

Research article

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Is there any relationship between C-reactive protein/albumin ratio and clinical severity of childhood community-acquired pneumonia

C-Reaktif Protein/Albümin Oranı ile Çocukluk Çağı Toplum Kökenli Pnömoninin Klinik Şiddeti Arasında İlişki Var mı?

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Abstract

Objectives: To investigate the relationship between the ratios of C-reactive protein (CRP)/albumin, neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), mean platelet volume (MPV)/platelet and erythrocyte sedimentation rate (ESR)/albumin in pediatric patients diagnosed with community-acquired pneumonia based on the severity of the disease.

Methods: This retrospective cross-sectional study included 52 patients with mild pneumonia, 30 with severe pneumonia, and 46 healthy controls. Whole blood parameters, CRP, ESR, and albumin values and ratios were recorded at the time of admission. The multivariate regression analysis, Pearson's correlation and ROC curve analyses were performed.

Results: The CRP/albumin, ESR/albumin, NLR and CRP values were significantly higher in the severe pneumonia group compared to both the other pneumonia group and the control group ($p < 0.005$). According to the regression and correlation analyses, these values were positively

correlated ($p < 0.001$). For CRP/Albumin ratio, ESR/albumin ratio calculated OR were 2.103 (CI: 1.675–2.639); 1.907 (CI: 1.552–2.344); respectively.

Conclusions: The data presented can be a guide in the follow-up and treatment of this patient group.

Keywords: albumin; children; C-reactive protein; erythrocyte sedimentation rate; pneumonia.

Özet

Amaç: Toplum kökenli pnömoni tanısı almış çocuklarda hastalığın şiddeti ile C-reaktif protein (CRP)/albumin, nötrofil/lenfosit (NLR), monosit/lenfosit (MLR), mean platelet volum (MPV)/platelet and eritrosit sedimentasyon hızı (ESR)/albumin oranları arasındaki ilişkinin değerlendirilmesi.

Metot: Retrospektif ve kesitsel olarak tasarlanan bu çalışmaya 52 hafif pnömoni olgusu, 30 ağır pnömoni olgusu, 46 sağlıklı kontrol dahil edildi. Tam kan sayımı, CRP, ESR, ve albumin değerleri ve oranları başvuru anında kaydedildi. Multivaryant regresyon, Pearson korelasyon analizi ve ROC eğrisi analizleri çalışıldı.

Bulgular: CRP/albumin, ESR/albumin, NLR ve CRP değerleri ağır pnömoni grubunda hafif pnömoni ve sağlıklı kontrole göre anlamlı şekilde yüksek bulundu ($p < 0.005$). Bu değerlerde benzer şekilde pozitif korelasyon tespit edildi ($p < 0.001$). CRP/albumin oranı ve ESR/albumin oranı için Odds oranı (OR) sırası ile 2.103 (CI: 1.675–2.639); 1.907 (CI: 1.552–2.344) olarak hesaplandı.

Sonuç: Sunulan veriler bu hastaların takip ve tedavisinde yol gösterici olabilir.

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Anahtar kelimeler: albumin; çocuk; C-reaktif protein; eritrosit sedimentasyon hızı; pnömoni.

Introduction

Community-acquired pneumonia (CAP) is an important disease, leading to mortality in children under the age of five years, especially in developing countries [1]. According to the data of the World Health Organization, approximately one million children die every year due to CAP and lower respiratory tract infection [2]. The diagnosis of CAP is made based on clinical, radiological and laboratory findings. International guidelines have developed various diagnostic criteria that are mainly based on clinical signs and symptoms. Lung radiology or biochemical markers do not have 100% sensitivity or specificity [3]. In addition to combating risk factors, such as low birth weight, malnutrition, poor hygiene, and insufficient and/or unsafe food, early and timely interventions to the disease contribute to reducing mortality among children. Although the incidence of CAP has decreased due to conjugated pneumococcal vaccines developed recently, viral and atypical factors have started to replace pneumococcal strains [3, 4]. Therefore, the need for laboratory parameters to be combined with clinical findings in diagnosis and prognosis has increased.

In recent studies, the role of many biochemical markers in diagnosis and prognosis in childhood pneumonia has been investigated. Among the most frequently researched are C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), white blood cell (WBC) count, mean platelet volume (MPV), platelet number, procalcitonin, and interleukin-1 [5, 6]. CRP is a positive acute-phase reactant elevated in many infections, autoimmune diseases. Although erythrocyte sedimentation rate (ESR) increases slower than CRP, it is a positive acute-phase reactant, especially observed in rheumatological diseases, malignancies, and infections. Albumin is a negative acute-phase reactant inversely correlated with the severity of inflammation in various diseases [7]. In studies conducted, the ratio of CRP/albumin has been found to be a more sensitive marker in many diseases from malignancies to cardiovascular disorders and from infections to autoimmune diseases [7, 8]. Although we could not find information about the ESR/Albumin ratio in the literature, it is known that ESR and albumin levels can be important guides in inflammation [9]. The ESR/albumin ratio may also be a sensitive marker in this regard [9].

To our knowledge, this is the first study to investigate the relationship of CRP/albumin and ESR/albumin with

childhood CAP. We aimed to investigate the relationship between the diagnosis and clinical severity of CAP and the CRP/albumin, ESR/albumin, NLR, and platelet/MPV values.

Materials and methods

This retrospective cross-sectional study included 52 patients diagnosed with mild pneumonia and 30 with severe pneumonia according to the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America (PIDS/IDSA) classification [10], and 46 healthy children as the control group. The inclusion criteria for the study were presenting at our healthy child polyclinic for follow-up regarding child growth and development or being brought in for routine health exams, being in the similar age range, having no chronic diseases, having neither malnutrition nor obesity, being born full-term, having no acute infection, having no anaemia or polycythaemia, and having no kidney, lung, or liver diseases. In the diagnosis of CAP from three to 72 months of age, radiographic findings (lobar infiltration, round infiltration, consolidation, and interstitial involvement) and the presence of a higher respiratory rate than normal for age were taken into consideration. In addition to radiographic involvement and follow-up, the presence of any of sign of dyspnea, fever, retraction, and pathological auscultation was noted. The PIDS/IDSA classification (need for oxygenation, $PaO_2/FiO_2 < 250$, two or more of the symptoms of multilobar involvement, dyspnea, retraction, apnea, or fever) was used in the diagnosis of severe pneumonia [10]. Patients with immune deficiency, malnutrition, chronic kidney disease, cystic fibrosis, diabetes mellitus requiring chronic drug use, and connective tissue disease (systemic lupus erythematosus, familial Mediterranean fever, juvenile idiopathic arthritis, etc.) and those with defined syndromes or syndromic appearance were excluded from the study. A further 42 patients were excluded from the study due to incomplete records. The patients diagnosed with pneumonia were followed up and treated by the same pediatrician. The patients' age, gender, physical examination findings at first admission, NLR, WBC/lymphocyte, platelet/MPV, CRP/MPV, CRP/albumin, ESR/albumin, and monocyte/lymphocyte (MLR) were recorded from the electronic files. Samples of patients were taken at the time of diagnosis, first day of hospitalization. The relationship between these ratios and the severity of the disease was investigated. In the study, the complete blood count analysis was performed using a flow cytometric method with an ABX-Pentra DX 120 (Horiba LTD, Japan) device, and serum CRP and albumin analysis were performed using the photometric method with a Cobas C501 (Roche Diagnostic, Germany) device and ESR analysis was performed using the Modified Westergren method with SDM-100 (Berkhun, Turkey). For haemogram, purple capped K2EDTA tubes; for biochemistry, tubes with gel; for sedimentation, tubes with sodium citrate were used. All of them were standardized. Prior to the study, the local ethics committee approval was received (2019/80576354-050-99/113), and the study was conducted in accordance with the principles of the Helsinki Declaration.

The Statistical Package for Social Sciences (SPSS) v. 22 for Windows (IBM SPSS Inc., Chicago, USA) was used for the analysis of the data. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. The categorical variables were presented as numbers and percentages. The numerical values between the pneumonia and severe pneumonia groups were compared using Student's

t-test and Mann-Whitney U test, while one-way ANOVA and the Kruskal-Wallis test were used to compare the data between the three groups. The chi-square and Fisher's exact tests were conducted to compare the categorical data. The diagnostic discrimination of independent predictors for severity was examined using multivariate regression analysis and area under the curve (AUC) in receiver operating characteristic (ROC) curve analyses. The Pearson correlation test was used to analyze the correlations between CRP/albumin and NLR, NLR and CRP, CRP/albumin and CRP, and NLR and ESR/albumin, and then the R^2 linear value was calculated. In statistical analysis, a p value of <0.05 was considered statistically significant at the 95% confidence interval (CI) and 5% margin of error.

Results

A total of 128 children, (52 with pneumonia, 30 with severe pneumonia, and 46 healthy controls) were included in the study. There were no significant differences in age and gender between the patient and control groups ($p=0.693$ and $p=0.203$, respectively). As expected, the complication rate and length of hospital stay were significantly higher in patients with severe pneumonia ($p=0.002$ and $p=0.001$, respectively). The CRP, ESR, albumin, neutrophil and lymphocyte values also significantly differed both between the pneumonia groups and the control group, as well as between the severe pneumonia and pneumonia groups ($p=0.019$, 0.03 , 0.001 , 0.004 , and 0.009 , respectively). Table 1 present the comparison of the demographic and laboratory parameters of the groups. The ratios of NLR, CRP/albumin and ESR/albumin were significantly higher in the severe pneumonia group ($p=0.045$, 0.016 , and 0.003 , respectively) (Table 2). In the ROC curve and

regression analyses, AUC was calculated as 0.830 (CI: $0.754-0.906$) for CRP/albumin, 0.787 (CI: $0.701-0.873$) for ESR/albumin, and 0.785 (CI: $0.698-0.871$) for CRP. The CRP/albumin ratio presented as a valuable marker with 86.7% sensitivity and 70.4% specificity (Figure 1). When analyzed by linear regression and Pearson's correlation analysis, the CRP/albumin ratio was strongly correlated with CRP ($R^2=0.967$, $p<0.001$) and weak positively correlated with NLR ($R^2=0.125$, $p<0.001$). A weak positive relationship was also detected between NLR and CRP and between ESR and NLR ($R^2=0.137$, $p=0.001$ and $R^2=0.054$, $p=0.008$, respectively) (Figure 2). When we separated patients into two groups according to hospitalization length as 6 days or above and 5 days or below, we found that a significant difference ($p=0.016$), CRP/Albumin ratio is significant high in the group of hospitalization length was 6 days or above (CRP/Albumin ratio was 0.95 ± 1.22 and 0.47 ± 0.53 ; respectively). For CRP/Albumin ratio, ESR/albumin ratio and NLR, calculated OR were 2.103 (CI: $1.675-2.639$); 1.907 (CI: $1.552-2.344$); 1.378 (CI: $0.668-2.845$) respectively.

Discussion

Pediatric CAP is one of the leading causes of child deaths that can be prevented by timely diagnosis and treatment. The guidelines developed for diagnosis and clinical scoring are mainly based on clinical signs and symptoms. Biomarker studies with high sensitivity and specificity gain importance due to the low rate of the production of

Table 1: Evaluation of some demographic and laboratory parameters between groups.

	Pneumonia	Severe pneumonia	Control	p ¹ -Value	p ² -Value
Age, years	3.404 ± 2.178	3.933 ± 2.258	4.228 ± 1.569	0.123	0.693
Gender, n (Male/Female)	29/23	12/18	19/27	0.247	0.203
Complication, n ^a (Right heart failure, pneumothorax, pleural effusion), %	3/52 (5.7)	10/30 (33.3)	–	–	0.002
Hospitalization, day (mean $\pm$ SD)	4.92 ± 0.737	7.10 ± 1.348	–	–	0.001
WBC, $\times 10^3/\text{mm}^3$	10.28 ± 4.32	11.51 ± 6.44	8.84 ± 2.60	0.036^b	0.306
Neutrophil, $\times 10^3/\mu\text{L}$	4.40 ± 3.32	7.11 ± 4.83	4.34 ± 2.56	0.001^b	0.004
Lymphocyte, $\times 10^3/\mu\text{L}$	4.67 ± 2.34	3.39 ± 1.56	3.60 ± 1.41	0.003^b	0.009
Monocyte, $\times 10^3/\mu\text{L}$	0.89 ± 0.46	1.16 ± 1.3	1.06 ± 1.4	0.516	0.172
Hb, g/dL (mean $\pm$ SD)	12.08 ± 1.52	12.36 ± 1.75	12.91 ± 1.51	0.035	0.457
Platelet, $\times 10^3/\mu\text{L}$	395.77 ± 129.57	348.73 ± 117.54	337.85 ± 87.39	0.113 ^b	0.106
MPV, fL	7.92 ± 0.78	8 ± 0.67	7.87 ± 0.63	0.732	0.633
CRP, mg/dL	1.96 ± 2.21	3.80 ± 4.74	0.13 ± 0.14	<0.001^b	0.019
ESR, mm/h	26.44 ± 22.6	38.63 ± 26.59	7.85 ± 4.1	<0.001^b	0.03
Albumin, g/dL	4.28 ± 0.42	3.93 ± 0.37	4.17 ± 0.34	0.001	0.001

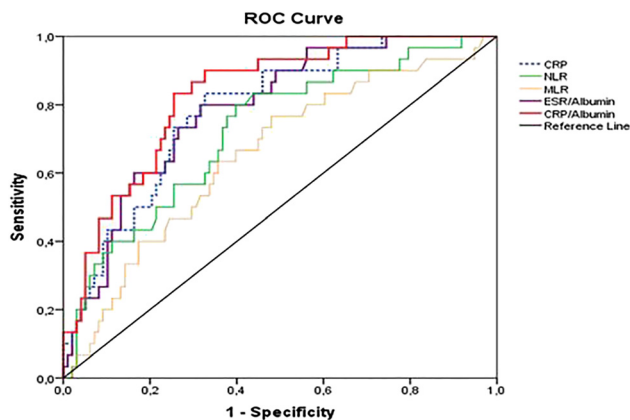
Mean $\pm$ SD are given. p¹-Value, between all groups, One way Anova; p²-Value, between pneumonia and severe pneumonia, Oneway Anova-Bonferonni test; ^aChi-square test. ^bKruskall Wallis test. Bold and italic p values are $p<0.005$.

Table 2: Comparison of some proportional values between groups.

	Pneumonia	Severe pneumonia	Control	p ¹ -Value	p ² -Value
NLR	1.47 ± 2.52	2.56 ± 1.90	1.5 ± 1.28	0.041	0.045
MLR	0.24 ± 0.21	0.36 ± 0.33	0.37 ± 0.6	0.233	0.042
WBC/Lymphocyte	2.79 ± 2.75	3.91 ± 2.15	2.78 ± 1.37	0.055	0.061
Plt/MPV	50.51 ± 17.22	44.54 ± 17.88	43.5 ± 13.05	0.074 ^a	0.140
CRP/MPV	0.25 ± 0.28	0.48 ± 0.63	0.017 ± 0.018	0.001	0.055
CRP/Albumin	0.46 ± 0.53	1.05 ± 1.26	0.032 ± 0.034	<0.001	0.016
ESR/Albumin	6.15 ± 5.69	9.24 ± 7.25	1.86 ± 0.91	<0.001	0.003

Mean ± SD are given. p¹-Value, between all groups, One way Anova; p²-Value, between pneumonia and severe pneumonia, Student-t test;

^aKruskall Wallis test. Bold and italic p values are p<0.005.

**Figure 1:** ROC curve analysis among CRP, CRP/Albumin, NLR, ESR/Albumin and MLR.

pathogen in blood culture and the need for at least seven to 10 days for the results. In previous studies, many markers, including WBC, NLR, CRP, procalcitonin, and IL-6 have been investigated [3, 5, 10]. In a study involving 394 suspected children with pneumonia, CRP and WBC were positively correlated with positive chest radiography and proven pneumonia [5]. In another study, with 92 children consisting of 46 patients of bacterial pneumonia, they investigated the diagnostic accuracy of procalcitonin as compared with C-reactive protein (CRP) and found the area under receiver characteristic curves for procalcitonin and CRP were 0.89 (95% CI=0.83–0.96) and 0.79 (95% CI=0.70–0.88), respectively [11]. According to guidelines based on many studies, for a complete blood cell count has weak recommendation; low-quality evidence but for acute phase reactant (ESR, CRP, procalcitonin) have strong recommendation; high-quality evidence [3, 10]. However, to the best of our knowledge, this is the first study to examine the relationship of clinical severity of pneumonia with CRP/albumin and ESR/albumin and in hospitalized children diagnosed with CAP. The CRP, ESR, neutrophil and lymphocyte values were found to be significantly

higher and albumin was significantly lower in the severe pneumonia group. Although the ratios of NLR, CRP/albumin and ESR/albumin were higher in the severe pneumonia group, there was no significant difference in the platelet, MPV, platelet/MPV and CRP/MPV values.

CRP is an important marker that induces cytokine release within eight to 12 h after acute inflammation and is either not affected or only minimally affected by age and sex, and thus it is often used in the diagnosis and follow-up of acute inflammation [12]. On the other hand, ESR seems to be important in the follow-up of chronic diseases, and it has been reported that it can be used to predict the duration of hospitalization in children with pneumonia [12, 13]. In a study conducted by Lee et al. with hospitalized children diagnosed with CAP, the AUC values were reported as 0.77 (95% CI=0.59–0.95) for CRP and 0.73 (95% CI=0.54–0.92) for ESR [14]. In the literature, CRP is presented as a more sensitive and specific marker for CAP but it is recommended to be used together with ESR because of the false positivity can be seen, such as obesity and trauma [15]. These results were similar to our study (Table 1, Table 3).

NLR is known to increase in inflammation and is induced especially by IL-6 and TNF released by T cells [16]. NLR, which is considered to be a predictor in many inflammatory events, was found to be higher in children diagnosed with Familial Mediterranean Fever during the attack and correlated with the clinical severity score in children with cystic fibrosis [17, 18]. In a study by Kartal et al. in children with CAP, a positive correlation was found between NLR and CRP, and it was emphasized that NLR could be an important marker, especially for hospitalized patients with CAP [19]. In another study, Bekdas et al. stated that NLR could be used to predict complications in children with pneumonia. In the same study, it was shown that the CRP/MPV ratio was a more sensitive and specific marker than NLR for complicated pneumonia cases. In the ROC analysis, the authors found AUC as 0.85 (95% CI=0.70–0.99) for CRP/MPV and 0.77.5 (95% CI=0.62–0.92)

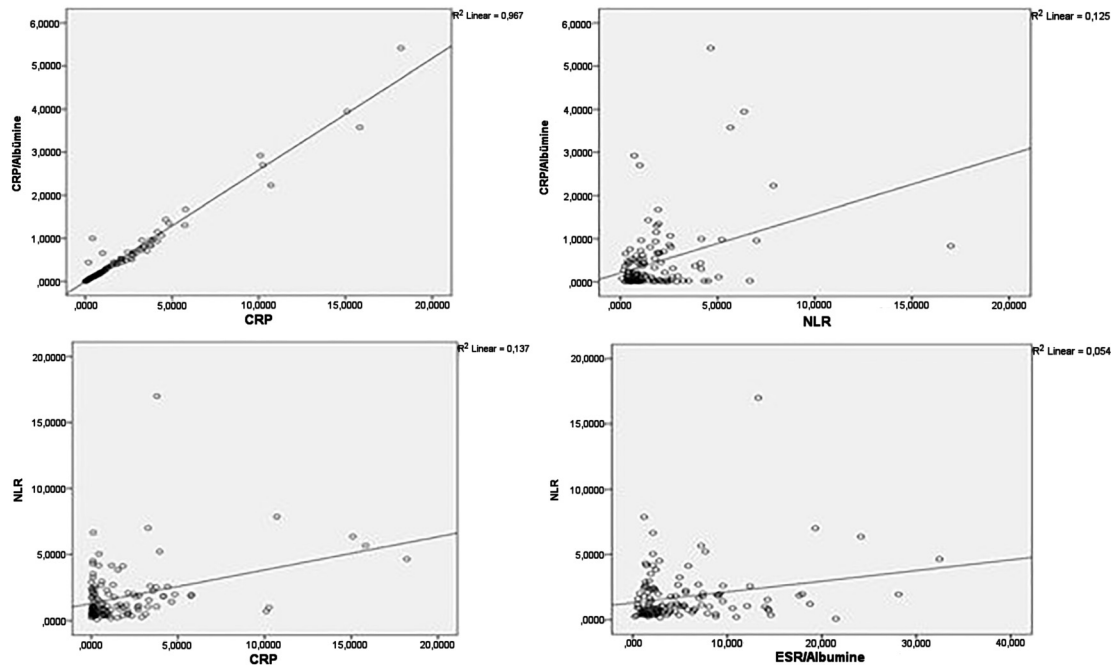


Figure 2: Significant correlation between CRP/Albumin and NLR; NLR and CRP; CRP/Albumin and CRP; NLR and ESR/Albumin; $p < 0.001$.

Table 3: Comparison of the ratios (CRP/Albumin, CRP, NLR, ESR/Albumin, MLR) according to ROC curve.

	Sensitivity (%)	Spesifity (%)	Cut-off value	AUC	p-Value	95% CI	
						Lower bound	Upper bound
CRP	83.3	67.3	0.742	0.785	<0.001	0.698	0.871
CRP/Albumin	86.7	70.4	0.215	0.830	<0.001	0.754	0.906
NLR	76.7	62.2	1.12	0.722	0.001	0.619	0.825
ESR/Albumin	80	68.4	3.85	0.787	<0.001	0.701	0.873
MLR	73.4	54.1	0.19	0.653	0.012	0.542	0.764

for NLR [20]. In our study, the CRP/MPV ratio did not statistically significantly differ between the groups (Table 2). The platelet count, MPV, and the ratios of these values have been investigated in relation to many inflammations, but considering that these ratios can also be affected by body mass index, age, gender, and drugs used, their role in routine diagnosis remains limited [21–23].

Better understanding the value of albumin in predicting the chronic process and prognosis of the disease and the role of CRP in the acute period and follow-up of inflammation leads to idea that the CRP/albumin ratio may be a more sensitive biomarker. As the severity of pneumonia increases in immune competent patients, cytokine storm (especially IL-1,6 and TNF alpha) appears more strongly, secondary CRP production increase in hepatocytes is inevitable [24]. In addition to the negative effect

of cytokine increase on albumin production is known, increase in metabolic rate in severe pneumonia, acute relative malnutrition, increase in vascular permeability with the effect of inflammation may cause low albumin [25]. CRP/Albumin ratio presents as a marker in the follow-up and prognosis of critical elderly patient [26]. In studies conducted to date, it has been shown that in many infections, malignancies and vasculitis, this ratio is correlated with the severity of inflammation and prognosis [27–30]. In a three-year prospective study in children with cystic fibrosis, the high CRP/albumin ratio was reported to be associated with <70% of forced expiratory volume in 1 s and was suggested as an important parameter in predicting lung function [31]. Other studies have also demonstrated the prognostic significance of albumin and CRP values in CAP diagnosis [32]. In a study conducted with 483 adults, it

was emphasized that the CRP/albumin ratio was associated with the severity of pneumonia and could be an independent and easily accessible prognostic marker for this disease [33]. To our knowledge, our study is the first to evaluate the relationship between CRP/albumin and the severity of childhood CAP.

ESR, which is another marker that is elevated in the inflammatory state, is affected by plasma immunoglobulins and fibrinogens [15]. Low albumin may lead to a false low measurement of ESR [15, 34]. This suggests that elevated ESR may be much more valuable than low albumin levels. Therefore, the ESR/albumin ratio can be used as a new prognostic marker in inflammatory diseases. However, there are not sufficient data about this ratio in the literature. In our study, we found the ratio of CRP/albumin to be more sensitive, but the ESR/albumin ratio was also valuable in terms of showing clinical severity (Figure 1, Figure 2).

The limitations of our study concern its retrospective nature and small sample size. Another limitation is that the parameters were not analyzed during the follow-up of patients. Prospective studies with larger patient populations are required.

In conclusion, CRP/albumin and ESR/albumin ratios may be used as markers for the severity of the childhood CAP. The data presented in this paper can be a guide for the follow-up and early treatment of this patient group.

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