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Serum C-reactive protein in dogs with paraplegia secondary to acute intervertebral disc extrusion

Max Foreman | Enzo Vettorato | Abby Caine | Paola Monti | Giunio Bruto Cherubini | Salih Eminaga

Dick White Referrals, Cambs, United Kingdom

Correspondence
Max H. Foreman, Dick White Referrals, Station Farm, London Road, Six Mile Bottom, Cambs CB8 0UH, United Kingdom.
Email: max.foreman@dwr.co.uk

Abstract

Background: Apart from the absence of nociception, there is no readily available prognostic test for dogs presenting with paraplegia secondary to acute intervertebral disc extrusion (IVDE).

Objective: To assess if serum C-reactive protein (CRP) can predict the postoperative outcome in paraplegic dogs undergoing surgery for IVDE and to assess the association between serum CRP and presence/absence of nociception on admission, and serum CRP and presence/absence of intramedullary changes seen on magnetic resonance imaging (MRI).

Animals: One hundred dogs that underwent surgery at our hospital between 2018 and 2020 because of acute paraplegia secondary to IVDE and in which serum CRP was measured.

Methods: Retrospective observational cohort study. Dogs were classified as 4 or 5 according to the modified Frankel score (MFS) depending on presence/absence of nociception, respectively. MRI images were reviewed and the T2-weighted hyperintensity: L2 vertebral body length was measured. Postoperative outcome was defined as positive if nociception, ambulation or both returned after decompressive surgery.

Results: The median (95% CI) serum CRP was 4 (4-5) and 6 (4-7) mg/L in MSF4 and MSF5, respectively ($P = .03$). A weak linear relationship ($R^2 = 0.049$, $P = .03$) was found between CRP and the T2-weighted hyperintensity: L2 vertebral length. Outcome data was available for 85 dogs: CRP was 4 (4-5) and 5 (4-10) mg/L in positive and negative outcome dogs, respectively ($P = .32$).

Conclusion and Clinical Importance: Serum CRP did not predict outcome after surgery in dogs with paraplegia secondary to IVDE.

Abbreviations: CI, confidence intervals; CK, creatine kinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; IL-6, interleukin-6; IVDE, intervertebral disc disease; MFS, modified Frankel score; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; STIR, short-tau inversion recovery; T2W, T2-weighted; VIF, variance inflation factor.

KEYWORDS
canine, intervertebral disc herniation, neurology, neurosurgery

1 | INTRODUCTION

Spinal cord injury secondary to acute intervertebral disc extrusion (IVDE) is a common clinical problem encountered in dogs, with clinical signs ranging from spinal hyperesthesia to paraplegia with absent nociception. In dogs with intact nociception, the prognosis for functional recovery is good,[1] however absent nociception is associated with guarded prognosis, with functional recovery in around 58% of cases.[2]

There are currently no readily available diagnostic tests to differentiate those dogs that will recover from those that will not after decompressive surgery.[3-10] The presence of an intramedullary T2-weighted (T2W) hyperintensity on magnetic resonance imaging (MRI) has been associated with a poorer outcome in dogs with thoracolumbar disc herniation,[11,12] with 1 study proposing a ratio of the length of the T2W-hyperintensity and the length of the vertebral body of L2 (T2W hyperintensity:L2 vertebral length) >4.57 being associated with increased risk of myelomalacia.[12]

C-reactive protein (CRP) is a major acute phase protein that is upregulated in response to infectious, immune-mediated, neoplastic or traumatic events.[13] In both adult human beings and children with traumatic brain injuries, CRP has been shown to be elevated on admission to hospital, suspected secondary to interleukin-6 (IL-6) release by activated glial cells.[14-16]

In dogs, serum CRP concentration increases after gastric mucosal injury,[17] inflammatory bowel disease,[18] intestinal obstruction,[19] acute pancreatitis,[20] polyarthritis,[21,22] pyometra,[23] pneumonia,[24] pemphigus,[25] systemic inflammatory response syndrome[26]and cancer[27] and infection with *Ehrlichia canis*[28] and *Leishmania infantum*.[29] Furthermore, CRP measurement has been used in the diagnosis and therapeutic monitoring of steroid responsive meningitis arteritis.[30-32]

The CRP response in dogs with acute spinal cord injuries is not fully understood. In the presence of intervertebral disc disease or lumbosacral stenosis, CRP was increased in neither serum[32,33] nor cerebrospinal fluid (CSF),[32] however information regarding the type of disc herniation, chronicity and severity of the injuries was not reported. Conversely, compared to control dogs, mean serum CRP was statistically elevated in 15 dogs with intervertebral disc herniation.[34] When stratified on the basis of severity of injury, another study reported significantly higher concentrations of CRP in the CSF of dogs with severe spinal cord injury when compared to those with mild-moderate injury.[35]

It is the authors' clinical impression that dogs with IVDE causing paraplegia with absent nociception have a worse postoperative outcome if serum CRP is elevated at presentation. If this is proven, CRP on admission could be an important prognostic indicator. Therefore, we designed this retrospective observational study on a cohort of dogs presenting with acute paraplegia secondary to IVDE to assess if serum CRP can predict postoperative outcome (main outcome), to assess the association between serum CRP and presence or absence of nociception on admission (secondary outcome), and serum CRP and presence of intramedullary changes seen in MRI (tertiary outcome).

2 | MATERIALS AND METHODS

2.1 | Case selection criteria

The medical records of dogs presented to the Neurology and Neurosurgery department at our institution with acute paraplegia (modified Frankel scores—MFS—4 and 5[1,36]) from February 2018 to March 2020 were retrieved from an electronic database and reviewed. Cases were excluded from the study if: the cause of the paraplegia was not an IVDE; serum CRP was not measured on admission; the dog had undergone another surgery within the previous week; there was anamnestic, clinical or laboratory evidence of a concurrent inflammatory disorder or any other disease that might have contributed to the increased CRP; clinical records were incomplete.

2.2 | Ethics statement

Ethical approval was not pursued because of the retrospective observational nature of the study. A written informed owner consent to use medical records, MRI studies and results of blood analysis for research purposes was obtained at the time of the animal's admission to the hospital.

2.3 | Retrospective review of medical records

The details obtained from the medical records, reported in Table 1, were recorded in a Microsoft Excel file.

2.4 | Diagnosis

Every dog referred to our institution was examined by a board-certified neurologist or a neurology resident directly supervised by the neurologist. An MFS was assigned to each case: MFS 4 = paraplegia with present nociception; MFS 5 = paraplegia with absent nociception.[1,36]

Preanesthetic hematological (Siemens Advia 2120) and biochemical (Olympus AU480) analysis, including CRP, were performed in each animal. Blood samples were collected via cephalic cannula or jugular venepuncture on presentation and analyzed either immediately or within 12 hours of blood collection. Serum CRP concentration was measured using an immunoturbidometric assay as described by Hillström et al.[37] Internal quality control procedures were performed

TABLE 1 Demographic and clinical information extracted from medical records of 100 dogs with IVDE

	MFS 4 (n = 55)	MFS 5 (n = 45)	*P* value	OR (95% CI)
Most represented breeds	Crossbreed = 17 French Bulldog = 10 Dachshund = 10 Cocker Spaniel = 4 Other: 14	Crossbreed = 13 French Bulldog = 9 Dachshund = 7 Cocker Spaniel = 4 Other: 12	.57	
Age (months)	72 (±2)	60 (±2)	.24	
Sex	Me: 8 Mn: 26 Fe: 6 Fn: 15	Me: 5 Mn: 19 Fe: 7 Fn: 14	.42	
Weight (kg)	12 (±7.1)	10.5 (±4.9)	.24	
Duration of clinical signs (h)	12 (12-48)	24 (12-24)	.81	
NSAID/steroid pretreatment (n)	NSAID: 24 Steroid: 3 None: 28	NSAID: 24 Steroid: 1 None: 20	.51	
CRP (mg/L)	4 (4-5)	6 (4-7)	.03	
CRP > 10 mg/L (n)	7	12	.12	2.49 (0.86-6.41)
CK (IU/L)	228 (177-346)	413 (295-704)	.03	
CK > 190 IU/L (n)	26	26	.2	2.14 (0.73-5.59)
Location of IVDE (n)	T3-L3: 51 L4-S3: 4	T3-L3: 37 L4-S3: 8	.13	2.75 (0.85-8.64)[a]
T2W:L2 > 4.57	Yes: 38 No: 17	Yes: 36 No: 9	.26	1.79 (0.69-4.24)
Outcome	Positive: 49 Negative: 2 Excluded: 4	Positive: 21 Negative: 13 Excluded: 11	<.0001	15.17 (3.20-69.95)
Urinalysis WBC/hpf > 2	Yes: 3 No: 35 Not performed: 13	Yes: 2 No: 23 Not performed: 9	>.99	

Abbreviations: CK, creatine kinase; CRP, C-reactive protein; Fe, female entire; Fn, female neutered; h, hours; IVDE, intervertebral disc extrusion; Me, male entire; MFS, modified Frankel score: 4 = presence of nociception, 5 = absence of nociception; Mn, male neutered; n, number of dogs; NSAID, nonsteroidal anti-inflammatory drug; T2W:L2, T2-weighted hyperintensity: L2 vertebral body length; WBC/hpf, white blood cells per high power field.
[a]Reciprocal odds ratio.

daily prior to analysis. A CRP < 10 mg/L was considered unremarkable. Given previous reports of dogs with paraspinal muscle changes concomitant to IVDE,[38,39] serum creatine kinase (CK) values were also extracted for each dog. A CK < 190 IU/L was considered unremarkable.

Magnetic resonance imaging was performed under general anesthesia within 15 hours of presentation (Hitachi Aperto Lucente 0.4 Tesla, Berkshire, UK). Sequences obtained included a combination of any or all of Fast Spin Echo T2W sagittal and transverse and Short Tau Inversion Recovery (STIR) sagittal and transverse images. For diagnosis, images were interpreted separately by both a board-certified radiologist and a board-certified neurologist, both aware of the animal's clinical information. However, for the purposes of this study, MRI images were retrospectively reviewed for the presence and length of T2W intramedullary hyperintensity by a board-certified radiologist (AC), blinded to clinical information and outcome. The ratio of T2W hyperintensity: L2 vertebral length was resultantly calculated.[11,12]

Urine samples were collected after indwelling catheter placement after surgery and were submitted for routine urinalysis and culture. A white blood cell count per high power field (WBC/hpf) > 2 was considered as a sign of urinary tract inflammation.

2.5 | Postoperative outcome

The postoperative outcome at 4 weeks after discharge from the hospital was classified as positive if neurological function was improved after surgery (regained conscious movement of the pelvic limbs, or return of nociception), or negative if the patient was euthanized because of a lack of improvement or if lack of nociception was persistent at 4 weeks after surgery.

2.6 | Statistical analysis

Univariate analysis was performed with Prism (version for MacOS, GraphPad Prism 8, CA 92037, USA). In particular, ordinal data were analyzed using Fisher's exact test; continuous data

were compared with Student t test or Mann-Whitney *U* test depending on their distribution (D'Agostino & Pearson test). A linear regression between CPR at presentation and T2W hyperintensity: L2 vertebral length was assessed. Mean ± SD or median (95% confidence intervals—CI) were used to report normal distributed and skewed data, respectively. Significant results were defined as $P < .05$.

Multivariate analysis was performed using SigmaStat 3.5 (SyStat Software Inc, CA 95131, USA). Forward Stepwise Regression was used to investigate if any of the variables considered in the univariate analysis (CRP, creatine kinase—CK, duration of clinical signs, presence/absence of nociception, and T2W hyperintensity: L2 vertebral length) could predict the dependent variable for outcome (no-improvement after surgery). A variance inflation factor (VIF) > 1.5 was considered as index of multicollinearity.

3 | RESULTS

3.1 | Blood analysis

Out of 232 retrieved cases, 132 were excluded and 100 were included in the study: 55 dogs were classified as MFS 4 and 45 dogs were classified as MFS 5 (Figure 1). No significant differences between the breed ($P = .57$), age ($P = .24$), sex ($P = .42$), body weight ($P = .24$), location of the disc extrusion classified as T3-L3 versus L4-S3 ($P = .13$), pretreatment with nonsteroidal anti-inflammatory drugs (NSAIDs)/corticosteroids ($P = .51$) and duration of clinical signs ($P = .81$) were found between groups (Table 1).

Serum CK > 190 IU/L was found in 54 of the 72 dogs in which it was measured [median (95% CI) = 295 (177-629) IU/L], and it was statistically higher ($P = .03$) in dogs with absent nociception (MFS 5).

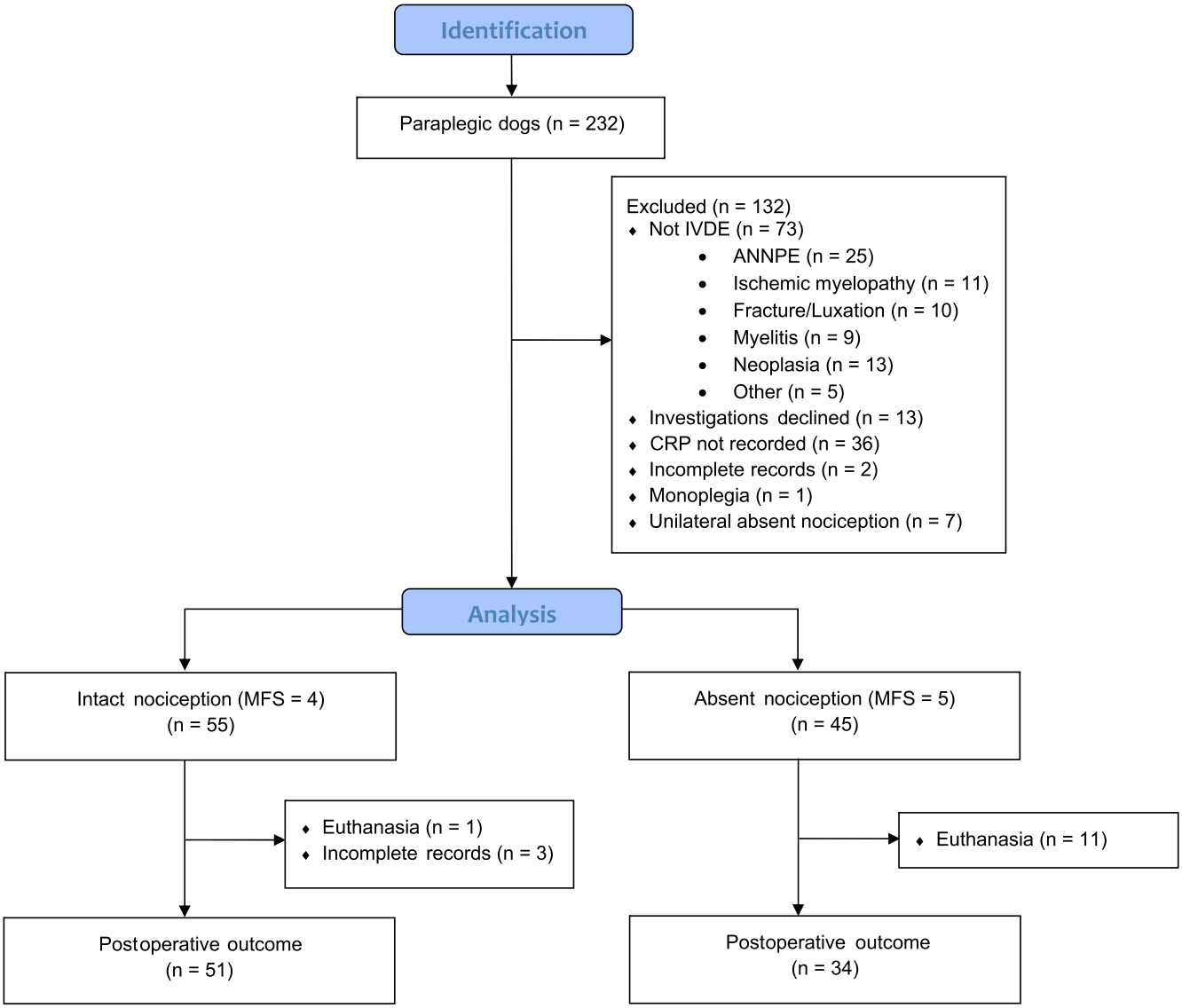

FIGURE 1 Flow diagram illustrating the inclusion and distribution of dogs in this study. ANNPE, acute noncompressive nucleus pulposus extrusion; CRP, C-reactive protein; IVDE, intervertebral disc extrusion; MFS, modified Frankel score; n, number of dogs

However, the number of dogs with CK > 190 IU/L was similar between groups (Table 1).

Overall, CRP was statistically higher in the MFS 5 group, with median (95% CI) CRP 4 (4-5) and 6 (4-7) mg/L in group MFS 4 and 5, respectively ($P = .03$). A serum CRP > 10 mg/L [25 (13-32) mg/L] was found in 19 out of 100 dogs (Table 1). Considering only the dogs with CRP > 10 mg/L, median (95% CI) CRP was 13 (12-28) and 28 (20-71) mg/L in group MFS 4 and 5, respectively ($P = .02$). On admission, the number of dogs on treatment with NSAID or a corticosteroid was similar between groups (Table 1), and no difference in CRP ($P = .16$) was found between dogs on treatment with an NSAID [5 (4-7)] and not [4 (4-7)].

3.2 | MRI findings

The mean ± SD of T2W hyperintensity: L2 vertebral length in the absent nociception (MFS 5) group (6.85 ± 2.77 cm) was not different ($P = .25$) from the intact nociception (MFS 4) group (6.23 ± 2.48 cm). Dogs with T2W hyperintensity: L2 vertebral length > 4.57 had a statistically higher ($P = .02$) serum CRP compared to those with T2W hyperintensity: L2 vertebral length < 4.57 : 5 (4-6) and 4 (3-5) mg/L respectively. Furthermore, while out of the 74 dogs with T2W hyperintensity: L2 vertebral length > 4.57, 18 dogs had a serum CRP > 10 mg/L, only 1 out of 26 dogs with T2W hyperintensity: L2 vertebral length < 4.57 had serum CRP > 10 [$P = .06$; reciprocal OR 6.07 (1.01-66.64)]. Despite a low R^2 value, a linear relationship between CRP at presentation and T2W hyperintensity: L2 vertebral length was found ($P = .03$; $R^2 = .049$), and the relationship can be described by CRP = 1.312* T2W hyperintensity: L2 vertebral length + 1.815.

3.3 | Outcome

Outcome data was available for 85 dogs. Of the 34 dogs that presented with absent nociception (MFS 5), 21 dogs had a positive outcome (62%) and 13 did not (7 dogs were euthanized between 2 and 15 days after surgery due to a lack of improvement or signs consistent with ascending myelomalacia, and 6 were persistently nociception negative at 4 weeks postsurgery). Of the 51 dogs that presented with intact nociception (MFS 4), 49 improved (96%) and 2 did not (1 dog was euthanized due to postoperative deterioration and 1 was persistently nociception negative at 4 weeks postsurgery). Therefore, dogs presenting with intact nociception (MFS 4) had around 15 times more chance to have a positive outcome after surgery (Table 1). There was no difference ($P = .32$) in serum CRP value between dogs that had a positive outcome [4 (4-5) mg/L] compared to those that did not [5 (4-10) mg/L]. Furthermore, the number of dogs with CRP > 10 mg/L was not different ($P > .99$) between dogs with positive (12 out of 70) and negative outcome (3 out of 15).

Postoperatively, an indwelling urinary catheter was placed in 63 out of 85 dogs (74.1%) and the prevalence of (WBC/hpf) > 2 was similar between groups (Table 1). Of the 5 dogs with WBC/hpf > 2, urinary culture was only positive in 1 case.

Forward stepwise regression was performed to investigate if any of the studied variables (CRP, CK, duration of clinical signs, presence or absence of nociception at presentation, and spinal cord hyperintensity: L2 vertebral length > 4.57) could predict a lack of improvement after surgery. A variance inflation factor (VIF) > 1.5 was considered as index of multicollinearity, and for this reason CK was excluded. The only variable that could predict a lack of improvement after surgery was absence of nociception on presentation ($R = 0.441$; $R^2 = 0.194$; $P < .001$).

4 | DISCUSSION

This study specifically evaluates the serum concentrations of CRP in dogs with severe spinal cord injury secondary to acute IVDE and includes the largest number of cases with serum CRP recorded for this condition. According to the results obtained, our hypothesis has been rejected: dogs with IVDE causing paraplegia with absent nociception do not have a worse postoperative outcome if serum CRP is elevated at presentation. Therefore, serum CRP cannot predict outcome in this cohort of dogs. Despite the serum CRP levels being higher in dogs presenting with absent nociception (MFS = 5) compared to those dogs with intact nociception (MFS = 4), serum CRP levels generally fall within the laboratory reference range (CRP < 10 mg/L), which is in agreement with previous assertions.[32,33] However, of those dogs with serum CRP > 10 mg/L, CRP was statistically higher in dogs with absent nociception compared to those with intact nociception.

Loss of nociception represents the most severe category of spinal injury, with injury to the spinal cord originating from a combination of primary injuries (contusion, compression, laceration, shearing and traction) as well as secondary injuries (vascular changes, free radical formation, ionic imbalances, excitotoxicity, apoptosis and inflammatory microglial responses).[40] Given that CRP has important roles in the complement pathway, apoptosis, nitric oxide release, phagocytosis and cytokine production,[41] higher CRP levels would be expected in injuries of greater severity, where a greater degree of these inflammatory processes are likely to be occurring.

Cerebrospinal fluid CRP concentration was found to be significantly positively correlated with CSF total protein concentration in dogs with spinal cord injury.[35] C-reactive protein is synthesized primarily in hepatocytes,[41] suggesting that CRP within the CSF is a marker of blood-spinal cord barrier disruption. This damage has been directly observed via spectrophotometry in rats after experimental spinal cord injury.[42] As well as intradural inflammation, significant epidural inflammation has been documented in dogs with IVDE,[43] with the degree of epidural inflammation inversely correlated with the ability to regain ambulation in 1 study.[44] It therefore follows that dogs with more severe spinal cord injury might have increased serum levels of CRP related to both intradural and epidural inflammation.

Production of CRP is predominantly under transcriptional control by IL-6, released at sites of trauma or inflammation. Both adipocytes[45]

and glial cells[16] have been implicated in IL-6 production, making sites of IVDE candidates for CRP induction. Cytokine transport mechanisms are known to exist across the blood-brain barrier; however, the IL-6 system in humans is saturable, and the mechanism of passage of efflux from the central nervous system to blood is unclear.[46] It is likely that individual variability in the degree of blood-spinal cord barrier disruption contributes to the variability of serum CRP seen in this study. Otherwise, saturability in the efflux transport system of IL-6 might prevent systemic release of CRP in response to CNS injury.

This relationship between serum CRP and spinal cord changes is supported in the data presented here, in that we also found a linear but weak relationship between serum CRP and intramedullary T2W hyperintensity: L2 vertebral length seen on MRI images. Several studies have investigated this MRI finding previously, with intramedullary T2W hyperintensity found to be related to neurological grade,[47,48] outcome[11] and risk of development of ascending-descending myelomalacia.[12] This report compares serum CRP concentrations and MRI findings. Intramedullary T2W hyperintensity can be due to oedema, inflammation, hemorrhage, gliosis, necrosis and myelomalacia, and therefore larger affected areas might give larger resultant increases in CRP. Although 1 study has associated CSF CRP concentrations with neurological grade,[35] further work is needed to assess whether MRI changes are correlated with CSF CRP levels.

A further contribution to the differing CRP levels between groups could also stem from differing degrees of muscular damage. The results presented here show that dogs with absent nociception have higher serum CK levels compared to those dogs with intact nociception. The specificity of serum CK measurement for the diagnosis of muscle disease is around 0.82, with the most likely cause of an increased CK in paraplegic dogs being prolonged decubitus.[49] Recent studies, however, have documented paravertebral muscle signal intensity changes on MRI in dogs with acute IVDE, with changes being more common and more extensive in dogs with more severe neurological grades.[38,39] The pathophysiological process behind these reported MRI signal changes remain unclear. It was beyond the scope of this study to assess for paravertebral muscle changes in the cases reported here, however it is possible that these paravertebral muscle changes could contribute to the increased CK seen in our absent nociception group.

Other sources of increased CRP in dogs with IVDE are also possible. Gastric mucosal injury occurs in dogs with acute IVDE,[50] although the majority of the dogs in that study had concurrently been treated with corticosteroids or NSAIDs, leading to debate as to the cause of the mucosal injury. Although 48% of our cases had received NSAIDs at the point of blood sampling, there was no difference in CRP between dogs pretreated with NSAIDs or without treatment. This suggests either that NSAIDs are not an important source of gastric mucosal injury, or the induced mucosal injury does not cause a relevant increase in serum CRP. Numbers of dogs pretreated with corticosteroids in this study were too low for statistical analysis. Dogs with intervertebral disc herniation also have increased canine pancreatic lipase,[51] however the relationship with true pancreatitis in these cases was not fully elucidated.

Urinary tract inflammation or infection are also an important potential source of inflammation in dogs with IVDE. Postoperative urinalysis performed in the majority of our cases identified increased urine white blood cell count in only 5 out of 63 dogs in which an indwelling urinary catheter was placed. In 3 of these dogs, CRP was >10 mg/L. While some of these cells could have been the result of the bladder catheterization, in only 1 case urinary culture was positive for bacteria. This case was not excluded from the study as the urine sample was collected postoperatively and not prior to blood sampling, so it is not possible to say whether this was present at the time of CRP analysis. Also, being a catheter-obtained sample, it is possible that this was a false-positive culture result. Therefore, while we cannot categorically rule out the influence of urinary tract inflammation or infection on CRP, we believe that the similar prevalence of WBC/hpf > 2 found between the 2 groups should not have influenced the results obtained in our study.

Despite statistically significant differences being present in serum CRP between the groups, the clinical relevance of these findings is debatable, especially considering the median CRP value was <10 mg/L in both groups and the 95% CI were overlapping. However, while the number of dogs with CRP > 10 mg/L was not statistically different between dogs with and without nociception, the odds ratio and 95% CI might suggest a potential clinical difference. Furthermore, considering those dogs with CRP > 10 mg/L, nociception negative dogs had significantly higher CRP values than dogs with present nociception, with the lower 95% CI being 20 mg/L. Even if significant intra- and interindividual biological variation in the serum CRP has been reported in dogs, it has been suggested that a 2-fold increase in CRP might signify a clinically important change.[52]

According to the multiple linear regression, serum CRP on presentation cannot predict outcome after surgery in the population of dogs studied. This finding is in agreement with a previous report of CSF CRP concentrations, which similarly found increased CRP in the CSF of dogs with severe spinal cord injury secondary to IVDE, but no association with the 42-day postsurgical recovery.[35] Although epidural inflammation is known to occur secondary to acute IVDE in dogs, and that the degree of this inflammation is inversely correlated with the ability to regain ambulation,[44] it is not clear whether the source of an increased serum CRP is the intradural inflammation, the epidural inflammation or a combination of both. Further work to assess all 3 of these factors concurrently would help to characterize this relationship.

One factor that has not been fully examined in the present study is the timing of measurement of CRP. Being an acute phase protein, CRP shows fast-onset elevated expression in response to inflammation. However, when the stimulus ends, CRP values decrease exponentially over 18-20 hours.[41] An acute IVDE is a source of inflammation in the spinal cord and epidural tissues, but with the exception of ascending-descending myelomalacia, there is no ongoing inflammatory stimulus. Given the rapid half-life, it is possible that those dogs with delayed presentation to our hospital could have already returned to normal levels prior to blood sampling.

Other limitations of this study include its retrospective nature, as well as the follow-up of patients being limited to the short-term. Negative outcome was categorized by euthanasia after surgery, or otherwise a lack of return of nociception at the 4-week postoperative recheck appointment. This time-point was chosen on the basis of a previous finding that 97% of dogs with severe spinal cord injury secondary to IVDE that eventually regain ambulation will have recovered nociception by the fourth week after surgery.[2] It is possible that several of the dogs with absent nociception might still have regained nociception, or otherwise could have regained ambulation without regaining nociception. Furthermore, it was not possible to elucidate the reason for euthanasia in those cases—whether it was due to neurological deterioration, postoperative complications or lack of neurological improvement. Finally, comorbidities such as gastric mucosal injury or pancreatitis were not fully ruled out in our cases and could contribute to an increased serum CRP.

5 | CONCLUSION

The findings of this study suggest that serum CRP in dogs with acute IVDE is commonly within the reference range, even if paraplegic with absent nociception. Minor differences can be seen in dogs on the basis of neurological grade; however, these are not clinically significant. While CRP level can be linearly related with T2W hyperintensity: L2 vertebral length on MRI, it cannot be used to predict outcome after surgery.

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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.

ORCID

Max Foreman https://orcid.org/0000-0002-2381-1389

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