Original Research Report

MORTALITY ASSESSMENT OF PEDIATRIC SEPTIC PATIENTS THROUGH PEDIATRIC SOFA+ANION GAP AND PELOD-2 SCORES

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ABSTRACT

Sepsis and septic shock are some of the causes of morbidity and mortality (50-60%) in pediatric patients treated in intensive care rooms. This study aimed to compare the accuracy of pediatric Sequential Organ Failure Assessment (pSOFA) score combined with anion gap (AG) score to Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score in the assessment of mortality in pediatric septic patients at the Resuscitation Room of Dr. Soetomo Geeneral Academic Hospital, Surabaya, Indonesia. This was a retrospective observational cohort study using pediatric sepsis diagnosis guidelines based on the 2016 Pediatric Sepsis Consensus and medical records between January-December 2018. All data of patients aged 1 month to 16 years with suspected infection at the Resuscitation Room were collected based on predisposing infections, signs of infection, and warning signs. Organ dysfunction was assessed by calculating the pSOFA+AG scores, PELOD-2 scores, and corrected anion gap (cAG) in the first 24 hours. Sepsis mortality was assessed by comparing the results of the pSOFA, pSOFA+AG, and PELOD-2. The results showed 94.9% sensitivity and 70.0% specificity (p<0.0001) in the pSOFA, 89.9% sensitivity and 71.3% specificity (p<0.0001) in the PELOD-2, 79.7% sensitivity and 65% specificity (p<0.0001) in the AG, 79.7% sensitivity and 73.8% specificity (p<0.0001) in the cAG, and 79.3% sensitivity (p<0.0001) in the pSOFA+AG. In conclusion, pSOFA was more sensitive than PELOD-2, while the use of pSOFA+AG was not more sensitive than PELOD-2 in assessing the mortality of pediatric septic patients.

Keywords: *Sepsis; pediatric Sequential Organ Failure Assessment (pSOFA); anion gap (AG); Pediatric Logistic Organ Dysfunction-2 (PELOD-2); pediatric patient mortality; child mortality*

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How to cite: Siampa, J. P., Arie Utariani, & Elizeus Hanindito. (2022). Mortality Assessment of Pediatric Septic Patients Through Pediatric Sofa+Anion Gap and Pelod-2 Scores. Folia Medica Indonesiana, 58(4), 298–304. https://doi.org/10.20473/fmi.v58i4.14726

pISSN:2355-8393 ● eISSN: 2599-056x ● doi: 10.20473/fmi.v58i4.14726 ● Fol Med Indones. 2022;58: 298-304
● Submitted 25 Aug. 2022 ● Received 29 Oct 2022 ● Accepted 18 Nov 2022 ● Published 5 Dec 2022

Highlights:

1. Sepsis and septic shock cause morbidity and mortality in pediatric patients.
2. The accuracy of pediatric sequential organ failure assessment and anion gap (pSOFA+AG) was compared with AG and pediatric logistic organ dysfunction-2 (AG+PELOD-2).
3. The mortality assessment of pediatric septic patients showed that pSOFA was more sensitive than PELOD-2, while pSOFA+AG was not more sensitive than PELOD-2.

INTRODUCTION

Sepsis is a common phenomenon surrounded by the uncertainty of major public health problems in children throughout the world (Hunt 2019, Wong 2022). The Surviving Sepsis Campaign (SSC), which aims to improve clinical outcomes for patients undergoing sepsis treatment, developed and approved international clinical practice guidelines for the management of sepsis (Rhodes et al. 2017, Levy et al. 2018). These guidelines consist of bundles that combine treatments for different components of sepsis. Adherence to the SSC package has remained a cornerstone in improving quality and clinical outcomes for patients with sepsis since the publication of the first SSC guidelines (Levy et al. 2018, You et al. 2022). Although understanding pathophysiology and therapy has increased, sepsis remains the leading cause of non-cardiac mortality in Intensive Care Units (ICU) (Handayani, N., et al. 2022). The high mortality rate in sepsis is frequently due to delays in identification and treatment (Pasaribu, F.M., Setyaningtyas, A., & Andarsini, M. R. (2021).

Sepsis diagnosis using the 2001 definition by the Surviving Sepsis Campaign (SSC) was too sensitive (96.9% sensitivity) and less specific (58.3% specificity), resulting in high antibiotic resistance due to the high use of antibiotics, as well as increased expenditure on facilities and infrastructure (Kawasaki 2017, Costa et al. 2018, Rijal & Ramdhoni 2018).

In 2001, the Society of Critical Care Medicine (SCCM) defined sepsis in children as an infection with two or three signs of Systemic Inflammatory Response Syndrome (SIRS). In 2005, the definition of sepsis in children still maintained

the signs and symptoms of SIRS, in addition to organ failure. The validity of SIRS for identification and risk stratification of septic patients is questionable because tachycardia and tachypnea are adaptive mechanisms that often appear in pediatric patients with fever and infection, so they are not further investigated in research. In 2012, SIRS was defined as a condition resulted from infection found through positive culture; or a large suspicion of infection seen from physical, laboratory, and radiological findings. Sepsis is SIRS with evidence of infection, while severe sepsis is the presence of sepsis with organ dysfunction (Handayani & Nugrohowati 2022). Septic shock happens when septic patients' blood pressure decreases after adequate fluid resuscitation or if hemodynamics requires vasopressor support (Randolph & McCulloh 2014, Schlapbach et al. 2017).

The latest sepsis definition in 2016 emphasizes that sepsis is distinguished from uncomplicated infection by the presence of life-threatening organ failure resulting from the regulation system failure of the host response against infection. The Sequential Organ Failure Assessment (SOFA) score is used to assess organ dysfunction in the 2016 SSC guidelines. The SOFA score has variables that are easily measured, available, and routinely checked in the the intensive care unit (ICU). This latest definition of sepsis is expected to be widespread (Gogia & Prasad 2016, Schlapbach et al. 2017, Matics & Sanchez-Pinto 2017).

In February 2018, an Intensive Care Medicine study by Schlapbach et al. (2018) issued a multicenter binational cohort prospective study of organ dysfunction scores through SOFA, quick SOFA (qSOFA), and Pediatric Logistic Organ Dysfunction-2 (PELOD-2) among pediatric patients with infectious diseases admitted to the ICU. These scores were compared with the criteria of SIRS to distinguish hospital mortality or length of stay in the ICU. The SOFA and PELOD-2 scores were significantly more accurate than SIRS and qSOFA in predicting mortality. Seymour et al. (in Costa et al. 2018) found the same results from the use of SOFA score in the diagnosis of sepsis among adult patients.

The prevalence and mortality of pediatric sepsis have become comparable to figures reported from adult ICUs in high-income countries (Hartman et al. 2013; Schlapbach et al. 2015; Weiss et al. 2015). Defining sepsis in the absence of a gold standard remains a challenge (Angus 2016). According to the 2001 consensus statement of the Society of Critical Care Medicine, pediatric sepsis is defined as an infection in which at least two of the four criteria of SIRS are met (Carcillo & Fields 2002, Goldstein et al. 2005). The 2005 consensus definition of pediatric sepsis retained the SIRS requirement and provided more specificity for definitions of organ failure (Goldstein et al. 2005). The validity of the SIRS criteria in identifying and risk-stratifying adult patients with sepsis has been questioned because of its demonstrated insufficient sensitivity and specificity (Kaukonen et al. 2015; Raith risk-stratifying adult patients with sepsis has been questioned because of its demonstrated insufficient sensitivity and specificity (Kaukonen et al. 2015; Raith et al. 2017). On the other hand, tachycardia and tachypnea indicate adaptive mechanisms that accompany febrile infections in pediatric patients, which include patients suffering from diseases with near-zero mortality, e.g. bronchiolitis (Schlapbach et al. 2017). Therefore, the face validity, construct validity, and sensitivity of the SIRS criteria were not examined in many critically ill pediatric patients (Schlapbach et al. 2018). However, current definitions of pediatric sepsis remain essentially based on sepsis-2, which poses a major obstacle to research, bench-marking, coding, and quality control (Schlapbach 2017, Schlapbach & Kissoon 2018). The implementation of the clinical criteria for identifying individuals with sepsis is consistent with the definition of sepsis-3 , which is based on the SOFA score. However, neither SOFA nor qSOFA has been developed for children (Schlapbach et al. 2018).

In addition to the scoring system above, other parameters can be used to assess mortality, e.g. the anion gap (AG). A prospective observational cohort study by Pongmanee & Vattanavanit (2017) assessed biomarkers (base excess and AG) used in the emergency room septic shock patients, in which lactate and AG showed a strong relationship indicating that the biomarkers can be used in the initial assessment of septic shock patients, especially if there is a high cut-off point of 15.8 and 18.5 for AG. Another retrospective observational study by Sneha et al. (2022) using the consensus conference criteria found no correlation in the changing trends of anion and lactate among 130 severe septic shock patients (15-65 years) in the ICU. AG cannot be considered a substitute for lactate testing. Assessment of AG value to predict the mortality of patients in pediatric intensive care unit (PICU) showed that the corrected anion gap (cAG) can be used by combining with other scoring systems to produce better results (Pongmanee & Vattanavanit 2017, Kim et al. 2017).

A study on emergency department patients with sepsis by Adams (2006) found that AG and serum lactate are correlated, but not codependent. Berkman et al. (2009) studied 1,419 patients with septic shock from the Emergency Department of Boston Hospital and concluded that AG is a good but not excellent screening test to help identifying elevated lactate in emergency department population at risk of sepsis. Park et al. (2008) conducted a study at the Medical and Surgical ICU of the Hospital of the University of Sao Paulo, Brazil, in September 2004–November 2005 and

concluded that acidosis resolution is attributable to the decrease of strong ion gap and lactate level. Several studies have been conducted to test the validity of the use of SOFA scores in pediatric patients by modifying some age-adjusted variables known as pediatric SOFA (pSOFA) scores which can significantly predict the mortality output and prognosis of septic pediatric patients. This study aimed to compare the accuracy of the pSOFA score combined with AG score to the PELOD-2 score in the assessment of mortality in septic pediatric patients at the Resuscitation Room of Dr. Soetomo General Academic Hospital,Surabaya, Indonesia.

MATERIALS AND METHODS

This study was a retrospective observational cohort conducted at the Resuscitation Room of Dr. Soetomo Hospital from January to December 2018. The inclusion criteria of this study were critically ill patients with suspected infections, aged 1 month to 16 years, who were treated in the Resuscitation Room. The exclusion criteria of this study were patients aged less than 1 month and more than 16 years; patients with a history of trauma, kidney disease, and died less than 24 hours; and patients referred to other hospitals who had been treated and previously given care. The assessment of suspected infection was based on the predisposing factors to infection (age, nutritional assessment of suspected infection was based on the predisposing factors to infection (age, nutritional factors, comorbidities, and history of therapy), signs of infection (hyperthermia/hypothermia, tachycardia, focus of infection, leukocytes, platelets, CRP, procalcitonin), and warning signs (loss of consciousness, cardiovascular disorders respiration disorder). The organ dysfunction of each patient was assessed using the pediatric SOFA, AG, cAG, and PELOD-2 in the first 24 hours. Then, each predictor of the mortality of the pediatric septic patients were measured and compared.

RESULTS

There were 139 patients fulfilling the inclusion and exclusion criteria, consisting of 80 (57.6%) boys and 59 (42.4%) girls, with mortality rates of 33 (55.9%) in male and 26 (41.1%) in female. The average age of the patients who died was 36.3 months (3 years) with a normal distribution and a value of p<0.92. In this study, the most commonly found diagnoses were pneumonia, found in 79 (56.8%) patients with a mortality rate of 35 (59.3%); meningoencephalitis, in 23 (16.5%) patients with a mortality rate of 6 (10.2%); and encephalitis, in 15 (10.8%) patients with a mortality of 9 (15.3%) patients.

Table 1. Patient's characteristics

	Outcome			
	Alive (n=80)	Died (n=59)	*p*-value	OR (CI 95%)
Age (months)	11 (1 - 180)	12 (1-192)	0.92	1 (0.993-1.006)
1-11	42 (53.2%)	27 (45.0%)		
12-23	11 (13.9%)	11 (18.3%)		
24-59	10 (12.7%)	6 (10.0%)		
60-143	12 (13.9%)	11 (20.0%)		
≥144	5 (6.3%)	4 (6.7%)		
Gender			0.74	1.122 (0.595-2.215)
Male	47 (58.8%)	33 (55.9%)		
Female	33 (41.2%)	26 (44.1%)		
Suspected sepsis				
Infection predisposition	2.82±1.088	3.05±1.007	0.21	1.229 (0.888-1.703)
Signs of infection	4.075±0.882	4.115±0.931	0.54	1.125 (0.772-1.639)
Warning sign	2.437±0.672	2.813±0.392	0.001	3.593 (1.744-7.400)
Diagnosis			*	*
Pneumonia	44 (55.0%)	35 (59.3%)		
Meningoencephalitis	17 (21.2%)	6 (10.2%)		
Encephalitis	6 (7.5%)	9 (15.3%)		
GEA	3 (3.8%)	3 (5.1%)		
Peritonitis	4 (5.0%)	1 (1.7%)		
Mean Value				
Lactate	1.473±0.905	4.516±1.742	<0.0001	4.903 (3.016-7.969)
Anion gap (AG)	16.69±5.241	25.398±6.897	<0.0001	1.275 (1.175-1.385)
Corrected AG (cAG)	17.667±5.342	26.591±6.694	<0.0001	1.289 (1.184-1.404)
pSOFA	6.137±2.822	11.508±2.254	<0.0001	2.079 (1.651-2.617)
PELOD-2	4.162±3.074	9.576±4.022	<0.0001	1.617 (1.371-1.907)

* Distribution frequency value without distribution test. p<0.05 showed that data distribution was not normal.

Table 2. Predictor analysis

Predictor	Alive	Dead	*p* Value	OR	CI Interval 95%
PELOD-2					
<6	57 (71.2%)	6 (10.2%)	<0.0001	1.619	0.289-9.067
≥6	23 (28.8%)	53 (89.9%)			
pSOFA					
<8	56 (70.0%)	3 (5.1%)	<0.0001	7.854	1.650-37.384
≥8	24 (30.0%)	56 (94.9%)			
AG					
<18.5	52 (65.0%)	12 (20.3%)	<0.0001	0	0
≥18.5	28 (35.0%)	47 (79.7%)			
cAG					
<21	59 (73.8%)	12 (20.3%)	<0.0001	2.846	0.774-10.465
≥21	21 (26.2%)	47 (79.7%)			
Lactate					
<2.6	73 (91.2%)	5 (8.5%)	<0.0001	47.148	13.221-168.129
≥2.6	7 (8.8%)	54 (92.5%)			
pSOFA + AG					
<8+<18.5	95.2%	4.8%	<0.0001	76.6	16.1-363.3
≥8+≥18.5	20.7%	79.3%			

p<0.005: significant, logistic regression; Chi square

In this study, relations of PELOD-2, pSOFA, AG, cAG, lactate, and pSOFA+AG scores with mortality were analyzed using logistic regression and Chi-square tests. The cut-off points of PELOD-2 score was 6, pSOFA 8, AG 18.5, cAG 21, and lactate 2.6. Furthermore, the sensitivity and specificity values of each predictor were calculated and summarized in Table 3.

Table 3. Sensitivity and specificity values

Predictor	AUC	*p*-value	Sensitivity	Specificity	NPV	PPV
PELOD-2	0.881	<0.0001	89.8%	71.3%	90.5%	69.7%
pSOFA	0.924	<0.0001	94.9%	70.0%	94.9%	70.0%
AG	0.843	<0.0001	79.7%	65.0%	81.3%	62.7%
cAG	0.852	<0.0001	79.7%	73.8%	83.1%	69.1%
Lactate	0.934	<0.0001	91.5%	91.3%	93.6%	88.5%

p <0.005: significant, logistic regression; Chi Square

The receiver operating characteristic (ROC) chart shows that the largest predictor area is the lactate area and then followed by the p-SOFA score, PELOD-2 score, and cAG, while the smallest area is the AG area with p<0.0001.

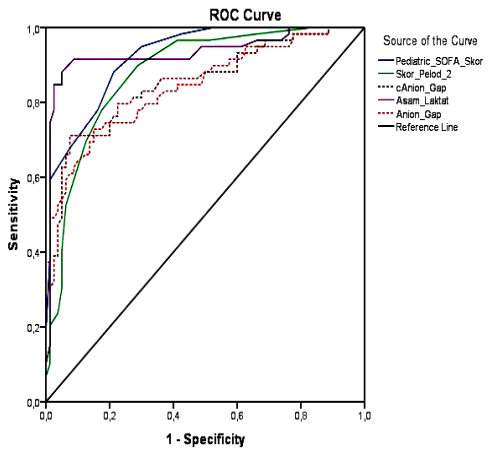

Figure 1. ROC chart of each predictor

In addition to analyzing the relationship between the predictors of mortality as described above, this study also analyzed the use of each predictor simultaneously (multivariate), so that its performance could be seen. Table 4 shows the results of the analysis.

Table 4. Performance of each mortality predictor

Predictor	Univariate			Multivariate		
	p-value	OR	CI 95%	*p*-value	OR	CI 95%
PELOD-2	<0.0001	1.6	1.3-1.9	0.58	1.6	0.3-9.1
pSOFA	<0.0001	2.0	1.6-2.6	0.01	7.8	1.6-7.4
AG	<0.0001	1.2	1.1-1.3	0.99	0	0
cAG	<0.0001	1.2	1.1-1.4	0.11	2.8	0.8-10.5
Lactate	<0.0001	4.9	3.0-7.9	<0.0001	47.1	13.2-168.1

p <0.005: significant, logistic regression; chi square

DISCUSSION

In this study, the highest distribution of age groups with sepsis diagnosis was children aged 1-11 months (49.6%). As stated by Kawasaki (2017), the incidence of sepsis in children is high, especially in infants (5.16 per 1,000), but decreases dramatically with age, especially at the age of 10-14 years. This is caused by the vulnerability of infants to infection, sepsis, and even to septic shock. In Indonesia, the incidence of sepsis is higher in the neonatal and infant group of less than 1 year compared to ages 1-18 years (9.7 versus 0.23 cases per 1,000) (Priyatiningsih et al. 2016).

In the findings of this study, the highest incidences of infection were caused by respiratory system infections (56.8%), central nervous system infections (27.3%), gastrointestinal infections (7.9%), and other infections (7.9%). Kawasaki (2017) reported similar findings that the highest sources of infection were from the bloodstream (67.8%) and respiratory tract (57.2%). In Indonesia, most patients with severe sepsis suffer from infections of respiratory tract (36-42%), bacteremia, and urinary tract (Priyatiningsih et al. 2016). A global study listed three most commonly found comorbid conditions that accompany pediatric patients with sepsis, i.e. the respiratory (30.3%), gastrointestinal (24.9%), and cardiovascular (24.0%) conditions (Weiss et al. 2015).

This study aimed to examine whether the use of pSOFA+AG compared with PELOD-2 was better in assessing the mortality of pediatric septic patients. The relationship between the predictors and mortality was the first analyzed in this study, which used the logistic regression statistical test and Chi-square test.

In the analysis of data obtained, if the PELOD-2 value was ≥6, the mortality rate was 89.8%. If PELOD-2 value was <6, then the mortality rate dropped to 10.2%,

with 0.881 area under the ROC curve (AUC), 89.8% sensitivity, 71.3% specificity, 0.697 positive predictive values (PPV), 1.6 odds ratio (OR), and <0.0001 p-value. From the results of this study, it was found that the PELOD-2 score had a significant relationship in assessing mortality.

The analysis of pSOFA scores showed a significant relationship to mortality with a p-value <0.0001, while the cut-off point of the pSOFA score from the logistic regression analysis was 8. The pSOFA score of ≥8 had a mortality rate of 94.9%. On the other hand, the pSOFA score of <8 decreased the mortality rate to 5.1%, with 0.924 AUC, 94.9% sensitivity, 70.0% specificity, 70.0% PPV, 7.8 OR, and <0.0001 p-value. This analysis showed that the pSOFA score had a strong and significant relationship with the mortality rate of pediatric septic patients.

This study also aimed to analyze the combined use of pSOFA and AG, so the relationship between the AG value and mortality was also studied. The results showed that the AG value in this study was significant for mortality with a p- value of <0.0001. The logistic regression test and Chi-square test resulted in the cut-off point value of the AG, which was 18.5. The AG value of ≥18.5 had 79.7% mortality rate, while the AG value of <18.5 had 20.3% mortality rate. When compared with pSOFA and PELOD-2, the mortality reduction from AG was not as large as those from pSOFA and PELOD-2. The analysis of AG values on mortality had an area of 0.84 AUC, 79.7% sensitivity, 65% specificity, 62.7% PPV, and <0.0001 p-value. From these results, the AG value showed lower sensitivity, specificity, and AUC when compared with pSOFA and PELOD-2.

The anion gap (AG) value is also influenced by albumin value. Therefore, the existence of hypoalbumin condition also affects the AG value. Most pediatric septic patients in this study had low albumin status, so the value of the cAG was also analyzed to recognize the mortality rate. The cAG value and mortality showed a significant relationship, with p-value <0.0001. The cut-off point value of the cAG was 21. The cAG value of ≥21 had 79.7% mortality rate. On the other hand, the cAG value of <21 decreased the mortality to 20.3%, with 0.852 AUC, 79.7% sensitivity, 73.8% specificity, 69.1% PPV, 2.8 OR, and <0.0001 p-value. This analysis showed that cAG was better in specificity, AUC, and PPV values compared to AG.

Lactate is a very significant and strong predictor of mortality. This predictor has been widely investigated and the results are all very significant. Therefore, this study also analyzed the relationship of lactate and mortality. This study showed a similar result as other studies that lactate had a significant relationshipwith mortality, with <0.0001 p-value and 4.9 OR. The lactate cut-off point in this study was 2.6. The lactate value of ≥2.6 had 91.5% mortality rate. On the other hand, the lactate value of <2.6 dropped mortality rate to 8.5%, with 0.934 RUC, 91.5% sensitivity, 91.3% specificity, 88.5% PPV, up to 47.1 OR, and <0.0001 p- value. Compared to the other predictors above, lactate was the best predictor in assessing mortality.

This study combined the use of pSOFA+AG and made the operational definition of this combination. The combination group was divided into for groups according to the cut-off point value, i.e. ≥8 pSOFA and ≥18.5 AG, <8 pSOFA and ≥18.5 AG, ≥8 pSOFA and <18.5 AG, and <8 pSOFA and <18.5 AG. The relationship between each group and its performance related to mortality was analyzed. The results of ≥8 pSOFA group and ≥18.5 AG were 79.3% mortality rate, with 76.6 OR, 95% CI of 16.1-363.3. As the p-values were <0.0001, the results were significant. The assessment of the performance of the pSOFA score itself resulted in 94.9% mortality rate with p<0.0001, indicating that the pSOFA was more sensitive compared to pSOFA+AG. The addition of AG did not improve the performance of pSOFA that was already good.

When analyzed separately (univariate), the performance of each predictor to mortality showed a strong and significant relationship, as seen in Table 4. On the other hand, if the predictors were analyzed simultaneously (multivariate) by seeing the dominance of each predictor, the pSOFA and lactate score were significant, in which pSOFA had a p-value=0.001 (OR 7.8, 95% CI 1.6-37.4), while lactate had a p-value<0.0001 (OR 47.1, 95% CI 13.2-168.1). In this study, the performance of pSOFA and lactate showed the two predictors as the best and most significant predictors compared to other predictors. The pSOFA scores were more sensitive than the PELOD-2 scores, meanwhile the addition of AG did not increase or improve the performance of the pSOFA score.

Strength and limitation

This study investigates the usage of pSOFA+AG compared to PELOD-2 in determining mortality in pediatric septic patients.

CONCLUSION

The pediatric SOFA (pSOFA) score is more sensitive than the PELOD-2 score in assessing the mortality of pediatric septic patients. The use of the pSOFA+AG score was not more sensitive than the PELOD-2 score in assessing the mortality of pediatric septic patients.

Acknowledgment

We would like to thank the Resuscitation Department, Anesthesia Department, and nurses of Dr. Soetomo Hospital, and also everyone that supported us in writing this research article. Thank you so much. We learned so much from you all.

Conflict of interest

No conflict of interest has been declared in this study.

Funding disclosure

This research was not funded by anyone or any institute.

Author contribution

Johaan Pawe Siampa conceptualized and designed the study, interpreted the data, and wrote the research manuscript. Arie Utariani and Elizeus Hanindito collected the data and checked the final result of the research.

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