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Effects of medical history and clinical factors on serum lipase activity and ultrasonographic evidence of pancreatitis: Analysis of 234 dogs

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Abstract

Background: Lipase measurements and ultrasonographic (US) evidence of pancreatitis correlate poorly.

Objectives: Identify explanations for discrepant lipase and pancreatic US results.

Animals: Two hundred and thirty-four dogs with gastrointestinal signs.

Methods: A retrospective study was conducted, in which lipase activity and US were performed within 30 hours. Medical history, clinical examination results, lipase activity, and US results were recorded.

Results: Lipase and US results were weakly correlated ($r_s = .25$, $P < .001$). At both evaluated time cut-offs, median lipase activities were significantly higher with shorter durations of clinical signs before presentation (≤2 days, 334 U/L; >2 days, 118 U/L; $P = .03$; ≤7 days, 334 U/L; >7 days, 99 U/L; $P = .004$), but US was not significantly more frequently positive. For both cut-offs (>216/≤216 U/L, >355/≤355 U/L; reference range, 24-108 U/L), median disease duration was significantly shorter (3 vs 4 days) with higher lipases. Previous pancreatitis episodes were significantly associated with an US diagnosis of pancreatitis ($P = .04$), but median lipase activities were not significantly higher (386 U/L vs 153 U/L; $P = .06$) in these dogs. Pancreatic US was significantly more often positive when the request contained "suspicion of pancreatitis" ($P < .001$) or "increased lipase" ($P = .01$). Only changes in pancreatic morphology, echogenicity, and peripancreatic mesentery were significantly associated with a positive US diagnosis, and also had significantly higher lipase activities.

Conclusions and Clinical Importance: Duration of clinical signs before presentation differently affects laboratory and US evidence of pancreatitis. Previous pancreatitis episodes and information given to radiologists influence US results. These findings can be helpful for future studies on pancreatitis in dogs.

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1 | INTRODUCTION

Pancreatitis is a common disease in dogs with a variable clinical picture. Presenting clinical signs (ie, vomiting, anorexia, abdominal pain) are not specific, and dogs can present with a single clinical sign. Histopathology is the diagnostic gold standard.[1,2] However, it is rarely used because of its invasive nature and inherent limitations, including the potential to miss localized or subclinical pancreatitis.[3,4] Therefore, pancreatitis is mostly a clinical diagnosis based on 3 cornerstones, namely clinical signs, laboratory abnormalities, and ultrasonography (US). Determination of serum lipase, either as a concentration (pancreatic lipase immunoreactivity [PLI]) or an activity (1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester [DGGR]-based lipase assays), has largely replaced histopathology as a surrogate gold standard for the diagnosis of pancreatitis in dogs.[5-11] Both tests have been shown to correlate strongly.[7,8,10,12-15] We have been using the LIPC Roche DGGR-based catalytic lipase assay since 2005 in our hospital. Assessments of the diagnostic utility of PLI and lipase activity versus a standardized histopathologic evaluation similar to what has been published in cats[16] or versus a standardized in-depth clinical evaluation are lacking. Because prospective clinical studies are inherently difficult to perform, correlations of serum lipase results with clinical findings and US findings suspicious for pancreatitis may help to better characterize this laboratory test.

Another diagnostic cornerstone of a clinical pancreatitis diagnosis is US. Whenever US results have been compared to the laboratory surrogate gold standard lipase (PLI or lipase activity), a clear discrepancy was found between both modalities with poor agreement and correlation of both tests.[14,17-20] Causes for this discrepancy have not been investigated. We assume duration of clinical signs before presentation plays a role, because circulating lipase very likely reflects the current state whereas recognizable US changes might lag behind, depending on when in the course of pancreatitis the patient is presented. Also, previous episodes of pancreatitis may have caused remnant pancreatic lesions still detectable ultrasonographically, which can be mistaken for an active process.[14] Therefore, we aimed to find explanations for the discrepancy between pancreatic US and lipase measurements. Our hypotheses were: (a) duration of clinical signs before presentation differently influences lipase and US results and (b) previous pancreatitis episodes as well as information given to radiologists affect the likelihood of an US diagnosis of pancreatitis. Secondary goals were to compare individual pancreatic US variables with the final pancreatic US diagnosis as well as with lipase results.

2 | MATERIALS AND METHODS

2.1 | Case selection and data collection

Cases were identified by searching medical records at the investigators' institution between January 1, 2016, and December 1, 2020. Inclusion criteria were clinical signs of gastrointestinal disease (vomiting, diarrhea, anorexia, abdominal pain, lethargy, or a combination of these signs), a Roche Colorimetric Lipase (LIPC) DGGR-based lipase activity measurement,[14] and abdominal US performed within 30 hours of blood sampling. Dogs with acute and chronic clinical signs were included. The PLI results were included when measured from the same blood sample. Cases were excluded if the US report did not mention the pancreas (Figure 1). Because prednisolone can increase PLI[21] as well as lipase acitivity[22] in dogs, and PLI often is increased in dogs with hyperadrenocorticism without clinical evidence of pancreatitis,[23] pretreatment with corticosteroids or a diagnosis of hyperadrenocorticism was an additional exclusion criterion. Concurrent azotemia was not an exclusion criterion, because neither experimentally induced acute kidney injury[24] nor chronic renal failure[25] has been shown to have significant effects on lipase activity and PLI, and correlation of lipase activity with serum creatinine concentration was poor in a recent study.[13]

2.2 | Medical history and clinicopathological variables

Presence of the following clinical signs was recorded: general clinical demeanor at presentation as judged by the attending clinician after taking the history and examining the dog (normal vs diminished), vomiting, hematemesis, diarrhea, hematochezia, anorexia, painful abdomen, obesity, as well as the clinical examination results. Duration of clinical signs was recorded exactly when the number of days was known. If owners stated that clinical signs had been present for 1 to 2 days, then the dogs were grouped into ≤2/>2 days for calculation. All dogs with clinical signs for at least 7 days were grouped into ≤7/>7 days for calculations.

2.3 | Lipase activity and PLI concentration

Lipase activity (reference range, 24-108 U/L) is included in the routine serum biochemistry panel and was measured using an in-house assay (LIPC, Roche on Cobas Integra 800, Roche Diagnostics, Rotkreuz, Switzerland).[14] Similar to interpretation of PLI concentrations, we originally had created a preliminary equivocal zone of 109-216 U/L that we considered a questionable range.[14] Pancreatic lipase immunoreactivity
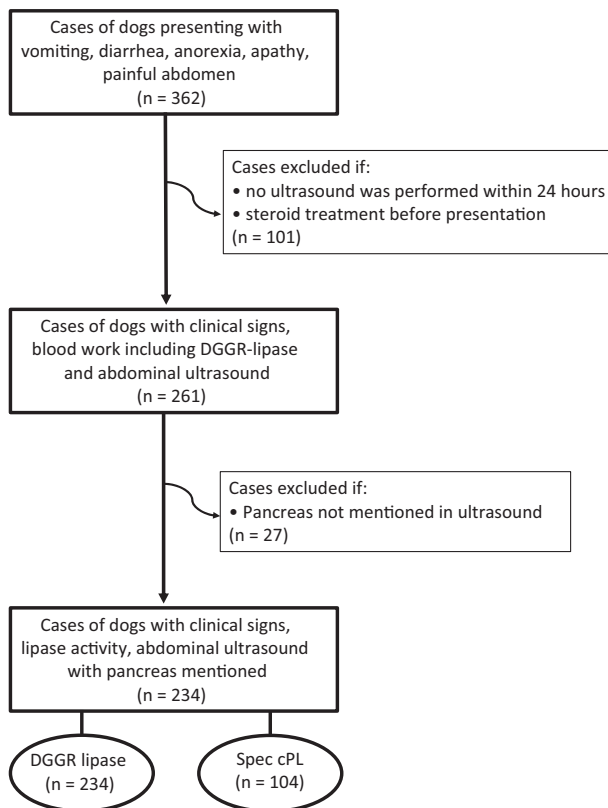
Cases of dogs presenting with vomiting, diarrhea, anorexia, apathy, painful abdomen (n = 362)

Cases excluded if:
• no ultrasound was performed within 24 hours
• steroid treatment before presentation
(n = 101)

Cases of dogs with clinical signs, blood work including DGGR-lipase and abdominal ultrasound (n = 261)

Cases excluded if:
• Pancreas not mentioned in ultrasound
(n = 27)

Cases of dogs with clinical signs, lipase activity, abdominal ultrasound with pancreas mentioned (n = 234)

DGGR lipase (n = 234)

Spec cPL (n = 104)

FIGURE 1 Flow diagram explaining patient selection

(reference range, 0-200 µg/L) was measured by IDEXX Laboratories (Diavet IDEXX, Switzerland) at the clinician's discretion.

2.4 | Pancreatic US diagnosis and US variables

Ultrasonography was performed either by a board-certified radiologist or a resident under supervision. Reports were written immediately after the examination. The results were taken as written in the original radiologists' reports and reviewed for each patient. The US diagnoses were divided into two groups using the verbatim description and diagnosis of the radiologist's report, namely (a) normal pancreas (ie, no US changes in the pancreas and the pancreas noted as normal) and (b) pancreatitis when the diagnosis in the radiology report was either pancreatitis or suspicion of pancreatitis. Eight descriptive imaging terms relating to the pancreas and gastrointestinal tract also were recorded.

2.5 | Statistical analyses

Spearman's rank correlation coefficients (r_s) of lipase activity, with PLI and the US results, were determined. Agreement between

lipase and US results was assessed using Cohen's kappa coefficient (κ). Linear regression analysis was used to calculate the goodness-of-fit (R^2) of truncated lipase activities with PLI results. Similar to PLI being reported only up to 1500 µg/L by the external laboratory, lipase activities >1500 U/L also were truncated at 1500 U/L for regression analysis. Kruskal Wallis and Mann-Whitney U-tests were applied to compare lipase activities between US categories. Associations among pancreatic US diagnosis and laboratory, as well as US variables, were assessed using chi-squared tests. For secondary and additional endpoints, exploratory data analysis was performed and P-values were used in an exploratory context.[26] Cramer's V and Hedge's g were used as measures for effect size for categorical and metric variables. All tests were performed 2-tailed using a 5% level of significance ($P = .05$). All statistical analyses were performed using SPSS version 25 (IBM Inc).

3 | RESULTS

3.1 | Dogs

A total of 362 client-owned dogs initially were identified that presented with ≥1 of the predefined clinical signs and had lipase activity measurements performed. Subsequently, 101 dogs were excluded because US was performed >30 hours after blood analysis or had corticosteroid treatment before presentation. A further 27 cases were excluded because the pancreas was not mentioned in the US report, leaving 234 dogs for analysis (Figure 1).

One hundred and thirty-one dogs were male and 103 were female. Median age was 8.9 years (interquartile range [IQR], 5.2-10.0 years). Median weight was 12.7 kg (IQR, 6.5-25.7 kg).

3.2 | Relationships between lipase activity and PLI concentration

Median lipase activity (n = 234) was 168 U/L (IQR, 61-567 U/L). Median PLI concentration (n = 104) was 569 µg/L (IQR, 114-1096 µg/L). Spearman's rank correlation coefficient (r_s) between lipase activity and PLI was very high ($r_s = .914$, $P = <.001$). Truncation of lipase activity results at 1500 U/L yielded an $r_s = .916$ ($P < .001$). Linear regression analyses indicated that lipase activity cut-offs corresponding PLI cut-offs ≤200/>400 µg/L were higher than previously suggested[14] at ≤179 U/L, and >355 U/L when all lipase activity results were truncated at 1500 U/L (goodness-of-fit for linear regression $R^2 = .812$ [lipase activity = 3.03 + 0.88 PLI]). Thirteen (6%) dogs were azotemic with a median serum creatinine concentration of 181 µmol/L (IQR, 152-273 µmol/L; reference range, 50-119 µmol/L). Median lipase activity in these 13 dogs was 762 U/L (IQR, 240-1158 U/L), and 5 of 13 dogs also had PLI

measured (median, 754 μg/L; IQR, 270-1500 μg/L). Agreement between lipase activity and PLI in azotemic dogs was 100% when applying both, the reference ranges and the >216/>355 U/L cut-off for lipase activity and >400 μg/L cut-off for PLI.

3.3 | Relationships between lipase activity and the pancreatic US diagnosis

Dogs with an US diagnosis of pancreatitis had significantly higher median lipase activity (411 U/L) than dogs with a normal pancreas (90 U/L; $P < .001$). Spearman's correlation coefficient documented a weak positive correlation between lipase activity and the US diagnosis ($r_s = .25$, $P < .001$). Truncation of lipase activity at 1500 U/L did not change r_s. No significant correlation was identified between PLI and the US diagnosis ($r_s = 0.095$, $P < .34$). Agreement between lipase activity >216 U/L and an US diagnosis of pancreatitis was fair ($\kappa = 0.251$; 95% CI, 0.126-0.376), and did not differ when using a

higher cut-off for lipase activity (≥355 U/L) from regression analysis ($\kappa = 0.280$; 95% CI, 0.155-0.405). Agreement between PLI >400 μg/L and an US diagnosis of pancreatitis was slight ($\kappa = 0.147$; 95% CI, −0.043 to 0.337).

3.4 | Correlation of medical history and clinical signs with lipase activity and the pancreatic US diagnosis

Previous pancreatitis episodes correlated significantly with an US diagnosis of pancreatitis, but not lipase activity (Table 1). Diminished general demeanor (160/231, 69%), anorexia (131/222, 59%), and vomiting (135/234, 58%) were the 3 most frequently recorded clinical signs. Diminished general demeanor, vomiting, and abdominal pain correlated significantly with lipase activity. Only diminished general demeanor, abdominal pain, and anorexia correlated significantly with an US diagnosis of pancreatitis (Table 1).

TABLE 1 Comparison of the presence of variables from clinical history and clinical variables with lipase activity and the US diagnosis

| | n/recorded information (%) | Median DGGR-lipase activity, U/L (IQR) | | | | US diagnosis (n, %) | | | |
		Present	Absent	Hedge's g	P-value	Normal pancreas	Pancreatitis	Cramer's V	P-value
Previous pancreatitis episodes	28/234 (12)	386 (102-1554)	153 (59-552)	.364	.06	10/129 (8)	18/105 (17)	.144	.04[a]
Clinical signs (present/absent):									
Diminished general demeanor	160/231 (69)	285 (65-1272)	87 (53-370)	.293	.01[a]	79/128 (62)	81/103 (79)	.194	.03[a]
Abdominal pain	73/199 (37)	370 (86-684)	114 (52-527)	.263	.03[a]	31/104 (30)	42/85 (49)	.210	.02[a]
Vomiting	135/234 (58)	337 (70-653)	102 (58-386)	.023	.01[a]	68/129 (53)	67/105 (64)	.112	.11
Hematemesis	19/234 (8)	554 (288-1600)	147 (59-548)	.382	.01[a]	8/129 (6)	11/105 (10)	.078	.34
Diarrhea	101/234 (43)	150 (52-539)	171 (63-586)	.064	.45	53/129 (41)	48/105 (46)	.046	.51
Hematochezia	40/234 (17)	165 (54-770)	167 (63-562)	.156	.81	23/129 (18)	17/105 (16)	.022	.86
Anorexia	131/223 (59)	177 (63-602)	102 (58-489)	.289	.12	64/122 (52)	67/101 (66)	.140	.04[a]

Note: This table denotes Mann Whitney *U*-test and chi-square (χ^2) comparisons of clinicopathological variables with lipase activity (median, IQR) and the US diagnosis respectively. For metric variables, Hedges g is used as effect size, for categorical data Cramer's *V* was calculated.
[a]Statistically significant value ($P < .05$).

TABLE 2 Differences between lipase activity results and the US diagnosis regarding duration of clinical signs

| Duration of clinical signs | n | Median DGGR-lipase (U/L) (IQR) | | | | US diagnosis (n, %) | | | |
		≤	>	Hedge's g	P-value	Normal	Pancreatitis	Cramer's V	P-value
≤2/>2 days	73/120	334 (81-726)	118 (58-550)	−.081	.03[a]	40 (53.3)/87 (55.8)	35 (46.7)/69 (44.2)	.023	.78
≤7/>7 days	138/55	334 (82-711)	99 (56-460)	−.149	.004[a]	68 (53.5)/60 (57.1)	59 (46.5)/45 (42.9)	.035	.60

Note: This table denotes Mann Whitney *U*-test comparisons of lipase activity (median, IQR) and the US diagnosis according to the duration of clinical signs. For metric variables Hedges g is used as effect size, for categorical data Cramer's *V* was calculated.
[a]Statistically significant value ($P < .05$).

TABLE 3 Comparison of information for radiologist, individual pancreatic and gastrointestinal US variables with lipase activity and the US diagnosis

Variables	n (% of 234)	Median lipase activity, U/L (IQR)				US diagnosis (n)			
		Yes	No	Hedge's g	P-value	Normal pancreas	Pancreatitis	Cramer's V	P-value
Pre-report radiologist									
Suspicion of pancreatitis (y/n)	50 (21)	386 (105-618)	140 (58-572)	.005	.06	16/129	34/105	.241	<.001[a]
Increased lipase (y/n)	32 (14)	508 (364-1525)	118 (58-527)	.466	<.001[a]	11/129	21/105	.166	.01[a]
Explicit mention of pancreatic parts									
Right (duodenal) limb (y/n)	38 (16)	449 (96-1054)	151 (59-539)	.325	.02[a]	9/129	29/105	.278	<.001[a]
Left (splenic) limb (y/n)	25 (11)	562 (177-1413)	147 (59-527)	.311	.001[a]	5/129	20/105	.244	<.001[a]
Pancreas body (y/n)	16 (7)	277 (91-1167)	167 (59-562)	.154	.24	2/129	14/105	.232	<.001[a]
Pancreas morphology									
Enlarged (y/n)	54 (23)	433 (105-1413)	118 (55-520)	.632	<.001[a]	4/129	50/105	.526	<.001[a]
Rounded contours (y/n)	48 (21)	469 (117-1700)	130 (57-513)	.391	<.001[a]	3/129	45/105	.499	<.001[a]
Pancreatic cysts, pseudocysts, masses (y/n)	4 (2)	1048 (32-2310)	167 (63-562)	.426	.92	2/129	2/105	.014	1.00
Pancreas echogenicity									
Normal (y/n)	120 (51)	109 (45-463)	370 (86-670)	−.374	<.001[a]	113/129	7/105	.805	<.001[a]
Hypoechogenic (y/n)	28 (12)	430 (101-856)	153 (59-552)	.306	.04[a]	3/129	25/105	.329	<.001[a]
Mixed echogenic (y/n)	53 (23)	289 (78-980)	157 (59-553)	.253	.13	7/129	46/105	.456	<.001[a]
Hypoechogenic and mixed (y/n)	23 (10)	472 (114-1554)	153 (59-552)	.495	.01[a]	2/129	21/105	.308	<.001[a]
Hyperechogenic (y/n)	11 (5)	125 (50-487)	168 (63-586)	−.325	.37	0/129	11/105	.246	<.001[a]
Dilated ducts/blood vessels									
Common bile duct (y/n)	5 (2)	370 (197-406)	164 (60-574)	.003	.32	2/129	3/105	−045	.66
Pancreatic ducts (y/n)	3 (1)	370 (197–406)	164 (60-572)	−.141	.35	0/129	3/105	.126	.09
Pancreatic vessels (y/n)	1 (0)	487	167 (61-574)	−.118	.61	0/129	1/105	.073	.45
Gastrointestinal tract									
Thickened gastric wall (y/n)	25 (11)	373 (114-670)	151 (59-562)	.061	.10	9/129	16/105	.132	.06
Loss of gastric wall layering (y/n)	16 (7)	151 (62-484)	169 (63-575)	−.245	.71	5/129	11/105	.129	.07
Gastric content (y/n)	95 (41)	168 (59-575)	165 (64-554)	−.026	.78	50/129	45/105	.038	.59
Corrugated duodenum (y/n)	222 (95)	376 (78-1054)	158 (60-562)	.153	.27	7/129	15/105	.151	.03[a]
Aperistalsis small intestines (y/n)	19 (8)	554 (117–1700)	157 (59–548)	.332	.03[a]	9/129	10/105	.046	.63
Thickened colon wall (y/n)	27 (12)	101 (42-428)	170 (67-575)	.005	.12	16/129	11/105	.030	.69

(Continues)

TABLE 3 (Continued)

| Variables | n (% of 234) | Median lipase activity, U/L (IQR) | | | | US diagnosis (n) | | | |
		Yes	No	Hedge's g	P-value	Normal pancreas	Pancreatitis	Cramer's V	P-value
Other									
Hyperechoic mesentery (y/n)	74 (32)	346 (64-1054)	153 (59-500)	.454	.04[a]	22/129	52/105	.347	<.001[a]
Peritoneal effusion (y/n)	58 (25)	366 (63-1413)	140 (59-527)	.635	.02[a]	24/129	34/105	.157	.02[a]

Note: This table denotes Mann Whitney U-test and Chi-square comparisons of the presence or absence of US variables with lipase activity (median, IQR) and the US diagnosis respectively. For metric variables Hedges g is used as effect size, for categorical data Cramer's V was calculated.
[a]Statistically significant value ($P < .05$).

3.5 | Duration of clinical signs before presentation

The median duration of clinical signs before presentation was significantly shorter in dogs with lipase activity >216 U/L (3 days, IQR 1-5 days) compared to dogs with lipase activity ≤216 U/L (4 days; IQR, 1-14 days; $P = .01$). Median duration of clinical signs before presentation also was significantly shorter (3 days; IQR, 1-5.5 days) for the >355 U/L cut-off compared to dogs with lipase activity ≤355 U/L (4 days; IQR, 1-14 days; $P = .04$). Duration of clinical signs before presentation was not significantly different between dogs with a normal pancreas and those with an US diagnosis of pancreatitis ($P = .40$). Median lipase activity was significantly higher in dogs that had more acute clinical signs (calculated for ≤2 days or ≤7 days before presentation) compared to dogs that had more prolonged clinical signs ($P = .03$ and .004, respectively). No significant difference was found between duration of clinical signs and the pancreatic US diagnosis (Table 2).

3.6 | Correlation of individual US variables with lipase activity and the pancreatic US diagnosis

3.6.1 | History for the radiologist

When the radiology request contained "suspicion of pancreatitis," the US diagnosis was significantly more often pancreatitis ($P < .001$), whereas lipase activities were not significantly higher ($P = .06$). Lipase activity was significantly higher ($P < .001$) and the US diagnosis ($P = .01$) was significantly more often positive, when the radiology request contained "increased lipase," lipase activity was significantly higher ($P < .001$) and the US diagnosis ($P = .01$) was significantly more often positive (Table 3). Chi-squared statistics on the significance of radiologist bias (information on "suspicion of pancreatitis" or "increased lipase") on the individual pancreatic US variables are given in Table 4.

3.6.2 | Pancreatic morphology

Lipase activity was significantly higher when an enlarged pancreas and rounded pancreatic contours were recorded ($P < .001$). Both

variables also were significantly associated with a final US diagnosis of pancreatitis ($P < .001$).

3.6.3 | Pancreas visualization

Visualization of the pancreas correlated significantly with the pancreatic US diagnosis but not with lipase activity (Table 3). Comments on the right and left lobe, respectively, were available in 16.3% and 10.7% of reports; the body was only specifically mentioned in 6.9% of cases. Lipase activity was significantly higher when visualization of the right and left lobe of the pancreas was mentioned.

3.6.4 | Pancreatic echogenicity

Lipase activity was significantly lower in dogs with normal pancreatic echogenicity ($P < .001$), and significantly higher in those with a hypoechoic ($P < .04$), or hypo- and mixed-echoic pancreatic echogenicity ($P < .01$). A normal echogenicity was significantly associated with a normal pancreas on US, whereas all recorded changes in echogenicity (hypoechoic, mixed echoic and hyperechoic pancreas parenchyma) were significantly associated with an US diagnosis of pancreatitis ($P < .001$; Table 3).

3.6.5 | Gastrointestinal tract involvement

Few gastrointestinal variables correlated with lipase activity or the pancreatic US diagnosis (Table 3). Dogs with aperistalsis of the small intestine had significantly higher lipase activity ($P = .03$), whereas a corrugated duodenum was significantly associated with an US diagnosis of pancreatitis ($P = .03$).

3.6.6 | Surrounding mesentery and peritoneal effusion

Dogs with hyperechoic mesentery and peritoneal effusion had significantly higher lipase activities ($P = .04$ and .02, respectively). Both

TABLE 4   Contingency table of the effect of possible radiologist bias on US variables (number of dogs, %)

		Radiology request contained: suspicion of pancreatitis (n, %)				Radiology request contained: increased lipase (n, %)			
		No	Yes	Cramer's V	P-value	No	Yes	Cramer's V	P-value
Parts of pancreas visualized									
Right (duodenal) limb	n	158 (86)	37 (74)	.137	.04[a]	172 (85)	24 (75)	.095	.15
	y	25 (14)	13 (26)			30 (15)	8 (56)		
Left (splenic) limb	n	167 (91)	41 (83)	.123	.06	182 (90)	27 (84)	.064	.33
	y	16 (9)	9 (18)			20 (10)	5 (16)		
Pancreas body	n	172 (94)	45 (90)	.065	.32	188 (93)	30 (94)	.009	.89
	y	11 (6)	5 (10)			14 (7)	2 (6)		
Pancreatic morphology									
Enlarged	n	145 (79)	34 (68)	.109	.13	156 (77)	24 (75)	.018	.82
	y	38 (21)	16 (32)			46 (23)	8 (25)		
Rounded contours	n	151 (83)	34 (68)	.147	.03[a]	159 (79)	27 (84)	.048	.50
	y	32 (18)	16 (32)			43 (21)	5 (16)		
Pancreatic cysts, pseudocysts, masses	n	179 (98)	49 (98)	.011	.87	199 (99)	30 (94)	.139	.09
	y	3 (2)	1 (2)			2 (1)	2 (6)		
Pancreatic echogenicity									
Normal	n	76 (42)	37 (74)	.267	<.001[a]	92 (46)	22 (69)	.160	.02[a]
	y	107 (58)	13 (26)			110 (55)	10 (31)		
Hypoechogenic	n	165 (90)	41 (82)	.105	.13	177 (88)	29 (91)	.032	.13
	y	18 (10)	9 (18)			25 (12)	3 (9)		
Mixed echogenic	n	143 (78)	37 (74)	.041	.57	162 (80)	19 (59)	.171	.01[a]
	y	40 (22)	13 (26)			40 (20)	13 (41)		
Hypoechogenic and mixed	n	170 (93)	40 (80)	.177	.01[a]	186 (92)	25 (78)	.161	.02[a]
	y	13 (7)	10 (20)			16 (8)	7 (23)		
Hyperechogenic	n	176 (96)	46 (92)	.081	.26	193 (96)	30 (94)	.029	.66
	y	7 (4)	4 (8)			9 (5)	2 (6)		
Dilated ducts/blood vessels									
Common bile duct	n	180 (98)	48 (96)	.067	.31	199 (98)	30 (94)	.113	.14
	y	3 (2)	2 (4)			3 (2)	2 (6)		
Pancreatic ducts	n	180 (98)	50 (100)	.060	.60	200 (99)	31 (97)	.065	.36
	y	3 (2)	0 (0)			2 (1)	1 (3)		
Pancreatic vessels	n	183 (100)	49 (98)	.126	.22	201 (99)	31 (100)	.026	.69
	y	0 (0)	1 (2)			1 (0.5)	0 (0)		
Gastrointestinal tract									
Thickened gastric wall	n	164 (90)	43 (86)	.054	.41	179 (89)	29 (91)	.017	.79
	y	18 (10)	7 (14)			22 (11)	3 (9)		
Loss of gastric wall layering	n	168 (92)	48 (96)	.060	.53	187 (93)	30 (92)	.010	.88
	y	14 (8)	2 (4)			14 (7)	2 (6)		
Gastric content	n	104 (57)	33 (66)	.074	.33	119 (59)	19 (59)	.001	.99
	y	78 (43)	17 (34)			82 (41)	13 (41)		
Corrugated duodenum	n	165 (90)	46 (92)	.026	.79	183 (91)	29 (91)	.000	1.00
	y	18 (10)	4 (8)			19 (9)	3 (9)		
Aperistalsis small intestines	n	165 (90)	49 (98)	.118	.08	185 (92)	30 (92)	.027	.75
	y	18 (10)	1 (2)			17 (8)	2 (6)		
Thickened colon wall	n	158 (86)	48 (96)	.124	.08	178 (88)	29 (91)	.027	.78

(Continues)

TABLE 4 (Continued)

		Radiology request contained: suspicion of pancreatitis (n, %)				Radiology request contained: increased lipase (n, %)			
		No	Yes	Cramer's V	P-value	No	Yes	Cramer's V	P-value
	y	25 (14)	2 (4)			24 (12)	3 (9)		
Other									
Hyperechoic mesentery	n	126 (69)	33 (66)	.025	.73	136 (67)	24 (75)	.057	.42
	y	57 (31)	17 (34)			66 (33)	8 (25)		
Peritoneal effusion	n	136 (74)	39 (78)	.035	.71	153 (76)	23 (72)	.031	.66
	y	47 (26)	11 (22)			49 (24)	9 (28)		

Note: This table denotes the Chi-square statistics of the influence of radiologist bias in terms of information on the suspicion of pancreatitis or increased lipase activity on the US variables. For categorical data, Cramer's V was calculated for effect size.
[a]Statistically significant value (P < .05).

variables also were significantly associated with a positive US diagnosis (P < .001 and .02, respectively; Table 3).

3.7 | Correlation of individual US variables and clinical variables

Associations between individual US variables and clinical signs can be found in Table S1. The dog's general demeanor correlated with an enlarged pancreas (P = .001) and rounded contours (P = .01), as well as various gastrointestinal signs. Vomiting correlated significantly with an enlarged pancreas (P = .04), rounded contours (P = .02), hypoechoic echogenicity (P = .02), as well as with most gastrointestinal signs (thickened gastric wall, loss of gastric wall layering, gastric content, corrugated duodenum). Other clinical signs including hematemesis, diarrhea, and hematochezia correlated significantly with gastrointestinal tract variables, but not with pancreatic variables. Anorexia correlated significantly with an enlarged pancreas, hyperechoic pancreas and hyperechoic mesentery.

4 | DISCUSSION

We aimed to find explanations for the weak correlation between laboratory and US evidence of pancreatitis in dogs.[14,17-20] Clinical signs, lipase measurement as the surrogate laboratory gold standard, and pancreatic US have never been correlated to detect information that could optimize a clinical diagnosis of pancreatitis. Improving our ability to clinically diagnose pancreatitis is important because pancreatic biopsy is highly invasive, focal lesions can be missed, and therapeutic consequences are limited.[3]

Lipase activity correlated strongly with PLI concentration, similar to previous reports.[7,8,10,12-15] Regression analysis between both assays identified higher lipase activity cut-offs than initially estimated.[14] The basis for currently used PLI cut-offs (≤200 μg/L/>400 μg/L) is unknown. Healthy dogs can have concentrations up to 279 μg/L,[27] and concentrations >200 μg/L can be found in clinically

healthy dogs with results up to 516.2 μg/L.[28] Reasoning for the suggested equivocal zone was that it is virtually impossible to rule out transient mild pancreatitis in clinically normal dogs.[29] Probably, some safety margin similar to the commonly used threshold of 3 × the upper limit of the reference range for lipase activity was built in.[13,30] Understandably, usage of these cut-offs has implications for comparisons with other tests.

We initially had performed all analyses with both lipase assays, assuming that attending clinicians did not request PLI concentrations whenever lipase activity was already markedly increased.[31] However, plotting the data indicated no discernible pattern (Figure S1). Significant associations between 1 lipase assay and clinical and US findings, but not the other lipase assay, may have been simply because of selection bias. To avoid skewed conclusions, we decided to focus on analyses related to lipase activity only. Showing the high correlation and agreement between both lipase assays, as well as the equally low correlation and agreement of both lipase assays with pancreatic US results, is helpful for readers unfamiliar with the lipase activity assay. Results illustrate that our study's principal findings very likely also apply to PLI results. However, prospective studies are needed to prove this hypothesis.

As shown before for lipase activity and PLI, we found only fair agreement and weak correlation between lipase activity and pancreatic US results.[14,17-20] Agreement remained low regardless of the cutoffs used. We believe that changes in serum lipase take place over a shorter time than do US changes, and increased lipase results reflect recent exocrine pancreatic cell damage that might not be visible ultrasonographically. Lipase activity half-life, as well as PLI half-life, was reported to be approximately 2 hours, suggesting that increased circulating lipase resulting from pancreatitis could be cleared from the circulation by <24 hours after cessation of pancreatic damage.[32,33]

A history of pancreatitis was significantly associated with an US diagnosis of pancreatitis, but not with lipase activity (Table 1). Previous episodes of pancreatitis may have left remnant changes that were interpreted as pancreatitis or contributed to an US diagnosis of pancreatitis. Recent data in humans suggested that it takes ≥3 episodes of acute pancreatitis (AP) without morphological changes to the

pancreas until morphological changes are detectable.[34] Only 0.3% of patients with a first episode of AP (n = 983), but 32% (n = 58) with a fifth episode of acute recurrent pancreatitis have either computer tomography, magnetic resonance imaging, US or endoscopic US-based morphological changes in the pancreas.[34] Such data are lacking in veterinary medicine, but our results give impetus to considering the comment "previous episode of pancreatitis" when interpreting pancreatic imaging results in dogs.

The effect of time on lipase results is visible when considering the duration of clinical signs before presentation. Dogs had significantly shorter duration of clinical signs when lipase activity was >216 U/L or >355 U/L. Similarly, lipase activity was significantly higher at both time cut-offs (<2d/<7d) when dogs were more acutely sick. Duration of clinical signs was not significantly associated with an US diagnosis of pancreatitis (Table 2). Effects of duration of clinical signs before presentation on lipase activity and pancreatic US has not been assessed previously. Emerging evidence suggests that duration of clinical signs before presentation indeed has an impact. In a recent study, dogs had repeated US examinations every 24 hours after admission. At presentation, 24/37 dogs (65%) had US findings suggestive of AP, whereas 10 dogs (27%) became positive on US examination within 2 days after hospitalization.[20] Similarly, the weak significant relationship between PLI concentrations and US pancreatic severity score found at baseline evaluation was lost when analyzed again for 12 dogs with repeated testing (days not specified).[19] This finding can be viewed as further indirect evidence that serum lipase and US results change at different rates.

Lipase activity was significantly higher for 4 clinical signs recorded as present in medical records, whereas 3 clinical signs were significantly associated with an US diagnosis of pancreatitis (Table 1). Only the clinical signs "diminished general demeanor" and abdominal pain had significant associations with both lipase activity and US results. Single clinical signs have never been compared with lipase results in dogs. Pancreatic lipase immunoreactivity and C-reactive protein correlated moderately (r_s = .42) with a clinical activity index in 13 dogs with pancreatitis.[35] However, this correlation was based on all time points from presentation until discharge, and no temporal association could be inferred from that study.[35] For clinicians, it seems relevant to see which clinical signs correlate most closely with lipase activity or US evidence of pancreatitis, because clinical severity scores are used primarily for research but not for daily patient evaluation. Clinical signs typically reflecting more acute disease, such as vomiting or hematemesis, are more likely reflected by high lipase results than US findings. This observation is similar to significantly higher lipase results but not significantly more positive US results, when shorter duration of clinical signs before presentation is considered (Table 2).

The classical US abnormalities associated with pancreatitis include variable degrees of a hypoechoic (hypo- and mixed-echoic), enlarged pancreas with rounded edges, surrounding hyperechoic mesentery with or without adjacent free fluid.[36] We found significantly higher lipase activities and significantly more US diagnoses of pancreatitis for these 5 abnormalities (Table 3). When evaluating clinical signs and their associations with US variables (Table S1), we could not identify clear patterns between individual clinical signs and US variables, and the final US diagnosis in our retrospective study. Hematemesis and hematochezia were more often significantly associated with US changes in the gastrointestinal tract and not with pancreatic changes. Diarrhea, although listed under inclusion criteria in all studies on pancreatitis in dogs, was neither significantly associated with any pancreatic US variable nor with the final US diagnosis or with lipase activities. When evaluating how many clinical signs correlated with which pancreatic US variable, an enlarged pancreas (3) and hyperechoic mesentery (3) had most associations, emphasizing their relevance in an US diagnosis of pancreatitis, especially because both US findings also significantly correlated with both lipase results and the final US diagnosis. An enlarged pancreas and mesenteric echogenicity were also significantly correlated with an US severity score of pancreatitis, but not to PLI concentrations in a recent study.[19]

No clinical sign is pathognomonic for pancreatitis, and dogs may display ≥1 signs and in various combinations. Few studies have reported prevalence of clinical signs in dogs with pancreatitis. Abdominal pain ranged from 15% to 62%, anorexia from 35% to 94%, vomiting from 50% to 90%, and diarrhea from 25% to 63%.[9,35,37,38] Assuming that serum lipase results most accurately reflect the actual state of pancreatic inflammation, vomiting, hematemesis, and abdominal pain would be the clinical signs most closely linked to pancreatitis (Table 1). Exact recording not only of presence, but also of frequency and severity of a clinical signs, as well as standardized pancreatic US reporting[39] will help further delineate associations between clinical presentations and US findings.

Ultrasonography is heavily dependent on operator skill and experience.[40-42] However, even when images were recently re-analyzed in a blinded fashion on the basis of more standardized US variables, correlation with concurrently measured PLI still was poor.[19] We found that visualization of the pancreas was significantly correlated with the US diagnosis, but it remained unclear exactly how much of the pancreas was seen. We could not determine if normal parts were not mentioned, or if all parts were examined but only abnormalities mentioned. In a recent retrospective study, correlations between clinical signs and affected pancreatic lobes were found (n = 293).[37] In that study, abdominal pain, vomiting, and diarrhea were significantly more commonly identified in diffuse pancreatitis, whereas anorexia was more prevalent in right-sided and diffuse pancreatitis.[37] In our study, abdominal pain, diminished clinical demeanor, and anorexia were significantly more common with an US diagnosis of pancreatitis (Table 1). Exact prospective recording of severity of clinical signs, as well as standardized pancreatic US reporting, will help delineate associations between clinical presentations and US findings.

Changes in pancreatic echogenicity and morphology were significantly different when the radiology request contained "suspicion of pancreatitis" or "increased lipase/actual lipase result" (Table 4). A suspicion of pancreatitis may have influenced ultrasonographers, resulting in a more focused search in the pancreatic region and greater weight assigned to subtle US findings. Significantly fewer dogs had normal pancreatic echogenicity when a "suspicion of pancreatitis" or

"increased lipase" was written on the request form (Table 4). Less clearly defined changes, such as mixed echogenicity, as well as the combination hypoechoic and mixed-echoic seemed more influenced by information given to radiologists, suggesting that in less clear cases (pancreas not clearly hypoechoic or hyperechoic), examiner bias is possible that may favor an US diagnosis of pancreatitis or suspicion of pancreatitis.

There were no significant associations of information given to radiologists with US gastrointestinal tract findings, suggesting that the medical history indeed had an effect on interpretation of pancreatic US findings. Similar possible biases from radiology request forms have been reported in cats undergoing imaging for pancreatitis, but numbers were too low to be significant.[41] When the radiology request contained "suspicion of pancreatitis," the US diagnosis was significantly more frequently positive, and lipase activity was not different (Table 3). When the request contained "increased lipase," lipase activities were also significantly higher. With all the caveats of a retrospective study, our findings suggest low agreement between a clinical suspicion of pancreatitis and the surrogate laboratory gold standard lipase in dogs presenting with gastrointestinal signs. Similarly, there was only a weak correlation between a retrospective clinical diagnosis of pancreatitis and an US pancreatic assessment severity score in a recent study.[19]

Corrugated duodenal walls were significantly associated with an US diagnosis of pancreatitis and corrugated intestines have been reported frequently as a typical extra-pancreatic finding in dogs with pancreatitis.[36,42-44] Corrugated duodenal walls did not correlate with lipase activity, indicating other primary intestinal disease or peritonitis might cause such lesions.[43] Aperistaltic small intestines have been less commonly reported to accompany pancreatitis in dogs, and although there was no significant correlation with an US diagnosis of pancreatitis, this finding correlated significantly with lipase activity, possibly reflecting more acute stages of pancreatitis.[42] We do not believe opioid analgesics interfered with our results because metimazole is our first-line drug in dogs with visceral pain.

A hyperechoic mesentery and peritoneal effusion surrounding the pancreas are highly suggestive of AP[44,45] and correlated significantly with both lipase activity and the US diagnosis in our study. Mesenteric echogenicity was also significantly correlated with a clinical diagnosis of pancreatitis but not with PLI in dogs presenting with gastrointestinal clinical signs.[19] We found no associations between the presence of a hyperechoic mesentery and peritoneal effusion and information given to radiologists on request forms ("suspicion of pancreatitis," "increased lipase"), suggesting that these US finding are more robust and less prone to variable interpretation.

Our study had some limitations. We could not determine frequency of clinical signs because all clinical signs were recorded as present when mentioned in the records, regardless of severity and frequency. Another limitation was that US examinations were carried out by multiple radiologists, and reporting was not standardized. When parts of the pancreas were not mentioned, we did not know if they were normal and thus not mentioned or not seen. The fact that almost all visualization (left limb, right limb, body) correlated with

lipase results and final US diagnosis makes it very likely that radiologists mentioned those parts when they felt they were abnormal. We purposely relied on US reports and did not re-evaluate saved static US images or loops. It is our experience that saved US images often do not fully reflect all changes seen during the examination, but only represent excerpts. Similar experiences were reported in a multi-institutional study on pancreatitis in dogs.[5] Also, evaluation of static ultrasound images is not free from drawbacks, because radiologists can differ markedly in their assessment of archived images.[46]

We would like to emphasize that our results refer to the LIPC Roche DGGR-lipase assay.[47] There are now several DGGR-based assays on the market with different reference ranges, and therefore our results cannot necessarily be applied to other assays.

In conclusion, we believe the following factors play a role in the interaction of clinical signs and lipase results with pancreatic US: duration of clinical signs before presentation, previous pancreatitis episodes, the different temporal dynamics of lipase activity and US changes, and possibly radiologist bias. Our results are a first explanation of the discrepancy between laboratory and US evidence of pancreatitis. Standardized prospective studies are needed that also take into account duration of disease before presentation. In the absence of a diagnostic gold standard, knowing which clinical signs and which US findings correlate most closely with lipase results at a given time in the disease process will markedly improve the clinical diagnosis of pancreatitis. A standardized criterion-based US examination and structured reporting of all parts of the pancreas are needed for future studies so as to better assess relationships between laboratory and US findings.[34] Serial assessments of both lipases and US would be ideal to explore how the factor time affects results of both tests.

CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

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