



The prognostic value of procalcitonin in critically ill cases of systematic inflammatory response syndrome in dogs

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Received: 4 July 2022 / Accepted: 11 November 2022 / Published online: 28 November 2022
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Abstract

Using markers for early diagnosis can help to reduce mortality and morbidity in systemic inflammatory response syndrome (SIRS). This study investigates the role of procalcitonin (PCT) as a prognostic value in dogs with SIRS in the intensive care unit. Fifty-five dogs were selected and studied. Blood samples were collected and investigated for PCT, white and red blood cells, iron, creatinine, platelet, glucose, albumin, urea, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), bandcell, body temperature, and hospitalized days and costs. The animals were grouped into survivors and deceased groups, and their results were compared. The results showed negative significant relations between PCT with hematocrit ($r^2=0.294$, $P<0.05$) and the serum concentration of iron ($r^2=0.280$, $P<0.05$) and also positive relation with IL-6 ($r^2=0.456$, $P<0.01$) and TNF- α ($r^2=0.391$, $P<0.01$). Significant relations were not seen between PCT with other parameters ($P>0.05$). The results also showed a significant relation between glucose and albumin with body temperature ($P<0.05$). The results showed that the serum concentrations of PCT, IL-6, and TNF- α were significantly higher in deceased dogs compared with survivors, while white blood cells, glucose, albumin, urea, lymphocyte, neutrophil, and body temperature were higher in survivors compared with others. PCT can be utilized as a prognostic value and helps early diagnosis in dogs with SIRS.

Keywords Early diagnosis · Procalcitonin · Prognostic values · SIRS

Introduction

Sepsis is known as one of the most common causes of morbidity and mortality in intensive care and is presented in different severities of systemic inflammatory response syndrome (SIRS) (Goggs and Letendre 2019). SIRS is an exaggerated defense response of the body against stressor factors, such as infection, trauma, and surgery for removing the endogenous and exogenous sources of the insult (Chakraborty and Burns 2019). The disease is known with signs such as abnormal body temperature, heart and respiratory rate, and leukocyte count (Pierini et al. 2019). The hematopoietic system and hematological disorders are also

seen in patients with SIRS (Napolitano 2017). The disease causes the increase in cytokines in the blood plasma by 2–6 times (Yelins'Ka et al. 2019). In dogs with SIRS, criteria are including body temperature <37.8 °C or >39.4 °C, heart rate >140 bpm, respiratory rate >30 breaths/min or $PCO_2 <32$ mmHg, white blood cells <6000 or $>16,000$ cells/ μ L, or $>3\%$ band neutrophils (Alves et al. 2020).

Clinicians have sought new tools to diagnose sepsis promptly. Early diagnosis and treatment may reduce mortality and morbidity (Rowe et al. 2018). A marker can help early detection and also distinguish between infectious and non-infectious causes of SIRS (Binnie et al. 2020). Traditional markers cannot be specific, such as heart and respiratory rates and white blood cell (WBC) count (Abedini et al. 2012). In addition, physicians are still faced with challenges in the correct use of antibiotics. The incorrect application of antibiotics not only increases mortalities but also leads to antibiotic-resistant, toxic side effects and healthcare costs (Gregoriano et al. 2020). Among biomarkers, procalcitonin is known to be a precise indicator of bacterial infection and/or severity of infection, and also good control of the success

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of a therapeutic procedure (Battaglia et al. 2021). It has been reported 79.00%, 84.00%, 69.00%, and 77.00% for sensitivity, specificity, sensitivity, and specificity (Yu et al. 2010).

Procalcitonin is an inactive propeptide of calcitonin released by C cells of the thyroid gland, hepatocytes, and peripheral monocytes. It has been reported as a useful biochemical marker to distinguish sepsis from other non-infectious causes of systemic inflammation (Rhodes et al. 2017). Indeed, pro-inflammatory cytokines stimulate the expression of genes responsible for the production of procalcitonin (Downes et al. 2020). Procalcitonin value is related to the severity of illness, and its changes are linked with severity of infection in patients (Tsui et al. 2021). Production of procalcitonin is increased 24 h after induction of infection. An appropriate treatment decreases its production, while incorrect treatment leads to future increases (Paudel et al. 2020). The serum concentration of procalcitonin is very low in healthy people while its concentration is higher in patients with infection (> 100 ng/mL) (Dever and Sheikh 2015).

Despite the role of procalcitonin as a value in human studies, it has not been still investigated as a prognostic value in dogs with SIRS. This new study works on the serum concentration of procalcitonin as a prognostic value in dogs with SIRS in the intensive care unit.

Materials and methods

Animals and protocols

This study was conducted in infectious and intensive care of a veterinary hospital for 7 months during 2020–2021 years. All the dogs with SIRS were studied. Animals with tachycardia, tachypnea, leukopenia, fever, and/or hypothermia were studied. Clinical examinations of dogs were conducted as reported by previous studies (Giunti et al. 2017). In the current study, all the efforts were conducted to minimize stress. All the experimental procedures were in agreement with protocols advised by the Ethical Committee of Islamic Azad University, Sciences and Research Branch (IR.IAU.SRB.REC.1400.048). All dogs with trauma, surgery, burning, and other diseases interfering with this study were excluded. Finally, 55 dogs were selected and studied. Vital signs were daily recorded.

Blood sampling

Blood samples were collected from all the dogs and transferred in two tubes with and without anticoagulant (Marschner et al. 2012). A complete blood count (CBC) was daily performed to monitor dogs. To evaluate serum samples, the blood samples

were centrifuged at 3000 rpm for 10 min. Sera were stored at -80 °C.

The measurement of biochemical parameters

To assess procalcitonin, specific kits (Procalcitonin Kryptor Sensitive B.R.A.H.M.S) were used as recommended by producer companies. To measure IL-6 and tumor necrosis factor- α (TNF- α), Bender Medsystem Kits were used and the results were reported as pg/mL. The serum concentration of glucose was assessed by glucose-hexokinase method using spectrophotometer (Biowave, S2100, England). The serum concentration of urease was assessed by Pars Azmoon Kit (UREA Berthelot, 18,940) as recommended by producer company. Creatinine was evaluated using Pars Azmoon Kit (UREA Berthelot, 18,940) based on recommendations of producer company. The serum concentration of iron was also assessed by Pars Azmoon Kit (BT-2000, 18,923) as recommended by producer company.

The measurement of CBC

The blood samples were analyzed for white and red blood cells, hematocrit, lymphocyte, monocytes, neutrophils, lymphocytes, and basophiles, as suggested by previous studies (Nazerian et al. 2013). At the end of the study, the animals were grouped and compared into survivors and deceased groups. Hospitalized days and treatment costs were also evaluated.

Data analysis

The blood samples were collected from 55 dogs, and sera were obtained from all the collected samples. The data were investigated for normality by Kolmogorov–Smirnov test in SPSS software (version 23). All the data were normalized and analyzed by *t* test. Pearson correlation was used to investigate the relationship between variables.

Results

The relation between parameters

Table 1 depicts the results for the relation between parameters. The results showed negative significant relations between procalcitonin with hematocrit ($r^2 = 0.294$, $P < 0.05$) and the serum concentration of iron ($r^2 = 0.280$, $P < 0.05$) and also positive relation with IL-6 ($r^2 = 0.456$, $P < 0.01$) and TNF- α ($r^2 = 0.391$, $P < 0.01$). Significant relations were not seen between procalcitonin with other parameters ($P > 0.05$). There were positive relations between hematocrit with red blood cells ($r^2 = 0.846$,

Table 1 Correlation between parameters

	Pro-C	Hct	WBC	RBC	Hb	Fe	Crt	Plt	Glu	Alb	
Pro-C											
Hct	-0.294*										
WBC	-0.228	0.260									
RBC	-0.159	0.846***	0.130								
Hb	0.239	0.959***	0.165	0.863**							
Fe	-0.280*	0.791***	0.173	0.769***	0.768***						
Crt	0.051	0.281*	0.109	0.201	0.0301	0.193					
Plt	0.180	-0.083	0.215	-0.026	-0.067	-0.087	0.009				
Glu	0.058	0.070	0.466**	0.047	0.025	0.087	0.210	0.017			
Alb	0.196	0.114	0.589**	0.014	0.088	-0.061	0.209	-0.034	0.642**		
Urea		Lymph	Neut	Eos	Mon	IL-6	TNF-α	Bandcell	Tem	Day	Cost
Pro-C	0.102	0.108	-0.146	0.102	-0.081	0.456**	0.391**	0.065	-0.005	0.083	0.055
Hct	0.013	0.099	0.241	-0.251	0.167	-0.011	0.025	0.178	0.051	0.095	0.058
WBC	0.322*	0.038	0.904**	0.363*	0.683**	0.486**	0.409**	0.304*	0.556**	0.310*	0.245
RBC	0.026	0.224	0.216	-0.260	0.126	0.038	0.052	-0.051	0.054	0.090	-0.051
Hb	0.010	0.110	0.158	-0.349*	-0.030	0.052	0.041	0.126	0.025	0.069	0.010
Fe	-0.116	-0.189	0.185	-0.192	-0.027	0.062	0.055	0.184	0.028	0.000	0.009
Crt	0.165	0.019	0.017	0.270	-0.275	0.032	0.047	0.118	0.324**	0.103	0.115
Plt	0.019	0.138	0.307*	0.412*	0.005	0.076	0.055	-0.256	0.060	0.180	0.175
Glu	0.375**	0.474**	0.501**	0.421*	0.357*	-0.303*	-0.296	0.348	0.837**	0.082	0.145
Alb	0.455**	0.551**	0.573**	0.430*	0.532*	-0.527*	0.402*	0.465*	0.733**	0.112	0.128
Urea	-	0.412**	0.327*	0.236	0.140	-0.376*	-0.334*	0.043	0.410**	0.007	0.027
Lymph			-0.173	0.355*	-0.350*	-0.264	-0.112	-0.098	0.607**	-0.191	-0.227
Neut				0.264	0.786**	-0.518**	-0.415**	0.291	0.521**	0.474**	0.425**
Eos					-0.455**	-0.322*	0.061	-0.361*	0.469*	0.018	0.018
Mon						-0.589*	-0.512*	0.353*	0.429*	0.475	0.362
IL-6							0.512	-0.371*	-0.447**	-0.321*	-0.203
TNF-α								-0.371*	-0.441**	-0.358*	-0.195
Bandcell									0.554	0.019	0.061
Tem										-0.154	-0.219
Day											0.961
Cost											

Pro-C Procalcitonin, Hct Hematocrit, WBC White Blood Cells, RBC Red Blood Cells, Hb Hemoglobin, Fe Iron, Crt Creatinine, Plt Platelet, Glu Glucose, Alb Albumin, Lymph Lymphocyte, Neut Neutrophil, Eos Eosinophil, Mon Monocyte, IL-6 Interleukin-6, TNF-α Tumor necrosis factor-α, Tem Temperature

Superscripts *, **, and *** show significant relationships at $P < 0.05$; $P < 0.001$ and $P < 0.0001$ respectively

Table 2 The concentrations of parameters and other characteristics in survivors and deceased groups

	Deceased	Survivors	T-statistic	P value
Pro-C	120.57 ± 34.71	89.83 ± 39.30	2.89	0.006
Hct (%)	25.05 ± 7.28	26.26 ± 8.53	-0.530	0.598
WBC (10 ³ /μL)	2427.78 ± 1295.15	3331.82 ± 995.90	-2.49	0.017
RBC (10 ⁶ /μL)	4.19 ± 1.02	4.20 ± 1.17	-0.007	0.995
Hb (%)	10.36 ± 2.99	10.49 ± 3.52	-0.140	0.890
Fe	84.35 ± 12.91	82.91 ± 13.34	0.387	0.700
Crt	0.97 ± 0.36	1.01 ± 0.35	-0.416	0.679
Plt (10 ³ /μL)	231.90 ± 148.80	265.88 ± 120.91	-0.915	0.364
Glu (mg/dL)	59.53 ± 27.88	81.06 ± 28.02	-2.76	0.008
Alb (mg/dL)	2.33 ± 0.55	3.37 ± 0.96	-5.058	0.0001
Urea	12.28 ± 5.38	19.72 ± 9.15	-3.30	0.007
Lymph	528.75 ± 245.15	1587.79 ± 1008.08	-4.96	0.001
Neut	1477.40 ± 1249.72	2376.25 ± 1086.77	-2.44	0.020
Eos	203.42 ± 129.76	330.87 ± 250.46	-1.70	0.102
Mon	34.70 ± 23.14	54.28 ± 26.80	-1.61	0.128
IL-6 (pg/mL)	896.78 ± 437.14	235.07 ± 122.19	5.52	0.001
TNF-α (ng/mL)	495.23 ± 63.52	245.52 ± 89.23	7.81	0.001
Bandcell	68.86 ± 29.63	61.17 ± 37.74	0.464	0.649
Tem (°C)	32.99 ± 8.18	37.50 ± 2.56	-2.98	0.004
Day	3.70 ± 1.84	4.38 ± 1.76	-1.35	0.181
Cost	1,432,500 ± 879,101	1,632,764 ± 856,510	-0.822	0.415

The data are presented as mean ± SD

Pro-C Procalcitonin, Hct Hematocrit, WBC White Blood Cells, RBC Red Blood Cells, Hb Hemoglobin, Fe Iron, Crt Creatinine, Plt Platelet, Glu Glucose, Alb Albumin, Lymph Lymphocyte, Neut Neutrophil, Eos Eosinophil, Mon Monocyte, IL-6 Interleukin-6, TNF-α Tumor Necrosis factor-α, Tem Temperature

$P < 0.001$), hemoglobin ($r^2 = 0.959$, $P < 0.001$), iron ($r^2 = 0.791$, $P < 0.001$), and creatinine ($r^2 = 0.281$, $P < 0.05$). The results also showed significant relations between white blood cells with glucose ($r^2 = 0.466$, $P < 0.01$), albumin ($r^2 = 0.589$, $P < 0.01$), urea ($r^2 = 0.322$, $P < 0.05$), neutrophil ($r^2 = 0.904$, $P < 0.001$), eosinophil ($r^2 = 0.363$, $P < 0.05$), monocyte ($r^2 = 0.983$, $P < 0.001$), IL-6 ($r^2 = 0.486$, $P < 0.001$), and TNF-α ($r^2 = 0.409$, $P < 0.001$). There were significant relations between stress indexes of glucose and albumin with body temperature. Other significant relations are shown in Table 1.

The concentrations of parameters in survivors and deceased groups

Table 2 shows the results for the concentrations of blood parameters and other parameters in survivors and deceased groups. The results showed significant differences between survivors and deceased groups for procalcitonin ($P = 0.006$), white blood cells ($P = 0.017$), glucose ($P = 0.008$), albumin ($P = 0.0001$), urea ($P = 0.007$), lymphocyte ($P = 0.001$), neutrophil ($P = 0.020$), IL-6 ($P = 0.001$), TNF-α ($P = 0.001$), and body temperature ($P = 0.004$). Based on findings, the serum concentrations of procalcitonin, IL-6, and TNF-α

were significantly higher in deceased dogs compared with survivors, while white blood cells, glucose, albumin, urea, lymphocyte, neutrophil, and body temperature were higher in survivors compared with others.

Discussion

The pathogenesis of sepsis and SIRS causes to involve a complex interplay of factors and dysregulation of immunity. Early diagnosis, differentiation, and prognosis of SIRS help human and veterinary medicine with the use of appropriate treatments (Thames et al. 2019). In the current study, procalcitonin was evaluated as a prognosis factor in dogs in ICU. Several studies have reported the increase in procalcitonin in patients with sepsis and SIRS (Mustafić et al. 2018; Patil and Patil 2020; Sharma et al. 2020). The increased bacterial infection leads to increased procalcitonin (Moustafa et al. 2021). However, the serum concentration of procalcitonin has not been evaluated in dogs with SIRS in the intensive care unit.

The results showed an inverse relation between procalcitonin with hematocrit and iron. The results are in agreement with previous studies for the relation between procalcitonin

with hematocrit in dogs with pyometra (Ahn et al. 2021). Our findings concur with other studies that reported a negative relationship between procalcitonin with hematocrit and iron in patients with coronary artery abnormalities (Liu et al. 2021). It has been also reported that an increase in serum concentration of procalcitonin concurs with a decrease in hematocrit and iron in patients with COVID-19 (Mertoglu et al. 2021). The increased serum concentration of procalcitonin could be attributed to greater inflammation and bacterial infection in patients in ICU. Iron and hematocrit deficiencies occur during infections (Riety and Nursyam 2022). The decreased hematocrit and iron could be attributed to repeated hemorrhages and the administration of agents affecting iron and hematocrit.

Based on the findings, procalcitonin can be considered as a prognostic value in dogs with SIRS. There was also a positive relationship between the serum concentrations of IL-6 and TNF- α with procalcitonin. Several studies have reported a significant relations between procalcitonin with IL-6 and TNF- α in rats with mild and severe pancreatitis (Soyalp et al. 2017) and white swine (Chalkias et al. 2021). The increased serum concentrations of pro-inflammatory cytokines are directly associated with the severity and mortality of human sepsis. In fact, the cytokines lead to an increase in the variety of pathologic reactions and hypotension and shock (Chalkias et al. 2021). In fact, IL-6 is the main cytokine responsible to induce the systemic changes and promotes postoperative neurological dysfunction (Chalkias et al. 2021). TNF- α is a pro-inflammatory cytokine that participates in several physiological and pathophysiological processes and may encourage monocyte/macrophage differentiation and tumor cell necrosis/apoptosis (Sedger and McDermott 2014). SIRS is largely mediated by pro-inflammatory cytokines, and a SIRS-like clinical picture can be induced by the administration of pro-inflammatory cytokines (Natanson et al. 1989). IL-6 is known as a good diagnostic and prognostic marker in people with SIRS (Pettilä et al. 2002; Reinhart et al. 2000), and this has also been confirmed in dogs with SIRS (Rau et al. 2007). The results indicate significant relations between procalcitonin with TNF- α and IL-6. In addition, the results showed increase of 1.3 times serum concentrations of procalcitonin in deceased dogs compared with survivors. In fact, the concentration of procalcitonin is significantly higher in dogs with a chronic condition of disease. The increased procalcitonin in deceased dogs means to be appropriate as a prognostic value in dogs with SIRS in ICU.

The results also showed increased serum concentrations of IL-6 and TNF- α in deceased dogs. The findings are in agreement with those reported by Ghazizadeh et al. who showed to be high procalcitonin concentration in the acute phase of sepsis (Ghazizadeh et al. 2021). Other studies have also reported an increase in inflammatory factors in dogs with systematic infection (Gommeren et al. 2018; Kuzi et al.

2020). It has been reported that procalcitonin concentration is a marker for distinguishing infectious episodes from non-infectious episodes (Haeusler et al. 2013). The results are also parallel with those reported by Neumann and others who reported higher serum concentration of procalcitonin in dogs with sepsis in the acute phase compared with control healthy dogs (Neumann 2022). In addition, white blood cells, glucose, albumin, urea, lymphocyte, neutrophil, and body temperature were higher in survivors compared with others. The increase in parameters implicates the presence of infection and fighting the body against disease. Fighting against disease requires an energy source, and the increased glucose is a response to supplying energy for fighting against disease (Suleiman et al. 2022). The increased white blood cells and pro-inflammatory cytokines in survivor dogs highlight greater immunity in them compared with deceased dogs. All the findings show to be appropriate and specific procalcitonin as a prognostic value in dogs with SIRS.

The results did not show significant differences between survivors and non-survivors for hospitalized costs and days, although costs and days were numerically lower in survivors compared with other groups. The decrease in hospitalized days directly reduces the costs for dog owners.

Conclusion

In sum, the serum concentration of procalcitonin was higher in dogs with SIRS and especially in deceased dogs compared with survivors. It shows that pro-calcitonin is a good value for the prognosis of SIRS. In addition, procalcitonin showed a strong and positive correlation with pro-inflammatory cytokines of IL-6 and TNF- α . Based on findings, procalcitonin is a good marker for early diagnosis of SIRS in dogs admitted to ICU. Using procalcitonin helps early diagnosis of SIRS and reduces hospitalized days and costs.

Acknowledgements Authors would like to appreciate Islamic Azad University, Science and Research Branch for their support.

Compliance with ethical standards

Funding This study was not supported by any funding.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All the experimental procedures were in agreement with protocols advised by Ethical Committee of Islamic Azad University, Sciences and Research Branch (IR.IAU.SRB.REC.1400.048).

Informed consent For this type of study informed consent is not required.

Consent for publication For this type of study consent for publication is not required.

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