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RESEARCH ARTICLE

Evaluation of C-Reactive Protein, Albumin, Neopterin, Urokinase Type Plasminogen Activator Receptor and Leukocyte Levels as Prognostic Parameters in Dogs with Parvoviral Enteritis

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ABSTRACT

The aim of this study was to determine the changes in C-reactive protein (CRP), albumin, neopterin (Np), urokinase type plasminogen activator receptor (uPAR) and leukocyte levels in dogs with parvoviral enteritis and to show the prognostic importance of these. In the study, a total of 48 dogs, 40 with parvoviral enteritis and 8 were healthy, were used. The dogs with parvoviral enteritis were divided into two subgroups, non-surviving (n=12) and surviving (n=28). The non-surviving dogs with parvoviral enteritis in the study had significantly ($p<0.05$) lower leukocyte levels than the control group and the surviving dogs with parvoviral enteritis. Serum albumin concentrations of non-surviving dogs with parvoviral enteritis were also significantly ($p<0.05$) lower than the control group. On the contrary, the CRP levels of the non-surviving and surviving dogs with parvoviral enteritis were significantly ($p<0.05$) higher than the control group. There was also no statistically significant difference between the groups in terms of Np and uPAR levels. The cut-off values of leukocyte, CRP and albumin were 4.5×10^9L, 120.50 mg/L and 2.28 g/dL, respectively. As a result, it can be stated that decreased leukocyte and albumin levels and increased CRP levels in dogs with parvoviral enteritis may be an indicator of poor prognosis. It was also determined that serum Np and uPAR levels in dogs with parvoviral enteritis do not have any prognostic importance.

Keywords: Parvoviral enteritis, C-reactive protein, neopterin, urokinase type plasminogen activator receptor, dog

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Parvoviral Enteritisli Köpeklerde Prognostik Parametreler Olarak C-Reaktif Protein, Albümin, Neopterin, Ürokinaz Tipi Plazminojen Aktivatör Reseptörü ve Lökosit Seviyelerinin Değerlendirilmesi

ÖZ

Bu çalışmanın amacı, parvoviral enteritisli köpeklerde C-reaktif protein (CRP), albumin, neopterin (Np), ürokinaz tipi plazminojen aktivatör reseptörü (uPAR) ve lökosit seviyelerindeki değişiklikleri belirlemek ve bunların prognostik önemini göstermekti. Çalışmada 40'ı parvoviral enteritisli ve 8'i sağlıklı olmak üzere toplam 48 köpek kullanıldı. Parvoviral enteritisli köpekler ölen (n=12) ve hayatta kalanlar (n=28) olarak iki gruba ayrıldı. Çalışmada ölen parvoviral enteritisli köpeklerin lökosit seviyesi kontrol grubu ve yaşayan parvoviral enteritisli köpeklere göre önemli düzeyde ($p<0.05$) düşük bulundu. Ölen parvoviral enteritisli köpeklerin serum albümin konsantrasyonları da kontrol grubundan önemli düzeyde ($p<0.05$) düşük bulundu. Aksine, ölen ve yaşayan parvoviral enteritisli köpeklerin CRP düzeyi kontrol grubuna göre önemli düzeyde ($p<0.05$) yüksek olarak tespit edildi. Np ve uPAR düzeyleri açısından ise gruplar arasında istatistiksel olarak anlamlı fark yoktu. Lökosit, CRP ve albüminin cut-off değerleri sırasıyla 4.5×10^9L, 120.50 mg/L ve 2.28 g/dL olarak tespit edildi. Sonuç olarak, parvoviral enteritisli köpeklerde azalmış lökosit ve albumin seviyeleri ile artmış CRP seviyelerinin kötü prognozun bir göstergesi olabileceği ifade edilebilir. Ayrıca serum Np ve uPAR düzeylerinin parvoviral enteritisli köpeklerde prognostik bir öneme sahip olmadığı belirlenmiştir.

Anahtar Kelimeler: Parvoviral enteritis, C-reactive protein, neopterin, ürokinaz plazminojen aktivatör reseptör, köpek

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INTRODUCTION

Canine parvoviral enteritis is an infectious viral disease which is caused by the canine parvovirus (CPV) type-2 from the Parvoviridae family. It is characterized by severe vomiting, hemorrhagic gastroenteritis and leukopenia (Kalli et al. 2010, Decaro and Buonavoglia 2012, Castro et al. 2013, Mylonakis et al. 2016). The disease is one of the common infections in puppies and morbidity and mortality rates are high in the disease (Kocaturk et al. 2010). The disease has two forms, enteritis and myocarditis (Nandi and Kumar 2010, Ford et al. 2017).

Most of the acute phase proteins formed during infectious diseases exhibit a non-specific immunological (inflammatory) response. Most of these proteins are glycoprotein-structured and are of liver origin. Increased acute phase proteins (for example, C-reactive protein and serum amyloid A) are called positive acute phase proteins while decreased acute phase proteins (for example albumin and transferrin) are called negative acute phase proteins (Cerón et al. 2005). CRP is the most important acute phase protein in dogs; it increases rapidly in infectious diseases and reaches its peak in 24-48 hours (Cerón et al. 2005, Schmidt and Eckersall 2015). When CRP binds to bacteria, it promotes complement binding which facilitates bacterial uptake of phagocytes, inhibits chemotaxis and regulates neutrophil function, and also induces anti-inflammatory cytokine production (Schmidt and Eckersall 2015). Increased CRP levels in patients with sepsis in human medicine were found to be associated with mortality (Koozi et al. 2020). Studies conducted in veterinary medicine have indicated that serum CRP, as one of the species-specific acute phase proteins, may provide information about diseases such as pancreatitis, neoplasias, sepsis, parvoviral enteritis, pyometra, systemic inflammatory response syndrome (SIRS), leishmaniosis, ehrlichiosis and babesiosis in dogs (Christensen et al. 2014, Ok et al. 2015, Daza González et al. 2019).

During the course of infectious diseases, Np as the end product of pteridine metabolism is released from monocytes and macrophages by interferon-gamma stimuli which are released from T lymphocytes (Berdowska and Zwirska-Korczala 2001). Increased Np concentrations have been reported in malignancies, infectious and autoimmune diseases where cellular immunological mechanisms are activated, and it has been suggested that these concentrations be used to evaluate the clinical course of diseases (Hoffmann et al. 2003, Pourakbari et al. 2010, Bastan et al. 2013, Ünüvar and Aslanhan 2019). In addition, significant increases in neopterin levels were detected in dogs with SIRS (Basbug et al. 2020) and trypanosomiasis (Rokos et al. 1992), cattle with Lumpy Skin Disease (Başbuğ et al. 2016), and calves with septicaemia (Ercan et al. 2016). Szczubiał et al. (2014) has been reported that in dogs with primary mammary cancer, the neopterin concentration is lower than in healthy animals.

uPAR is released mainly from neutrophils, endothelial and peripheral mononuclear blood cells (Donadello et al. 2012). It is involved in various immunological functions such as cell adhesion, migration, differentiation and proliferation. It has been stated that uPAR can be a potential biomarker for diseases in human medicine (Donadello et al. 2012, Çekmez et al. 2014). Although uPAR has been reported as a potential prognostic marker in sepsis, pulmonary and malignant diseases in human individuals and it can be used in intensive care units in human medicine (Stephens et al. 1997, Donadello et al. 2012, Wu et al. 2013), no literature on its use in veterinary medicine has been found in the literature.

This study aimed to determine the prognostic significance of CRP, albumin, neopterin, uPAR and leukocyte levels in dogs with parvoviral enteritis.

MATERIAL and METHODS

This study was approved by the Local Ethics Committee for Animal Experiments, Sivas Cumhuriyet University (approval number: 2016-81). The animal material of the study consisted of 40 dogs aged 6-18 weeks (7.07±1.2 weeks) of both genders (22 female, 18 male) and different breeds (25 Anatolian shepherd dogs, 5 Golden retriever, 5 Rottweiler, 3 Pointer, 2 German shepherd dogs) which had parvoviral enteritis, and which had been brought to the Internal Medicine Clinic at the Veterinary Faculty, Sivas Cumhuriyet University for examination and treatment, and 8 healthy dogs (control group) without any symptoms of disease. The dogs in the control group were of different breeds (4 Anatolian shepherd dogs, 1 Rottweiler, 1 Rottweiler, 1 Pointer, 1 German shepherd dogs), genders (5 female, 3 male) and were different ages 6-18 weeks old (6.92±0.4 weeks). Also, the dogs between 2.5-15 kg (parvoviral enteritis 5.03±0.4 kg, control 5.25±0.9 kg) were included in the study. Parvoviral enteritis in dogs was diagnosed by clinical symptoms, fecal antigen test and hematological findings.

The dogs with parvoviral enteritis and the healthy were examined for giardia and coccidiosis, and those with negative results were included in the study. The dogs were divided into two groups, surviving and non-surviving, after a follow-up of the health statuses of the dogs subsequent to the treatment.

After all clinical examinations, 5 ml of blood samples were taken from the vena cephalica antebrachi of the dogs to the tubes with anticoagulant and without anticoagulant once before treatment. In the blood samples with EDTA the levels of leukocyte,

erythrocyte, hematocrits, hemoglobin and platelets were determined by a hematological analyzer (BC-2800 Vet hematology analyzer, Mindray Bio-Medical Electronics Co. Ltd., Nanshan, Shenzhen). The blood samples with no anticoagulant were centrifuged at 3000 rpm for 10 min, and the serum samples were collected by centrifugation. These samples were stored at -80°C until biochemical analyses were performed. Serum albumin concentrations were measured on an automated analyzer (BS 200 chemistry analyzer, Mindray Bio-Medical Electronics Co. Ltd, Nanshan, Shenzhen) using commercial test kits. The levels of Canine CRP (Tri-Delta Phase CRP, Tri-Delta Diagnostic, Boonton Township, NJ), Np (Canine Neopterin ELISA Kit, Yehua Biological Technology Co. Ltd, Shanghai) and uPAR (Canine uPAR ELISA Kit, Sunred Biological Technology Co. Ltd, Shanghai) were determined using species specific ELISA kits according to the manufacturer's instructions. Absorbances were measured using a microplate reader (Thermo Multiskan GO Microplate Spectrophotometer, Waltham, Massachusetts).

In all the dogs included in the study, stool examination was performed with an antigen test kit (SNAP Parvo Test, Idexx, Westbrook, ME) without cross-reaction to modified live vaccines.

Treatment

All dogs with parvoviral enteritis were kept under observation for seven days in the infectious disease unit of the clinic. The sick dogs were given intravenous fluid containing balanced electrolyte solution to correct dehydration via intravenous catheter, which was placed in the vena cephalica antebrachi. Fluid therapy was continued until vomiting disappeared and food intake began. All dogs with parvoviral enteritis were administered with 50 mg/kg ceftriaxone (Desefin 1 gr IV, Deva, Istanbul) once a day. In addition, 2 mg/kg ranitidine (Ulcuran, Abfar, Istanbul), 0.2 mg/kg (Metpamid, Recordati, Istanbul) and 250 mg transaminic acid (Transamine 10%, Fako Istanbul) were administered twice a day, and 500 mg ascorbic acid (Injacom C, Ceva Animal Science, Istanbul) and B-complex vitamin (Bemiks, Zentiva, Istanbul) were administered once a day.

Statistical Methods

The data were shown with mean and standard error. The ANOVA test was used to determine the difference between the groups. $p<0.05$ was accepted as statistically significant. The Receiver Operating Characteristic (ROC) curve was used to determine a cut-off value for non-surviving and surviving dogs with parvoviral enteritis in terms of CRP, albumin and leukocyte measurements. Likelihood Ratio (LR) was calculated for each cut-off threshold and the highest LR was considered as the optimal cut-off point. The Pearson correlation coefficient was used to quantify the relationship between CRP, neopterin, uPAR, albumin and leukocyte. For analysis of the data, the SPSS software program (Version 15.0, SPSS Inc. Ltd. Chicago USA) was used.

RESULTS

The dogs with parvoviral enteritis were observed to have loss of appetite, decreased interest in the environment, depressed appearance, vomiting, bloody diarrhea and dehyration. Despite intensive care, 12 of dogs with parvoviral enteritis died within the first 48 hours. Also, all animals were followed for 1 week and information was obtained from the owners. Necropsy was performed on dogs that non-survivors and the diagnosis of parvoviral enteritis was confirmed in the necropsy.

The results of hematological analysis of the dogs with parvoviral enteritis and healthy are given in Table 1. The leukocyte levels of non-surviving dogs with parvoviral enteritis were found to be significantly ($p<0.05$) lower than those of the control group and surviving dogs with parvoviral enteritis.

The changes in CRP, Np, uPAR and albumin levels of the dogs with parvoviral enteritis and healthy are shown in Table 2. The CRP levels of the non-surviving and surviving dogs with parvoviral enteritis were significantly ($p<0.05$) higher than the control group. On the contrary, the serum albumin concentration of non-surviving dogs with parvoviral enteritis was found to be significantly ($p<0.05$) lower than that of the control group. Albumin showed a negative correlation with CRP, while it showed a positive correlation with leukocyte (Table 3).

The cut-off values, sensitivity, specificity, and area under the curve of CRP, albumin and leukocyte levels of surviving and non-surviving dogs with parvoviral enteritis are given in Table 4. The cut-off values for CRP, albumin and leukocyte levels were determined as 120.5 (mg/L), 2.28 (g/dL) and 4.5 ($\times 10^9$L), respectively.

Table 1: Clinical finding and hematological parameters in the dogs with parvoviral enteritis and healthy

Parameters	Healthy group	Survivors	Non- Survivors
Leukocyte ($\times10^9$L)	9.35 ± 0.77[a]	9.86 ± 1.10[a]	3.69 ± 1.17[b]
Erythrocyte ($\times10^{12}$L)	5.32 ± 0.38	5.24 ± 0.19	5.99 ± 0.23
HCT (%)	36.85 ± 2.81	33.31 ± 2.08	41.68 ± 2.90
Hg (g/dL)	10.31 ± 1.00	8.73 ± 0.60	11.45 ± 0.66
PLT ($\times10^9$L)	383.75 ± 37.92	398.52 ± 60.66	396.92 ± 37.44
Temperature (°C)	38.41 ± 0.11	38.72 0.19	37.97 ± 0.27

HCT; hematocrit, Hg; hemoglobin, PLT; platelet. a, b: the difference between the average values with different letters in the same row is significant ($p<0.05$).

Table 2: CRP, neopterin, uPAR and albumin levels in the dogs with parvoviral enteritis and healthy

Parameters	Healthy group	Survivors	Non- Survivors
CRP (mg/L)	9.20 ± 2.64[b]	111.30 ± 6.12[a]	133.04 ± 3.48[a]
Neopterin (nmol/mL)	13.28 ± 3.70	8.22 ± 0.49	10.44 ± 1.83
uPAR (ng/mL)	2.59 ± 0.73	1.64 ± 0.10	2.02 ± 0.29
Albumin (g/dL)	2.47 ± 0.29[a]	2.44 ± 0.60[ab]	2.21 ± 0.65[b]

CRP; C-reactive protein, uPAR; urokinase type plasminogen activator receptor. a, b: the difference between the average values with different letters in the same row is significant ($p<0.05$).

Table 3. Pearson correlation coefficient between CRP, neopterin, uPAR, albumin and leukocyte in the dogs with parvoviral enteritis and healthy

Parameters	Neopterin	uPAR	Albumin	Leukocyte
CRP	-,242	-,232	-,358*	-,251
Neopterin		,909**	,046	-,043
uPAR			,040	-,090
Albumin				,445**

CRP; C-reactive protein, uPAR; urokinase type plasminogen activator receptor. *Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)

Table 4: Cut-off, sensitivity, specificity and area under the curve values of CRP, albumin and leukocyte in the dogs with parvoviral enteritis and healthy

Parameters	CRP (mg/L)	Albumin (g/dL)	Leukocyte ($\times10^9$L)
AUC	0.68	0.72	0.90
Cut off	120.50	2.28	4.5
Sensitivity (%)	92.3	69.2	84.6
Specificity (%)	54.0	71.4	92.6
p	0.073	0.029	< 0.001
SEM	0.082	0.087	0.069

AUC; Area under the curve, SEM; standard error of mean, CRP; C-reactive protein

DISCUSSION

Myocarditis, sepsis, systemic inflammatory response syndrome (SIRS) and endotoxemia that develop as a result of CPV infection may be the cause of death (Turk et al. 1990, Otto et al. 1997, Prittie 2004). In this study, changes in serum CRP, uPAR, Np, albumin and leukocyte levels and the prognostic

significance of these in dogs with parvoviral enteritis were evaluated.

CRP is a sensitive marker of inflammation, tissue damage and infection. An increased CRP level has been reported as a potential indicative marker of poor prognosis which is related to the inflammatory response (Kocaturk et al. 2010, Kocaturk et al. 2015). CRP is the major acute phase protein used in the evaluation of inflammation in dogs and is synthesized in the liver by stimulation of cytokines secreted mainly from the inflamed tissue. The CRP level has been reported to reach peak values after 48 hours and to return to normal levels within 1-2 weeks (Cerón et al. 2005). Healthy dogs have a very low level of serum CRP (Schmidt and Eckersall 2015). In human and veterinary medicine, CRP measurement is a test which shows inflammation and it has also been reported as a potential prognostic marker in some diseases (Cerón et al. 2005, Kocaturk et al. 2010, Nandi and Kumar 2010). In dogs with parvoviral enteritis, serum levels of CRP may be 10 times higher than in healthy subjects; it may be a biomarker that shows the severity of the disease. McClure et al. (2013) have been reported that although serum CRP concentration was associated with outcome in puppies with parvoviral enteritis, it did not prove to be a good predictor of outcome when used alone. Kocaturk et al. (2010) reported that mortality rate was 91% in dogs with parvoviral enteritis which had CRP levels above 92.4 mg/L. In our study, serum CRP levels were found to be significantly ($p<0.05$) higher in the surviving and non-surviving dogs with parvoviral enteritis compared to the control group. When the cut-off value for CRP was evaluated as 120.5 mg/L to differentiate survivors from non-survivors, the sensitivity and specificity were determined as 92.3% and 54.0% respectively. While significant increases in CRP level are mainly observed in bacterial infections in dogs, the increase in viral infections is at smaller levels (Gruys et al. 2005). In studies conducted (Kocaturk et al. 2010, Kocaturk et al. 2015), it has been reported that secondary bacterial infections and sepsis may develop in dogs with parvoviral enteritis. This explains this increase in CRP level in dogs with parvoviral enteritis. In addition, this suggests that increased CRP may be evaluated as a sign of poor prognosis in the dogs with parvoviral enteritis in consistent with other studies.

In medical practice, inflammatory mediators such as serum Np and uPAR are analyzed to identify the extent of inflammation in different infectious diseases and to provide information about clinical prognosis (Berdowska and Zwirska-Korczala 2001, Donadello et al. 2012, Grove et al. 2014). Neopterin is released by macrophages in response to stimuli of cytokines such as interferon-γ in infectious patients (Hoffmann et al. 2003). It has been stated that Np levels may be a prognostic factor in patients with sepsis (Tasdelen Fisgin et al. 2010). Nevertheless, viral infections have been reported to increase Np levels in blood before the appearance of clinical symptoms (Chan et al. 2006, Başbuğ et al. 2016). Kaufmann et al. (1998) reported that Np may provide more valuable information than CRP in the determination of the severity of pancreatitis in human medicine. Başbuğ et al. (2016) reported a positive correlation between the clinical appearance of lumpy skin disease and blood Np level in cattle. Rokos et al. (1992) has been reported that an increase in serum neopterin levels in dogs after Trypanosoma infection and this supports the activation of the cellular immune system. Basbug et al. (2020) has been stated that serum neopterin levels significantly increased in dogs with SIRS compared to healthy dogs. In contrast, Szczubiał et al. (2014) has been reported that in dogs with primary mammary cancer, the neopterin concentration is lower than in healthy animals, and this low neopterin level may be associated with impaired cell-mediated immunity. In another study (Strasser et al. 2003), they reported that a significant reduction in neopterin level was observed in dogs following polyvalent vaccination. In this study, it was found that serum Np levels were low in dogs with parvoviral enteritis compared to the control group, but there was no statistical difference. Decreased neopterin levels in dogs with parvoviral enteritis may be associated with impaired cell-mediated immunity.

It is reported that uPAR can be evaluated as one of the indicators of inflammation in human medicine (Wu et al. 2013, Genua et al. 2015). uPAR, which is released from cells such as monocytes, macrophages, neutrophil, T cells, and endothelial, is considered as a marker for fibrinolysis and inflammation (Plesner et al. 1997, Genua et al. 2015). Increased uPAR levels have been reported as a marker for immune system activation in conditions such as inflammation and infection (Mondino and Blasi 2004, Genua et al. 2015). Florquin et al. (2001) reported that uPAR was significantly increased in experimental endotoxemia and urosepsis models. In this study, it was found that serum uPAR levels were low in dogs with parvoviral enteritis compared to the control group, but there was no statistical difference. The decrease in uPAR levels of dogs with parvoviral enteritis may be associated with leukopenia due to bone marrow and lymphoid tissue damage. Because uPAR is secreted by cells such as monocytes, macrophages, neutrophil and T cells.

Protein losses and hypoalbuminemia due to enteropathies are common signs (Willard 2015). Plasma protein and albumin levels were decreased in the dogs with parvoviral enteritis (Kocaturk et al. 2010, Bastan et al. 2013). It has been reported that the cause of this decrease is enteritis and/or haemorrhagic diarrhea, anorexia and malabsorption (Wingfield and Raffe 2002). Many studies have found a positive correlation between low albumin levels and morbidity and mortality (Mazzaferro et al. 2002, Kalli et al. 2010, Kocaturk et al. 2010). Albumin is also a negative acute phase protein and its concentration is

reduced by 25% during the inflammatory response (Cerón et al. 2005, Eckersall 2008). Albumin has a low clinical value in the diagnosis and monitoring of inflammation, although its measurement is easier. Decreased albumin level is a marker for the acute phase reaction in dogs and cats with infection and inflammation. However, their sensitivity and specificity rates are not as high as CRP for clinical or subclinical diseases (Christensen et al. 2014, Torrente et al. 2015). In this study, serum albumin levels decreased in the non-surviving and surviving dogs with parvoviral enteritis compared to the control group. However, only the decrease in serum albumin levels of the non-surviving dogs with parvoviral enteritis was statistically significant ($p<0.05$). In this study, the cut off value for albumin was found to be 2.28 g/dL; its sensitivity and specificity were 69.2% and 71.4%, respectively. According to the results of the study, the serum albumin level in the dogs with parvoviral enteritis is useful in the evaluating of the prognosis of the disease and low albumin levels may be a marker of poor prognosis.

The predominant hematological abnormality in dogs with parvoviral enteritis is leukopenia, because bone marrow precursors and the lymphoid tissues are destroyed (Turk et al. 1990). There was a relationship between leukopenia and death in dogs with parvoviral enteritis. Furthermore, leukopenia may also be an important tool for determining the prognosis (Willard 2015). Macartney et al. (1984) reported that panleukopenia, which is characterized with lymphopenia and granulocytopenia, is a significant laboratory finding in the first 72 hours when the clinical symptoms of dogs with parvoviral enteritis are observed. It has been stated that the severity of leukopenia is positively correlated with the clinical pattern of the disease in dogs with parvoviral enteritis, that the total leukocyte counts increases with recovery and that the leukocyte counts may be used in the determination of the prognosis of the disease (Macartney et al. 1984, Kuffer et al. 1997). In this study, a significant ($p<0.05$) decrease in leukocyte level was found in the non-surviving dogs with parvoviral enteritis compared to the surviving dogs with parvoviral enteritis and the control group. In addition, the sensitivity and specificity of leukocyte counts were determined as 84.6% and 92.6% respectively when the cut-off value used was $4.5x10^9$L. These results may provide important knowledge on the prognosis of the disease in dogs with parvoviral enteritis. Furthermore, a low leukocyte count may be a marker of poor prognosis.

In conclusion, it was evaluated that decrease in albumin and leukocyte levels and increase in CRP levels in dogs with parvoviral enteritis may be predictors of poor prognosis. In addition, serum Np and uPAR levels in dogs with parvoviral enteritis were found to have no prognostic significance.

Conflict of Interest: The authors declare that there is no conflict of interest.

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