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ORIGINAL ARTICLE

Metabolic syndrome increases cardiovascular risk in a population with prediabetes: A prospective study in a cohort of Chinese adults

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ABSTRACT

Aims/Introduction: The prevalence of prediabetes has become a global epidemic, and prediabetes is often accompanied with metabolic syndrome (MS). However, the association between MS and cardiovascular (CV) risk among individuals with prediabetes in China remains unknown. The present study aimed to identify the relationship of MS with CV risk in Chinese adults with prediabetes.

Materials and Methods: Altogether, 19,464 participants with prediabetes were enrolled at baseline and were followed up prospectively. Prediabetes is defined as a fasting plasma glucose level between 5.6 and 6.9 mmol/L, and with neither a history of diabetes nor current use of hypoglycemic drugs. Participants were classified on the basis of the presence of MS, according to the definition of the International Diabetes Federation. Main outcomes include major CV events. Incidence rates were expressed in cumulative incidence and person-years incidence. Cox proportional hazards analysis was used to estimate the risk of major CV events.

Results: At baseline, the mean age was 51.9 ± 11.4 years, and 85.6% (n = 16,663) were men. During a median follow-up period of 10.0 years, a total of 1,169 major CV events occurred, including 921 strokes and 273 cases of myocardial infarction. The cumulative incidences were 9.0% (8.1–10.0%), 6.8% (6.0–7.6%) and 2.5% (2.0–3.0%) for total CV events, strokes and myocardial infarction. Regardless of the risk of total CV events, or the risk of stroke or myocardial infarction, the number of prediabetes individuals with MS was higher than those without, and the hazard ratio was 1.50 (95% confidence interval 1.31–1.73), 1.42 (95% confidence interval 1.21–1.67), 1.78 (95% confidence interval 1.34–2.36), respectively.

Conclusions: Among the Chinese population with prediabetes, the risk for major CV events was significantly higher in those with MS than those without.

INTRODUCTION

With global population growth, and aging, change of lifestyle and dietary patterns, the proportion of the population with diabetes[1], as well as prediabetes[2], has increased rapidly. It was estimated that the worldwide prevalence of diabetes might approach 422 million[1], and 840 million people currently live with prediabetes[3]. A national cross-sectional survey in China suggested that approximately 493.4 million adults lived with prediabetes in 2010[4]. A recent meta-analysis reported that prediabetes is the precursor stage of diabetes, and the yearly progression rate to diabetes is 3.5–7.0%[5]. Furthermore, prediabetes is considered to be an increased risk factor for cardiovascular complications[3,6]. Therefore, it would be more cost-effective to screen and manage the high-risk subgroups among individuals with prediabetes.

In addition, prediabetes is often accompanied with the manifestation of much broader underlying disorders[7,8], including metabolic syndrome (MS), a highly prevalent, multifaceted disease characterized by a series of abnormalities that include abdominal obesity, hypertension, dyslipidemia and elevated

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fasting plasma glucose fasting plasma glucose (FPG). Evidence exists to support that individuals with MS are at significant risk of developing diabetes[9]. In addition, individuals with MS are at high risk of developing cardiovascular disease (CVD)[9,10]. The Botnia study showed that the risk for stroke and coronary heart disease was increased threefold in individuals with MS[10].

In theory, individuals with prediabetes and MS should have a higher risk of developing CVD than those without MS, which has been affirmed by a cohort study in Iran[11]. However, to the best of our knowledge, there is little research about the association between MS and major CV events in China, where the burden of prediabetes is more severe[4]. In the current study, we analyzed data collected from the Kailuan study to investigate the impact of MS on major CV events in a Chinese prediabetes population.

METHODS

Study Population

A large prediabetes subgroup of the Kailuan cohort was included in the current study. The Kailuan study is a prospective cohort study and workforce survey carried out in the community of Kailuan in Tangshan, a large and littoral industrial city located in the Hebei province of China. The detailed study design and characteristics of the study population have been described previously[12]. Briefly, 101,510 working and retired employees of Kailuan Corporation, aged ≥18 years participated in a biennial health examination between June 2006 and October 2007. All participants completed questionnaires on demographics and other variables, clinical examinations were carried out by trained medical personnel, and laboratory assessments were carried out in Kailuan General Hospital and its 10 affiliated hospitals. The examination data were recorded and maintained in dedicated health records.

The employees were included in the study population if they met the following criteria: aged 18–85 years; with prediabetes according to American Diabetes Association 2003 criteria (FPG between 100 mg/dL [5.6 mmol/L] and 125 mg/dL [6.9 mmol/L]), without a self-reported history of diabetes and taking hypoglycemic drugs)[13]; having completed information for MS (according to the definition of the International Diabetes Federation): central adiposity (defined as waist circumference [WC] ≥90 cm in men and ≥80 cm in women) plus two or more of the following four factors: raised triglycerides (>1.7 mmol/L); reduced high-density lipoprotein cholesterol (HDL-C; <1.03 mmol/L in men and <1.29 mmol/L in women); raised blood pressure (BP; systolic ≥130 mmHg or diastolic ≥85 mmHg); and raised FPG (≥5.6 mmol/L))[14]. Because the present participants are prediabetes and met one of the diagnostic criteria for MS, we agreed that as long as central obesity was met, plus one of the following conditions (raised triglycerides, reduced HDL-cholesterol, raised BP), we could diagnose MS. Those with a history of myocardial infarction (MI), stroke, any malignant cancer or end-stage kidney disease (defined as estimated glomerular filtration rate <15 mL/min/1.73 m^2) at baseline were excluded. Finally a total of 19,464 participants (16,663 men, 85.6%) with prediabetes were included in the analysis.

The current study was approved by the ethics committee of Kailuan General Hospital in accordance with the Declaration of Helsinki, and written informed consent was obtained from each participant.

Data Collection

Follow up started from the completion of the health examination in 2006–2007, and the end of follow up was the first occurrence of the defined main outcomes on 31 December 2016. Questionnaires were administered by research doctors in person, documenting their sociodemographic status (e.g., sex, age, education, economic status), lifestyle habits (e.g., alcohol consumption, smoking status, physical activity), and personal and family health history (e.g., hypertension, diabetes, CVD).

Anthropometric measurements including WC and BP were collected according to a standard protocol[13]. WC was averaged to 0.1 cm, and central obesity was defined as WC ≥90 cm and ≥80 cm for men and women, respectively[14].

Following the standard recommended procedures, BP was measured using a standardized mercury sphygmomanometer. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken at a 5-min intervals twice after participants had been sitting for at least 15 min. If these two readings differed by >5 mmHg, then a third measurement was carried out. The average of these readings was used for analysis.

Serum samples were collected in ethylenediaminetetraacetic acid tubes after an overnight fast, and were taken at 07.00–09.00 hours the next morning. Biochemical measurements including FPG, serum creatinine, high-sensitivity C-reactive protein (hs-CRP), triglyceride and HDL-C were tested using a Hitachi 7600 auto-analyzer (Hitachi, Tokyo, Japan). Measurement of FBG was carried out using the Hexokinase method (BioSino Bio-Technology & Science Inc., Beijing, China). Serum creatinine was measured using the Jaffe's assay, and estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration Study equations. Urine protein concentration was assessed by a dry chemistry method with the H12-MA test assay (Changchun Dirui Medical Technology Co., Ltd., Changchun, China) using a semiquantitative dipstick test. All biochemical variables were measured at the central laboratory of the Kailuan General Hospital.

Study Outcomes

Primary outcomes were first occurrence of major CV events, which were defined as either non-fatal MI or stroke (including ischemic stroke, subarachnoid hemorrhage and intracerebral hemorrhage). The diagnosis of CV events was confirmed through medical record review, using the World Health Organization criteria[15,16]. Total CV events was defined as the sum of the first occurrence of major CV events. A biennial personal interview was used to collected information on major CV

events, and was confirmed by evaluation of claim data from medical insurance combined with medical records and discharge summaries from Kailuan General Hospital and its 10 affiliated hospitals. Because of the current insurance coverage rules in the Kailuan population, individuals who seek medical care outside this hospital network might not have their health insurance costs reimbursed. This ensures a high accuracy of screening the outcomes of interest in the Kailuan population. The outcomes were collected and recorded every 6 months. All outcomes were validated by the Data Safety Monitoring Board and the Arbitration Committee for Clinical Outcomes.

Other Covariates

According to the definition of MS from the International Diabetes Federation[14], raised BP was defined as SBP ≥130 mmHg or DBP ≥85 mmHg, or treatment for previously diagnosed hypertension. Raised TG was defined as TG ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality. Reduced HDL-C was defined as HDL-C <40 mg/dL (1.03 mmol/L) and <50 mg/dL (1.29 mmol/L) for men and women, respectively. Raised FPG was defined as FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or urine protein dipstick reading ≥1+. Fatty liver was diagnosed using a color ultrasonic diagnostic apparatus with the presence of at least two of the following indicators: (i) hypoechogenicity of the liver far field; (ii) hyperechogenicity of the liver near field (bright liver), and stronger than the kidney cortex; and (iii) blurring intrahepatic tubular structure.

Statistical Analysis

The baseline characteristics were described and compared among participants with and without MS. Continuous variables were described by mean ± standard deviation and median (quartile) for normal distribution and abnormal distribution, respectively. Categorical variables are presented by number (percentage). The continuous variables were compared using Student's *t*-test and a non-parametric test for normal distribution data and abnormal distribution data, respectively, whereas categorical variables were compared using χ^2-tests.

Based on the presence of MS, the prediabetic population was divided into two groups. The incidence rate of predefined outcomes was calculated as a whole and among different groups, and was compared using the log–rank test. Incidence rates were expressed in cumulative incidence, as well as person-years incidence.

Cox proportional hazards models were used to assess the risk of major CV events. *P*-value and hazard ratios with 95% confidence intervals (CIs) were reported. All analyses were adjusted for none (model 1), adjusted for age, sex (model 2) and further adjusted for baseline heart rate, hs-CRP, smoking status (current smoker or not), income (>800 RMB per capita income vs <800 RMB per capita income), education level (high school or above vs below high school level), physical activity (defined as self-reported exercise frequently or not), alcohol consumption (current drinker or not), CKD (yes vs no) and fatty liver (yes vs no; model 3). All *P*-values were calculated from two-tailed tests of statistical significance. A *P*-value <0.05 was considered to be statistically significant. All statistical analyses were carried out with SPSS System version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics of Study Population

The detailed approach for participants' selection is shown in Figure 1. After exclusion, overall 19,464 participants with prediabetes with valid data were enrolled in the analyses. The mean age of this cohort was 51.9 ± 11.4 years, and 85.6% (n = 16,663) were men. The baseline characteristics of the entire study population and stratified by the presence of MS are shown in Table 1. In general, individuals with MS were significantly older, had lower educational level and higher income, as compared with those without MS. In addition, the levels of heart rate, WC, BP, FPG, TG, hs-CRP, and the percentage of CKD, fatty liver and current smoker were significantly higher in participants with MS than those without (P < 0.001; Table 1).

Incidence Rate of Major CV Events

The results of the incidence rate of adverse outcomes stratified by MS are shown in Table 2. During a median follow-up period of 10.0 years (interquartile range 9.8–10.2 years), 1,169 (6.0%) total CV events occurred, which included 921 strokes and 273 cases of MI. Overall, the incidence rates of total CV events, strokes and MI were 617.9, 483.8 and 141.2 per 100,000 person-years, respectively. Obviously, participants with MS had a higher cumulative incidence than those without MS, and the cumulative incidences were 9.0% (8.1–10.0%), 6.8% (6.0–7.6%) and 2.5% (2.0–3.0%) for total CV events, strokes and MI (Table 2).

Effect of MS on Adverse Outcomes

The results of multivariate Cox proportional hazard regression analysis are shown in Table 3. After adjusting for age and sex, compared with participants without MS, the participants with MS were associated with notably higher risk of MI, strokes and total CV events, whose hazard ratio was 1.92 (95% CI 1.49–2.48), 1.46 (95% CI 1.26–1.69) and 1.57 (95% CI 1.38–1.79), respectively (model 2). The above findings did not substantially change after adjusting for multivariate factors, such as smoking status, CKD and other risk factors (model 3).

DISCUSSION

This is the first prospective community-based cohort study identifying the association of MS and major CV events among a large East Asian population with prediabetes. Just as we expected, we found that participants with MS had evidently

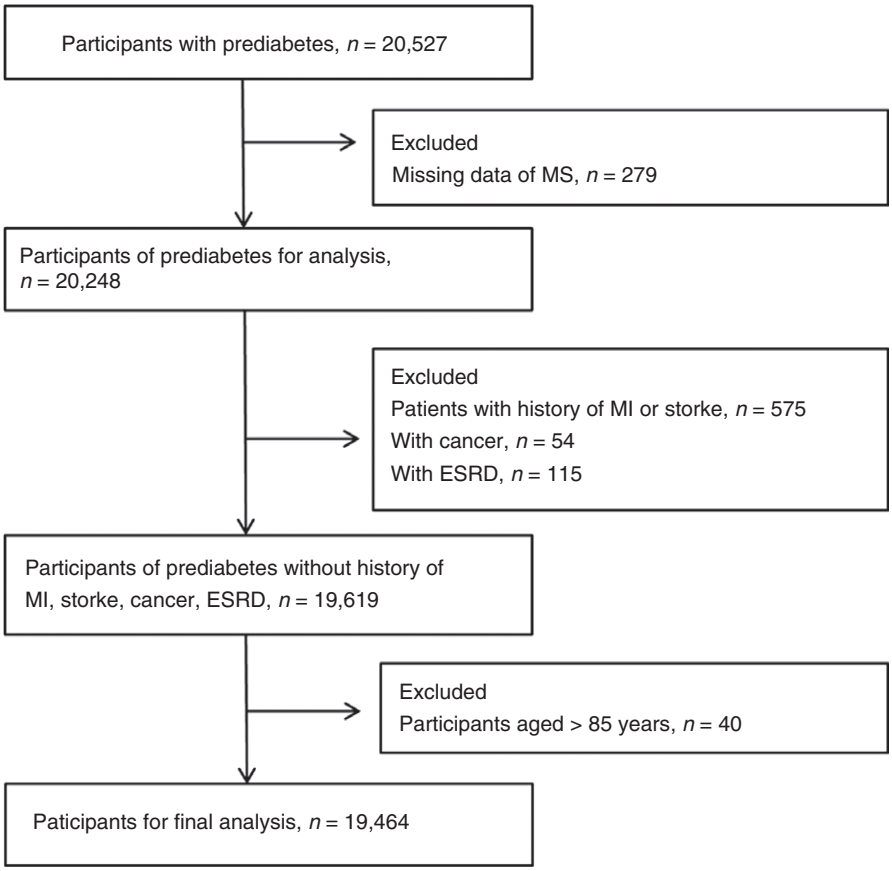

Figure 1 | Detailed approach for participant selection. ESRD, end-stage renal disease; MI, myocardial infarction; MS, metabolic syndrome.

increased risk of MI, strokes or total CV events. The present findings enrich the knowledge on the association between MS and adverse outcomes in the Chinese population with prediabetes, which would be helpful for easier screening of those high-risk individuals among the prediabetes population, so that they could be targeted for prevention strategies accordingly.

To the best of our knowledge, there was only one cohort study that investigated the association between MS and CVD in a population with prediabetes. A study carried out in Iran, including 4,018 Iranian participants aged ≥40 years, showed that prediabetic individuals with MS had an increased risk of CVD by 2.45-fold compared with those with prediabetes but without MS[11]. Likewise, the present results showed that among 19,464 Chinese participants aged ≥18 years, the risk of major CV events increased by 50% in prediabetic individuals with MS compared with those without. Thus, when prediabetes combines with MS, the risk of major CV events is dramatically increased.

Furthermore, the present showed that other CV risk factors, such as higher CRP, higher prevalence of CKD and fatter liver, were grouped in prediabetes individuals with MS, which might partly account for the excess CV risk in these individuals. In particular, the prevalence of fatty liver was significantly higher in the participants with MS than those without. Except for WC and TG, fatty liver was also a marker for visceral fat and a strong predictor for CV events[17]. Therefore, taking MS into account was more valuable to target the high-risk subgroup in prediabetes.

Several studies have showed that the prevalence of prediabetes and MS overlapped, although not precisely[18–20]. For example, the Finnish Diabetes Prevention Study showed that >10,000 obese participants with prediabetes, 78% of men and 72% of women also fulfilled the criteria for MS[19]. However, among 19,464 participants with prediabetes in the present study, 19% fulfilled the criteria for MS. Inclusion of the non-obese population and lack of measurement of oral glucose tolerance test might be the main reasons for the present result to be underestimated. The high prevalence of both prediabetes and MS in the same individuals not only highlighted the importance of routinely evaluating prediabetes patients for MS, but also showed that both conditions likely had a common metabolic soil. Obesity and insulin resistance are the common factors.

The mechanisms of the association of prediabetes and MS with CVD are incompletely understood, but likely have a common metabolic soil. First, insulin resistance is a common factor.

Table 1 | Baseline characteristics of 19,464 participants with prediabetes

Characteristics	All patients	Without MS	With MS	*P*-value
n (%)	19,464	15,775 (81.0)	3,689 (19.0)	–
Age (years)	51.9 ± 11.4	51.2 ± 11.4	54.7 ± 10.8	<0.001
Male, *n* (%)	16,663 (85.6)	13,769 (87.3)	2,894 (78.4)	<0.001
Education ≥high school, *n* (%)	3,551 (18.2)	2,930 (18.6)	621 (16.8)	0.007
Income ≥800 RMB, *n* (%)	3,063 (15.7)	2,239 (14.20)	824 (22.3)	<0.001
Heart rate (b.p.m.)	75.4 ± 10.7	75.3 ± 10.7	76.0 ± 10.7	<0.001
Waist circumference (cm)	87.9 ± 9.9	85.8 ± 9.1	97.1 ± 7.6	<0.001
SBP (mmHg)	133.8 ± 21.0	131.3 ± 20.7	144.8 ± 19.0	<0.001
DBP (mmHg)	85.3 ± 11.8	83.9 ± 11.4	91.1 ± 11.5	<0.001
FPG (mmol/L)	6.04 ± 0.36	6.03 ± 0.35	6.09 ± 0.37	<0.001
HDL-C (mmol/L)	1.54 ± 0.40	1.55 ± 0.38	1.46 ± 0.44	<0.001
TG (mmol/L)	1.4 (1.0–2.1)	1.2 (0.9–1.7)	2.3 (1.8–3.3)	<0.001
hs-CRP (mmol/L)	0.9 (0.3–2.1)	0.8 (0.3–1.9)	1.4 (0.6–3.4)	<0.001
Current drinker, *n* (%)	4,201 (21.6)	3,463 (22.0)	738 (20.0)	0.005
Current smoker, *n* (%)	6,529 (33.5)	1,253 (12.5)	1,335 (14.3)	<0.001
Physical activity, *n* (%)	2,987 (15.3)	2,329 (14.8)	658 (17.8)	<0.001
Kidney injury, *n* (%)	4,051 (20.8)	3,086 (19.6)	965 (26.2)	<0.001
Fatty liver, *n* (%)	7,543 (38.8)	5,039 (31.9)	2,504 (67.9)	<0.001

Continuous variables were described by mean ± standard deviation (normal distribution)/median (quartile; abnormal distribution); categorical variables were presented by number (percentage). DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; TG, triglyceride.

Table 2 | Incidence rate of adverse outcomes stratified by metabolic syndrome

Group	*n*	No. CV events	Cumulative incidence (95% CI)	Per 100,000 person-years
Total CV events				
Total	19,464	1,169	6.0 (5.6–6.3)	617.9
Without MS	15,775	836	5.3 (4.9–5.6)	543.5
With MS	3,689	333	9.0 (8.1–10.0)	941.3
P-value for log–rank test	–	–	<0.001	–
Stroke				
Total	19,464	921	4.7 (4.4–5.0)	483.8
Without MS	15,775	671	4.3 (3.9–4.6)	434.0
With MS	3,689	250	6.8 (6.0–7.6)	697.9
P-value for log–rank test	–	–	<0.001	–
MI				
Total	19,464	273	1.4 (1.2–1.6)	141.2
Without MS	15,775	182	1.2 (1.0–1.3)	116.1
With MS	3,689	91	2.5 (2.0–3.0)	248.9
P-value for log–rank test	–	–	<0.001	–

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Most individuals with prediabetes exist along with insulin resistance[21], and most persons with MS are insulin resistant[22], too. The role of insulin resistance in causing hyperglycemia is well established, which contributes to the increased risk of both CVD and diabetes[8]. Furthermore, many researchers believe that insulin resistance mediates all metabolic risk factors for MS[24]. Another factor is obesity, which always exists in both conditions[19]. Excess adipose tissue releases excess fatty acids and a variety of adipokines, which seemingly elicit metabolic risk factors that predispose to CVD[23]. At the same time, individuals with central obesity usually also have insulin resistance[8], which in turn further contributes to the increased risk of CVD.

Several studies suggest that the long-term damage of end organs associated with diabetes might start in prediabetes[25–27]. Because current methods of treating diabetes do not prevent all the complications associated with the condition, prevention and

Table 3 | Hazard ratios of major cardiovascular events

Group	Model 1	Model 2	Model 3
Total CV events			
Without MS	1	1	1
With MS	1.73 (1.52–1.96)	1.57 (1.38–1.79)	1.50 (1.31–1.73)
Stroke			
Without MS	1	1	1
With MS	1.61 (1.39–1.86)	1.46 (1.26–1.69)	1.42 (1.21–1.67)
MI			
Without MS	1	1	1
With MS	2.14 (1.67–2.76)	1.92 (1.49–2.48)	1.78 (1.34–2.36)

Model 1 was stratified for metabolic syndrome (MS); model 2 was further adjusted for age and sex; model 3 was further adjusted for smoking status, alcohol consumption, income, education, physical exercise, kidney injury, fatty liver, heart rate and high-sensitivity C-reactive protein. CV, cardiovascular; MI, myocardial infarction.

treatment of prediabetes is preferable, especially for those individuals with prediabetes with MS. As ascertainment of MS is simple using clinical measurements and a blood test, we highlight the utility of these simple measurements to identify high-risk individuals for early intervention. It might be possible to risk-stratify individuals with prediabetes by MS, and they should complete the following goals: (i) lifestyle modification training; (ii) 150 min per week of physical activity; and (iii) weight loss (7% of bodyweight)[28]. If these goals are not achieved, pharmacological interventions might be taken into consideration.

The present study had some strengths, including the large sample size, prospective design and long-term follow-up period. Nevertheless, the current study also had some limitations that should be mentioned. First, our study was based on a population in north China, and the ratio between sexes was imbalanced with a majority of men, so the results might limit generalizability of the study findings to women. Second, we failed to assess the influence of any changes on the results, because we only used the baseline information without reflecting the variation of the variables during the follow-up period. Third, in the present study, individuals with prediabetes were defined by a single FBG measurement, but no oral glucose tolerance test was carried out, which could result in the inclusion of individuals with diabetes. However, a national survey in China reported that the prevalence of prediabetes measured by FBG was 27.2%, and the prevalence of diabetes identified by IGT was just 3.5%[4]. Thus, the proportion of individuals who were misclassified as prediabetes was low, and unlikely to influence the present results.

In conclusion, among individuals with prediabetes in China, the risk for a major CV event was significantly higher in the group with MS than the group without MS. Therefore, among individuals with prediabetes, MS should be included for the risk stratification, and it is an important marker for long-term adverse outcomes. These results might better guide public policymakers to develop strategies towards high-risk individuals among huge the prediabetes population.

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DISCLOSURE

The authors declare no conflict of interest.

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