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The impact of clinical presentation, presence of SIRS and organ dysfunction on mortality in bitches with pyometra

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ABSTRACT: This retrospective study evaluated the impact of the clinical presentation of pyometra on the morbidity and mortality of the affected bitches. The medical records of 47 bitches surgically treated for pyometra between May and December 2017 were evaluated. The admission data were analyzed to classify the animals according to the clinical presentation of pyometra, presence of systemic inflammatory response syndrome (SIRS) and organic dysfunctions (cardiovascular, neurological, renal, and hemostatic). The outcomes were recorded for up to 14 days. The overall mortality rate was 13%. Open and closed pyometra were identified in 62% (n= 29) and 38% (n= 18) of the cases, respectively. The SIRS was present in 44 (94%) bitches, and 27 (57%) had at least one organ dysfunction. The most prevalent dysfunction was hemostatic, followed by neurological, cardiovascular, and renal dysfunction. The clinical presentation of pyometra and the presence of SIRS did not correlate with each other, or with the presence of organ dysfunction and mortality. However, cumulative organ dysfunction (r=0.532, P=<0.001) and the presence of neurological (r= -0.371; P=0.012) and renal dysfunction (r=0.303; P=0.041) were correlated with mortality. Thus, the identification of organ dysfunction through physical examination and routine laboratory analysis proved to be more effective in identifying and predicting the critically ill patients than the SIRS criteria or clinical presentation of the disease.
Key words: dog, open cervix, closed cervix, kidney dysfunction, neurological dysfunction.

O impacto da apresentação clínica, presença de SIRS e disfunção de órgãos em cadelas com piometra

RESUMO: O objetivo deste estudo retrospectivo foi avaliar o impacto da apresentação clínica da piometra na morbimortalidade das cadelas afetadas. Foram avaliados os registros clínicos de 47 cadelas tratadas cirurgicamente para piometra entre maio e dezembro de 2017. Os dados recolhidos na admissão foram analisados para classificar os animais quanto à apresentação clínica da piometra, presença de critérios da Síndrome da Resposta Inflamatória Sistêmica (SRIS) e disfunções orgânicas – cardiovascular, neurológica, renal e hemostática. Foi registrado o desfecho durante 14 dias. A mortalidade global foi de 13%. Piometra aberta e fechada foram identificadas em 62% (n= 29) e 38% (n= 18) respectivamente. SRIS esteve presente em 44 (94%) cadelas e 27 (57%) tiveram pelo menos uma disfunção orgânica. A disfunção mais prevalente foi a hemostática, seguida da neurológica, cardiovascular e renal. A apresentação clínica da piometra e a presença de SRIS não se correlacionaram entre si ou com presença de disfunção orgânica e mortalidade. No entanto, a quantidade de disfunções orgânicas (r=0.532, P=<0.001) e a presença das disfunções neurológica (r= -0.371; P=0.012) e renal (r=0.303; P=0.041) foram correlacionados com mortalidade. Assim, a identificação de disfunções orgânicas através do exame físico e análises laboratoriais de rotina mostrou-se mais eficaz na identificação e previsão de pacientes críticos do que os critérios de SRIS ou a apresentação clínica da doença.
Palavras-chave: cão, cérvix aberta, cérvix fechada, disfunção renal, disfunção neurológica.

INTRODUCTION

Pyometra is a common disease in intact female dogs that are middle aged to elderly. It causes moderate-to-severe illness, and in most cases, critical care and early surgical treatment are necessary (HAGMAN, 2018). Although, it has been described that distinguishing between open or closed cervix in pyometra is important from a clinical point of view (JOHNSON, 2006; JITPEAN et al., 2017; HAGMAN, 2018), this identification might be difficult because of the grooming habits of the species and the progression of the disease (JOHNSON, 2006; HAGMAN, 2018). Pyometra may initially present as a closed cervix and progress to an open cervix due to multifactorial causes such

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as time to diagnosis, etiologic agent, and individual host characteristics (HAGMAN, 2018). However, the veterinary literature describes the closed cervix pyometra as having a poor prognosis (JOHNSON, 2006; JITPEAN et al., 2017; HAGMAN, 2018).

Regardless of the clinical presentation, bitches with pyometra may show clinical signs of systemic inflammatory response (SIRS) and sepsis, which can progress to multiple organ dysfunction and death if not properly treated (HAGMAN, 2018). Most pyometra studies in dogs have discussed sepsis and morbidity/mortality using the SIRS criteria and other inflammatory biomarkers (EGENVALL et al., 2001; JITPEAN et al., 2014; JITPEAN et al., 2017). Since the clinical presentation and physiopathology of sepsis are similar in humans and dogs (OTTO, 2007), it is possible that the methodology used to diagnose SIRS will overestimate the condition in dogs as has been reported for humans (CHURPEK et al., 2015), and may not reflect the real morbidity and prognosis of the patient.

Sepsis is defined as a potentially fatal organ dysfunction caused by a dysregulated host response to an infection (SINGER et al., 2016). This definition emerged almost three decades after the first consensus, which conditioned sepsis to the presence of SIRS in the face of an infection (BONE et al., 1992; LEVY et al., 2003). SIRS, both in humans and dogs, has a defined and validated criteria for identification (two or more of the following clinical criteria: tachycardia, tachypnea, hypo- or hyperthermia, and leukocytosis with immature cells) and can be initiated by various infectious or non-infectious causes (BONE et al., 1992; HAUPTMAN et al, 1997). However, in the last decade, several studies have highlighted the limitations of these criteria for the definition and diagnosis of sepsis in humans and dogs (WELZL et al., 2001; OTTO, 2007; CHURPEK et al., 2015). In addition to the low specificity of this diagnostic tool, more recent studies have pointed the low sensitivity, especially in more critically ill patients with multiple organ dysfunction (MODS) and depletion of pro-inflammatory responses (CHURPEK et al., 2015; KAUKONEN et al., 2015; HAAS et al., 2016). Thus, sepsis was redefined, and new diagnostic tools were proposed through the Third International Consensus (SEPSIS-3 – SINGER et al., 2016), giving greater importance to the identification of organ dysfunctions to the detriment of the predominant inflammatory approach.

As observed in human medicine, veterinary studies have also demonstrated that organ dysfunction has a crucial impact on the mortality of septic animals (WELZL et al., 2001; KENNEY et al., 2010; ATECA et al., 2014; ALVES et al., 2019). The most common organ systems affected by sepsis included the renal, cardiovascular, respiratory, hepatic, hematologic, neurologic, gastrointestinal, endocrine, and immune systems (VINCENT et al., 1996; KENNEY et al., 2010; ATECA et al., 2014). Human studies have shown that even a modest degree of organ dysfunction is associated with an increased risk of mortality (VINCENT et al., 1996; SEYMOUR et al., 2016). However, an early recognition of a sepsis-induced organ dysfunction and an appropriate approach significantly improve patient outcomes (CHURPEK et al., 2015; SINGER et al., 2016).

Therefore, the general objective of this retrospective study was to evaluate the impact of the clinical presentation of pyometra on morbidity and mortality in affected bitches. In addition, we evaluated the correlation between SIRS and organ dysfunction criteria for mortality in these patients.

MATERIALS AND METHODS

This retrospective study was performed using the medical records (May to December 2017) from the Veterinary Teaching Hospital of the Federal Rural University of Rio de Janeiro (VTH - UFRRJ, Seropédica, Brazil). The inclusion criteria were bitches admitted or referred to the hospital with an ultrasonographic examination and clinical findings suggestive of pyometra; only the data collected at admission (clinical and laboratory tests before any therapeutic procedure) were included and analyzed. However, all the animals received clinical stabilization when necessary, antibiotic administration until the second hour of admission, and ovariohysterectomy performed as soon as possible (6-12 hours) after admission. Animals that presented with comorbidities with possible systemic repercussions were excluded.

All the animals' characteristics (breed, age, and body weight), anamnesis, and clinical data were also reviewed. Heart rate (HR, beats per minute); respiratory rate (RR, breaths per minute); Doppler systolic blood pressure (SBP, mmHg); rectal temperature (Celsius); capillary refill time (CPT, seconds) and mental status, using the Glasgow Pediatric Coma Scale modified for dogs (Andrade et al., 2010) (Table 1) were extracted from the medical records. Blood hematological and biochemical analyses were recorded (blood glucose measured at a specific point-of-care). The medical management provided by the attending veterinarian was reviewed to confirm that all the bitches received individual pre- and post-operative care including clinical stabilization

Table 1 - The Pediatric Glasgow Coma Scale Modified for Dogs, used in clinical care to assess the mental status at the Veterinary Teaching Hospital of the Federal Rural University of Rio de Janeiro (UFRRJ, Seropedica, Brazil).

Indicator	Criteria/response	Score
Eye opening	Spontaneous	4
	Verbal stimulation/command	3
	Verbal stimulation/command/shouting	3
	Painful stimulus	2
	Without opening	1
Better response to vocalization	Bark/growl	5
	Angry crying	4
	Crying in pain	3
	Yawn to pain	2
	No reply	1
Best motor response	Spontaneous and normal movement	6
	Touch reaction	5
	Reaction to pain	4
	Abnormal flexion - decortication	3
	Abnormal extension - decerebration	2
	None	1
Total		15

Adapted from ANDRADE et al., 2010.

prior to surgery, antibiotics for 14 days, analgesics, and other supportive drugs. The outcome was defined as the surgical discharge after complete remission of symptoms (alive) or cause of death (dead) for up to 14 days postoperatively.

The clinical presentation of pyometra was classified as open or closed cervix according to the presence or absence of vulvar discharge, respectively, based on the information reported by the owner or clinical examination. SIRS was confirmed if the patient met at least two of the four criteria described in table 2. Organ dysfunction was classified as renal, cardiovascular, hemostatic, and neurological, using the criteria described in table 2.

Statistical analyses were performed first with all the dogs and then separately for comparison between groups. The bitches were categorized according to the breed classification of the Confederação Brasileira de Cinofilia (CBKC) into: small size (breeds with a body weight standard of up to 15 kg; n= 18), medium (breeds with a body weight standard between 15 and 25 kg; n= 4), large (breeds with a standard body weight above 25 kg; n= 5), and mixed breeds (n= 20). Subsequently, the animals were allocated to the open cervix *versus* closed cervix groups [identified as open (n= 29) and closed (n= 18)]; survivor *versus* non-survivor groups [identified as alive (n= 41) and dead (n= 6)], and bitches without organic dysfunction *versus* those that presented at least one organ dysfunction [identified as **no-dysfunction (n= 20)** and **with dysfunction (n= 27**)]. In the group of animals with organ dysfunction, a subdivision was performed to identify the most severe patients, who had 2 or more organ dysfunctions (**≥ 2 dysfunctions, n= 14**). The number of organ dysfunctions was considered a categorical variable. Bitches were classified as **positive** (n= 44) or **negative** (n= 3) according to the SIRS criteria. These groups were analyzed separately and compared using descriptive statistics and testing applications. The Shapiro–Wilks test was used to assess the continuous variables for normality. The t-test and Mann–Whitney rank sum test were used to compare the continuous variables between groups with normal and non-normal distributions, respectively. The chi-square test was used to determine whether the variables were significantly associated with the clinical presentation, SIRS, organ dysfunction, and outcome. Spearman's correlation analysis was used to test for correlations between the parameters. All statistical analyses were performed using the statistical software package SigmaPlot 11.0, with $P \leq 0.05$.

RESULTS AND DISCUSSION

Historically, it is believed that the clinical presentation of pyometra, with a closed or open

Table 2 - Criteria to identify organ dysfunctions and SIRS in bitches with pyometra. Veterinary Teaching Hospital of the Federal Rural University of Rio de Janeiro (UFRRJ, Seropedica, Brazil).

Organ Dysfunction	Criteria
Renal	Creatinine > 1.7 mg/dL
Cardiovascular	Systolic blood pressure < 90 mmHg
Hemostatic	Platelet counts < 200,000/µL
Neurologic	Glasgow Coma Scale modified for dogs[18] ≤13 points
SIRS*	Criteria
Body temperature	<38.1 ºC or >39.2 ºC
Heart rate	>120 bpm
Respiratory rate	>20 bpm
Total white blood cell count	<6,000 or >17,000/µL

*adapted from HAUPTMAN et al., 1997.

cervix, can contribute to the severity of the disease, since a closed cervix can cause a higher incidence of sepsis and worsen the prognosis (JOHNSON, 2006; JITPEAN et al., 2017; HAGMAN, 2018). This concept alone can lead a veterinarian to treat an open cervix through clinical approaches (FIENI et al., 2014) and ignore the importance of early removal of the focus of infection (HAGMAN, 2018). Results of our study indicated that the most relevant aspect for predicting morbidity and prognosis in pyometra was the identification of sepsis based on the organ dysfunction criteria (SINGER et al., 2016). Our data also highlight that the clinical presentations of pyometra and SIRS are not significant criteria for risk stratification, especially in early care.

A total of 48 dogs met the inclusion criteria. However, one dog was excluded because of hematologic abnormalities suggestive of a lymphoma. Of the 47 medical records, 25% (n=12) contained descriptions of comorbidities without systemic repercussions; therefore these were not excluded. Small breast lumps (n=4), focal dermatopathies (n=4), mild periodontal disease (n=2) and ophthalmic disorders (n=2) were described. In this population, patient characteristics such as age, reproductive history, and clinical signs of pyometra, were similar to those described in previous studies (EGENVALL et al., 2001; JITPEAN et al., 2014; HAGMAN, 2018). The mean age of the population was 9±4 years and the mean body weight was 10[1.6-37.2] kg. The mixed breed bitches were the majority (43%), followed by small (38%), large (11%), and medium (8%) breeds. The most prevalent symptoms highlighted by the owners were a lack of appetite, prostration, changes in urination and diarrhea. The medical history, anamnesis, and physical examination data at admission are presented in table 3.

Pyometra in dogs is commonly diagnosed between 4 weeks and 4 months after estrus, when the uterus is suitable for fetal development, but is also susceptible to bacterial growth (JOHNSON, 2006; HAGMAN, 2018). Pyometra is life-threatening when there is an unbalanced immune reaction owing to a systemic inflammatory response with tissue and organ dysfunction (HAAS et al., 2016; KARLSSON et al., 2016). In the current study, the average time between the last estrus and admission of the bitch, as reported by the owners, was 44±27 days. Forty one bitches (87%) survived, and 6 (13%) died. The mean time from admission to death was 3±1 days. None of the animals was euthanized. The mortality rates reported in the literature range from 4.3 to 10% (EGENVALL et al., 2001; JITPEAN et al., 2014; JITPEAN et al., 2017). Our slightly higher mortality rate can be explained by the location where the study was conducted - a rural area, in which most dogs are kept outside, which can delay owners in early identification of the disease.

Considering the clinical presentation of pyometra, 29 (62%) patients were classified as open cervix and 18 (38%) as closed cervix. None of the clinical presentations of pyometra was not associated with the presence of SIRS (P=0.650), organ dysfunction (P=0.411), or outcome (P=0.806). The parameters evaluated in the physical examination at admission (Table 3) also did not differ significantly between the bitches with open or closed pyometra. Only the study by JITPEAN et al. (2017) suggested that the closed-cervix was worse due to a higher incidence of SIRS and severe general clinical conditions at admission; however, as demonstrated in the same study, the presence of complications and prolonged postoperative hospitalization in the closed

Table 3 - Variables of the admission clinical examination of 47 bitches with pyometra treated in the Veterinary Teaching Hospital of the UFRRJ, Seropedica, Brazil (May to December 2017).

	all animals n=47	open cervix n=29	closed cervix n=18	*alive n=41*	*dead n=6*	*no-dysfunction n=20*	*with dysfunction n=27*	*SIRS criteria n=44*	*≥2dysfunction n=14*
Age *(years)*	9±4	9±3	8±4	8±4	10±3	8±4	10±3	9±3	9±4
Body weight *(kg)*	10.0 [1.6-37.2]	8.4 [1.6-37.2]	10.5 [2.7-28.0]	10.0 [2.3-37.2]	8.7 [1.6-25.6]	10.5 [2.3-37.2]	8.6 [1.6-35.0]	10 [1.6-37.2]	6.5 [1.6-25.6]
Body score *(1 to 5)*	3 [2–5]	3 [2-5]	3 [2-4]	3 [2-5]	3 [2-3]	3 [2-5]	3 [2-4]	3 [2-5]	3 [2-3]
Last heat *(days)*	30 [4-120]	30 [4-120]	30 [20-90]	30 [4-90]	25 [4-120]	30 [4-90]	30 [4-120]	30 [4-120]	25 [4-120]
Previous pregnancy	14 (30%)	7 (24%)	7 (39%)	25 (61%)	4 (66%)	6 (30%)	8 (30%)	14 (32%)	4 (28%)
Prostration	34 (72%)	22 (76%)	12 (67%)	28 (68%)	6 (100%)	12 (60%)	22 (81%)	33 (75%)	14 (100%)
Inappetence	38 (81%)	24 (83%)	14 (78%)	13 (32%)	1 (17%)	14 (70%)	24 (89%)	38 (86%)	13 (93%)
Changes in urination	10 (21%)	5 (17%)	5 (28%)	9 (22%)	1 (17%)	5 (25%)	5 (18%)	10 (23%)	3 (21%)
Diarrhea	10 (21%)	6 (21%)	4 (22%)	33 (80%)	5 (83%)	6 (30%)	4 (15%)	10 (23%)	2 (14%)
HR *beats/min*	120±27	126±30	121±21	122±26	138±32	119±19	128±31	126±27	136±29
RR *breaths/min*	42 [16-80]	40 [20-80]	54 [16-80]	44 [16-80]	39 [24-75]	58 [16-80]†	38 [20-80]†	43 [16-80]	31 [20-76]
SBP *mmHg*	118±28	113±28	124±27	120±24*	94±40*	131±20†	107±28†	117±28	101±28
T *º Celsius*	38.5 [32.7-40.8]	38.5 [32.7-40.3]	38.3 [34.7-40.8]	38.5 [36.5-40.8]	37.4 [32.7-39.6]	38.6 [36.5-40.8]	38.3 [32.7-40.2]	38.5 [32.7-40.8]	38.0 [32.7-40.1]
CRT *seconds*	2 [1-5]	2 [1-4]	2 [1-5]	2 [1-4]	3 [1-5]	2 [1-4]	2 [1-5]	2 [1-5]	2 [1-5]
GCS *1 to 15 score*	15 [11-15]	15 [11-15]	15 [13-15]	15 [11-15] *	13 [11-15]*	15 [15-15]†	15 [11-15]†	15 [11-15] ‡	13 [11-15]‡
GLU *mg/dL*	88 [17-180]	85 [25-163]	91 [17-180]	89 [25-180]	73 [17-138]	91 [60-129]	85 [17-180]	89 [17-180]	84 [17-180]
Deaths	06 (13%)	4 (14%)	2 (11%)	0 (0%)	06 (100%)	0 (0%)	6 (22%)	6 (14%)	6 (43%)

HR: heart rate; RR: respiratory rate, SBP: systolic blood pressure; T: rectal temperature; CRT: capilar refil time; GCS: Glasgow coma scale; GLU: plasma glucose
* Significant difference between alive and dead groups; † significant difference between with dysfunction and no-dysfunction groups; ‡ significant difference between SIRS criteria and ≥2 dysfunction groups.

pyometra group did not differ significantly from the open cervix group.

The SIRS was present in 94% (n=44) of bitches admitted with pyometra and did not correlate with mortality (r= 0.099; P=0.334), clinical presentation of pyometra (r= 0.026; P= 0.858), or presence of organic dysfunction (r= 0.127; P=0.365). This result is important, since the presence of SIRS associated with a suspected or confirmed infectious focus remains one of the diagnostic methods for sepsis in dogs (HAUPTMAN et al., 1997), even after the proven limitations of this method for humans (SINGER et al., 2016). The incidence of SIRS in our study was higher compared with other reported in studies using the same cut-off values (ATECA et al., 2014; JITPEAN et al., 2014; JITPEAN et al., 2017). However, we believe that this result was influenced by the regional climate - high temperatures and humidity, which physiologically increased the respiratory rate. Indeed, 98% of the patients had a respiratory rate of >20 bpm. For example, if a cut-off value of >40 bpm was used, 89% of the samples would have SIRS. Similarly, a high incidence of SIRS (87%) was observed in another study from South Africa (WELZL et al., 2001) in the dogs with babesiosis. The authors observed that only 4 out of the 91 dogs studied had a respiratory rate below 20 bpm and the presence of SIRS had no significant impact on the outcome. Although, the SIRS criteria validated for dogs by HAUPTMAN (1997) are widely used, their cut-off values require a critical analysis because the physiological range for temperature, heart rate,

and respiratory rate varies substantially in dogs according to age, and are also affected by pain, stress, dehydration (ATECA et al., 2014; ALVES et al., 2019) and environment conditions. Several studies have highlighted this limitation in the SIRS criteria for humans (CHURPEK et al., 2015; KAUKONEN et al., 2015; SEYMOUR et al., 2016) and dogs (WELZL et al., 2001; ATECA et al., 2014; ALVES et al., 2019), including studies on canine pyometra (KARLSSON et al., 2016; JITPEAN et al., 2017). If the SIRS criteria are still considered for clinical diagnosis, we suggest keeping in mind that they are unspecific, and their association with biomarkers may be useful to understand the severity of the disease.

The results of the hematologic and biochemical variables are listed in table 4. The mean RBC count (4.6±1.3 x106/µL) and hemoglobin (10.3±3 g/dL) were lower than the baseline values, indicating a mild normocytic normochromic anemia in all the groups, with no statistical difference. This reflects the chronicity of the disease, the reduction in bone marrow erythropoiesis, lack of available iron, and loss of erythrocytes to the uterus (KUPLULU et al., 2009; HAAS et al., 2016). The animals also presented hyperproteinemia (8.4±1.4 g/dL) with hypoalbuminemia (1.8 [1.1–3.4] g/dL), corroborating the inflammatory character of the disease. Hypoalbuminemia and hyperproteinemia are also frequently observed in pyometra, reflecting the loss of albumin due to increased vascular permeability and increased production of gamma globulins (KARLSSON et al., 2016; HAGMAN, 2018). Albumin is considered a negative acute-phase protein because the serum concentrations decrease in inflammation and/or infection, and may be valuable as a negative prognostic biomarker for survival (ATECA et al., 2014). Our results demonstrated significantly lower albumin levels in bitches with organ dysfunction than in those without it (P=0.034).

Moderate to severe leukocytosis or leukopenia is also a common finding in bitches with pyometra (KARLSSON et al., 2016; JITPEAN et al., 2017; HAGMAN, 2018). In our study, 79% (37) of the bitches had leukocytosis and 4% (02) had leukopenia; no difference was found between the groups, which may have been due to the number of animals. HAAS et al. (2016) analyzed the activation of serum neutrophil chemokines (CXCL8) in relation to symptom severity in dogs with infection, and observed that only dogs with mild symptoms had significantly higher values than healthy dogs; however, the values of healthy dogs and those with severe symptoms were similar. Similar findings have been reported previously (DECLUE et al., 2012; KARLSSON et al., 2016). Therefore, as demonstrated in humans (KAUKONEN et al., 2015), septic dogs with more severe clinical conditions do not necessarily present a systemic inflammatory response owing, to a weak or deficient immune response (HAAS et al., 2016). Furthermore, our study identified significantly lower eosinophil counts in bitches that presented with organ dysfunction than in those without it (P=0.008). Eosinophils undergo apoptosis due to cytokine production in bacterial sepsis and eosinopenia is considered a sepsis prognostic marker in humans (MERINO et al., 2012). Although, this finding has been less explored in the veterinary literature, similar results have been demonstrated in septic dogs (ALVES et al., 2019).

Twenty bitches (43%) had no organ dysfunction, and 27 (57%) had one or more organ dysfunctions. The non-survivor group had significantly more organ dysfunction than the survivor group ($P < 0.001$). The median of organic dysfunctions presented by the group was 1 [0-3] for alive, and 2 [2-4] for dead. There was a positive and moderate correlation between the number of organ dysfunctions and mortality ($r=0.532$, $P=<0.001$). These results are in line with the new definition of sepsis for humans (SINGER et al., 2016) and highlight, also for dogs, the predictive value of organic dysfunctions in the outcome of bitches with pyometra sepsis. In humans, the predictive validity of the Sequential [Sepsis related] Organ Failure Assessment (SOFA) score (VINCENT et al., 1996) is significantly greater than that of the SIRS, supporting its use in clinical criteria for sepsis (SEYMOUR et al., 2016; SINGER et al., 2016). To our knowledge, no studies have yet validated the cut-off values for organ dysfunction in dogs; however, some studies have documented their incidence and association with mortality rates (KENNEY et al., 2010; ATECA et al., 2014). In this study, the criteria used to classify dogs as having organ dysfunction were adapted from the SOFA scoring system (VINCENT et al., 1996); however, the results were not stratified in severity but only as present or absent. This methodology showed that 57% (27) of the bitches had at least one organ dysfunction at the time of admission, and 30% (14) of these were also classified with MODS (bitches that had two or more dysfunctional organ systems, identified as ≥ 2 dysfunctions). In a retrospective study of dogs with severe wounds, ATECA et al. (2014), reported that 73% of dogs had at least one organ dysfunction and the overall mortality rate was 15%; KENNEY et al., (2010) observed that 78% of dogs with gastrointestinal tract leakage had at least

Table 4 - Admission laboratory analysis of 47 bitches with pyometra attended at the Veterinary Teaching Hospital of the UFRRJ, Seropédica, Brazil (May to December 2017).

	all animals n=47	open cervix n=29	closed cervix n=18	alive n=41	dead n=6	no-dysfunction n=20	withdysfunction n=27	SIRS criteria n=44	≥2 dysfunction n=14
Red blood cells 5.5 – 8.5 x10^6/µL	4.6±1.3	4.8±1.3	4.4±1.2	4.6±1.3	4.9±1.1	4.9±1.3	4.5±1.3	4.5±1.2	4.4±1.2
Hemoglobin 12.0 – 18.0 g/dL	10.3±3.0	10.5±3.0	10.0±2.9	10.3±3.0	10.2±3.1	11.1±3.0	9.8±3.0	10.0±2.8	9.5±3.0
Packed cell volume 37–55 %	31±8	31±8	30±8	31±8	31±8	33±8	30±8	30±8	29±8
Total white blood cells 6–17 x10^3/µL	32.3 [4.0-102.1]	37.8 [59-102.1]	23.2 [4.0-90.33]	31.5 [4.0-102.1]	37.0 [8.1-91.8]	31.9 [7.7-90.3]	33.8 [4.0-102.1]	34.1 [4.0-102.1]	46.1 [4.0-102.1]
Band neutrophils 0 – 3%	1 [0-26]	2 [0-11]	0 [0-26]	1 [0-26]	1 [0-5]	1 [0-26]	1 [0-11]	1 [0-26]	3 [0-10]
Segmented neutrophils 3.0–11.4 x10^3/µL	24.5 [3.4-84.9]	28.9 [4.6-84.9]	17.5 [3.4-66.0]	24.5 [3.4-84.9]	27.2 [5.7-76.1]	24.2 [5.9-58.7]	25.6 [3.4-84.9]	25.6 [3.4-84.9]	38.1 [3.4-84.9]
Lymphocytes 1.0 – 4.8 x10^3/µL	1.8 [0.06-10.1]	1.7 [0.06-9.1]	2.6 [0.4-10.1]	1.8 [0.06-10.1]	2.6 [0.9-7.4]	3.1 [1.0-9.1]†	1.2 [0.6-10.1]†	1.8 [0.6-10.1]	1.5 [0.4-7.4]
Monocytes 150 – 1,350 x10^3/µL	1.4 [0.24-10.21]	2.3 [0.32-10.21]	0.91 [0.24-7.61]	1.28 [0.24-10.21]	2.42 [0.78-9.22]	1.0 [0.32-7.6]	2.2 [0.24-10.21]	2.09 [0.24-10.21]	3,.49 [0.24-10.21]
Eosinophils 100 – 750/µL	172 [0-2,632]	38 [0-1,569]	253 [0-2,632]	220 [0-2,632]	0 [0-918]	315 [0-2632]†	0 [0-1,328]†	181 [0-2,632]‡	0 [0-918]‡
Platelets 200 – 500 x10^3/µL	220 [20-654]	236±153	261±172	262±162	137±72	311 [203-654]†	140 [20-486]†	212 [20-654]‡	142 [30-334]‡
Total protein 5.4 – 7.5 g/dL	8.4±1.4	8.5±1.4	8.2±1.5	8.5±1.4	7.8±1.7	8.2±1.4	8.6±1.4	8.4±1.4	8.3±1.4
Albumin 2.3 – 3.1 g/dL	1.8 [1.1-3.4]	1.8±0.5	2.0±0.6	1.8 [1.1-3.4]	1.7 [1.2-2.3]	2.1 [1.1-3.4]†	1.7 [1.2-3.2]†	1.8 [1.1-3.4]	1.7 [1.2-2.4]
Phosphatase alkaline 1–114U/L	142 [29-950]	146 [30-403]	121 [29-950]	137 [29-950]	165 [193-317]	104 [51-950]	165 [29-484]	145 [29-950]	165 [30-484]
Alanine transferase 10–109 U/L	28 [5-139]	22 [5-70]	35 [10-139]	28 [10-139]	31 [5-33]	28 [10-139]	28 [5-113]	28 [5-139]	31 [5–75]
Creatinine 0.5 – 1.7 mg/dL	0.9 [0.3-2.5]	0.9 [0.3-2.5]	0.8 [0.5-2.2]	0.9 [0.3-2.3]*	1.7 [0.5-2.5]*	0.8 [0.3-1.4]†	1.1 [0.5-2.5]†	0.9 [0.3-2.5]	1.3 [05-2.5]

Reference values by MEYER & HARVEY (2004).
*Significant difference between alive and dead groups; † significant difference between with dysfunction and no-dysfunction groups; ‡ significant difference between SIRS criteria and ≥2dysfunction groups.

one organ dysfunction and the overall mortality rate was 47%; CRNOGAJ et al. (2017) observed organ dysfunction in 27.5% of cases of canine babesiosis with a mortality rate of 10%. Although, the incidence, morbidity and mortality may differ according to the underlying disease, these studies also demonstrated a positive correlation between the amount of organ dysfunction and mortality (KENNEY et al., 2010; ATECA et al., 2014). MODS, in rare studies where it is addressed in dogs, is also associated with the evolution and worsening of an infectious condition and sepsis. KENNEY et al. (2010) observed MODS in 50% of the patients, and mortality rate was 70% in the same group. ATECA et al. (2014) reported a mortality rate of 69% in animals that developed four or more organ dysfunctions. Our results reinforce the correlation between MODS and mortality in bitches with pyometra, since the number of organ dysfunctions had an impact on mortality ($p<0.001$) and 100% of the bitches that died had two or more organ dysfunctions.

The most prevalent dysfunction was hemostatic (40%), followed by neurological (25%), cardiovascular (21%), and renal (15%) dysfunctions. In a study on sepsis-induced hemostatic changes in dogs, LLEWELLYN et al. (2017) observed that in addition to thrombocytopenia, there was an increase in the volume, size, and acute consumption of platelets. Although, some studies have demonstrated that hemostatic dysfunction has a predictive value for sepsis (LLEWELLYN et al., 2017) based on our results, it has no prognostic value for unfavorable outcomes in bitches with pyometra. In this study, the neurological dysfunction was also highly prevalent and weakly correlated with mortality ($r= -0.371$; $P=0.012$). In older people with sepsis, the prevalence of this dysfunction is high, affecting not only morbidity and mortality, but also the quality of life of survivors (SINGER et al., 2016; ROWE & MCKOY, 2017). Almost no studies on sepsis and organ dysfunction in animals have examined the level of consciousness (KENNEY et al., 2010; ATECA et al., 2014; ALVES et al., 2019). However, prostration/apathy and inappetence are commonly reported (JOHNSON, 2006; HAGMAN, 2018), and in some cases may be related to septic encephalopathy (SINGER et al., 2016; ROWE & MCKOY, 2017). This highlights the importance of identifying this dysfunction in older dogs with suspected sepsis and investigating its impact on the cognition and quality of life of these animals. The cardiovascular dysfunction plays an important role in sepsis owing to its direct influence on microcirculatory, cytotoxic, and microsomal dysfunctions (SINGER et al., 2016). Although, our results did not show a correlation with mortality, SBP values were significantly lower ($P=0.024$) in patients who had ≥ 1 organ dysfunction and died. Renal dysfunction, although, less prevalent in the general population, was observed in 67% of the non-surviving bitches and was weakly correlated with mortality ($r=0.303$; $P=0.041$). In sepsis, acute kidney injury is multifactorial and the increase in serum creatinine is a late marker of this dysfunction (SINGER et al., 2016; GASSER et al., 2020). In pyometra, tubular and glomerular lesions are added because of an exacerbated stimulation of the immune system by the bacterial agent, which induce the formation of circulating immune complexes that precipitate in the glomeruli (MADDENS et al., 2010; GASSER et al., 2020). Recently, Gasser et al. (2020) demonstrated that, although,only 20% of the bitches with pyometra presented creatinine levels above the reference, all the animals had some degree of renal histopathologic damage.

Our study had a small number of patients, which consequently limited the statistical analyses. As the focus of the study was only on the patients' admission data, it was not possible to include parameters such as fluid resuscitation or vasopressor requirements in the criteria used for cardiovascular dysfunction, thus limiting the information on this dysfunction. Finally, it was not possible to perform microbiological analysis of the uterine contents of all bitches; however, all females presented purulent exudate in the excised uterine lumen, corroborating the suspicion of an infectious focus that allowed the investigation of sepsis and organ dysfunction (SINGER et al., 2016).

CONCLUSION

Based on our results, we can conclude that: (1) the clinical presentation of pyometra had no impact on morbidity and mortality of the disease in the studied population; and therefore, the authors recommend not using this parameter alone for the staging and prognosis of bitches; (2) bitches with pyometra and SIRS do not necessarily have organ dysfunction and sepsis; therefore, this criterion, in the present study, was not a good method to identify patients more likely to have a worse outcome; and (3) the identification of organ dysfunction, through physical examination and routine laboratory analysis proved to be more effective in identifying and predicting the critically ill patients, and thus optimizing an early and more aggressive approach to patients with a greater risk of mortality.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Conceptualization: AJRP, VCTL, CDB and CMMC. Data acquisition: AJRP, VCTL, MESLF, LCO, BTB and FFPCB. Design of methodology and data analysis: AJRP, CMMC, CDB and FBK. AJRP prepared the draft of the manuscript. All authors critically revised the manuscript and approved of the final version.

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