% (50-99%), positive likelihood ratio was 4.1 (1-103), negative likelihood ratio was 0.29 (0.01-1), and prevalence was 37% (10-79%). Only 13 (32%) tests had PLR >10 and only 10 (25%) tests had NLR <0.1.

Measures of accuracy for radiographic tests and ultrasonographic tests are summarized in tables 5 and 6, respectively. Subjective assessment of sROC plots (figure 2) and paired forest plots of sensitivity and specificity (figure 3) revealed a high level of heterogeneity for results of both radiographic and ultrasonographic tests. In general, confidence intervals were wider for tests based on radiographic measurements and included 50% in several instances. Specificity estimates for several tests based on ultrasonographic measurements were close to 100%.

For the sub-group of 14 radiographic tests for cardiac or pericardial disease that were based on measurements of the cardiac silhouette, the median (range) sensitivity was 76% (40-90%), specificity was 76% (58-89%), positive likelihood ratio was 3.1 (1.4-4.8), and negative likelihood ratio was 0.32 (0.15-0.71). Area under the sROC curve for this sub-group was subjectively slightly less than that for all radiographic tests (figure 4).

For the sub-group of 5 ultrasonographic tests for adrenal endocrinopathy that were based on measurement of adrenal gland thickness, the median (range) sensitivity was 77% (73-97%), specificity was 94% (80-98%), positive likelihood ratio was 12.5 (3.9-52), and negative likelihood ratio was 0.24 (0.04-0.29). Area under the sROC curve for this sub-group appeared to be the same as that for all ultrasonographic tests (figure 5).

Discussion

Search

Radiologic measurements used in studies retrieved by search were predominantly linear[15,33] or ratio[20,21,26,27,36], with relatively few examples of angle[28], area[18] or volume[17,32] measurements. The studies retrieved by this search represent a more heterogeneous group than is usually obtained by systematic reviews focused on a single diagnosis. Retrieved studies of radiologic measurements varied with species, modality, anatomy, diagnosis, study design, measurement method, and cut-off points, hence the differences observed between studies reflect real differences in study procedures and patients. As a result, there was limited potential for meta-analysis. In order to optimally compare measures of test accuracy obtained in different studies retrieved by systematic review, it is necessary for the definition of disease to be constant, the same test must be used, the thresholds between categories of test result (i.e. positive and negative) must be constant, and the spectrum of patients studied must be similar with respect to prevalence and severity of disease.[8-10,41] Useful synthesis of test results may still be possible if some of these criteria are not satisfied; however, none of these criteria can be applied to studies included in the present review, which was deliberately broad in scope in order to enable generalizable conclusions about the diagnostic value of making radiologic measurements.

It is noteworthy that 169 papers describing radiologic measurements of normal subjects were retrieved by search (figure 1), which is a much larger number than papers about radiologic measurements for diagnostic purposes. This difference suggests that the majority of reported anatomic measurements have either not been tested for diagnostic use or not found to be useful clinically. These possibilities merit further study.

Quality assessment

It is important to consider the methodologic quality of studies reporting accuracy of diagnostic tests because differences in study design are associated with significant variations in results.[12] Abundant guidance is available to promote higher standards of methodological quality in clinical research studies, including the STARD guidelines for reporting studies of diagnostic accuracy[42], the STROBE guidelines for observational studies[43], and the CONSORT guidelines for reporting randomized trials.[44] QUADAS-2 was developed specifically as a tool to assesses methodological quality of primary studies in order to identify risks of bias in the results of studies retrieved by systematic review.[13-15] Methodological weaknesses contributing to exaggerated results for diagnostic imaging tests can be found in many studies.[12,45,46] Of the various methodological weaknesses that make studies vulnerable to bias, the most serious are non-consecutive inclusion of patients, retrospective data collection, and use of healthy control subjects.[12] Multiple methodological weaknesses were identified in the studies retrieved by search, including case-control design (89% studies), *post hoc* determination of cut-off value (85% studies), non-consecutive inclusion of patients (at least 65% studies), use of multiple reference tests for patients under study (65% studies), and retrospective data collection (at least 58% studies). Incomplete reporting of methods is another well-recognized deficiency in diagnostic imaging studies[12] that was observed frequently in studies retrieved by the present systematic review. None of the studies retrieved by the present systematic review had a low risk of bias in all methodological domains.

Healthy subjects were included in the control group used for calculation of test accuracy in 54% studies. Studies of diagnostic tests that use healthy volunteers as a control group may be useful as 'Phase 1' research, which aims to identify tests with potential clinical utility, but these results cannot be assumed to apply in a clinical setting in which all test subjects are patients.[47] A control group for 'Phase 2' studies intended to estimate test accuracy in clinical patients should comprise subjects who are identical to the test or treatment group in all aspects that affect the outcome except the variable, result or intervention being studied.[48,49] Failure to utilize a suitably comparable control group is a frequent methodological flaw in clinical research papers.[12,45,46,50] For example, the study by Eom et al[22] described use of ultrasonography to measure the width of the tracheal rings and reported that thoracic inlet tracheal ring width-first tracheal ring width ratio >1.4 was a highly accurate test for tracheal collapse in small breed dogs. Eom et al reported zero false negatives and zero false positives (sensitivity and specificity = 100%), i.e. there was a complete lack of overlap in tracheal dimensions of affected and control dogs. Unfortunately, this finding is unrealistic because dogs of breeds prone to collapsing trachea, such as Yorkshire terriers and Pomeranians, have a congenital defect in tracheal cartilage that gets gradually weaker over time[51], and it is the occurrence of a comorbidity, such as cardiac disease, heat stress, endotracheal intubation or exposure to smoke, that triggers clinical signs.[52,53] Hence any representative sample of dogs at risk of tracheal collapse should include dogs with a continuous range of tracheal dimensions and degrees of tracheal collapse from normal to markedly abnormal. The wide separation between case and control groups in this study is an example of selection bias[12,48] that will inflate estimates of sensitivity and specificity. It should also be noted that dogs in this study were assigned to case or control groups on the basis of survey radiography, which is insensitive for tracheal collapse[54], and therefore not suitable as a reference test for this condition. This is an example of imperfect-standard bias.[48]

Measures of accuracy

Overall, the accuracy of diagnostic tests based on radiologic measurements was moderate, with median sensitivity 77% and specificity 82%. In many instances the confidence intervals for estimates of sensitivity and specificity were very wide, which is a function of analyzing small numbers of subjects.[55] The results of several of the studies with low numbers of subjects included zero false negatives or false positives. Calculations using these data result in sensitivity or specificity of 100% and likelihood ratios equal to infinity or zero. To avoid extreme calculated values, the results of any study with zero false positives or false negatives were modified by adding 0.5 subjects into each cell of the 2x2 table.[9] This approach produced slightly more conservative estimates for these studies. Likelihood ratios were calculated for studies retrieved by search because they give an indication of a test's ability to rule in or rule out a condition.[56] High likelihood ratios (e.g. PLR >10) indicate that the test may be useful to rule in disease, while low likelihood ratios (e.g. NLR <0.1) may be useful to rule out disease. In this series, only 13 (32%) tests had PLR >10 and only 10 (25%) tests had NLR <0.1.

Sub-group analysis of the 14 radiographic tests based on measurements of the cardiac silhouette found modest diagnostic performance with a subjectively reduced area under the sROC curve for this sub-group than that for all radiographic tests. The range encompassed by these results likely reflects differences in cardiac pathophysiology between cats and dogs and between canine breeds, which have differing predisposition to cardiac conditions.[57] For example, conditions that result in cardiac dilatation or eccentric hypertrophy are more likely to cause a recognizable increase in the external dimensions of the heart than conditions resulting in concentric hypertrophy or dysrhythmias.[58]

Sub-group analysis of the 5 ultrasonographic tests that were based on measurement of adrenal gland thickness found a similar area under the sROC curve for this sub-group as for all ultrasonographic tests. Although diagnosis of adrenal gland dysfunction depends primarily on endocrinologic testing, ultrasonography has a potential role as a means of supporting a diagnosis of adrenal gland dysfunction[59,60], and in distinguishing adrenal-dependent from pituitary-dependent hyperadrenocorticism.[16] However, the finding that 3 of the 5 ultrasonographic tests for adrenal endocrinopathy included in this review had zero false positives or false negatives indicates that these estimates of diagnostic performance are probably inflated. Although a perfect diagnostic test would have zero false positives or false negatives, this is not a realistic expectation. In clinical practice, inconclusive results are inevitable and should be reported in studies about diagnostic tests.[61] Given that few studies about diagnostic tests report sample size calculations[55], it is suggested that zero false positives or false negatives could be considered a *post hoc* criterion of inadequate sample size.

The moderate median values for sensitivity and specificity of tests based on radiologic measurements included in the present review primarily reflect the fact that the normal size ranges for many anatomical structures are very wide, hence there is marked overlap between normal and pathologic ranges.[62] In this respect it is noteworthy that dogs exhibit enormous phenotypic variation compared to other mammals[63-65], which makes them particularly ill-suited to diagnosis based on measurement because that variation exaggerates the overlap between normal and abnormal ranges. Even for structures that would not be expected to vary greatly with conformation, wide normal size ranges may be observed. For example, abdominal lymph nodes in dogs are variable in size and number in CT images[66], which complicates interpretation of size in clinical patients. In humans, differences in interpretation of the status of lymph nodes is the most frequent cause of disagreement in reinterpreted CT scans of cancer patients.[67] The association between lymph node size and occurrence of metastasis to that node appears to be relatively weak, hence assessment of lymph node size alone is insufficient for accurate clinical staging of neoplasia, such as oral malignant melanoma in dogs.[68] When a significant risk of lymphatic metastasis exists, cytologic or histologic examination of regional lymph nodes is indicated, regardless of the size of those nodes.[68]

Limitations

Systematic reviews often use a multiple electronic databases to maximize the likelihood of retrieving all available empirical evidence. The present study was based on a search done using only the ISI Web of Knowledge[SM]. We chose this approach because this database includes over 140 veterinary journals, because it interfaces directly with our preferred citation database, and for simplicity. This search strategy satisfies the minimum recommendations of the PRISMA Statement[10]; however, it is possible that additional applicable studies might have been retrieved if the search had used multiple electronic databases.

In typical test research, the use of an individual diagnostic test is evaluated in order to estimate sensitivity and specificity; however, this kind of test research is only pertinent to clinical situations in which diagnosis is likely to be based on the results of that one test (such as screening).[69,70] In usual clinical practice, the results of a test are always judged in the context of existing information, including results of prior tests, and a more relevant objective of diagnostic test performance assessment is to identify the added value (i.e. the incremental increase in diagnostic accuracy) that occurs when the test is used.[70] Robust estimates of the added value of diagnostic tests require multivariable methods, in which the probability of disease is a function of all diagnostic variables.[70] Many authors of studies included in the present systematic review over-estimated the potential diagnostic impact of radiologic measurements because they calculated the accuracy of the test based on measurement without taking into account the accuracy of concurrent subjective image interpretation. The two studies that compared accuracy of radiologic measurements to subjective image interpretation alone for dogs with suspected intestinal obstruction[20] and dogs with suspected cardiac disease[26] found no differences. In other words, observers making radiologic measurements were no more accurate than when they relied on subjective assessment alone. These findings applied equally to experienced and inexperienced observers.[20,26]

Use of measurements may seem appealing to those who are uncertain about their ability to reach correct conclusions based on subjective assessment of the images alone. Although radiologic measurements (e.g. the vertebral heart scale[7]) have been recommended for use by inexperienced observers, these same observers may have difficulty making the measurements if selection of landmarks relies on subjective interpretation.[20] Furthermore, emphasis on measurements is unwarranted when the pathologic effects of disease are invariably multiple and all the imaging signs must be recognized for optimal interpretation. The trained eye and brain can integrate multiple features that cannot be described with a single measurement.[71-73] Radiologic interpretation is a skill that must be refined by experience rather than by recourse to measurements.[74]

Conclusions

For tests based on radiologic measurements that were included in this systematic review, median sensitivity and specificity were only moderate, estimates of test accuracy in many instances were likely exaggerated because of deficiencies in study methodology, and observers making radiologic measurements were no more accurate than when they relied on subjective assessment alone. Overall, evidence is weak that radiologic measurements of structures in radiologic images of dogs and cats are useful for diagnosis. Although measurements may have value in the descriptive part of a radiology report, they should not be emphasized as a basis for diagnosis in either teaching or clinical imaging reports.

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Table 1. Summary of diagnostic tests based on radiographic measurements

First author	Year	Species	Diagnosis	Design	Data collection	Cut-off value for positive result
Ciasca	2013	Dog	Intestinal obstruction	Case-control	Retrospective	Maximal small intestinal diameter >1.7 depth of fifth lumbar vertebra
Gatineau-a	2011	Dog	Hip arthritis	Cross-sectional	Prospective	Dorsal acetabular slope >7.5 degrees at 6m as predictor of arthritis at 24m
Gatineau-b	2011	Dog	Hip arthritis	Cross-sectional	Prospective	Distraction index >0.68 at 6m as predictor of hip arthritis at 24m
Guglielmini-a	2012	Dog	PE vs cardiac disease without PE	Case-control	Retrospective	VHS >11.9 on lateral radiographs
Guglielmini-b	2012	Dog	PE vs cardiac disease without PE	Case-control	Retrospective	Global sphericity <1.17
Lamb	2000	Dog	Cardiac vs non-cardiac	Case-control	Retrospective	VHS >10.7 on lateral radiographs
Lamb-a	2001	Dog	Cardiac disease in Boxers	Case-control	Retrospective	VHS >11.6 on lateral radiographs
Lamb-b	2001	Dog	Cardiac disease in Labradors	Case-control	Retrospective	VHS >10.9 on lateral radiographs
Lamb-c	2001	Dog	Cardiac disease in GSD	Case-control	Retrospective	VHS >10.2 on lateral radiographs
Lamb-d	2001	Dog	Cardiac disease in Dobermanns	Case-control	Retrospective	VHS >10.5 on lateral radiographs
Lamb-e	2001	Dog	Cardiac disease in CKCS	Case-control	Retrospective	VHS >11.1 on lateral radiographs
Lamb-f	2001	Dog	Cardiac disease in Yorkshire terriers	Case-control	Retrospective	VHS >10.4 on lateral radiographs
Le Roux	2012	Dog	Left atrial enlargement	Case-control	Retrospective	Bifurcation angle >76.6 degrees
Moise-a	1986	Cat	Cardiomyopathy	Case-control	Indeterminate	Heart length >5.95cm
Moise-b	1986	Cat	Cardiomyopathy	Case-control	Indeterminate	Heart width at atrial level >3.99cm
Moise-c	1986	Cat	Cardiomyopathy	Case-control	Indeterminate	Heart width at ventricular level >3.47cm
Moise-d	1986	Cat	Cardiomyopathy	Case-control	Indeterminate	Heart width on dorsoventral radiograph >4.47cm
Torres	2005	Dog	Hip arthritis	Cross-sectional	Indeterminate	Distraction index >0.35 as predictor of hip arthritis at 5y
Trevail-a	2011	Cat	Constipation vs normal	Case-control	Retrospective	Maximal colonic diameter >1.28 length of fifth lumbar vertebra
Trevail-b	2011	Cat	Megacolon vs constipation	Case-control	Retrospective	Maximal colonic diameter >1.48 length of fifth lumbar vertebra
Wray	2006	Dog	Myasthenia gravis vs megaesophagus	Cross-sectional	Retrospective	Relative esophageal diameter >0.65 = non-myasthenia megaoesophagus
Pineiro[a]	2000	Dog	AI HAC vs AD HAC	Case-control	Retrospective	Maximal adrenal diameter ratio >2.08 = AI HAC

PE, pericardial effusion; GSD, German shepherd dog; CKCS, Cavalier King Charles spaniel; AI, adrenocorticotropic hormone independent; AD, adrenocorticotropic hormone dependent; HAC, hyperadrenocorticism

[a] CT test

Table 2. Summary of diagnostic tests based on ultrasonographic measurements

First author	Year	Species	Diagnosis	Design	Data collection	Cut-off value for positive result
Barthez	1995	Dog	Pituitary-dependent HAC	Case-control	Prospective	Left adrenal gland maximal diameter >7.4mm
Benchekroun	2010	Dog	Adrenal- vs pituitary-dependent HAC	Case-control	Retrospective	For adrenal gland dependent HAC, thickness of smaller gland <5mm
Brömel	2005	Dog	Hypothyroidism	Case-control	Prospective	Total thyroid gland volume <424.6mm^3
Brown-a	2005	Dog	Mitral insufficiency	Case-control	Retrospective	Index of change in left ventricular internal area >2.1
Brown-b	2005	Dog	Congestive heart failure	Case-control	Retrospective	Index of left atrial dimension >1.55 for heart failure
Choi	2011	Dog	Pituitary-dependent HAC	Case-control	Retrospective	Left adrenal maximal diameter >6.0mm
D'Anjou-a	2004	Dog & cat	Extrahepatic portosystemic shunt	Case-control	Retrospective	Portal vein-aorta ratio <0.65
D'Anjou-b	2004	Dog & cat	Extrahepatic portosystemic shunt	Case-control	Retrospective	Portal vein-caudal vena cava ratio <0.70
Eom	2008	Dog	Tracheal collapse	Case-control	Indeterminate	Thoracic inlet tracheal ring width-first tracheal ring ratio >1.4
Grooters	1996	Dog	Pituitary-dependent HAC	Case-control	Prospective	Either adrenal gland >7mm thick
Leveille	1996	Cat	Common bile duct obstruction	Case-control	Indeterminate	Common bile duct diameter 5mm or more
Reese	2005	Dog	Hypothyroidism	Case-control	Retrospective	Thyroid gland volume (<0.05ml/kg)
Reusch	2000	Dog	Chronic vs acute renal failure	Case-control	Prospective	Parathyroid maximal longitudinal dimension >4mm = Chronic renal failure
Rudorf-a	2005	Dog	IBD duodenum	Case-control	Retrospective	Duodenal wall thickness >4.2mm
Rudorf-b	2005	Dog	IBD jejunum	Case-control	Retrospective	Jejunal wall thickness >3.3mm
Wenger	2010	Dog	Hypoadrenocorticism	Case-control	Indeterminate	Left adrenal gland thickness <3.2mm
Wisner	1994	Cat	Hyperthyroidism	Case-control	Indeterminate	Total thyroid gland volume >215 mm^3
Zwingenberger	2010	Cat	Small intestinal lymphoma	Case-control	Retrospective	Muscularis layer thickness >0.5 submucosal layer thickness

HAC, hyperadrenocorticism; IBD, inflammatory bowel disease

Table 3. Results of methodological quality assessment of radiographic measurement studies retrieved by systematic review

		Patient selection Signaling questions			Risk of bias	Index test Signaling questions		Risk of bias	Reference standard Signaling questions		Risk of bias	Flow/timing Signaling questions				Risk of bias
First author	Year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?		Was the index test interpreted without knowledge of the reference standard?	Was the cut-off value pre-specified?		Is the reference standard likely to correctly classify patients?	Was the reference standard interpreted without knowledge of the index test?		Was there a suitable interval between the index test and reference standard?	Did all patients receive a reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?	
Ciasca	2013	N	N	U	H	Y	N	L	Y	Y	L	Y	Y	N	Y	L
Gatineau[a]	2011	U	Y	U	L	Y	N	L	Y	U	L	Y	Y	Y	N	L
Guglielmini[a]	2012	U	N	N	H	Y	N	H	Y	Y	L	Y	Y	N	Y	H
Lamb	2000	N	N	U	H	Y	Y	L	U	Y	L	Y	Y	N	N	H
Lamb[b]	2001	N	N	U	H	Y	N	L	U	Y	L	Y	Y	N	Y	H
Le Roux	2012	N	N	N	H	U	N	H	Y	Y	L	Y	Y	Y	Y	L
Moise[c]	1986	Y	N	U	H	Y	N	H	Y	Y	L	U	Y	N	N	H
Torres	2005	U	Y	U	U	U	N	H	Y	U	L	Y	Y	Y	Y	L
Trevail[a]	2011	N	N	Y	H	U	N	H	Y	Y	L	Y	Y	Y	Y	L
Wray	2006	U	Y	N	H	Y	N	H	Y	Y	L	Y	Y	Y	Y	L
Pineiro[d]	2000	N	N	U	H	Y	N	H	Y	Y	L	U	Y	N	Y	L

Y, yes; N, no; H, high; L, low; U, unclear (insufficient data).

[a] study includes 2 tests; [b] study includes 6 tests; [c] study includes 4 tests; [d] CT test

Table 4. Results of methodological quality assessment of ultrasonographic measurement studies retrieved by systematic review

		Patient selection				Index test			Reference standard			Flow/timing				
		Signaling questions			Risk of bias	Signaling questions		Risk of bias	Signaling questions		Risk of bias	Signaling questions				Risk of bias
First author	Year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?		Was the index test interpreted without knowledge of the reference standard?	Was the cut-off value pre-specified?		Is the reference standard likely to correctly classify patients?	Was the reference standard interpreted without knowledge of the index test?		Was there a suitable interval between the index test and reference standard?	Did all patients receive a reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?	
Barthez	1995	N	N	N	H	U	Y	L	Y	U	L	U	N	N	Y	H
Benchekroun	2010	N	N	N	H	Y	N	H	Y	U	L	U	Y	N	Y	H
Bromel	2005	U	N	N	H	Y	N	H	Y	Y	L	Y	Y	N	Y	L
Brown[a]	2005	N	N	N	H	N	N	H	Y	N	H	U	Y	Y	Y	L
Choi	2011	U	N	N	H	U	N	H	Y	U	L	U	N	N	Y	H
D'Anjou[a]	2004	N	N	U	H	U	N	H	Y	U	L	U	Y	N	N	H
Eom	2008	N	N	N	H	U	N	H	N	U	H	U	Y	Y	Y	L
Grooters	1996	N	N	U	H	U	N	H	Y	U	L	U	Y	N	Y	H
Leveille	1996	N	N	U	H	Y	N	H	N	U	H	U	Y	N	Y	H
Reese	2005	N	N	N	H	Y	N	H	Y	Y	L	Y	Y	N	Y	L
Reusch	2000	N	N	U	H	U	N	H	Y	U	L	U	Y	N	U	H
Rudorf[a]	2005	N	N	U	H	Y	Y	L	Y	Y	L	U	Y	Y	Y	L
Wenger	2010	U	N	U	H	Y	N	H	Y	Y	L	Y	Y	N	Y	L
Wisner	1994	U	N	Y	H	N	N	H	Y	Y	L	Y	Y	N	Y	L
Zwingenberger	2010	N	N	Y	H	U	Y	L	Y	Y	L	N	Y	Y	Y	L

Y, yes; N, no; H, high; L, low; U, unclear (insufficient data)

[a] study includes 2 tests

Table 5. Performance of diagnostic tests based on radiographic measurements

First author	Year	n	TP	FP	FN	TN	Sensitivity %	95% CI	Specificity %	95% CI	PLR	95% CI	NLR	95% CI	Prevalence %
Ciasca	2013	85	25	16	12	32	67	52-80	67	53-78	2.0	1.3-3.2	0.49	0.29-0.81	44
Gatineau-a	2011	73	15	11	5	42	75	53-89	79	67-88	3.6	2.0-6.5	0.32	0.15-0.68	27
Gatineau-b	2011	70	14	12	6	38	70	48-86	76	63-86	2.9	1.65-5.2	0.40	0.20-0.79	29
Guglielmini-a	2012	151	46	34	5	66	90	79-96	66	56-75	2.7	2.0-3.5	0.15	0.06-0.35	34
Guglielmini-b	2012	151	44	29	7	71	86	74-93	71	62-79	3.0	2.2-4.1	0.19	0.10-0.39	34
Lamb	2000	100	38	10	12	40	76	63-86	80	67-89	3.8	2.1-6.8	0.30	0.18-0.50	50
Lamb-a	2001	55	13	14	9	19	59	39-71	58	41-73	1.4	0.82-2.4	0.71	0.40-1.3	40
Lamb-b	2001	64	12	15	7	30	64	41-81	66	52-79	1.9	1.1-3.2	0.55	0.30-1.0	30
Lamb-c	2001	60	16	10	5	29	76	55-89	75	59-85	3.0	1.7-5.4	0.32	0.15-0.70	35
Lamb-d	2001	52	14	10	6	22	70	48-86	69	51-82	2.2	1.2-4.0	0.44	0.22-0.89	38
Lamb-e	2001	48	17	6	4	21	80	60-92	78	59-89	3.6	1.75-7.6	0.25	0.10-0.61	44
Lamb-f	2001	41	10	5	2	24	83	55-95	83	67-92	4.8	2.1-11.2	0.20	0.06-0.72	29
Le Roux	2012	106	21	6	31	48	40	28-54	89	78-95	3.6	1.6-8.3	0.67	0.53-0.86	49
Moise-a	1986	43	8	5	4	26	67	39-86	84	67-93	4.1	1.7-10.1	0.40	0.18-0.90	28
Moise-b	1986	43	8	7	4	24	67	39-86	77	60-89	3.0	1.4-6.3	0.43	0.20-1.0	28
Moise-c	1986	43	9	7	3	24	75	47-91	77	60-89	3.3	1.6-6.9	0.32	0.12-0.88	28
Moise-d	1986	41	8	8	2	23	80	49-94	74	59-86	3.1	1.6-6.1	0.27	0.08-0.95	24
Torres	2005	60	40	4	1	15	98	87-100	79	57-92	4.6	1.9-11.1	0.03	0.004-0.22	68
Trevail-a	2011	89	37	6	2	44	95	83-99	88	76-94	7.9	3.7-16.8	0.06	0.015-0.23	44
Trevail-b	2011	39	19	2	7	11	73	54-86	85	58-96	4.8	1.3-17.4	0.32	0.16-0.63	67
Wray	2006	66	16	22	4	24	80	58-92	52	38-66	1.7	1.2-2.4	0.38	0.15-0.96	30
Pineiro[a]	2000	64	**18.5**	**1.5**	**0.5**	**45.5**	97	79-100	97	87-99	30.5	6.3-148	0.03	0.002-0.42	30
Median (range)		62 (39-151)	16 (8-46)	9 (2-34)	5 (0-31)	28 (11-71)	76 (40-98)		77 (52-97)		3.2 (1.4-30.5)		0.32 (0.03-0.71)		34 (24-68)

n, number of subjects studied; TP, true positives; FP, false positives; TN, true negatives; FN, false negatives; CI confidence interval; PLR, likelihood ratio for a positive result; NLR, likelihood ratio for a negative result. Values in bold type have had 0.5 added to permit calculation of likelihood ratios (see text).
[a] CT test.

Table 6. Performance of diagnostic tests based on ultrasonographic measurements

First author	Year	n	TP	FP	FN	TN	Sensitivity %	95% CI	Specificity %	95% CI	PLR	95% CI	NLR	95% CI	Prevalence %
Barthez	1995	42	17	4	5	16	77	57-90	80	58-92	3.9	1.6-9.6	0.28	0.13-0.63	52
Benchekroun	2010	47	**19.5**	**0.5**	**1.5**	**27.5**	93	74-98	98	85-100	52.0	3.3-813	0.07	0.02-0.34	40
Bromel	2005	47	**4.5**	**0.5**	**7.5**	**36.5**	38	17-65	99	88-100	28.0	1.6-479	0.63	0.41-0.98	23
Brown-a	2005	223	159	1	17	46	90	85-94	98	89-100	42.5	6.1-295	0.10	0.06-0.16	79
Brown-b	2005	176	56	19	18	83	70	65-84	81	73-88	4.1	2.65-6.2	0.30	0.20-0.45	42
Choi	2011	211	16	11	6	178	73	52-87	94	90-97	12.5	6.7-23.4	0.29	0.15-0.57	10
D'Anjou-a	2004	81	**28.5**	**5.5**	**0.5**	**48.0**	98	85-100	90	79-95	9.7	4.4-21.3	0.02	0.001-0.3	35
D'Anjou-b	2004	78	29	1	1	47	97	83-99	98	89-100	46.4	6.7-323	0.03	0.005-0.23	38
Eom	2008	129	**78.5**	**0.5**	**0.5**	**51.5**	99	94-100	99	91-100	103	6.6-1630	0.01	0.0-0.10	61
Grooters	1996	20	**8.5**	**0.5**	**2.5**	**10.5**	77	48-93	96	68-100	17.0	1.1-260	0.24	0.08-0.71	50
Leveille	1996	35	**7.5**	**0.5**	**0.5**	**28.5**	94	60-99	98	85-100	54.0	3.5-854	0.06	0.004-0.93	20
Reese	2005	166	43	5	10	108	81	69-89	96	90-98	18.3	7.7-43.6	0.2	0.11-0.35	32
Reusch	2000	43	12	2	1	28	92	67-99	93	79-98	13.9	3.6-53.3	0.08	0.013-0.54	39
Rudorf-a	2005	300	35	116	34	115	50	39-61	50	43-56	1.0	0.77-1.3	1.00	0.77-1.3	23
Rudorf-b	2005	305	37	116	37	115	50	39-61	50	43-56	1.0	0.77-1.3	1.00	0.77-1.3	24
Wenger	2010	54	29	2	1	22	97	83-99	92	74-98	11.6	3.1-43.8	0.036	0.005-0.25	56
Wisner	1994	20	**13.5**	**0.5**	**1.5**	**6.5**	90	66-98	93	56-99	12.6	0.87-183	0.11	0.023-0.50	75
Zwingenberger	2010	142	30	8	32	72	48	36-61	90	82-95	4.8	2.4-9.8	0.57	0.45-0.74	44
Median (range)		80 (20-305)	29 (5-159)	2 (0-116)	4 (0-37)	47 (7-178)	86 (38-99)		94 (50-99)		13.3 (1.0-103.0)		0.16 (0.01-1.0)		40 (10-79)

n, number of subjects studied; TP, true positives; FP, false positives; TN, true negatives; FN, false negatives; CI confidence interval; PLR, likelihood ratio for a positive result; NLR, likelihood ratio for a negative result. Values in bold type have had 0.5 added to permit calculation of likelihood ratios (see text).

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Legends

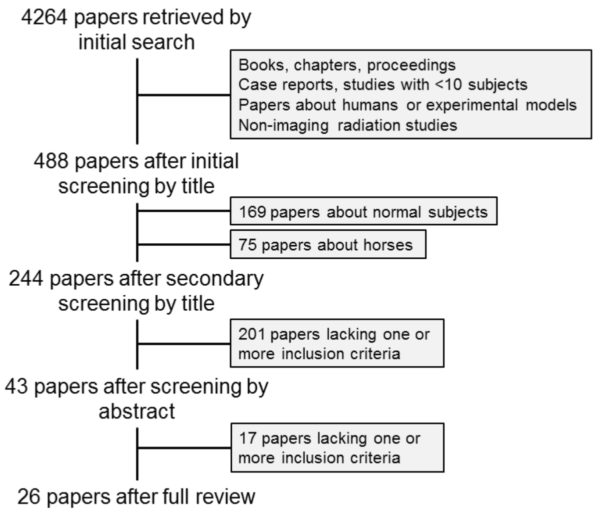
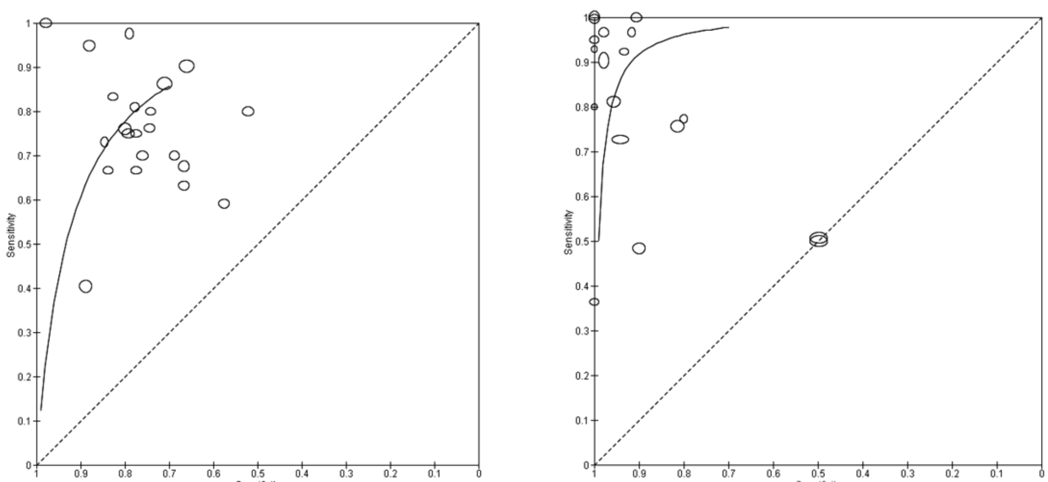
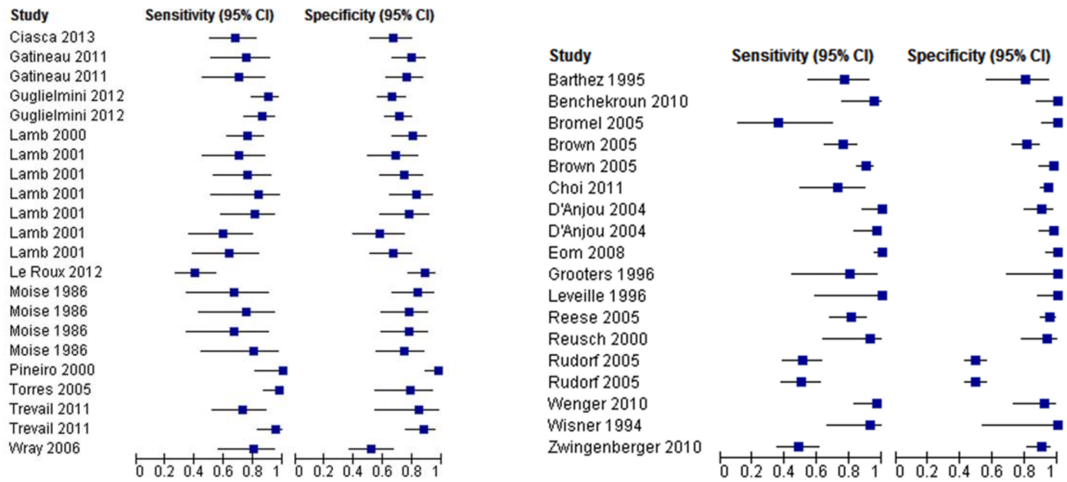


Figure 1. Schematic to illustrate numbers of papers retrieved by the search.



A B

Figure 2. Summary receiver-operating characteristic plots of results of A) 22 tests based on radiographic measurements and B) 18 tests based on ultrasonographic measurements. In each instance, results of individual tests are widely scattered. The size of data points is proportional to sample size.



A B

Figure 3. Forest plots of results of A) 22 tests based on radiographic measurements and B) 18 tests based on ultrasonographic measurements. In general, confidence intervals are wider for tests based on radiographic measurements and include 0.5 (50%) in several instances. Specificity estimates for many tests based on ultrasonographic measurements are close to 1.0 (100%). Multiple tests derived from a single study are presented in the same order as in Tables 1 & 2.

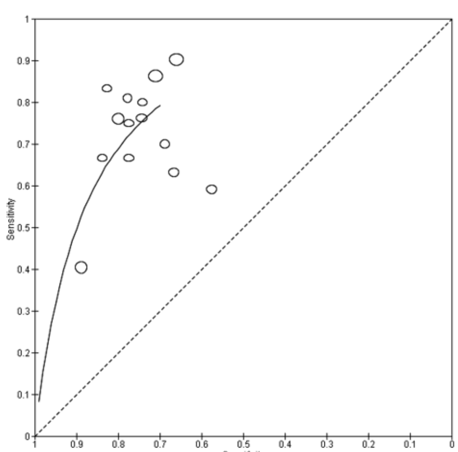


Figure 4. Summary receiver-operating characteristic plot of results of 14 radiographic tests for cardiac or pericardial disease based on measurements of the cardiac silhouette. The results of individual tests are widely scattered. The area under the curve for this sub-group is subjectively slightly less than that for all radiographic tests (compare with figure 2A).

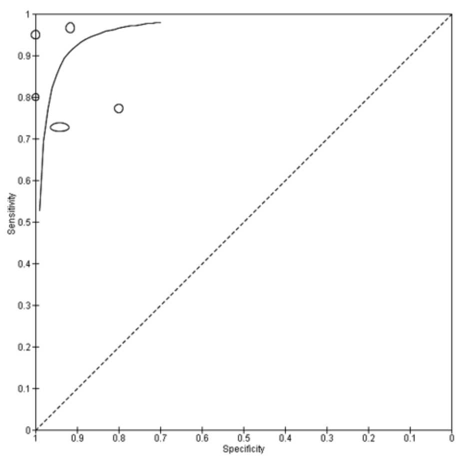


Figure 5. Summary receiver-operating characteristic plot of results of 5 tests based on ultrasonographic measurements. The area under the curve for this sub-group appears to be the same as that for all ultrasonographic tests (compare with figure 2B).