RISK OF TUBERCULOSIS IN CHILDBEARING-AGE WOMEN WITH DIABETIC MELLITUS AND MALNUTRITION IN EASTERN INDONESIA BASED ON THE 2018 NATIONAL BASIC HEALTH SURVEY

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Abstract. Diabetes mellitus has previously been identified as a comorbidity among tuberculosis patients due to a weak immune system. Malnutrition, on the other hand, is still a public health issue and a risk factor for tuberculosis. This study aimed to investigate the risk of tuberculosis in childbearing-age women who have diabetes and malnutrition in East Indonesia. The secondary data of this study were from the 2018 National Large Cross-Sectional Survey. To describe national representatives, a multistage sample was used as a sampling method. However, this analysis was limited to the East Indonesia Region with 13 provinces prevalence of malnutrition is highly found there. The logistic regression in complex samples was used to examine the risk of tuberculosis in diabetic patients and was adjusted for nutrition status and other factors. The samples of this study were 82,252 participants. The prevalence of malnutrition was determined to be undernutrition (17.8%), overweight (12.1%), and 20.9% of obese status. The prevalence of tuberculosis is 0.1% while the prevalence of diabetes mellitus diagnosed by doctors is 1.1%. Results of this study shows that determinant of tuberculosis are being diabetic patients (adjusted odds ratio (aOR) = 7.45; 95% confidence interval (CI): 3.80-14.60, $p<0.001$), chronic energy malnutrition (CEM) (aOR = 3.30; 95% CI: 2.20-4.90, $p<0.001$), age group 20-35 (aOR = 1.75; 95% CI: 0.90-3.10, $p=0.002$), age group 36-59 (aOR = 2.70; 95% CI: 1.60-4.50, $p<0.001$). We concluded that patients with diabetes are the most vulnerable to has tuberculosis.

Keywords: diabetic mellitus, malnutrition, risk-factor, tuberculosis, women childbearing age

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INTRODUCTION

Tuberculosis (TB) is an infectious disease that still becomes a global public health concern in developing countries. It is estimated that 10 million people lived with TB by 2020, and 1.5 million of them died. TB ranks the 13th of the world's leading causes of death (WHO, 2022). The global commitment to end TB has set targets to reduce deaths (WHO, 2021a) by 90% by 2020 and reduce TB incidence by 80% by 2035; these numbers are higher than those in 2015 data (WHO, 2021a; WHO, 2015). Meanwhile, after China and India, Indonesia has the highest global incidence of TB. It implies that a significant effort is required to realize the global target of ending TB.

Many factors are identified as a determinant of TB; as an infectious disease, TB gets more severe because people have low immunity (Yorke *et al*, 2017). Previous research has found that TB is comorbid with communicable and non-communicable diseases (Asturiningtyas *et al*, 2021; Bates *et al*, 2015). Comorbidities can significantly weaken immune systems, leading to more severe illness (Bates *et al*, 2015). A previous study has found that diabetes mellitus (DM) increases the risk of active TB (Restrepo, 2016). DM patients who are also infected with TB are more likely to develop TB and suffer from more severe TB (Yorke *et al*, 2017). DM and TB can also worsen health complications if they are not treated properly (CDC, 2022).

Otherwise, changes in epidemiology patterns show that DM has spread rapidly in recent years (Khan *et al*, 2019). This spread is estimated to continue for three to quarter fold during the last three decades, and a higher number of approximately 7,862 cases per 100,000 population is predicted to occur in 2040 (Khan *et al*, 2019). Another source estimates that the number of DM cases in 2045 is approximately 693 million people (Cho *et al*, 2018). DM also became the world's leading cause of death in 2019 and has killed

up to 1.5 million people (WHO, 2021b). Meanwhile, the prevalence of DM is increased by obesity and lifestyle; these two factors are influenced by rapid economic development and urbanization. The prevalence of DM was reported for Southeast Asia (Zheng *et al*, 2018), and 58% of this prevalence also suffers from TB. China, India, and Indonesia are three countries with high prevalence of TB and DM (Khan *et al*, 2019).

The 2017 burden of the disease shows that TB and DM are public health issues in Indonesia. TB wasone of the five leading causes of disease burden in 2017. Meanwhile, DM, which is also a risk factor for TB, became the third largest contributor to the burden of disease. At the same time, malnutrition was another problem in developing countries.

Based on the National Basic Health Survey, malnutrition is a public health issue in Indonesia because approximately one-third of children under five are stunted, more than 40% of pregnant women suffer from anemia, and 18.3% of childbearing age women suffer from undernutrition (MOH RI, 2019). Meanwhile, the problem of overweight and obesity in adults has increased five times as high as that in 2013 (MOH RI, 2019). By 2030, TB is targeted to end; new TB cases could be reduced by controlling vulnerable groups, such as DM patients and malnutrition people (Byashalira *et al*, 2022; van Crevel and Critchley, 2021). This paper aims to analyze the risk of TB in childbearing-age women with DM and malnutrition in East Indonesia.

MATERIALS AND METHODS

This study used secondary data from the 2018 Basic Health Research (Riskesdas) survey, which was organized by the National Institute of Health Research and Development of the Ministry of Health. The sample was selected using the multistage sample method and the census block serving method as the primary sampling unit with a proportional probability size. The stratification was then done according to urban and rural areas. The national representative sample consisted of 2,500 census blocks with subsamples drawn from 30,000 census blocks as the total samples in

34 provinces (MOH RI, 2019).

However, this paper only investigated cases in Eastern Indonesia, consisting of 13 provinces. Based on the Lemeshow method (Lwanga and Lameshow, 1991), the minimum target sample size was expected in this study with an absolute accuracy of 95% of the confidence interval. Based on these data, the sample size of this study was adequate even after considering the inclusion and exclusion criteria, which were more than 80%.

The inclusion criteria of this study were childbearing-age women aged 10-59 years, and not pregnant. Weight, height, and body mass index (BMI) and mid upper arm circumference (MUAC) were used to assess the nutritional status of the childbearing-age women. A standardized measuring instrument for height with a precision of 0.1 cm was used to determine the anthropometric scale. If the BMI value had been less than 18.5 kg/m^2, the women had been classified as undernutrition. Meanwhile, if the BMI value had been more than 27 kg/m^2, the women had been classified as overweight. Finally, if the BMI had been more than 30 kg/m^2, the women were classified as obese. When the middle upper arm circumference (MUAC) was less than 23.5 kg/m^2, it was classified as chronic energy malnutrition (CEM). Abdominal circumference 90-110 cm was classified central obesity category 1; abdominal circumference >110 cm was classified central obesity category 2. Meanwhile, DM and TB were classified based on the doctor's diagnosis and respondents' interview. The socioeconomic level was represented by a quintile index, with Q1 indicating very low socioeconomic status, Q2 indicating low economic status, and Q3 indicating middle socioeconomic status. Q4: Economic status in the upper middle; Q5: highest level of economic status. This categorization is based on a wealth index derived from a survey and analyzed using principal component analysis (Ahmad, 2015). The secondary data provided a socioeconomic indicator that was divided into five quartiles (Q1-Q5). The median of the index value is represented by Quartile 3 (Q3). Furthermore, index value lower than the median (Q3), indicating very low economic status (Q1) and low economic status (Q2). While the index with the highest Q3 value indicates upper middle socioeconomic status (Q4) and high economic status (Q5).

We visualized the cases of malnutrition, TB, and DM on maps. We used administrative maps of provinces and districts with a scale of 1:50,000 from the Geospatial Information Agency of Indonesia. This map was publicly available at https://tanahair.indonesia.go.id/. All the spatial visualization processes employed QGIS version 3.22 which is open source and is available freely at https://qgis.org/en/site/.

The data were then analyzed using Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp, Armonk, NY). The results of this calculation were then tested using multivariate logistic regression.

The Indonesian Health Research and Development Ethics Committee approved this study for ethical reasons with number of ethics LB.02.01/2/KE.024/2018.

RESULTS

This study examined 82,252 childbearing women. Maps of the malnutrition proportion and cases of DM and TB in Eastern Indonesia are presented in Fig 1. This study has determined the percentages of the prevalence of malnutrition: 17.8% for undernutrition, 12.1% for overweight, and 20.9% for obesity. The prevalence of TB is 0.12% while the prevalence of DM diagnosed by doctors is 1.1%. The characteristics of the research participants are presented in Table 1.

Table 1 shows that the proportion of TB in Eastern Indonesia is 0.12, with this proportion increasing with age. Rural areas had a higher proportion of TB than urban areas; otherwise, the proportion of TB decreased as education level increased. TB prevalence was higher in diabetes patients than in non-diabetics. People with chronic energy malnutrition (CEM) have a higher proportion of TB than people with normal nutrition status.

Table 2 reveals that more risk of getting tuberculosis was found in person with diabetic (aOR = 7.45; 95% CI: 3.8-14.6, p<0,001) whilst in chronic energy malnutrition, aOR = 3.3, 95% CI: 2.2-4.9, p<0,001; in the age group 20-35, aOR = 1.75, 95% CI: 0.9-3.1, p=0.002) and in the age group 36-59, aOR = 2.6, 95% CI: 1.6-4.5, p<0.00.

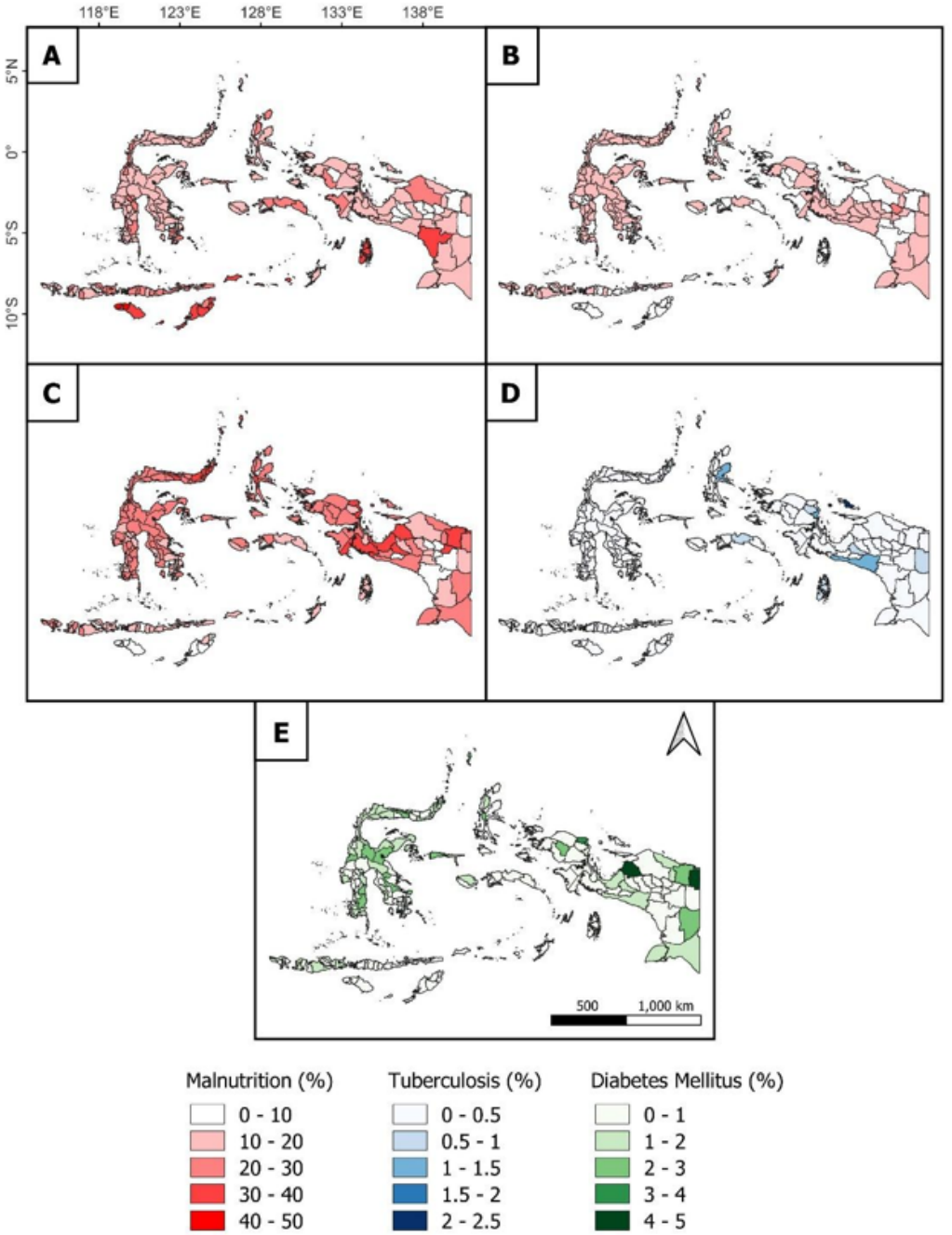

Fig 1 - Map of malnutrition, tuberculosis and diabetes mellitus in Eastern Indonesia

A: Undernutrition; B: Overweight; C: Obesity; D: Tuberculosis; E: Diabetes mellitus

Table 1

Proportion of respondents TB based on characteristic, DM status and nutrition status

Demographic characteristics	Tuberculosis (%)	Confidence interval (%)		Number
		Lower	Upper	
Age				
10-19 years old	0.06	0.04	0.11	21,674
20-35 years old	0.09	0.05	0.15	29,702
35-59 years old	0.18	0.13	0.27	30,875
Socio economic status*				
Quintile 1	0.10	0.06	0.16	20,708
Quintile 2	0.07	0.04	0.13	14,976
Quintile 3	0.14	0.07	0.28	14,913
Quintile 4	0.12	0.08	0.20	14,932
Quintile 5	0.15	0.07	0.29	16,724
Area				
Urban	0.10	0.06	0.17	32,638
Rural	0.13	0.09	0.17	49,614
Education level†				
Low	0.14	0.10	0.21	38,765
Middle	0.11	0.07	0.17	35,579
High	0.03	0.01	0.10	7,909

Table 1 (cont)

Demographic characteristics	Tuberculosis (%)	Confidence interval (%)		Number
		Lower	Upper	
Job category				
Government/Private company	0.08	0.03	0.25	7,008
Farmer/Fisherman/Self employed	0.12	0.07	0.19	25,132
Driver, laborer	0.00	0.00	0.00	2,147
Un-employed	0.13	0.09	0.18	47,965
Diabetes mellitus				
No	0.11	0.08	0.14	81,371
Yes	1.09	0.53	2.21	881
CEM				
No	0.08	0.06	0.11	69,258
Yes	0.28	0.18	0.44	12,994
Proportion TB in Eastern Indonesia	0.12	0.09	0.15	82,252

CEM: chronic energy malnutrition (the condition when middle upper arm circumference or MUAC was less than 23.5 centimeters); DM: diabetes mellitus; TB: tuberculosis

*Socio economic status (Quintile 1: very low economic status; Quintile 2: low economic status; Quintile 3: middle economic status; Quintile 4: upper middle economic status; Quintile 5: high economic status)

†Education (Low: duration of study <9 years; Middle: duration of study 9-12 years, High: duration of study >12 years)

Table 2
Multivariate analysis of risk factors of TB in people with DM and malnutrition

Characteristic	B	aOR (95% CI)	*p*-value
Age			
10-19 years old			<0.001
20-35 years old	0.56	1.75 (0.98-3.12)	0.06
>35 years old	0.98	2.66 (1.57-4.52)	<0.001
Diabetes mellitus	2.01	7.45(3.80-14.61)	<0.001
Educational level*			
Low			0.02
Middle	-0.37	0.69 (0.47-1.03)	0.07
High	-1.27	0.28 (0.10-0.78)	0.01
Nutrition Status			
CEM	1.19	3.30 (2.21-4.94)	<0.001
Constant	-7.35		<0.001

*Education (Low: duration of study <9 years; Middle: duration of study 9-12 years, High: duration of study >12 years)
aOR: adjusted odd ratio; B: coefficient; CEM: chronic energy malnutrition (the condition when middle upper arm circumference or MUAC was less than 23.5 centimeters); CI: confidence interval

Further multivariate analysis shows risks of DM increase by age, ie at age 20-35 years (aOR = 4.02; 95% CI: 1.61-10.05, p<0.003); at age >35 years (aOR = 43.5; 95% CI: 18.05-105.11, p<0.0001). Risks also increase by socio economic status, ie at Q2 (aOR = 1.56; 95% CI: 1.21-2.02, p<0.001); Q3 (aOR =1.78; 95% CI: 1.39-2.28, p<0.001); Q4 (aOR = 2.08; 95% CI: 1.64-2.64, p<0.001); Q5 (aOR = 2.49; 95% CI: 1.98-3.14, p<0.001). People with different category of abdominal obesity have different risks, *ie* category 1 (aOR = 1.29; 95% CI: 1.12-1.50, p=0.001). People living in urban area have an aOR of 1.31; 95% CI: 1.14-1.52, p<0.001) (Table 3).

Table 3
Multivariate analysis risk factor of diabetes mellitus

Demographic characteristic	B	aOR (95% CI)	*p*-value
Age			
10-19 years old			<0.001
20-35 years old	1.392	4.02 (1.61-10.05)	0.003
>35 years old	3.774	43.56 (18.05-105.11)	<0.001
Abdominal circumference			0.003
Category 1 (90-110 cm)	0.258	1.29 (1.12-1.50)	0.001
Category 2 (>110 cm)	0.098	1.10 (0.64-1.89)	0.722
Socio economic status*			
Quintile 1			<0.001
Quintile 2	0.447	1.56 (1.21-2.02)	0.001
Quintile 3	0.578	1.78 (1.39-2.28)	<0.001
Quintile 4	0.733	2.08 (1.64-2.64)	<0.001
Quintile 5	0.913	2.49 (1.98-3.14)	<0.001
Area (Urban)	0.273	1.31 (1.14-1.52)	<0.001
Constant	-8.216		<0.001

*Socio economic status (Quintile 1: very low economic status; Quintile 2: low economic status; Quintile 3: middle economic status; Quintile 4: upper middle economic status; Quintile 5: high economic status)
aOR: adjusted odd ratio; B: coefficient; CI: confidence interval; cm: centimeter

DISCUSSION

Tuberculosis is caused by the bacteria Mycobacterium tuberculosis and affects the lungs. It spreads from person to person through germs in the air particles inhaled by others (WHO, 2022).

However, humans have different immune factors to fight against the pathogen, so that only 5-10% of people exposed to TB germs will develop

into TB disease (active TB); such a condition links to a breakdown in immune surveillance (WHO, 2022).

As a result, people with malnutrition, metabolic diseases (DM or chronic lung disease), and immune disorders (HIV and autoimmunity) are more likely to contract TB (Bates *et al*, 2015). Previous research in Indonesia has found that the most common non-communicable disease (NCD) comorbidities among people with TB are asthma (13.3%), hypertension (11.2%), diabetes (7.7%), and heart disease (5.5%) (Asturiningtyas *et al*, 2021). The study also discovers that people with DM are more likely to develop TB than people without DM. Moreover, the comorbidity of TB and DM patients has been discovered (Yorke *et al*, 2017). The prevalence of TB among DM patients in several countries ranges from 0.1 to 45%. A study in Thailand has found that DM is found in approximately 6.0-16.3% of TB patients (Buasroung *et al*, 2022).

DM worsens the conditions of TB patients and increases the risk of complications (Yorke *et al*, 2017). A prospective cohort study of 216 subjects in Thailand has revealed that patients with TB and DM are 76% more likely to have other comorbidities (Buasroung *et al*, 2022). Patients with TB who also have DM are more likely to have other underlying conditions than those without DM; these conditions include dyslipidemia (73.9% *vs* 28.2%), hypertension (66.3% *vs* 27.4%), cardiovascular disease (25% *vs* 11.3%), obesity (22.8% *vs* 9.7%), and chronic kidney disease (19.6% *vs* 9.7%). Moreover, patients with TB and DM have a higher 6-month mortality rate (14% *vs* 3%) and a higher proportion of treatment complications (Buasroung *et al*, 2022). These findings are similar to those of the previous study by Huangfu *et al* (2019), who conducted systematic reviews and meta-analyses with 1,004 publications from 1980 to 2018. Moreover, DM is associated with an increased risk of poor TB treatment outcomes, with a risk 1.88; 1.66 and 1.98 on mortality; relapse and development of primary MDR-TB, respectively (Huangfu *et al*, 2019).

Some systematic review reveals similar results that DM increases the risk of failure and death as well as death and relapse in TB patients (Baker

et al, 2011; van Crevel and Critchley, 2021). This present study emphasizes the importance of paying more attention to TB treatment in people with DM. The treatment may include testing for suspected diabetes, improving glucose control, and increasing clinical and therapeutic monitoring (Baker *et al*, 2011; van Crevel and Critchley, 2021)

The findings of this study denote that DM is highly risky for childbearing-age women with TB. DM, on the other hand, is a metabolic disorder because pancreatic tissues produce insufficient insulin to transport glucose to the cell (WHO, 2021b). Immune systems are influenced by the increase in body glucose levels. Obese women are more likely to develop DM (Kautzky-Willer *et al*, 2016). This condition means that obese women who live with TB patients are at a higher risk of contracting TB because they have weak immune systems. Moreover, malnourished women could not be ignored because they are also at risk of contracting TB as they have weak immune systems.

A systematic review has revealed that human mechanisms of immune systems are related to TB and DM. Hyperglycemia is a risk factor for lung cavity swelling and lung lobe lesions and is commonly found in TB and DM patients with uncontrolled blood sugar (Wei *et al*, 2022; Yorke *et al*, 2017). A systematic review has also revealed that the absolute numbers of T lymphocytes, CD8+ T lymphocytes, and B lymphocytes in DM and TB patients are lower than those in non-DM and TB patients (Wei *et al*, 2022). Thus, weak immune systems and the complexity of diseases are influenced (Yorke *et al*, 2017).

The immune system is a human defense mechanism that protects against pathogens, such as bacteria (Davis, 2008). People with DM have a systemic immune response disorder caused by high blood glucose levels. As a result, T cells are protected against infectious disease sources (Wei *et al*, 2022; Yorke *et al*, 2017). Furthermore, many factors have been identified as immune response determinants; malnutrition is a factor that influences immune strength.

The findings of this research show that undernutrition status affects almost 20% of childbearing-age women in eastern Indonesia. The risk of TB in undernutritious people is nearly three times as high as that in people with normal nutrition status. Malnutrition disrupts the balance of essential enzyme metabolism, which controls the immune system (Saeed *et al*, 2016). Every nutrient plays a role in immunity systems. Protein-energy deficiency causes lymphoid organ atrophy, such as the thymus, lymph nodes, and tonsils (Yaqooob and Calder, 2015). Moreover, the number of lymphocytes in the blood and the ability of natural killer cells decrease; these decreases are proportional to the degree of malnutrition (Alwarawrah *et al*, 2018; Yaqooob and Calder, 2015).

In addition to protein energy deficiency, other nutrient deficiencies, such as Vitamins A, B, C, D, and E, caretonoid, folic acid, zinc, iron, and selenium, can impair the immune system due to the unique roles of each nutrient (Smedman, 2007). In other words, well-balanced micronutrients boost immune systems against pathogens, such as the mycobacterium of tuberculosis (Smedman, 2007; Yaqooob and Calder, 2015).

The government needs to implement an integrated screening program to increase the number of cases of Tuberculosis with Diabetes Mellitus (TB2DM). We can expand our case finding to high-risk populations like those with diabetes mellitus (blood glucose screening) or obesity and malnutrition in TB patient through integrated unit for non-communicable disease to improve early detection for TB with diabetic mellitus.

In summary, diabetic patients and malnutrition are particularly vulnerable to active tuberculosis. Tuberculosis and Noncommunicable Disease Integrated Programs are required to increase case finding of TB cases and prevent TB severity to get underlying condition.

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CONFLICT OF INTEREST DISCLOSURE

All author declares no conflict of interest of this study.

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