Pancreatitis is a common disease in dogs, with a variable clinical presentation, progression, and outcome. Dogs with mild or chronic relapsing pancreatitis may be treated on an outpatient basis, but severely affected individuals require fluid therapy and comprehensive supportive care and may experience pancreatic necrosis, multiple-organ failure, and hemorrhagic disorders.1–3 Mortality rates for dogs with acute pancreatitis presented to teaching hospitals range from 19% to 58%.4–6 Determining an individual’s prognosis at the time of diagnosis may facilitate decisions regarding the need for prompt hospitalization or referral to a specialist facility.

Serum concentrations of both amylase and lipase have been shown to correlate poorly with short-term prognosis, although marked elevations of pancreas-specific lipase activity have been associated with increased disease severity and worse outcome.9–13 Recently, 2 scoring systems, namely the Canine Acute Pancreatitis Severity score and the simplified Canine Acute Pancreatitis Severity score, were demonstrated to reliably predict death within 30 days of admission.5 These scores incorporate the following 4 findings: ionized hypocalcemia, increased serum creatinine concentration, prolongation of clotting times and/or significant thrombocytopenia, and either a diagnosis

**OBJECTIVE**
To determine the prognostic value of serum C-reactive protein (CRP) in dogs with pancreatitis.

**ANIMALS**
503 client-owned animals with pancreatic lipase immunoreactivity (PLI) > 600 µg/L.

**METHODS**
Routine submissions to the Texas A&M Gastrointestinal Laboratory were monitored for canine samples with PLI > 600 µg/L. Clinics were emailed 2 weeks after PLI measurement and asked the following questions: (1) was the dog hospitalized, and (2) is the patient alive? If a response was received, serum CRP concentration was measured using leftover serum.

**RESULTS**
Paired PLI and CRP results were available for 503 dogs. Median PLI was 984 µg/L (range, 603 to 2,001 µg/L); median CRP was 9.9 mg/L (range, 9.9 to 395.3 mg/L; ref: < 10 mg/L). Inpatient care was provided to 136 dogs (27.0%); 49 dogs (9.7%) died or were euthanized. Median PLI values for dogs that died versus survived were similar. Median CRP was higher in hospitalized dogs (36.1 vs 9.9 mg/L; P < .0001) and those that died (37.2 vs 9.9 mg/L; P < .0001). Compared to dogs with CRP < 10 mg/L, those with CRP > 10 mg/L were 5.3 times more likely to die (CI, 2.7 to 10.2) and 5.7 times (CI, 3.7 to 8.7) more likely to be hospitalized.

**CLINICAL RELEVANCE**
In dogs with PLI > 600 µg/L, CRP > 10 mg/L was associated with increased risk of hospitalization or death. This biomarker may provide prognostic information in dogs with evidence of pancreatitis and guide decisions regarding hospitalization or referral.

Keywords: C-reactive protein, pancreatitis, biomarker, pancreas, outcome
of a systemic inflammatory response syndrome or respiratory rate ≥ 24 breaths/min.

C-reactive protein (CRP) may also provide prognostic information in patients with pancreatitis. CRP is a positive acute phase protein that is produced by the liver in response to inflammatory cytokines. The liver produces CRP within 4 to 24 hours of initiation of inflammation, with peak levels occurring 24 to 48 hours after the initial insult. Increases in serum CRP concentrations have been reported in dogs with a variety of inflammatory diseases, such as pneumonia, diskospondylitis, immune-mediated polyarthritis, and neoplasia, and are routinely noted in dogs with pancreatitis. In people with pancreatitis, CRP has been shown to correlate with disease severity and provide useful prognostic information.

Previous studies have evaluated the prognostic value of serum CRP in dogs with pancreatitis. In a study of 31 hospitalized patients, CRP values were not predictive of death, although all were above the upper limit of the reference interval at the time of admission. Also, higher serum CRP concentrations were noted in dogs with higher disease severity scores. In another study, CRP was measured in 13 hospitalized dogs and was found to correlate with a clinical severity score; only 2 dogs died, but both had CRP concentrations at the time of admission that were > 10-fold the upper limit of the reference interval. CRP was also increased > 3-fold in 12 dogs admitted to specialty centers for management of acute pancreatitis; mean CRP at admission was higher in the nonsurvivors (𝑛 = 3), but this did not reach statistical significance. In a study describing 65 dogs, CRP at presentation was not predictive of outcome at day 15, although there was a trend toward increased mortality for dogs with CRP > 10 times the upper limit of the reference interval. Serial CRP measurements were reported in a subset of dogs that were hospitalized (𝑛 = 22); median values of serum CRP on the third and fourth days were significantly higher in the nonsurvivors. CRP was determined in 71 dogs admitted to a teaching hospital with a diagnosis of acute pancreatitis; absolute values for CRP were not reported, but a higher CRP-to-albumin ratio was associated with a significant risk of mortality.

Taken as a whole, these previous studies raise uncertainty regarding the prognostic value of serum CRP concentrations in dogs hospitalized for pancreatitis and suggest that CRP at the time of diagnosis may add little useful information. However, these reports primarily describe patients hospitalized at specialty centers and likely represent dogs with more severe disease. In addition, modest case numbers may limit the reliability of the data. The aim of our study was to evaluate the prognostic value of CRP in a large cohort of dogs with biochemical evidence of pancreatitis, examined at both first-opinion clinics and referral/emergency hospitals. We hypothesized that dogs with increased serum CRP concentrations would be more likely to require hospitalization and less likely to survive than those with CRP within the reference range.

Methods

Case selection

The Texas A&M Gastrointestinal Laboratory database was prospectively searched daily or every other day between June 2022 and October 2022 for submissions of serum samples from dogs for which serum pancreatic lipase immunoreactivity (PLI) was > 600 µg/L. A brief survey was subsequently sent by email to the submitting clinic, 14 or 15 days after the sample was received at the laboratory. The survey included just 2 questions and required a 2-word response:

1. Was this patient treated as an OUTPATIENT or was it HOSPITALIZED (which would include day-time-only care as well as overnight care)?
2. Is this patient ALIVE or DEAD?

If an email response was received, laboratory personnel retrieved the frozen aliquot of surplus serum associated with that particular PLI accession. This was then submitted for measurement of CRP concentration.

PLI measurement

Pancreatic lipase immunoreactivity was determined using a commercial ELISA (Spec cPL; Texas A&M University Gastrointestinal Laboratory). A result > 400 µg/L is regarded as indicative of active pancreatic inflammation. The upper limit of the working range of the assay is 2,000 µg/L; results above this were listed as 2,001 µg/L for statistical purposes. Surplus serum was automatically stored after analysis at −20 °C.

CRP measurement

CRP was measured on thawed serum using the Gentian CRP immunoassay on a Beckmann AU480 chemistry analyzer within 1 to 2 weeks of receiving an email response from the submitting clinic. All results within the reference interval (0 to 10 mg/L) were reported by the laboratory as < 10 mg/L; these were listed as 9.9 mg/L for statistical purposes. A CRP of 10 to 30 mg/L is consistent with mild or early inflammation. Values > 30 mg/L are indicative of severe systemic inflammation.

Data collection

Patient identifier and signalment (ie, age, breed, and sexual status) were obtained from the submission document for each eligible sample. Online information regarding the submitting clinic was used to categorize the practice as either first opinion or specialty/referral/emergency. The level of care provided to each patient (hospitalization vs outpatient), its survival status (dead vs alive), PLI result (in µg/L), and CRP value (in mg/L) were also tabulated.

Statistical analysis

A commercial software program (Prism 9; GraphPad Software) was used for statistical analyses. Normality was evaluated using the D’Agostino and Pearson tests. Nonparametric data are presented as median and range. Correlation between CRP and PLI was investigated using the Spearman rank
correlation coefficient. The Mann-Whitney test was used to evaluate the relationship between both PLI and CRP with respect to level of care and survival. Odds ratios were calculated using the Fisher exact test, and the 95% CIs are provided. Values of \( P < .05 \) were considered significant.

Results

Study population

A total of 965 surveys were sent during the study period; 503 (52.1%) responses were received. The median interval between PLI measurement and receipt of the survey response was 14 days (range, 14 to 83 days); 97.2% of survey responses were returned 14 to 21 days after measurement of serum PLI. Approximately half (51.7%) of the responses came from first-opinion practices.

Surplus serum was available in all instances; paired results for PLI and CRP were therefore generated for 503 individuals. The study population included 22 intact females, 204 spayed females, 12 intact males, and 256 neutered males; sexual status was not reported for 9 animals. Seventy-two breeds were represented, with mixed breed (n = 156), Yorkshire Terrier (27), Dachshund (20), Chihuahua (19), Boxer (18), German Shepherd Dog (13), Labrador Retriever (11), Cavalier King Charles Spaniel (10), and Pomeranian (10) being the most common. Age was reported for 479 dogs and ranged from 0.5 to 19 years, with a median of 11 years.

Inpatient care was provided to 136 (27.0%) dogs; 367 (73.0%) were treated as outpatients. Forty-nine (9.7%) dogs had died or had been euthanized prior to return of the survey. The mortality rate for dogs treated as outpatients was 5.2% (19/367); 22.1% (30/136) of dogs receiving inpatient care died or were euthanized (Table 1).

| Patient age did not impact the likelihood of hospitalization (median, 11 years; range, 0.5 to 6.5 years) versus outpatient care (median, 10.75 years; range, 0.5 to 19 years) or death/euthanasia (median, 12 years; range, 1 to 15.75 years) versus survival beyond 2 weeks (median, 10.8 years; range, 0.5 to 19 years). |
| Serum PLI concentrations |
| Then median PLI for dogs included in the study population was 984 \( \mu \text{g/L} \) (range, 603 to 2,001 \( \mu \text{g/L} \)). Serum PLI concentrations for dogs that were hospitalized were significantly higher (median, 1,175 \( \mu \text{g/L} \); range, 601 to 2,001 \( \mu \text{g/L} \)) than those for dogs receiving outpatient care (median, 952 \( \mu \text{g/L} \); range, 603 to 2,001 \( \mu \text{g/L} \); \( P = .0014 \)). Serum PLI concentrations for dogs that died (median, 1,180 \( \mu \text{g/L} \); range, 603 to 2,001 \( \mu \text{g/L} \)) were higher than in those that lived (median, 983.5 \( \mu \text{g/L} \); range, 601 to 2,001 \( \mu \text{g/L} \)), but this difference did not reach statistical significance (\( P = .286 \); Figure 1). |

![Figure 1](image1)

Table 1—Treatment (outpatient vs hospitalized) and short-term outcome (alive vs died/euthanized) for 503 dogs with serum pancreatic lipase immunoreactivity > 600 \( \mu \text{g/L} \).

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Hospitalized</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>348</td>
<td>106</td>
<td>454 (90.3%)</td>
</tr>
<tr>
<td>Dead</td>
<td>19</td>
<td>30</td>
<td>49 (9.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>367 (73%)</td>
<td>136 (27%)</td>
<td>503</td>
</tr>
</tbody>
</table>

Serum CRP concentrations

The median CRP concentration was 9.9 mg/L (range, 9.9 to 395.3 mg/L); CRP was within the reference interval in 300 of 503 (59.6%) dogs. There was weak positive correlation between serum PLI and CRP concentrations (\( r = 0.136 \); CI, 0.047 to 0.224; \( P = .0022 \); Figure 2).

Serum CRP concentrations were significantly higher for hospitalized dogs (median, 36.1 mg/L; range, 9.9 to 395.3 mg/L) than for dogs that were treated as outpatients (median, 9.9 mg/L; 9.9 to 269 mg/L; \( P < .0001 \)). Only 41 of 300 (13.7%) dogs with CRP < 10 mg/L were hospitalized, whereas 32 of 41 (78%) with CRP > 100 mg/L were hospitalized. Serum CRP concentrations were significantly higher for dogs that died (median, 37.2 mg/L; range, 9.9 to 231.9 mg/L) than those that survived (median, 9.9 mg/L; range, 9.9 to 395.3 mg/L; \( P < .0001 \); Figure 3). Almost all (288/300 [96%]) of the dogs with CRP < 10 mg/L survived. Compared to dogs with a CRP < 10 mg/L, those with CRP > 10 mg/L were 5.7 times more likely to be hospitalized (CI, 3.7 to 8.7; \( P < .0001 \)) and 5.4 times more likely to die (CI, 2.7 to 10.2; \( P < .0001 \)). A total of 114 (22.7%)
dogs had CRP > 30 mg/L; almost a quarter (22.8%; n = 26) of these dogs died or were euthanized. The OR of death for dogs with CRP > 30 mg/L compared to those with CRP < 10 mg/L was 7.1 (CI, 3.5 to 14.3; P < .0001). A total of 21 (4.2%) dogs had CRP > 100 mg/L; 11 (52.4%) of these were nonsurvivors.

Discussion

We hypothesized that CRP concentrations would be predictive of more severe clinical disease and correspond with a more uncertain prognosis for dogs with PLI > 600 µg/L. Both hypotheses were confirmed: dogs with CRP above the reference interval (ie, > 10 mg/L) were both more likely to be hospitalized or die than those with CRP < 10 mg/L. We also demonstrated that dogs with CRP concentrations consistent with severe inflammation (ie, > 30 mg/L) were 7 times more likely to be nonsurvivors than those with a normal CRP. Although a CRP within the reference interval carried a positive predictive value for survival > 95%, this result does not guarantee a successful outcome, as almost a quarter (12/49 [24.5%]) of the dogs that died or were euthanized had CRP < 10 mg/L.

Our findings differ from previous studies that did not identify any differences of serum CRP concentrations between dogs that survived and those that did not.10,11,14 This likely reflects the fact that we looked at a different patient population: the majority of dogs described here were treated on an outpatient basis, whereas most previous studies have focused on hospitalized dogs. This assumption is supported by the relatively low mortality rate (< 10%) in our patient population and the fact that the CRP was within the reference interval in the majority (59.6%) of our cases. These animals were presumably unwell due to the local effects of pancreatic inflammation but did not have a more widespread inflammatory response. It is reasonable to conclude that hospitalized animals are inherently more systemically compromised and therefore expected to routinely have substantially increased CRP concentrations. Our findings do share some similarities with a previous study10 that included nonhospitalized patients (n = 65) and demonstrated a trend toward increased mortality in dogs with markedly elevated serum CRP concentrations. In that study, only 2 of 14 dogs with a normal CRP died, whereas 6 of 15 with a > 10-fold increase in CRP did not survive (P = .1147).10

We demonstrated a weak positive correlation between serum PLI and CRP concentrations in our patient population (r = 0.136). This finding is not surprising, as PLI measurements are not considered to be a reliable indicator of disease severity.4,12,15,25,26 Pancreatic lipase is released into the systemic circulation within minutes of damage to pancreatic acinar cells but has a short half-life (approx 2 hours).27 If the trigger for pancreatic inflammation is transient, PLI may therefore rapidly decrease. However, the extrapancreatic effects of acinar damage, such as activation of systemic inflammatory responses, vasculitis, peritonitis, dysregulation of hemostasis, etc, may take hours or days to fully to manifest and may persist and promulgate despite resolution of the initial acinar insult. As CRP is expected to peak 24 to 48 hours after the initiation of a systemic inflammatory response and will persist until the underlying process resolves, synthesis of this biomarker is unlikely to correlate closely with the release of lipase.
by injured pancreatic acinar cells. The half-life of CRP is also substantially longer, at about 19 hours. It is noteworthy that CRP and PLI were more strongly positively correlated in a study of 31 hospitalized patients ($r = 0.52$). Interestingly, neither analyte was found to be predictive of mortality in that patient population. Our results regarding correlation may have been impacted by the fact that PLI measurements were not diluted and instead reported as 2,001 µg/L when they were above 2,000 µg/L, whereas values in excess of 30,000 µg/L were reported in the other study.

There were several limitations to the study presented here, primarily related to the lack of clinical information about any of the dogs included. We deliberately decided against asking questions in our survey regarding patient history, physical examination findings, results of imaging studies, etc, as we felt this would discourage participation. Instead, we opted for a 2-word questionnaire design, in which the recipients could simply type 2 words and return the email. This strategy resulted in an impressive response rate, although we do not know what prompted the clinician to measure this patient’s PLI on this particular occasion.

Establishing a clinical diagnosis of pancreatitis in dogs generally relies on the documentation of appropriate clinical signs, along with specific supportive evidence from measurement of pancreas-specific lipase activity and/or results of abdominal imaging studies (transabdominal ultrasonography or CT). A definitive diagnosis of pancreatitis requires histopathological examination of affected tissues and is therefore rarely established antemortem. In the absence of any clinical information, we recognize that we did not meet the standard criteria for establishing a definitive diagnosis of pancreatitis in the dogs included in our study and are instead relying solely on the PLI value. Numerous groups have evaluated the reliability of the PLI assay used here, and there are various estimates of its sensitivity and specificity. For the purposes of this study, we were most concerned with the latter, as we used this biomarker as the sole criterion for a diagnosis of pancreatitis. Using a cutoff of 400 µg/L, specificity ranges from 74.1% to 100%, depending on the reference standard used. Recognizing that specificity is likely to improve as PLI increases, we set the threshold for inclusion in our study at PLI > 600 µg/L to minimize the risk of including dogs without pancreatitis. The authors recognize that relying exclusively on PLI measurements in the absence of any other clinical information was a significant limitation to this study. However, it is reasonable to assume that measurement of PLI was prompted by a clinical history or physical examination findings suggestive of this condition.

Another limitation of this study was the lack of information regarding the cause of death (natural or euthanasia) and conditions beyond the diagnosis of pancreatitis that may have influenced mortality. Concurrent diseases, patient age, and financial limitations may all have played a role in this outcome and could have potentially impacted the reliability of our data. In addition, the nature of the survey used in this study precluded us from defining a specific time period (eg, 14 days from sample collection) within which to assess patient mortality. The submitting clinics were consistently contacted 14 to 15 days after receipt of the sample at the laboratory, but we did not establish the date of sample collection and did not specify a deadline for inclusion of survey responses. Most responses were received within a few days, so almost all of the data presented here represent outcomes over a 2- to 3-week period following sample collection, but we were unable to be more precise. However, we feel that the large number of samples included in this study mitigates the effect of a loosely defined postdiagnosis window.

To our knowledge, this study was the largest evaluating CRP in dogs with biochemical evidence of pancreatitis and demonstrates that measurement of CRP may provide useful prognostic information for this condition, as a serum CRP concentration within the reference interval (ie, < 10 mg/L) had a positive predictive value for survival beyond 2 weeks of 96%. Our results also indicate that pancreatitis has variable clinical impact in dogs and studies focusing on patients presented to referral hospitals may not adequately reflect the spectrum of clinical disease seen in first-opinion practice. The findings presented here also suggest that CRP > 10 mg/L indicates more extensive systemic involvement, an increased need for hospital care, and a correspondingly more guarded prognosis. As CRP can now be measured using in-clinic devices, patient-side measurement of CRP may help guide decisions regarding hospitalization or referral to a 24-hour care facility. However, the authors would advise caution when applying the findings from this study to other CRP measurement systems, and further work is clearly needed to compare results across different devices and methodologies. Given the limitations of this study and the overlap of mortality rates between groups, additional large-scale, prospective studies evaluating CRP in dogs with pancreatitis are warranted. Ideally, these studies would include patient populations that adequately represent the range of clinical compromise seen in dogs with this condition.

Acknowledgments

The authors thank the practitioners who supported this study by responding to the questionnaire.

Disclosures

The Texas A&M Gastrointestinal Laboratory offers measurement of both Spec cPL and C-reactive protein on a fee-for-service basis. Dr. Jörg Steiner (Director) and Robynne Gomez (Assistant Director) are both affiliated with the Gastrointestinal Laboratory at Texas A&M University. No AI-assisted technologies were used in the generation of this manuscript.

Funding

The authors have nothing to disclose.
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