

Correlation Between Prematurity and The Onset of Neonatal Sepsis: A Cross-Sectional Study in NICU of a Tertiary Hospital in East Java, Indonesia

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ABSTRACT

INTRODUCTION: The incidence of neonatal sepsis in developing countries is still high, reaching 170 out of 1000 births. An increased premature birth rate has become the leading cause of death in children under five years old. Studies examining the correlation between prematurity and neonatal sepsis onset have not been widely reported. Therefore, we assessed the correlation between gestational age and the onset of sepsis in neonatal patients.

METHODS: Hospital-based cross-sectional study was performed on all neonates diagnosed with neonatal sepsis in the NICU of a tertiary referral hospital in East Java between 1 January 2019 – 31 December 2019. Logistic regression was used to analyze the obtained data. P-value <0.05 was considered statistically significant.

RESULTS: Of the 241 patients identified with neonatal sepsis at Dr. Soetomo General Hospital in 2019, we found that 161 patients met the inclusion criteria, with most patients being early-onset sepsis patients (67.7%), low birth weight (75.8%), premature (65.2%), singleton deliveries (92.5%), and cesarean section births (65.2%). Statistical analysis showed a non-significant correlation between prematurity and the onset of neonatal sepsis ($p>0.05$).

CONCLUSION: Although preterm birth is often reported as one of the most important risk factors of neonatal sepsis, prematurity does not appear to be an independent risk factor of neonatal sepsis onset

Keywords: Neonatal Sepsis, Risk Factor, Prematurity, Gestational Age, Age of Onset.

INTRODUCTION

The World Health Organisation (WHO) has identified sepsis as a major global health problem [1]. From 1979-2019, the global rate of neonatal

sepsis remains high, reaching 2824 out of 100.000 birth [2]. Low-income countries have the highest incidence of neonatal sepsis [3]. Various factors contribute to the increased risk of neonatal sepsis. Prematurity and low birth weight are frequently

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cited as the most significant risk factors for neonatal sepsis [3–5]. Additional data showed an increase in reported premature births worldwide, contributing to the leading cause of death in children under five [4,5]. Thus, prematurity and sepsis should not be underestimated.

Sepsis is a term used to indicate potentially fatal organ failure caused by a malfunction in the body's immune response to infection [6]. The immune system of infants in the early months of life is still in an immature developmental stage and has little immunological memory. Decreased function of neutrophils and low concentrations of immunoglobulins increase the susceptibility of neonates to an invasive infection [7]. Preterm neonates are known to have less immune function than term neonates, making preterm neonates more vulnerable to infection [8].

Neonatal sepsis can be divided into early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS occurs within 0-3 days of birth and is often associated with vertical transmission from mother to newborn. Vertical transmission of infection may occur intrapartum, from contact with the maternal genital tract, or during childbirth. LOS is diagnosed between 72 hours post-partum and 28 days. The most important source of infection for LOS is the horizontal transmission. Examples of LOS sources include infection transmission from healthcare workers, invasive devices used in neonatal health management, and hospital or community environmental exposure [9,10].

Clinical manifestations of neonatal sepsis can vary and occasionally present without obvious signs of infection [7,11]. The current gold standard for diagnosing sepsis is blood culture. However, the neonate's past exposure to empiric antibiotics and limited blood volume can influence blood culture sensitivity. These factors may make blood culture an unreliable method for organism isolation and identification of sepsis [12]. In addition, the time it takes from collection to isolation of the infectious organism may take up to 48 hours, further limiting its utility. As a result, therapy is often initiated before infectious etiology is known. Despite these limitations, therapeutic management should be initiated in patients with suspected sepsis [13]. For these reasons, identifying independent risk factors for neonatal sepsis plays an important role in managing susceptible patients and aims to reduce the incidence of death [14].

Pre-maturity of a newborn is defined as a gestation of less than 37 weeks [15]. Two out of three preterm births occur spontaneously, while others occur due to maternal medical conditions or fetal complications, such as pre-eclampsia or intrauterine growth restriction (IUGR) [16]. Significant risk factors for premature birth include advanced maternal age, pregnancy education level, number of deliveries, twin pregnancies, minimal or no prenatal treatment, and male fetal gender [17].

Meta-analysis and systematic review of the literature have shown that prematurity is frequently reported as one of the most common risk factors for both EOS and LOS in neonates [18]. Immune system dysfunction, immaturity, as well as the lack of maternal IgG antibodies in premature neonates contribute to an increased risk of infection [7]. Studies of prematurity as a risk factor for neonatal sepsis comparing EOS and LOS patients have not been widely reported. As a result, this study aims to assess the correlation between gestational age and the onset of sepsis in neonatal patients.

METHODS

A cross-sectional, retrospective analysis was conducted at Dr. Soetomo General Hospital, Surabaya, the largest referral hospital in East Java, Indonesia. Data were obtained from the medical record center of Dr. Soetomo General Hospital Surabaya, Indonesia, from January to December 2019. Data analysis utilized a consecutive non-random sampling technique that fulfilled the inclusion and exclusion criteria. The neonates were divided into two groups, early-onset sepsis (EOS) patients and lately-onset sepsis (LOS) patients. Identified variables include gender, birth weight, gestational age, type of birth, mode of delivery, referred patient status, patient outcome and mother's age.

Our inclusion criteria consisted of the following criteria: age 0–28 days neonates admitted to the NICU of Dr. Soetomo General Hospital and diagnosed with neonatal sepsis based on clinical manifestations and laboratory tests assessed by physicians. Clinical features considered in this study were temperature instability (fever $\geq 38.0^{\circ}\text{C}$ and hypothermia $\leq 36.5^{\circ}\text{C}$), apnea, tachypnea, chest retraction, nasal flaring, tachycardia, cyanosis, hypotonia, hyporeflexia, and jaundice [7]. The laboratory test components of a sepsis

screen include a total leucocyte count of $<5000/\text{cumm}$ or $>20.000/\text{cumm}$, an absolute neutrophil count $<2 \times 109/\text{L}$, I:T ratio of >0.2 and a C-Reactive Protein (CRP) $>1\text{mg}/\text{L}$ [19,20]. The exclusion criteria included neonates with incomplete medical record data and/or laboratory results.

In total, 161 out of 241 possible patients fit our inclusion criteria and were subsequently divided

into three categories based on gestational age, including extreme premature infants (<28 weeks), very premature infants (28 - <32 weeks), and late premature infants (32 - <47 weeks) [15].

This research used secondary data obtained from the medical record center of Dr. Soetomo General Hospital Surabaya, Indonesia. Ethical clearance was approved by the ethical committee of Dr. Soetomo

Table 1: Characteristic of Neonatal Sepsis Patients

Variable	EOS (n=109)	LOS (n=52)	Total (n=161)
Gender			
Male	58 (53,2%)	34 (65,4%)	92 (57,1%)
Female	51 (46,8%)	18 (34,6%)	69 (42,9%)
Birth Weight			
Low ($<2500\text{gr}$)	88 (80,7%)	34 (65,4%)	122 (75,8%)
Normal (2500 – 4000 gr)	20 (18,3%)	18 (34,6%)	38 (23,6%)
High ($>4000\text{gr}$)	1 (0,9%)	0	1 (0,6%)
	$1876 \pm 747,79$	$2076 \pm 763,48$	$1941 \pm 756,35$
Gestational Age			
Premature (<37 weeks)	74 (67,9%)	32 (61,5%)	106 (65,2%)
Term (37–42 weeks)	35 (32,1%)	20 (38,5%)	55 (34,8%)
	$33,53 \pm 4,11$	$34,13 \pm 4,06$	$33,72 \pm 4,11$
Birth			
Singleton	100 (91,7%)	49 (94,2%)	149 (92,5%)
Twin	9 (8,3%)	3 (5,8%)	12 (7,5%)
Mode of Delivery			
Spontaneous	35 (32,1%)	18 (34,6%)	53 (32,9%)
SC	71 (65,1%)	34 (65,4%)	105 (65,2%)
Others (Vacuum extraction and Forceps)	3 (2,8%)	0	3 (1,9%)
Referred Patient			
Yes	29 (26,6%)	31 (59,6%)	60 (37,3%)
No	80 (73,4%)	21 (40,4%)	101 (62,7%)
Outcome			
Alive	59 (54,1%)	31 (59,6%)	90 (55,9%)
Dead	50 (45,9%)	21 (40,4%)	71 (44,1%)
Mother's Age			
≤ 20 years old	6 (5,5%)	3 (5,8%)	9 (5,6%)
21–35 years old	72 (66,1%)	35 (67,3%)	107 (66,5%)
≥ 36 years old	31 (28,4%)	14 (26,9%)	45 (28%)
	$30,56 \pm 6,52$	$30,61 \pm 6,68$	$30,58 \pm 6,55$

Hospital Surabaya, Indonesia (approval number 0401/105/XI/2020). Information gathered from patient's medical records during this study is kept confidential. The data obtained were analyzed using SPSS 25 application. Univariate analysis was used to describe patient characteristics, mean \pm SD was used for continuous data, and frequency with percentages was used for categorical data. Logistic regression was calculated to evaluate the

correlation between prematurity and gestational age in EOS and LOS patients. Calculating odds ratio (OR) with a 95% confidence interval (95% CI) was used to estimate the correlation magnitude. The p-value is significant if the value is less than 0.05.

RESULTS

Of the patients included in the analysis, 109 were

Table 2: Characteristic of Neonatal Sepsis Premature Patients

Variable	Premature (n=106)	Aterm (n=55)	Total (n=161)
Onset			
EOS	74 (69,8%)	35 (63,6%)	109 (67,8%)
LOS	32 (30,2%)	20 (36,4%)	52 (32,2%)
Gender			
Male	61 (57,5%)	31 (56,4%)	92 (57,1%)
Female	45 (42,5%)	24 (43,6%)	69 (42,9%)
Birth Weight			
Low (<2500gr)	97 (91,5%)	25 (45,5%)	122 (75,8%)
Normal (2500 – 4000 gr)	9 (8,5%)	29 (52,7%)	38 (23,6%)
High (>4000 gr)	0	1 (1,8%)	1 (0,6%)
	1591 \pm 555,52	2617 \pm 623,25	1941 \pm 756,35
Birth			
Singleton	94 (88,7%)	55 (100%)	149 (92,5%)
Twin	12 (11,3%)	0	12 (7,5%)
Mode of Delivery			
Spontaneous	38 (35,8%)	15 (27,3%)	53 (32,9%)
SC	66 (62,3%)	39 (70,9%)	105 (65,2%)
Others (Vacuum extraction and Forceps)	2 (1,9%)	1 (1,8%)	3 (1,9%)
Referred Patient			
Yes	28 (26,4%)	32 (58,2%)	60 (37,3%)
No	78 (73,6%)	23 (41,8%)	101 (62,7%)
Outcome			
Alive	55 (51,9%)	35 (63,6%)	90 (55,9%)
Dead	51 (48,1%)	20 (36,4%)	71 (44,1%)
Mother's Age			
\leq 20 years old	6 (5,5%)	3 (5,5%)	9 (5,6%)
21–35 years old	72 (66,1%)	35 (63,6%)	107 (66,5%)
\geq 36 years old	28 (26,4%)	17 (30,9%)	45 (27,9%)
	30,31 \pm 6,63	31,1 \pm 6,43	30,58 \pm 6,55

found to be EOS (67.7%) and 52 LOS (32.3%). The patient characteristics in both categories were found to be similar. However, as many as 59.6% of LOS patients were referral cases, while most EOS patients were born in Dr. Soetomo General Hospital (73.4%). The mean age for the patients' mothers was calculated to be between 30 and 31 years old (Table 1).

We found that most neonates with sepsis were a singleton birth (92.5%) and born via caesarean section (65.2%) with low birth weight (LBW) (75.8%) and premature gestational age (65.2%) (Table 1). Patient characteristics in premature and term patients were found to be similar. Of note, 91.5% of premature patients with neonatal sepsis also had a low birth weight, with a mean birth weight of 1.591 gram (Table 2).

Most patients in both EOS and LOS categories had a mean gestational age of between 33-34 weeks (67.9% vs. 61.5%). Logistic regression analysis for EOS and LOS patients with their respective gestational age categories can be seen in Table 3. There was no statistical correlation between prematurity and the onset time of neonatal sepsis ($p>0.05$).

DISCUSSION

Neonatal sepsis is a life-threatening condition resulting from a bloodstream infection, in which bacteria, viruses or fungi are present during the first 28 days of life [6]. Premature infants are at a higher risk of acquiring sepsis than children and adults because of their immature immune

systems [21]. Many risk factors lead to neonatal sepsis, including maternal, neonatal (host), and nosocomial factors. A greater number of predisposing factors present in a patient could lead to a higher risk of developing sepsis. Some factors other than prematurity are being discussed in this study seeing that there could be a correlation among prematurity and onset of the disease with other neonatal risk factors. Neonatal risk factors involved in developing sepsis in neonates that we investigated include onset of the disease, mode of delivery, birth weight, referral status, and prematurity.

In this study, the prevalence of EOS patients was higher than that of LOS patients. Both premature and term neonates were more likely to be EOS patients than LOS. These findings are consistent with other studies conducted in other areas, such as Lampung, Denpasar, Ghana, and Bangladesh [22–24]. The high incidence of preterm birth and low birth weight neonates may explain the higher prevalence of EOS compared to LOS in this study, which are known as risk factors of EOS [25]. Other risk factors for EOS in developing countries, such as Indonesia, include inadequate antenatal treatment, high rates of home birth, poor treatment practices of the umbilical cord and unhygienic birth, as well as late recognition of conditions that increase risk of infection in the mother or infant [26].

Most analyzed patients were born via cesarean section delivery (65.2%). Infants born premature and the term had two times the number of birth via SC compared to spontaneous birth. Other

Table 3: Correlation between Prematurity with Neonatal Sepsis Onset

Variable	EOS (n=109)	LOS (n=52)	Total (n=161)	Logistic Regression Analysis		
				OR	CI 95%	p-value
Premature						
Extremely premature (<28 weeks)	5 (4,6%)	4 (7,7%)	9 (5,6%)	4,324	0,504-39,081	0,182
Very premature (28 – <32 weeks)	29 (26,6%)	19 (36,5%)	48 (29,8%)	1,017	0,457-2,267	0,966
Late premature (32 – <37 weeks)	31 (28,4%)	17 (32,7%)	48 (29,8%)	1,236	0,538-2,836	0,618
A term	44 (40,4%)	12 (23,1%)	56 (34,8%)		Reference	

studies in Jakarta and Medan had similar findings [27,28]. This finding could be because, as Dr. Soetomo General Hospital is the largest tertiary referral hospital in East Java, there are many complicated cases. Most neonatal sepsis patients and/or mothers have an underlying condition requiring emergency cesarean section treatment. Another possible explanation is the high number of mothers aged >36 years old (28%). Mothers of

advanced age have pre-existing conditions and more commonly obstetrical complications than younger women, which contribute to a greater caesarean delivery rate before labour and labour induction [29].

No significant correlation between the mode of delivery and neonatal sepsis onset was found ($p > 0,05$). This is consistent with the finding of no

Table 4: Correlation between Neonatal Characteristics with Neonatal Sepsis Onset

Variable	EOS (n=109)	LOS (n=52)	Total (n=161)	Logistic Regression Analysis		
				OR	CI 95%	p-value
Gender						
Male	58 (63,0%)	34 (37,0%)	92 (57,1%)	0,602	0,304-1,193	0,144
Female	51 (73,9%)	18 (26,1%)	69 (42,9%)			
Birth Weight						
Low (<2500gr)	88 (80,7%)	34 (65,4%)	122 (75,8%)	2,329	1,101-4,930	0,535
Normal (2500 – 4000 gr)	20 (18,3%)	28 (34,6%)	38 (23,6%)	0,952	0,866-1,048	0,348
High (>4000 gr)	1 (0,9%)	0 (0,0%)	1 (0,6%)		Reference	
Birth						
Singleton	100 (91,7%)	49 (94,2%)	149 (92,5%)	0,680	0,176-2,626	0,574
Twin	9 (8,3%)	(5,8%)	12 (7,5%)			
Mode of Delivery						
Spontaneous	35 (32,1%)	18 (34,6%)	53 (32,9%)	0,588	0,048-7,218	0,220
SC	71 (65,1%)	34 (65,4%)	105 (65,2%)	1,259	0,107-14,785	0,234
Others (Vacuum extraction and Forceps)	3 (2,8%)	0 (0,0%)	3 (1,9%)		Reference	
Referred Patient						
Yes	29 (26,6%)	31 (59,6%)	60 (37,3%)	0,246	0,122-0,494	0,000
No	80 (73,4%)	21 (40,4%)	101 (62,7%)			
Outcome						
Alive	59 (54,1%)	31 (59,6%)	90 (55,9%)	0,799	0,409-1,562	0,512
Dead	50 (45,9%)	21 (40,4%)	71 (44,1%)			
Mother's Age						
≥36 years old	31 (28,4%)	14 (26,9%)	45 (28,0%)	2,521	0,573-11,095	0,221
21–35 years old	73 (66,1%)	35 (67,3%)	107 (66,5%)	1,610	0,417-6,213	0,489
<20 years old	6 (5,5%)	3 (5,8%)	9 (5,6%)		Reference	

apparent difference in the percentage of infants born via SC (65,1% vs 65,4%) and spontaneous delivery (32,1% vs 34,6%) in EOS compared to LOS. Similar findings were reported in a national cohort study by Olivier et al. in Canada. Infants born by cesarean section or vaginal delivery did not correlate with the onset of neonatal sepsis (OR = 0.99; 95% CI: 0.87 – 1.12). However, the probability of LOS caused by coagulase-negative Staphylococcal neonatal sepsis (CONS)-associated infection was significantly higher among individuals who gave birth via cesarean section [30]. Although no direct exposure to vaginal bacteria occurs in SC, lacerations from medical equipment during delivery can be an entry point for microorganisms that cause the patient could undergo sepsis with a probability of 0.1–3.1%. Beyond this, the immunity of neonates following cesarean delivery may also be vulnerable due to the long duration of hospitalization and delayed initiation of breastfeeding [23,29]. In this regard, future studies are needed to clarify the correlation between mode of delivery with neonatal sepsis onset.

In the analyzed patients, 75.8% were identified as having low birth weight (LBW). LBW is a common finding in neonatal sepsis patients and is considered a strong risk factor [24,32]. Similar studies of the factors related to neonatal sepsis have shown inconsistent and varied results, though several meta-analyses and literature reviews maintain low birth weight as a factor that can increase the risk of infection due to immature organ function, decreased maternal immunoglobulin (IgG) reserves, inhibited antibody-forming ability, and decreased ability to consume breast milk, which causes malnutrition and prolongation of hospital stay [32,33]. Higher percentage of low birth weight infants (80,7%) was found in EOS compared to LOS (65,4%). However, no significant correlation was found between birth weight and neonatal sepsis onset ($p>0,05$). Several factors could explain the high percentage of LBW infants, 65.2% of the neonatal sepsis patients studied were born via SC. In previous studies by Barros et al. and Murta et al., negative pregnancy outcomes such as premature birth and low birth weight were found to be linked with an increased occurrence of spontaneous CS [30,31]. More than half of preterm and LBW deliveries performed by CS were planned [32]. This might be owing to the misuse of planned

CS, which has been shown to be connected with term LBW deliveries, particularly in private facilities [33]. Another possible explanation could be a relatively high percentage of mothers aged >36 years old (28%). In older women, there is a general decline in physiological and reproductive functions, resulting in poor fetal development and LBW infants. Pregnant women > 36 years old also have an increased risk of premature birth resulting in the occurrence of LBW in infants [36]. This could explain the higher number of LBW infants in EOS compared to LOS, where a greater number of mothers aged >36 years was identified. In this study, 91.5% of premature patients with neonatal sepsis had a low birth weight. This finding is consistent with studies done in Ethiopia, Nigeria and Afghanistan[31,37,38]. Onwuanaku, et al. found preterm birth to be the major cause of low birth weight [37]. Premature infants with low birth weight require longer intensive treatment in hospitals, increasing the risk of nosocomial sepsis [38].

A total of 37,3% neonatal sepsis patients studied were referred cases. This number is considerably higher than other referral hospitals in Indonesia (1.5%-3.7%) [39]. In this study, referral status significantly correlated with neonatal sepsis onset ($p<0,05$). Although most patients in this study were born in Dr. Soetomo General Hospital, 59.6% ($n=31$) of LOS patients were referred, 2 times greater than EOS patients (26,6%). This finding is consistent with a previous study where delivery outside of Dr. Soetomo General Hospital was significantly associated with LOS (p -value = 0.01, OR 31.69 (95%CI 3.83-262.03) [25]. Another study conducted by Murthy, et al. found that referred patients had a significantly higher risk for neonatal sepsis in India. The increased incidence of neonatal sepsis might be related to the lack of availability of pediatrician or other medical personnel to the patient during pregnancy and delivery leading to an increased risk of infection from poor hygiene, unmonitored pregnancy health, poor umbilical cord care, lack of breastfeeding, aspiration of feeds and undetected symptoms of neonatal sepsis. The non-specific symptoms of neonatal sepsis may have caused the parents only to get medical care when the symptoms worsen or become life-threatening. LOS is diagnosed if the onset is over 72 hours post-partum and mainly occurs from post-natal nosocomial infection or

community-acquired illnesses. Patients with underlying respiratory and cardiovascular disease, prolonged hospitalization, surgery, and invasive interventions such as intravascular catheterization and mechanical ventilation may also increase the risk of LOS [18].

Neonates are highly susceptible to disease, with prematurity increasing susceptibility to infection. One mode of protection from infection in term infants is antibodies transferred from mother to fetus. These antibodies protect against specific infections that the mother has experienced. In premature infants, the amount of IgG is less than that of term infants, increasing the susceptibility of these neonates to infection. Beyond this, immaturity of the cellular immune system, such as limited bactericidal ability and an incompletely functioning complement system further reduces the immune system function of these patients. Decreased function of neutrophils and low concentrations of immunoglobulins also increase the susceptibility of preterm infants to infection obtained from invasive procedures [34].

Prematurity is often reported as one of the most important neonatal sepsis risk factors and commonly found in both EOS and LOS cases [18]. Most EOS and LOS patients were premature babies (67.9% vs. 61.5%). These results are consistent with other studies of risk factors for neonatal sepsis [16,25,34].

Our analysis found no statistically significant correlation between prematurity and EOS or LOS. This finding aligns with the study by Ogundare et al. conducted in Nigeria but contradicts the study by Al-Matary et al. conducted in Saudi Arabia [25,34]. A study in South-East Nigeria found that prematurity was more likely to be associated with LOS due to prolonged hospitalization and increased chance of nosocomial infection [35]. The geographical differences might influence various patterns of neonatal sepsis, including factors that determine the onset of infection [36].

Another reason for our statistical finding is numerous underlying medical reasons among mothers who should give birth prematurely. Based on the delivery mode and indication for surgery, preterm birth can be divided into four subtypes: spontaneous preterm birth, spontaneous preterm

birth with premature rupture of membranes (PROM), cesarean section without PROM, and preterm birth with induction of labour [37]. Intra-amniotic infections such as chorioamnionitis can induce spontaneous preterm birth. Intrapartum sepsis is caused by the passage of contaminated amniotic fluid into the fetus. When preterm membranes rupture after 18 hours, the risk of EOS in the newborn increases by 1%, with an estimated risk of 1-4% [17]. Thus, the cause of preterm birth should also be examined when considering the risk level for neonates developing sepsis.

Other factors not discussed in this study include a mother's history of UTIs in the third trimester, which coincides with preterm birth and APGAR score at 5 minutes < 7, which has been identified as a significant risk factor [23]. In addition, social or ethnic factors need to be considered to be associated with neonatal sepsis. These may include inadequate or poor prenatal treatment, low maternal socioeconomic status, poor maternal nutrition, substance abuse by the mother, male gender, and African-American mothers (higher GBS colonization rate) [6].

Neonates are vulnerable to infection with many factors that may result in newborn morbidity and mortality. These factors can be addressed through a combined, holistic approach to the effective medical care of the mother and her neonate during pregnancy, delivery and after birth [29].

The limitation of this study is the inability to find a standardized scoring for neonatal sepsis risk factors worldwide or nationwide. Standardized scoring could benefit this study by determining the severity of neonatal sepsis risk factors between patients.

CONCLUSION

There is no significant correlation between prematurity and neonatal sepsis onset. Although preterm birth is often reported as one of the most important risk factors for neonatal sepsis, prematurity does not appear to be an independent risk factor for the onset of neonatal sepsis.

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