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Research Article

The association between miR-155 promoter polymorphism and risk of sepsis in a Chinese Han population

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Abstract

Background: miR-155 has been demonstrated play a critical role in the pathogenesis of sepsis. Little is known about the potential clinical relevance of genetic variants in the promoter of miR-155 and sepsis risk. Aims：This study aims to evaluate the association between miR-155 promoter rs767649 T>A polymorphism and the sepsis onset and development. Study Design: we carried out this hospital-based case-control study to investigate whether the genetic polymorphism of rs767649 was associated with the risk and progression of sepsis in a Chinese Han population. Methods: A total of 579 sepsis patients and 748 matched healthy controls of Chinese Han population were consecutively enrolled. Pyrosequencing and polymerase chain reaction-length polymorphism method was conducted to determine the genotype of the rs767649 site. Results: No significant association was observed between rs767649 T > A polymorphism and the sepsis susceptibility, but subgroup analysis revealed rs767649 SNP may a risk factor for sepsis progression. Conclusion: Our data initially indicated that miR-155 promoter rs767649 T>A polymorphism may not a genetic risk factor for sepsis occurrence but is associated with the development of sepsis in Chinese Han population. However, extensive studies are needed to gain more reliable and authentic results.

Key words: Sepsis; miR-155; Polymorphism; rs767649

INTRODUCTION

Sepsis is characterized as a life-threatening organ dysfunction caused by a dysregulated host response to infection(1). Despite much advance in antibiotics and other supportive care has been made, sepsis remains the major cause of death in intensive care units(2-4). As a complex condition, multiple genes and gene-environment interactions play a vital role for the risk, development and clinical outcome of sepsis(5-7). Currently, increasing evidence indicated that genetic polymorphism within the inflammatory-related genes have been found related to the prognosis of sepsis(8-10). These genetic variants may help to explain the existence of genetic background caused interindividual discrepancies in both cytokine production and clinical prognosis of sepsis patients despite the same standardized therapy. Therefore, functional and association studies involving single nucleotide polymorphisms (SNPs) in essential genes might useful to provided genetically insights in molecular pathophysiology of sepsis and might develop strategic approaches for prevention of sepsis.

MicroRNAs (miRNAs) are a class of 21 to 25 nucleotide noncoding RNAs molecules, which involved in regulating eukaryotic gene expression at the posttranscriptional level by sequence-specific targeting mRNA cleavage or by inhibiting mRNA translation, have recently emerged as critical regulators in variety of biological systems and physiological as well as pathological functions ranging from embryonic development, homeostasis, inflammatory and autoimmune diseases(11-18). MiR-155, one of the best characterized miRNAs, is strongly induced and emerged as a key transcriptional regulator in inflammation-related diseases, such as cancer and sepsis, and could serve as a promising marker for the diagnosis and prognosis of sepsis(17, 19-22). To date, accumulative evidence indicates that genetic variants in regulation regions of miRNAs have attracted much attention these years since they are capable of altering miRNA expression, consequently affecting downstream biological events and disease risk(23-25). Recently, considerable efforts have been made to identify genetic variations of miRNAs that may modulate their function and expression and eventually affecting sepsis susceptibility, development and prognosis(26, 27). The rs767649 polymorphism, located in the miR-155 promoter region, was recently reported acts as a functional SNP that could alter miR-155 expression(28, 29). Several lines of evidence have confirmed that the MiR-155 genetic polymorphism are associated with the risk and survival of various inflammation-related diseases, such as hepatocellular carcinoma and lung cancer(30, 31). For instance, recently discovered a positive association between the rs767649 polymorphism and the risk of cervical cancer, indicating that rs767649 might be a causal variant for cervical cancer susceptibility(29). In addition, functional variant rs767649 was found might contribute to the increased risk and poor prognosis of hepatocellular carcinoma, highlighting the importance of miR-155 in the prevention and

prognosis of hepatocellular carcinoma(30). Although several studies have suggested correlations between MiR-155 and sepsis, nevertheless, the links between the rs767649 genetic variants in relation to the onset and development of sepsis has not yet been elucidated(21, 32).

Given the evidence that MiR-155 significantly involved in pathogenic mechanism and development of sepsis and several related SNPs positively contributed to the risk of inflammatory diseases, we carried out this hospital-based case-control study to investigate whether the genetic polymorphism of rs767649 was associated with the risk and progression of sepsis in a Chinese Han population.

MATERIALS AND METHODS

Study population

A hospital-based case-control study was performed to evaluate SNP in the promoter region of miR-155 and sepsis risk. A total of 579 sepsis patients (316 males and 263 females) diagnosed according to the Third International Consensus for Sepsis and Septic Shock (1) were consecutively recruited between July 2016 and August 2018. All sepsis patients were inter-viewed to collect general information including the following clinical parameters: age, sex, source of infection, dysfunctional organs, blood microbiological cultures, base-line laboratory data, procalcitonin (PCT), Acute Physiology and Chronic Health Evaluation (APACHE) II score and sepsis related organ failure assessment (SOFA) score. Patients who suffered from cancer, autoimmune diseases, HIV, other organic or blood diseases were excluded from this study. At the same period time, 748 matched healthy controls (386 males and 362 females) free from any history of sepsis, cancer, autoimmune diseases, inflammatory and chronic infectious diseases were enrolled from the Medical Examination Center of this hospital. All participants were unrelated Chinese Han ethnic and older than 18 years. The peripheral blood samples were collected from the enrolled patients upon the sepsis were diagnosed. The study was approved by the Ethics Committee of the Affiliated Hospital and all subjects or their legal representatives provided informed consent for this study.

DNA isolation and genotyping

Genomic DNA of the enrolled subjects was extraction and the isolation from the peripheral blood leucocytes using the TIANamp Blood DNA extraction Kit (Tian Gen Biotech, Beijing, China) following the protocol of the manufacturer and the concentration was quantified by ultraviolet spectrophotometry and stored at -80 °C until used.

The rs767649 polymorphism was genotyped according to A SNaPshot Multiplex Kit (Genesky Biotechnologies, Inc., Shanghai, China). Briefly, the Polymerase chain reaction (PCR) primer pairs used to amplify the MiR-155 promoter region containing rs767649 site was 5'-ATATAACACATTATCAAAAACACCGT -3' (forward) and 5'-ATTAGAGCACTCAGAAAAGCGT-3' (reverse). SNaPshot PCR reaction was conducted in a final volume of 10 μl (5 μl of the SNaPshot Multiplex Kit reagent (ABI), 1 μl of the primer mix, 2 μl of the templates and 2 μl of ddH2O). The PCR

reaction procedures described as follows: 95°C for 2 minutes (denaturation), 11 cycles of DNA amplification were performed using Taq PCR: 94°C for 20 s at (denaturation), 65°C for 40 s (annealing), and 72°C for 90 s (extension), followed by 24 cycles of DNA amplification: 94°C for 20 s (denaturation), 59°C for 30 s (annealing), and 72°C for 90 s (extension). Extension products were purified (37°C for 1 h, 75°C for 15 min) by incubation with 1U of shrimp alkaline phosphatase (Takara: Otsu, Shiga, Japan). Additionally, 0.5 μL of the purified products was mixed with Liz120 Size Standard and 9 μL of Hi-Di formamide (95°C for 5 min) and finally analyzed by ABI 3730xl genetic sequence Analyzer and Gene Mapper 4.1 (Applied Biosystems, Carlsbad, CA, USA). In addition, ten percent of the random samples were selected as the validation group for quality control, yielding a 100% concordance. Power analyses exhibited 100% power for rs767649 to test a genotype relative risk with an odds ratio of 2.0 at the significance level of 0.05 in this study.

Statistical analyses

Genotype and allele distribution between the patients and controls of miR-155 (rs767649) polymorphism was calculated by Chi-squared test or Fisher's exact test, and the P-value was adjusted by the Bonferroni correction in multiple-time statistics. Power analysis was performed by quanto 1.2 software. Statistical analyses were analysis by the SPSS version 19.0 (IBM, NY, USA), and statistical significance was defined as a $p < 0.05$.

RESULTS

Procedures

The process of the clinical studies mainly included the subject collect, primary analysis and subgroup analysis (Figure 1). Among the 772 cases diagnosed with sepsis, 193 were excluded who did not meet the sepsis protocol initiated, 62 in whom the data was incomplete, 31 were duplicate, and the ineligible due to age, malignant tumors, diabetes and autoimmune disease were 17，29, 32 and 22 respectively. A total, 579 sepsis patients and 748 matched healthy controls were included in the primary analysis to evaluate the association between miR-155 promoter SNP and sepsis susceptibility. After the primary analysis, the sepsis patients were divided into sepsis group and septic shock group as defined by sepsis severity to further explore the genotype and allele distributions on sepsis development

Clinical characteristics

Table 1 shows the baseline characteristics of study participants in the sepsis and control groups (579 sepsis cases and748 cont¬rols). The mean ages of the sepsis cases and controls were 55.09 (± 12.67 years) and 57.47 years (± 13.71 years), respectively. There were no significant diffe¬rences in age or sex distri¬butions between the sepsis cases and controls. Lung tract (65.8%), abdominal (11.8%), and bloodstream infections (14.2%) were the most frequent infections in terms of location. Gram-ne¬gative (36.1%) and fungal infections (17.3%) were the primary infection types, while polymicrobial infec¬tion accounted for 13.8%. The main pathogens bacte¬ria identified in the present study were Acinetobacter baumannii (32.8%),

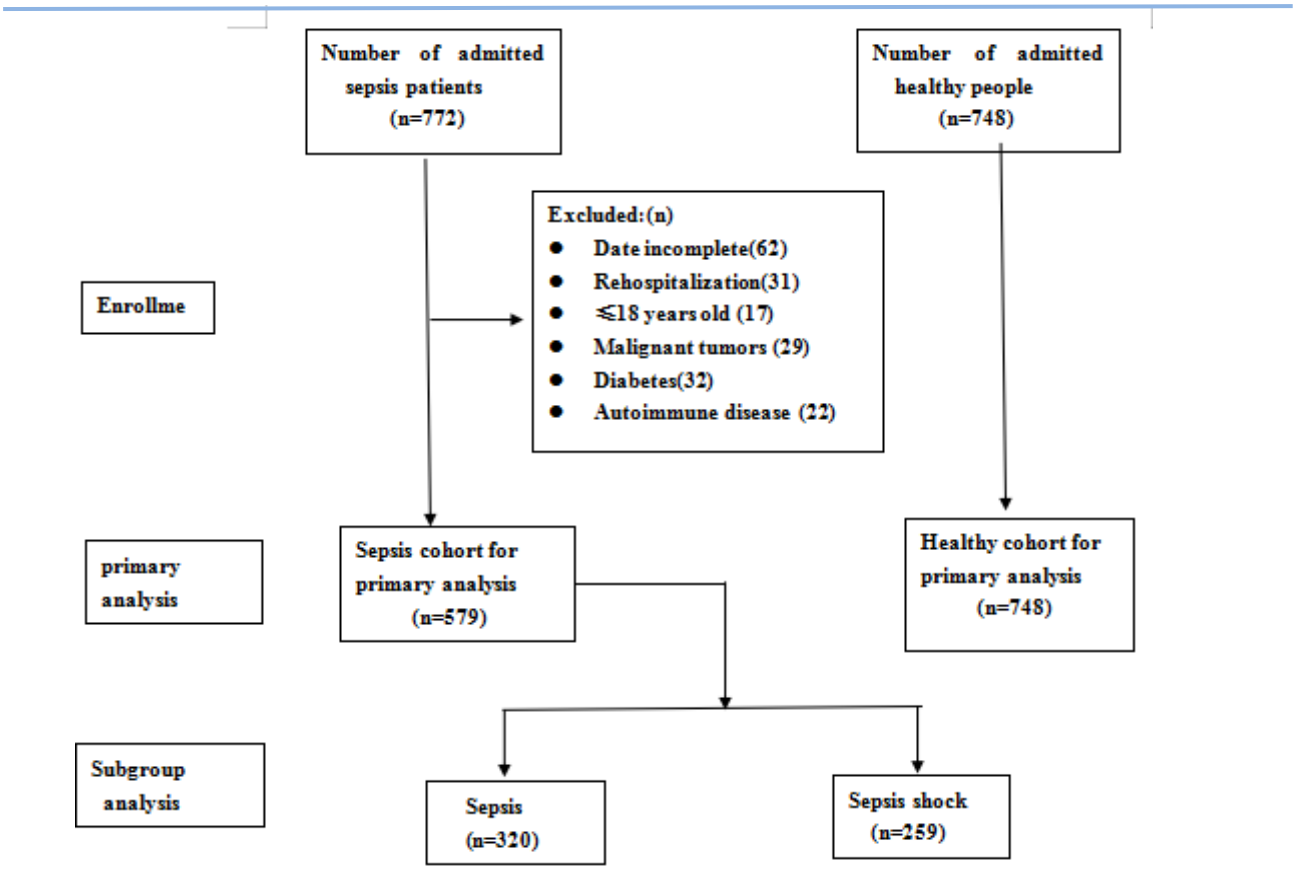

Figure 1. Procedure of the study

Escherichia coli (8.6%), Pseudomonas aeruginosa (6.9%) and Staphylococcus aureus (9.8%). The sepsis cases consisted of 320 sepsis (55.3%), 259 sepsis shock (44.7%). The 28-day ICU mortality rate was 23.6% in this study.

Clinical characteristics

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Table2 shows the baseline characteristics of study participants in the sepsis and sepsis shock (320 sepsis cases and 259 sepsis shock).

Table 1. Clinical characteristics of sepsis patients and healthy control

Variable	Sepsis (n=579) N(%)	Control (n=748) N(%)	P value
Demographics			
Age, years, mean ± SD	55.09±12.67	57.47±13.71	0.9102
Male/female, number	316/263	386/362	0.2820
Sepsis status, n(%)			
sepsis	320(55.3)	N.A	
Sepsis shock	259(44.7)	N.A	
Source of infection, n(%)			
Respiratory tract infection	381(65.8)	N.A	
Primary bloodstream infection	82(14.2)	N.A	
Abdominal infection	69(11.8)	N.A	
Urinary tract infection	18(3.1)	N.A	
Catheter-associated infection	19(3.3)	N.A	
Brain	30(5.2)	N.A	
Others	20(3.5)	N.A	
Infection types, n(%)			
Gram-positive	58(10.0)	N.A	
Gram-negative	209(36.1)	N.A	
Mixed Gram-negative and -positive	62(10.7)	N.A	
Fungus	100(17.3)	N.A	
Polymicrobial	80(13.8)	N.A	
Negative blood culture	70(12.1)	N.A	
Pathogenic bacteria, n(%)			
Acinetobacter baumannii	190(32.8)	N.A	
Monilia albican	40(6.9)	N.A	
Yeast sample sporphyte	46(7.9)	N.A	
Aspergillus	35(6.1)	N.A	
Klebsiella pneumoniae	44(7.6)	N.A	
Pseudomonas aeruginosa	40(6.9)	N.A	
Staphylococcus aureus	57(9.8)	N.A	
Escherichia coli	50(8.6)	N.A	
Others	77(13.4)	N.A	

APACHE II score	23.8±7.1	N.A
28-day mortality, n (%)	136(23.6)	N.A

N.A: not applicable; APACHE II: Acute Physiology and Chronic Health Evaluation II; Continuous data are expressed as the mean ± SD.

Table 2. Clinical characteristics of the sepsis patients and healthy controls

Variable	Sepsis (n=320) N(%)	Sepsis shock (n=259) N(%)
Demographics		
Age, years, mean ± SD	55.09±12.67	57.47±13.71
Male/female, number	172/148	144/115
Source of infection, n(%)		
Respiratory tract infection	179(55.9)	202(78.0)
Primary bloodstream infection	50(15.6)	32(12.4)
Abdominal infection	39(12.2)	30(11.6)
Urinary tract infection	12(3.8)	6(2.3)
Catheter-associated infection	13(4.1)	6(2.3)
Brain	18(5.6)	12(4.6)
Others	9(2.8)	11(4.2)
Infection types, n(%)		
Gram-positive	30(9.4)	28(10.8)
Gram-negative	99(30.9)	110(42.5)
Mixed Gram-negative and -positive	40(12.5)	22(8.5)
Fungus	57(17.8)	43(16.6)
Polymicrobial	50(15.6)	30(11.6)
Negative blood culture	44(13.8)	26(10.0)
Pathogenic bacteria, n(%)		
Acinetobacter baumannii	102(31.9)	88(34.0)
Monilia albican	22(6.9)	18(6.9)
Yeast sample sporphyte	27(8.4)	19(7.3)
Aspergillus	21(6.5)	14(5.4)
Klebsiella pneumoniae	25(7.8)	19(7.3)
Pseudomonas aeruginosa	24(7.5)	16(6.1)
Staphylococcus aureus	30(9.4)	27(10.4)

Escherichia coli	29(9.1)	21(8.1)
Others	40(12.5)	37(14.3)
APACHE II score	23.8±7.1	N.A
28-day mortality, n (%)	53(16.6)	83（32.0）

N.A.: not applicable; APACHE II: Acute Physiology and Chronic Health Evaluation II; Continuous data are expressed as the mean ± SD.

Effect of miR-155 polymorphism on the susceptibility to sepsis

To evaluate the association of miR-155 promoter polymorphisms with sepsis susceptibility, the genotype and allele distributions of the rs767649 in sepsis patients and healthy individuals were calculated. As shown in Tables 3, no significant differences in genotypes or allele frequencies were detected between the sepsis patients and healthy controls, suggesting that the rs767649 T > A polymorphisms may not a risk factor for sepsis susceptibility. Genotype distribution in the sepsis patients and control subjects was in agreement with the Hardy-Weinberg equilibrium (P > 0.05, data not shown).

Effects of miR-155 polymorphisms on sepsis progression

To further evaluate the rs767649 polymorphism on sepsis progression, we separated the 579 cases into sepsis subgroup (320) and septic shock subgroup (259) according the sepsis severity (Table 4). We found that the allele frequencies of rs767649 T>A is higher in septic shock than sepsis patients, suggesting that these polymorphisms may affect the progression of sepsis.

Table 3. Frequencies of the rs767649 genotypes/alleles in the sepsis patients and controls

SNP	Sepsis n=579(%)	Control n=748(%)	P	P*	OR (95% CI)
rs767649					
TT	229(39.6)	303(40.5)	0.672	0.735	-
AT	244(42.1)	322(43.0)	-	-	-
AA	106(18.3)	123(16.5)	-	-	-
TT+AT	473(81.7)	625(83.5)	0.380	0.735	0.930(0.797, 1.087)
AT+AA	350(60.4)	445(59.5)	0.735	0.735	1.023(0.902 ,1.159)
T	702(60.6)	928(62.0)	-	-	1.000 (reference)
A	456(39.4)	568(38.0)	0.459	0.735	0.967(0.885 ,1.056)

OR: odds ratio; 95% CI: 95% confidence interval; *False discovery rate-adjusted P-value for multiple hypotheses testing using the Benjamin-Hochberg method

Table 4. Genotype and allele frequencies distribution in the different sepsis status

SNP	Sepsis (n=320)	Septic shock (n=259)	P1	P*	
rs767649					
TT	142(44.4)	87(33.6)	0.030	0.040	-
AT	123(38.4)	121(46.7)	-	-	-
AA	55(17.2)	51(19.7)	-	-	-
TT+AT	265(82.8)	208(80.3)	0.451	0.451	0.926(0.758 ,1.131)
AT+AA	178(55.6)	172(66.4)	0.010	0.040	0.820(0.710 ,0.948)
T	407(63.6)	295(56.9)	-	-	1.000 (reference)
A	233(36.4)	223(43.1)	0.022	0.040	1.135(1.017 ,1.266)

P1: sepsis vs septic shock. *False discovery rate-adjusted P-value for multiple hypotheses testing using the Benjamin-Hochberg method.

DISCUSSION

In the present study, we explored the role of miR-155 genetic polymorphism (rs767649 T>A) with susceptibility and development of sepsis in a Chinese Han population by conducting a hospital-based case-control study. To the best of our knowledge, the present study was the first to investigate the relevance of miR-155 genetic polymorphism with the risk and progression of sepsis. No significant association was observed between rs767649 T>A polymorphism and the occurrence of sepsis. But secondary analysis revealed rs767649 SNP may affect sepsis progression.

Sepsis is defined as life-threatening organ dysfunction that develops as a dysregulated host response to infection, and is associated with both host genetic factors, environmental triggers and the immune balance(1, 5-7). Among patients with infections, the risk factors for the development and prognosis for sepsis are less well characterized, but comorbidities and host hereditary factor in addition to gene-environment reciprocal factors. Host genetics probably contribute to the risk of acquiring an infection as well as the risk of developing sepsis from an infection(33, 34). There has been considerable interest in the identification of genetic factors for the risk, progression and clinical outcomes of sepsis and the common sequence variations within candidate genes involved in inflammatory responses have received particular attention(5, 35, 36). SNPs are the most common type of genetic variant in the human genome. Increasing efforts are underway to identify SNPs in candidate inflammatory-related genes that may be related to the prognosis and clinical outcomes of sepsis. Multiplying evidence have confirmed that

the miRNAs promoter SNPs are involved in inflammation-related diseases(27).

miR-155 is processed from the noncoding RNA transcript of the bic gene located on chromosome 21, which is a major regulator of inflammation and immunity, and it is induced in response to a variety of inflammatory factors(37-39). For instance, it has been shown that miR-155 is induced by bacterial lipopolysaccharide (LPS) in a human monocytic cell line(40, 41). In addition, miR-155 has been proposed to increase the translation of TNF-a transcripts either by acting at the 3'UTR of TNF-a mRNA to release its self-inhibitory effects or by increasing TNF-a mRNA stability(42). Moreover, miR-155 has been identified and characterized as a component of the primary macrophage response to different types of inflammatory mediators(43).

Emerging evidence suggested that polymorphism located in the promoter of miR-155 influence the expression level of miR-155 and could serve as a promising marker for the diagnosis and prognosis of various inflammation-related diseases by influence relevant inflammation process(44, 45). For instance, a presently investigation suggested that rs767649 in the regulation region of miR-155 was positively associated with the increased risk and poor prognosis of non-small cell lung cancer (NSCLC), and specifically interacted with chemotherapy or radiotherapy for NSCLC survival(31). Another previous study has shown evidence that the rs767649 polymorphism, locating in the miR-155 promoter region, was significantly associated with cervical cancer (CC) risk, especially among the subgroups with older age, postmenopausal status, and early-medium stages of cancer and functional studies showed that miR-155 was overexpressed in CC tissues and rs767649 could dampen the promoter activity of miR-155, indicating that rs767649 might be a causal variant for CC susceptibility(29). As the rs767649 T allele could enhance the expression of miR-155, which played a oncogenic role in lung cancer, they proposed that rs767649 might influence lung cancer risk through modulating the binding of NF-κB, which resulting in enhanced miR-155 expression. Therefore, it is rational to postulate that miR-155 promoter polymorphism might associated with the risk of sepsis. Nerveless, in our present study, no significant association was observed between rs767649 polymorphism and the occurrence of sepsis, suggesting that the miR-155 promoter SNP may not confers sepsis onset in a Chinese Han population，but affect the progression of sepsis。

Nevertheless, several potential limitations in this study should be acknowledged. First, the sample size in this study was insufficient, and all subjects were of Chinese Han ethnic may leading to nonrepresentative results. Second, all individuals were of Chinese Han ethnic perhaps leading to nonrepresentative results. Therefore, further biological studies with larger populations and different ethnic backgrounds are expected to validate our tentative conclusions. Second, patients with specific diseases in the samples that could not eliminate, may yield conflicting results regarding miR-155 polymorphisms and the sepsis risk. In addition, other functional polymorphisms may interfere with miR-155 expression, and these integrated effects should be studied for better

estimation of individual risk of the onset or development of sepsis.

DECLARATIONS

1) ***Consent to publication***
We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement, and followed publication ethics.
2) ***Ethical approval and consent to participants***
Not applicable.
3) ***Disclosure of conflict of interests***
We declare that no conflict of interest exists.
4) ***Funding***
None
5) ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article.
6) ***Authors' Contributions***
Authors contributed to this paper with the design (ZPF), literature search (ZPF), drafting (ZPF), revision (ZPF and YJY), editing (ZPF and YJY) and final approval (ZPF).
7) ***Acknowledgement***
None
8) ***Authors' biography***
None

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