Received: 3 May 2021 | Accepted: 3 May 2021

DOI: 10.1111/jvim.16165

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

LETTER TO THE EDITOR

Letter regarding "ACVIM consensus statement on pancreatitis in cats"

Dear Editor,

With interest we read the "ACVIM consensus statement on pancreatitis in cats." It was our impression that information regarding comparisons of Spec feline pancreas-specific lipase (fPL) and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR)-lipase (LIPC Roche, Roche Diagnostics Corp., Indianapolis, IN), as well as their performances compared to pancreatic ultrasound was incomplete. A consensus statement should aim to be comprehensive in summarizing the existing literature. If information about Spec fPL at the level of an abstract[1] is deemed sufficient evidence, then also abstracts from other authors on the topic should have been included.

The authors state that clinical signs of pancreatitis in cats are nonspecific and that results of CBC, biochemistry, and urinalysis are "not specific for the diagnosis of either acute or chronic pancreatitis in cats" but help eliminating other differential diagnoses. In the absence of pancreatic histology, this would leave ultrasonography for the clinical evaluation of the pancreas.

We know from retrospective studies that ultrasonography and serum lipase measured as Spec fPL or DGGR-lipase activity (used as surrogate gold standard for pancreatitis) agree poorly in cats. This has not only been shown by us (n = 161 cats),[2] but also by colleagues in France (n = 62 cats) where the agreement between Spec fPL and pancreatic ultrasonography was very low (Cohen's kappa [κ] = 0.11).[3] The situation is the same in dogs. Clearly, such results depend on study design, operator skills, machine quality, and used cutoff values of laboratory tests. But still, at this point all available studies in cats and dogs highlight a discrepancy between ultrasonography and serum lipase results in the diagnosis of pancreatitis.

On the 1 hand, acute pancreatitis may not get picked up ultrasonographically in the early phase when differences between acoustic impedance of abnormal and normal pancreas are still too small. In a recent study, one third (14/48, 36%) of dogs with suspected acute pancreatitis had a normal pancreas at initial presentation but ultrasonographic evidence of pancreatitis 2 to 3 days later.[4] The same probably applies to cats, but serial ultrasonographic monitoring has not been studied so far. On the other hand, when considering how common chronic pancreatitis is found histologically in cats,[5] silent chronic pancreatitis without relevant enzyme release but with sufficient ultrasonographically detectable pancreatic parenchymal remodeling may account for many false-positive diagnoses.

The authors allude to lipase and ultrasound stating: "There is poor agreement between the ultrasonographic diagnosis of pancreatitis and DGGR-lipase (cutoff, 26 U/L) or Spec fPL (cutoff, >5.4 μg/L), with $\kappa = 0.22$ and $\kappa = 0.26$". But it is not mentioned that even the highest agreements among ultrasonography and a high Spec fPL (cutoff >16 μg/L; $\kappa = 0.33$), and a high DGGR-lipase (cutoff >57 U/L; $\kappa = 0.37$) still appear too low to be clinically useful.[2]

The currently used Spec fPL cutoffs are based on results of 141 cats with "clinical signs consistent with pancreatitis" and 41 healthy cats.[1] In a presumably retrospective study, 2 internists blinded to Spec fPL divided cats into 6 groups with different probabilities of having pancreatitis based on history, clinical examination, CBC, biochemistry panel, urinalysis, ultrasonography, and clinical outcome (no specifics given on ultrasound, outcome, follow-up). Data have never been published beyond an abstract, thus we do not know whether cats had acute or more chronic disease, and most importantly when considering the often nonspecific clinical picture, how much importance was placed on the results of ultrasonography. However, using these cutoffs has consequences when comparing diagnostic tests for pancreatitis.

The authors state that "agreement between DGGR-lipase (>26 U/L) and Spec fPL (>5.3 μg/L) has been reported to have a κ of 0.681 and 0.70." But an almost perfect agreement ($\kappa = 0.82$) from a prospective study (n = 60) using the same cutoffs is not mentioned.[5] Also when increasing the DGGR-lipase cutoff to >34 U/L, a higher agreement ($\kappa = 0.76$) with Spec fPL (>5.3 μg/L) was found (n = 251)[6] (reference lacking in consensus statement). These differences illustrate the difficult comparison of diagnostic tests using different cutoffs. It should be noted that there is no "gray-zone concept,"[1] but only 1 reference interval available for DGGR-lipase (8-26 U/L; n = 80 healthy cats).[6] This obviously further complicates comparisons of tests. The authors also state that κ values of 0.7 are "considered good when comparing results of subjective diagnostic modalities, but less so for objective ones," and they rate a κ of 0.7, as "indicating discordance." We believe, the limitations of a statistical approach comparing the agreement of 2 methods without actually knowing the true state of disease should have been clarified in the consensus statement. For calculation of *k* values and also sensitivity/specificity, it is necessary to dichotomize results of serum lipase results. This type of allocation can underestimate a relationship in the dataset. Most probably, it is

more realistic to look at lipase results as continuous variables that are surrogates for the degree of pancreatic injury, than to dichotomize a test to absence or presence of disease. Therefore, inclusion of published Spearman correlation coefficients between Spec fPL and DGGR-lipase ($r_s = 0.83$, n = 251,[6] $r_s = 0.83$, n = 161)[2] would have been helpful. The same DGGR-lipase assay (LIPC Roche) also correlated highly with Spec fPL in cats in a study from Canada ($r_s = 0.92$, n = 40).[7]

Similar sensitivities and a tendency towards higher specificity for the DGGR-lipase compared to Spec fPL were found in the only study evaluating both assays against a gold standard (standardized, detailed histologic assessment of the entire pancreas; n = 60).[5] We added a logistic regression analysis (and Akaike information criterion [AIC] as a model selection criterion) to assess if the histological disease activity index was better explained by variations in Spec fPL or DGGR-lipase. Results indicated that the DGGR assay performs better than Spec fPL in terms of explaining the variability in the histological disease activity index.[5]

We did not "postulate that mild infiltration of the pancreas with inflammatory cells should be considered normal." Instead, we clearly stated that the relevance of mild lymphocytic pancreatic inflammation in cats is currently unknown.[5] Our decision to define lymphocytic inflammation affecting <10% of a section as normal was based on previous work where small nests of lymphocytes were considered normal.[8] When considering mild lymphocytic infiltration as normal, sensitivity of Spec fPL (cutoff >5.3 μg/L) increased from 42.1% to 61.1%.[5] This was slightly lower than the sensitivity of 67% reported for the previously used fPLI radioimmunoassay.[8] The sensitivity of DGGR-lipase (cutoff >26 U/L) increased from 36.5% to 78.6% when considering mild lymphocytic infiltration as normal.[5] Specificity of both lipase assays was 100% when mild lymphocytic inflammation was considered indicative of pancreatitis (n = 3). When considering this as normal, the number of healthy cats increased to 42 and the specificity decreased to 61.1% for Spec fPL and to 66.7% for DGGR-lipase.[5] These data were not given in the consensus statement.

In summary, existing knowledge on the comparison of Spec fPL with DGGR-lipase has not been presented in full detail. It seems useless to constantly harp on the "pancreas specificity" of the Spec fPL assay when it is obvious that Spec fPL and DGGR-lipase are highly correlated, and when studies proving superior diagnostic performance of Spec fPL are lacking. It should be acknowledged that retrospective ultrasonography results are of limited use for evaluating diagnostic performance of lipases, and we clearly need well-designed prospective studies to address this crucial point. At present, we can only conclude that both tests appear equally suitable for the diagnosis of pancreatitis in cats. Any assessment of a diagnostic test should also take into account cost and turnaround time of results, as both factors are critical to generating more knowledge about pancreatitis in cats.

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