Original Study

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Use of C-reactive protein to predict outcome in dogs with systemic inflammatory response syndrome or sepsis

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Abstract

Background – There is a high mortality rate in patients with systemic inflammatory response syndrome (SIRS) or sepsis. Therefore, an early diagnosis and prognostic assessment is important for optimal therapeutic intervention. The objective of the study was to evaluate if baseline values and changes in serum C-reactive protein (CRP) might predict survival in dogs with SIRS and sepsis.
Design – Prospective study; July 2004 to July 2005.
Setting – Small Animal Clinic, Berlin, Clinic of Small Animal Medicine, Munich.
Animals – Sixty-one dogs.
Measurements and Main Results – For the CRP analysis blood was drawn on day 0, 1, and 2; CRP was measured using a commercial ELISA test kit. Thirteen dogs suffered from nonseptic SIRS and 48 dogs from sepsis. The 14-day survival rate was 61% (69% nonseptic SIRS, 58% sepsis). Serum CRP was higher in sick dogs compared with controls ($P < 0.001$). Over the 3-day period surviving dogs ($n = 31$) displayed a significantly greater decrease in CRP than nonsurvivors ($n = 10$) ($P = 0.001$). No correlation was found between the initial CRP concentrations and the survival rate. The changes in CRP corresponded to the survival rate ($P = 0.01$).
Conclusion – There was no significant relationship between the survival rate in dogs with nonseptic SIRS or sepsis and the initial serum CRP concentrations. There was a correlation between decreasing CRP concentrations and recovery from disease. However, the changes in CRP concentrations over a 3-day period correctly predicted survival in 94% of dogs and death in 30% of the dogs (false positive rate 22%).

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Introduction

Both sepsis and systemic inflammatory response syndrome (SIRS) are diseases that occur with increasing incidence in human medicine (USA: rates of 1.5–8% per year).[1,2] They have a high mortality rate (third most likely cause of death in Germany, tenth most likely in the USA).[3,4] Less is published on the incidence of SIRS or sepsis in veterinary medicine. In 1 study the number of septic dogs at the University of Pennsylvania Veterinary Teaching Hospital increased from 1 per 1000 hospital cases in 1988 to 3.5 in 1998; mortality rates of 33–50% have been described for dogs with sepsis.[5–8] Information about the mortality rates of dogs with SIRS is rarely available. Early recognition of sepsis and SIRS in both human and veterinary medicine is important in order to initiate effective treatment and to assess the outcome of these patients.

SIRS can be caused by various infectious or noninfectious agents. The term sepsis is used if a patient is suffering from SIRS due to a histologic, microbiologic, or gross confirmation (purulent exudates) of infection.[9,10] Standard definitions for SIRS and sepsis in hu-

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mans were established in 1992 at the Consensus Conference of ACCP/SCCM.[9] Hauptman et al[10] and de Laforcade et al[5] modified these criteria for SIRS and sepsis with respect to dogs. Severe sepsis is present if the sepsis is associated with organ failure, decreased perfusion, or hypotension.[9] Septic shock is defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction.[9]

In human and veterinary medicine C-reactive protein (CRP) is an inflammatory marker. CRP is synthesized mainly by the liver as part of the acute-phase response after stimulation of hepatocytes by proinflammatory cytokines (interleukin-6, interleukin-1, and tumor necrosis factor-α).[11] Acute-phase proteins indicate the presence of infectious or inflammatory processes, but they do not indicate underlying causes.[12] In cases of acute and severe inflammation in humans a thousandfold increase of CRP has been described.[13] Human CRP has a short half-life of approximately 7 hours; it is used as a sepsis marker, and it was applied as a useful marker to determine the duration of antibiotic treatment in neonatal septicemia.[14–18] In dogs, CRP is increased in various disorders; the increase is correlated to the degree and course of the illness.[19–21] For example, CRP levels have been studied in dogs with pancreatitis, pyometra, pneumonia, ehrlichiosis, leishmaniasis, or postsurgical trauma.[11,19,20,22–24] In the majority of these studies the dogs were not classified according to the standard definitions for SIRS or sepsis. Thus, only sporadic information is available on CRP concentrations in dogs suffering from sepsis versus noninfectious SIRS.

The objective of this study was to measure serum concentrations of CRP initially and over a 3-day period in dogs suffering from nonseptic SIRS and sepsis. A possible correlation between the survival rate and the CRP concentration was evaluated.

Material and Methods

Patients

Dogs suffering from nonseptic SIRS or sepsis that were presented to the Small Animal Clinic, Berlin or at the Clinic of Small Animal Medicine, Munich from July, 2004 to July, 2005 were eligible for inclusion to the study. Inclusion criteria were SIRS or sepsis criteria present at day 0 in dogs weighing at least 2 kg, using criteria modified for dogs according to de Laforcade et al[5] and Hauptman et al[10] (Table 1). The dogs were divided into 2 groups: dogs with nonseptic SIRS (group 1) and dogs with sepsis (group 2). When dogs were euthanized rather than died of natural causes, only those judged to be moribund with end-stage disease at the time of euthanasia were included in the study. Patients that were euthanized because of financial concerns and patients that could not be allocated with 100% accuracy to either 1 of the groups were excluded. Dogs were only enrolled in the study if the owners consented to hospitalization and treatment and for their dog to be enrolled, and if the patients' records were completed successfully. Dogs were examined clinically at least 4 times a day over a time period of 3 days (days 0, 1, and 2). Day 0 corresponded to the day of the first examination, which was either the day of hospital admission or the day the dogs developed nonseptic SIRS or sepsis in the hospital. Classification to the nonseptic SIRS or sepsis group was based on the presence of classifying criteria on day 0. The dogs had to have documented classifying criteria at least 4 times during the examinations on day 0 and have a predisposing disease.

Table 1: Inclusion criteria for SIRS or sepsis, modified after de Laforcade et al,[5] and Hauptman et al[10]

SIRS = ≥ 2 of the following criteria	
Hypo- or hyperthermia (°C)	<37.8 or >39.4
Tachycardia (heart rate [/min])	>140
Tachypnea (respiratory rate [/min])	>20
Leukopenia or leukocytosis (WBC [× 10^9/L])	<6.0 or >16.0
Immature (band) neutrophils	>3%

Sepsis = SIRS + infection (histological, microbiological, and/or gross confirmation [purulent exudate] of infection).
SIRS, systemic inflammatory response syndrome.

Dogs were monitored for 14 days; those alive at 14 days were considered to be survivors. The following blood samples were taken on days 0, 1, and 2: EDTA-anticoagulated blood samples for hematologic analyses,[a] lithium-heparin plasma samples for clinical chemistry analytes,[b,c] and serum samples for CRP measurement. Serum for CRP analysis was stored at −70°C until analyzed. On day 0, at least 1 bacteriologic culture[d] of the blood was performed. To avoid contamination, strict aseptic sampling was performed including thorough shaving and disinfection of the sampling site and strict use of sterile gloves. The culture bottles were incubated at 37°C. Blood cultures were routinely examined aerobically and anaerobically. In dogs with a macroscopically identifiable source of infection, a swab[e] for culture or cytologic analysis was taken. In all cases aerobic cultures were performed; depending on the septic focus an anaerobic culture was performed in addition. In cases of suspected urinary tract infection, urine obtained with a catheter or by cystocentesis was submitted for bacteriologic culture. Dogs were also included in the septic group without a positive culture, as long as a macroscopic septic focus and a positive cytology (numerous neutrophilic granulocytes with phagocytized bacteria) were present.

Controls

Aliquots of the blood from 15 control dogs were used for serum CRP measurements. These dogs had been presented to the Small Animal Clinic, Berlin for blood donations or elective procedures (eg, castrations). For these dogs the physical examination as well as results of CBCs and clinical chemistry were within reference intervals.

Determination of CRP

CRP from canine serum was determined according to the manufacturer's instructions using a commercial ELISA test kit,[f] a solid-phase sandwich immunoassay that has been validated for use in dogs.[25] Absolute concentrations of CRP were established on days 0, 1, and 2. Differences between days 2 and 0 were calculated to evaluate the changes of serum CRP.

Statistics

The data were evaluated using a computer software program.[g] To describe the distribution of serum CRP concentrations, maximum, minimum, and median were used. Box plots were used for graphical illustration. To describe the changes of the CRP values the difference between day 2 and day 0 was calculated. The Mann-Whitney *U*-test was used to evaluate differences in the mortality rate between dogs with nonseptic SIRS and sepsis. The same test was used to evaluate differences in the CRP concentrations between sick and healthy dogs, survivors and nonsurvivors, and dogs with nonseptic SIRS and sepsis. Binary logistic regression was used to analyze dependency of mortality from CRP concentration on day 0, as well as the change of this parameter from day 0 to day 2. Statistical significance was set at $P < 0.05$.

Results

Patients

Sixty-one dogs (Berlin $n = 38$, Munich $n = 23$) of 30 different breeds were enrolled. Twelve dogs were mixed-breed. Thirty-five of 61 (57%) dogs were male, 8 of 35 were castrated, and 26 of 61 (43%) were female, 5 of 26 were spayed. The dogs had a median age of 9 years (range, 6 mo to 14 y).

Thirteen dogs were categorized into the nonseptic SIRS group and 48 were categorized into the septic group.

Of the dogs with sepsis, 8 dogs had a positive blood culture (pyometra [$n = 2$], abscess of tarsal joint/skin, parvoviral enteritis, myiasis, salmonellosis, peritonitis/hepatic abscess/pneumonia, underlying cause not identified) (Table 2). Twenty-six dogs had positive bacteriologic culture results (samples from: urine; feces; swabs of wounds, abdominal cavity, prostate, tonsils, or uterine contents; and tracheobronchial lavage) (Table 2); and were diagnosed with abscesses of the skin ($n = 6$), peritonitis ($n = 5$; intestinal perforation [$n = 3$], lymphoma/intestinal perforation, gastric perforation), prostatic abscesses ($n = 4$), pyometra ($n = 4$), pneumonia ($n = 4$), mastitis ($n = 1$), pyelonephritis ($n = 1$), necrotizing purulent tonsillitis ($n = 1$). Fourteen dogs had a macroscopic septic focus and a positive cytology (Table 2); they were diagnosed with pneumonia ($n = 3$; 2 dogs also had neoplasia), peritonitis ($n = 3$; intestinal perforation, perforating bite wound, purulent cholecystitis), prostatic abscess ($n = 2$), pyometra ($n = 2$), parvoviral enteritis ($n = 2$), abscess of the skin/polytrauma ($n = 1$), pneumonia/pancreatitis/pyoderma ($n = 1$). In 7 of 48 dogs more than 1 of the criteria for inclusion as septic were met.

All 13 dogs with nonseptic SIRS had a negative blood culture (Table 3). Two dogs were diagnosed with pancreatitis and 1 dog had splenic neoplasia. Seven dogs had negative bacteriologic cultures from urine, bile, cerebrospinal fluid, or swabs of the abdominal cavity (Table 3). These dogs were diagnosed with pancreatitis, heat stroke, gastric ulcer, mesenteric infarct, steroid-responsive meningitis, fever of unknown origin, and juvenile cellulitis. Three dogs had cytologic samples that did not have evidence for bacterial infection (sterile peritonitis [$n = 2$], uterine hemorrhage) (Table 3).

The gastrointestinal (29%) and urogenital tract (23%) were affected most frequently, followed by diseases of the skin (16%) and of the respiratory tract (12%), miscellaneous diseases (10%), neoplasia (5%), and musculoskeletal diseases (3%).

Median duration of hospitalization was 5 days (range, 0–32 d).

The survival rate at 14 days was 61% (37/61). Twenty-four of the 61 (39%) dogs died ($n = 7$) or were euthanized ($n = 17$). Nine of 13 (69%) dogs suffering from nonseptic SIRS versus 28 of 48 (58%) dogs with sepsis survived. As far as the nonsurvivors were concerned, 25% (6/24) died ($n = 1$) or were euthanized ($n = 5$) on the first day of presentation (day 0), and 42% (10/24) died ($n = 4$) or were euthanized ($n = 6$) on day 1 or day 2. Eight dogs died ($n = 2$) or were euthanized ($n = 6$) after day 2.

Microbiologic analyses

Bacteriologic culture of the blood was performed in 54 of 61 dogs; 46 of these were negative. In 8 of 54 (15%) dogs, the culture was positive (single organism infections). In 4 of the cultures, *Escherichia coli* was isolated. Further pathogens included β-hemolytic *Staphylococcus intermedius*, *Salmonella typhimurium*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumanii* ($n = 1$

Table 2: Diseases and microbiologic test results in 48 dogs with sepsis

Disease	Microbiological tests
Pyometra	Blood culture: *Escherichia coli*, urine culture: *E. coli*
Pyometra	Blood culture: *E. coli*, vaginal smear/uterine content: *E. coli*
Pyometra	Blood culture negative, vaginal smear/uterine content: *E. coli*, *Clostridium perfringens*
Pyometra	Blood culture negative, vaginal smear/uterine content: *Klebsiella spp*.
Pyometra	Blood culture negative, vaginal smear/uterine content: *E. coli*
Pyometra	Blood culture negative, vaginal smear/uterine content: *E. coli*, urine culture negative
Pyometra	Blood culture negative, cytology of uterine content: neutrophils, phagocytized bacteria
Pyometra	Blood culture negative, vaginal smear – cytology: cocci, urine culture negative
Abscess (tarsal joint/skin)	Blood culture: methicillin-resistant *Staphylococcus aureus*, synovial fluid negative
Abscess of the skin	Blood culture negative, wound swab: *Streptococcus canis*
Abscess of the skin	Blood culture negative, wound swab: *Staphylococcus intermedius*, *Pasteurella multocida*
Abscess of the skin	Blood culture negative, skin swab: *Streptococcus spp*.
Abscess of the skin	Blood culture negative, wound swab: *Acinetobacter spp*.
Abscess of the skin	Blood culture not performed, skin swab: *Staphylococcus spp*.
Abscess of the skin	Blood culture not performed, skin swab: *Prevotella spp*.
Abscess of the skin/polytrauma	Blood culture negative, cytology: neutrophils, phagocytized bacteria
Pneumonia and hepatopathy	Blood culture negative, intranasal swab: *Acinetobacter baumanii*, *Enterococcus spp*.
Pneumonia	Blood culture negative, tracheal lavage: *S. canis*, *Pasteurella spp.*, *S. intermedius*, *Klebsiella pneumoniae*
Pneumonia	Blood culture negative, trachael lavage: *E. coli*
Pneumonia	Blood culture not performed, tracheal lavage: *Streptococcus spp*.
Aspiration pneumonia (leukemia)	Blood culture negative, cytology tracheal lavage: neutrophils, phagocytized bacteria
Aspiration pneumonia	Blood culture negative, cytology tracheal lavage: neutrophils, phagocytized bacteria
Aspiration pneumonia (thyroid adenocarcinoma)	Blood culture negative, urine culture negative, cytology tracheal lavage: neutrophils, phagocytized bacteria
Pneumonia/pancreatitis/pyoderma	Blood culture negative, skin swab: *Staphylococcus spp*., cytology tracheal lavage: neutrophils, phagocytized bacteria
Peritonitis/hepatic abscess/pneumonia	Blood culture: β-haemolytic *S. intermedius*, swab abdominal cavity: *Staphylococcus spp*.
Peritonitis (intestinal perforation)	Blood culture not performed, swab abdominal cavity: *E. coli*, *Enterococcus spp.*, *C. perfringens*, *Proteus mirabilis*
Peritonitis (lymphoma)	Blood culture negative, swab abdominal cavity: *E. coli*, *Enterococcus spp.*, *C. perfringens*, *Prevotella spp*.
Peritonitis (gastric perforation)	Blood culture negative, swab abdominal cavity: *S. intermedius*
Intestinal and gastric foreign bodies (peritonitis, intestinal perforation)	Blood culture negative, cytology abdominal cavity: neutrophils, phagocytized bacteria
Peritonitis (perforating bite)	Blood culture negative, cytology abdominal cavity: neutrophils, phagocytized bacteria
Peritonitis (purulent cholecystitis)	Blood culture negative, histopathological evidence of purulent cholecystitis
Intestinal and gastric foreign bodies (peritonitis, intestinal perforation)	Blood culture negative, swab abdominal cavity: *Pseudomonas aeruginosa*, *C. perfringens*
Intestinal foreign body (intestinal perforation)	Blood culture negative, urine culture: *P. mirabilis*, cytology abdominal cavity: neutrophils, phagocytized bacteria
Prostatic abscess	Blood culture negative, swab prostate: *S. canis*, urine culture: *E. coli*, *S. canis*
Prostatic abscess (peritonitis)	Blood culture negative, swab prostate: *E. coli*, urine culture: *E. coli*
Prostatic abscess	Blood culture negative, swab prostate: *E. coli*, wound swab: *E. coli*, *P. mirabilis*, *Clostridium spp*., hemolytic *Streptococcus spp*.
Prostatic abscess	Blood culture not performed, swab prostate: *E. coli*
Prostatic abscess	Blood culture negative, urine culture negative, cytology: neutrophils, phagocytized bacteria
Prostatic abscess	Blood culture negative, cytology: neutrophils, phagocytized bacteria
Parvoviral enteritis	Blood culture: *A. baumanii*
Parvoviral enteritis	Blood culture negative, fecal parvovirus test positive
Parvoviral enteritis	Blood culture negative, fecal parvovirus test positive
Myiasis	Blood culture: *E. coli*
Salmonellosis	Blood culture: *Salmonella typhimurium*, fecal culture: *E. coli*, *S. enterica* subsp enterica, *C. perfringens*
Mastitis	Blood culture not performed, swab of mammary gland secretion: *S. intermedius*
Pyelonephritis	Blood culture not performed, urine culture: *E. coli*
Necrotizing purulent tonsillitis	Blood culture negative, swab tonsils: *S. intermedius*, β-hemolytic *Streptococcus spp*.
Underlying disease not identified	Blood culture: *E. coli*, urine culture negative

Table 3: Diseases and microbiologic test results in 13 dogs with nonseptic SIRS

Disease	Microbiological tests
Pancreatitis	Blood culture negative, no further test
Pancreatitis	Blood culture negative, no further test
Pancreatitis	Blood culture negative, bile culture negative, urine culture negative
Splenic neoplasm	Blood culture negative, no further test
Heat stroke	Blood culture negative, urine culture negative
Gastric ulcer	Blood culture negative, urine culture negative
Mesenteric infarct	Blood culture negative, swab abdominal cavity negative
Steroid-responsive meningitis	Blood culture negative, PCR negative for *Toxoplasma*, *Neospora*, CSF: bacterial culture negative (cytology: pleocytosis, no bacteria, fungi or parasites); CSF IgA increased
Fever of unknown origin	Blood culture negative, urine culture negative, serology/PCR for *Anaplasma*, *Borrelia*, *Ehrlichia*, *Babesia*, and *Leishmania* negative, (histopathology of intra-abdominal lymph nodes: no evidence for infectious disease)
Juvenile cellulitis	Blood culture negative, microbiological culture skin biopsy negative
Intestinal foreign body (without intestinal perforation)	Blood culture negative, cytology abdominal cavity: no bacteria
Peritonitis (uroabdomen)	Blood culture negative, cytology abdominal cavity (modified transudate): no bacteria
Uterine hemorrhage	Blood culture negative, cytology uterine content: few neutrophils, no bacteria

SIRS, systemic inflammatory response syndrome.

of each). Twenty-eight of 61 dogs enrolled had received antimicrobial drugs before the initial examination. Twenty-two of these 28 (79%) patients were categorized as septic; 3 of the 22 dogs had a positive blood culture. Six dogs were categorized as nonseptic.

Bacteriologic culture of relevant fluid/tissue samples was performed in 44 dogs (53 samples). Of these 53 cultures, 35 were positive (66%). In the 43 positive bacteriologic cultures (blood and other samples combined), *E. coli* was the most frequent isolate (14/43, [33%, 8 of the isolates were part of a polymicrobial infection]). Overall, there was a higher incidence of infections caused by single organism gram-negative bacteria (20/43, 46%) than of infections caused by single organism gram-positive bacteria (12/43, 28%). Multiple isolates were obtained in 11 of 43 (26%) dogs. In 19 cases aerobic and anaerobic cultures were performed; 8 of the isolates were anaerobic.

CRP

Concentrations of serum CRP ranged from 1.9 to 4.3 μg/mL in the control group (median, 2.4 μg/mL, $n = 15$). In the clinically ill dogs, CRP values were significantly higher than the control group on day 0 ranging from 1 to 632 μg/mL (median, 182 μg/mL) ($P < 0.001$). Only 1 dog with nonseptic SIRS displayed values within the reference interval on days 0 and 1; this dog survived (Figure 1a).

There were no differences detected in serum CRP concentrations on days 0, 1, and 2 between dogs with nonseptic SIRS and dogs with sepsis. There were no differences detected in serum CRP concentrations on days 0, 1, and 2 between survivors and nonsurvivors (Figure 1a–c).

The change in serum CRP from day 0 to day 2 was calculated for 41 dogs (Table 4). An increase in CRP was observed in 10 of 41 (24%) dogs; the increase ranged from 6 to 493 μg/mL (median, 45 μg/mL). Seven of these dogs were nonsurvivors (70%) with 2 being from the nonseptic SIRS and 5 being from the sepsis group. Concentrations of serum CRP decreased in 31 of 41 (76%) dogs; the decrease ranged from 377 to 2 μg/mL (median, 128 μg/mL). Three of these 31 (10%) dogs were nonsurvivors and had sepsis. The survivors displayed a significantly greater decrease in CRP than the nonsurvivors ($P = 0.001$) (Table 4 and Figure 1d).

Binary logistic regression revealed no relationship between serum CRP concentrations on day 0 and the odds of death or survival in the sick dogs. The change in CRP from day 0 to day 2 was significantly related to the survival rate ($P = 0.01$). However, using binary logistic regression, survival was correctly predicted in 29 of 31 (94%) dogs, but death was correctly predicted in only 3 of 10 (30%) dogs. In other words, the prediction accuracy was 88% overall; 2 survivors were predicted to die and 7 nonsurvivors were predicted to survive.

Discussion

The mortality rate for sepsis in dogs is high. Therefore, a tool that can assist with prognosis may be an important factor for the owner of the dog and for the veterinarian in their decision about further therapeutic options and intensive care measures. The objective of this study was to examine serum CRP concentrations to

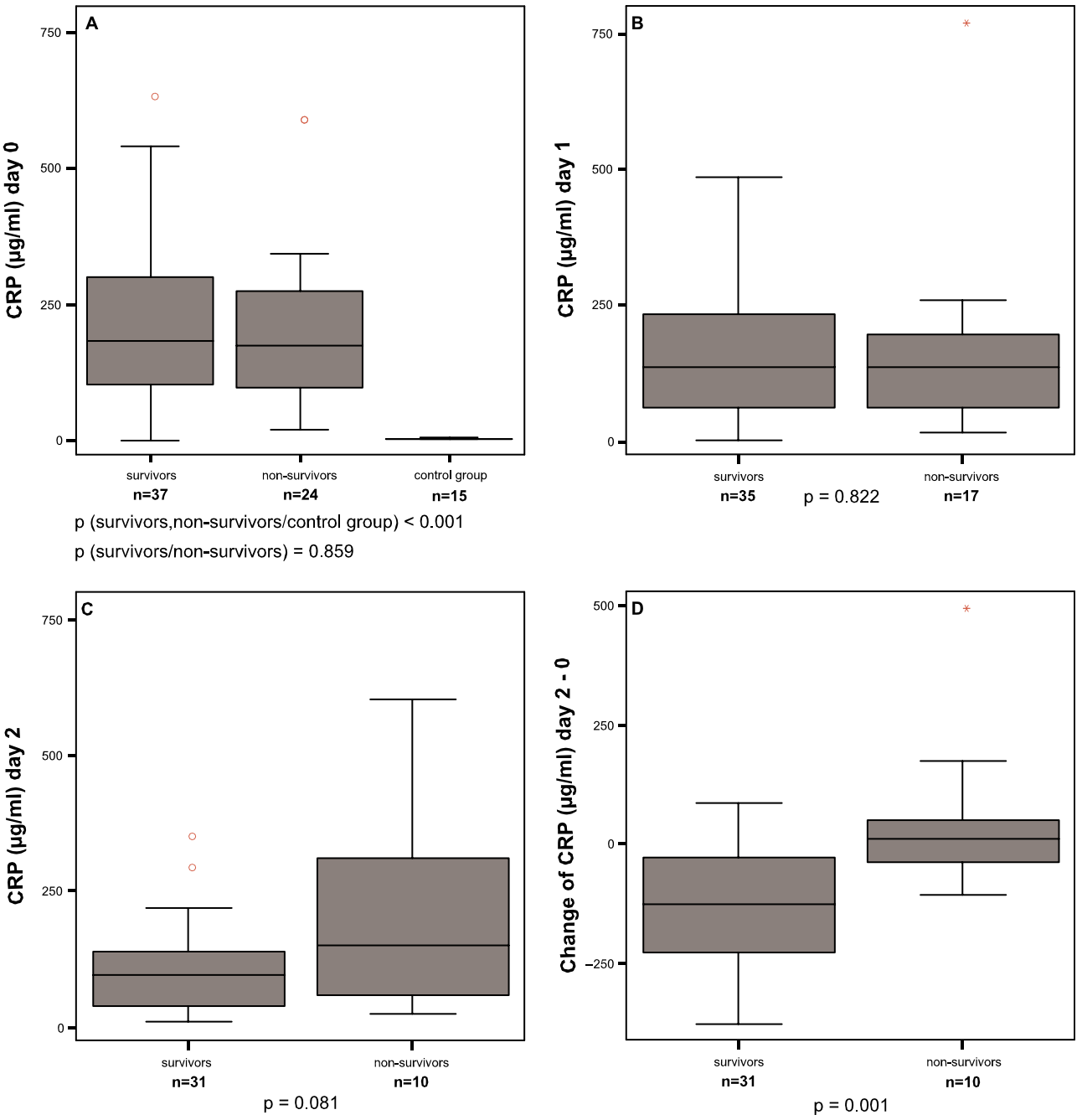

Figure 1: C-reactive protein (CRP) concentrations in dogs with nonseptic systemic inflammatory response syndrome or sepsis on day 0 (A, control group [1.9–4.3 µg/mL]), day 1 (B), and day 2 (C), differentiated according to death or survival, and change in CRP concentration from day 0 to 2 in survivors and nonsurvivors (D); increase: day 2 minus day 0 equals a positive difference, decrease: day 2 minus day 0 equals a negative difference (outliers with circle are values, which lie between $1\frac{1}{2}$ to 3 boxlengths outside the box. *Values that lie more than 3 boxlengths outside the box).

determine if they might be useful prognostic indicators for dogs with sepsis and nonseptic SIRS.

In this study, the survival rate of the dogs diagnosed with sepsis (58%) was lower than the survival rate of the dogs diagnosed with nonseptic SIRS (69%). The survival rate of 58% for dogs with sepsis corresponded to other canine studies, which reported ranges of 50–67%.[5–7]

Table 4: Concentration of serum CRP on day 0, 1, and 2 and the change of serum CRP from day 0 to day 2 in dogs with nonseptic SIRS and sepsis

	CRP concentration (μg/mL)			
Group	**Day 0**	**Day 1**	**Day 2**	**Change from day 0 to day 2**
Nonseptic SIRS				
n	13	13	7	7
Range	1–315	2–244	29–311	− 280 to 78
Median	142	83	116	− 9
Sepsis				
n	48	39	34	34
Range	9–632	16–769	10–603	− 377 to 493
Median	187	142	97	− 88
Survivors				
n	37	35	31	31
Range	1–632	2–486	10–353	− 377 to 87
Median	182	137	96	− 128
Nonsurvivors				
n	24	17	10	10
Range	20–589	17–769	26–603	− 108 to 493
Median	175	137	153	11

Change of serum CRP concentration from day 0 to 2; increase: day 2 minus day 0 equals a positive difference, decrease: day 2 minus day 0 equals a negative difference.
CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.

In this study, 15% of the bacteriologic cultures of blood were positive. This corresponded to a study in human medicine, where the percentage of positive cultures was similar.[26] The detected infectious agents corresponded to the pathogens isolated in other studies in veterinary medicine: gram-negative pathogens were isolated more often than gram-positive pathogens.[5,7,27] In human medicine, the incidence of gram-negative sepsis appears to be decreasing from its levels in the 1970s and 1980s, whereas the incidence of gram-positive sepsis is increasing.[3,14,28]

The allocation of the dogs to the septic and the nonseptic SIRS groups was performed as accurately as possible. Twenty-eight dogs had been treated with antimicrobial drugs before the bacteriologic cultures, which was a limitation for this clinical study. However, in 22 of these dogs the microbiologic or cytologic evaluation provided evidence of a bacterial infection in spite of treatment. In 6 of these 28 dogs (eg, suffering from pancreatitis or heat stroke), there was no evidence to support a septic component to their disease; therefore they were allocated to the SIRS group. Another limitation of the study was that for most dogs only 1 blood culture was taken, although 3 cultures are recommended.[29] Dogs were euthanized when judged to be moribund with end-stage disease. If financial concerns were the reason for euthanasia, the dogs were excluded from the study. However, because different clinicians were involved, different criteria might have led to the decision for euthanasia; a bias toward euthanasia based on survival odds seemed unlikely but could not be excluded completely. Another limitation of the study was the fact that 4 dogs with neoplastic disease fulfilled the criteria for nonseptic SIRS or sepsis and were included in the study. However, it is known that serum CRP can be elevated in dogs with neoplasia.[19,30] Whether the elevation in these dogs was mainly due to sepsis/SIRS or due to neoplasia could not be established, because CRP concentrations have been reported to be markedly elevated in dogs with various tumors.[19]

CRP is an acute phase protein. As expected, concentrations of serum CRP were significantly higher in sick than in healthy dogs. In this study, dogs with sepsis did not have significantly higher CRP concentrations on day 0, 1, or 2 than dogs with nonseptic SIRS. In a study by Castelli et al,[15] significantly higher CRP levels were present in humans suffering from sepsis or severe sepsis than in those with SIRS or no SIRS (medicosurgical patients without trauma or SIRS). Both for humans and for animals CRP is a useful parameter to indicate inflammation.[18,31] CRP was the only inflammatory marker in dogs with pyometra that was related to morbidity.[32] However, a high CRP value in patients with SIRS only predicted increased hospitalization.[32]

There was no statistical difference in the CRP levels in dogs with sepsis versus dogs with nonseptic SIRS. In humans with sepsis a relationship between a decrease in CRP and recovery has been observed.[33] Therefore, CRP has been used as a marker for an effective antimicrobial therapy.[34] In contrast to the nonsurvivors with nonseptic SIRS or sepsis in this study, the surviving dogs displayed a significant decrease in CRP. This suggests that it may be possible to make presumptions regarding the odds of survival. The change in serum CRP from day 0 to day 2 significantly predicted the odds of survival ($P = 0.01$). However, this value successfully predicted outcome in only 29 of 31 surviving dogs and 3 of 10 nonsurviving dogs. In this study, this translated into an inaccurate outcome prediction in 22% of the dogs.

Scoring systems are used in human medicine and have been suggested in veterinary medicine for assessing organ dysfunction and survival.[35–37] King et al[36] developed a system for early objective prediction of survival, which could be applied to all critically ill dogs with naturally occurring disease. The survival prediction index had an 86.3% concordance with the outcome.[36] CRP might be a useful parameter to improve this result. Although it is tempting to apply the SPI to guide management of the individual animal, the pre-

diction applies to populations rather than to individuals.[36] In a follow-up study, serial estimation of survival prediction indices did not improve the prediction of survival in critically ill dogs.[37] In our study, serum CRP changes correlated significantly with the odds of survival. Therefore, serial monitoring of CRP might be a useful parameter to include in future scoring systems.

Serum CRP alone did not represent an adequate parameter for the evaluation of survival odds, neither for individual dogs nor for populations. Using CRP exclusively as the basis for decisions about therapy or euthanasia is not feasible. However, careful interpretation of CRP values and especially of the serial changes of the concentrations in addition to clinical examination and hematologic and biochemical parameters might be useful in assessing the severity of the disease. Further studies should address serial changes in CRP in dogs with severe sepsis or septic shock and the utility of measuring CRP in inflammatory effusions.

Footnotes

[a] CELL-DYN 3500, Abbott, Wiesbaden, Germany.
[b] KONELAB 30i, Thermo Clinical Labsystems, Dreieich, Germany.
[c] Hitachi 911, Roche, Mannheim, Germany.
[d] OXOID SIGNAL blood culture system, Oxoid limited, Hampshire, UK.
[e] BBL Culture Swab Collection & Transport System, Copan for Becton, Dickinson and Company, Sparks, MD.
[f] Phase Range Canine C-Reactive Protein Assay, Tridelta Development Ltd, Wicklow, Ireland.
[g] SPSS 14.0 for Windows, SPSS Inc, Chicago, IL.

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