Influence of Hypertension on the Survival of Non-Small Cell Lung Cancer Patients with Type 2 Diabetes Mellitus

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Hypertension and diabetes mellitus (DM) are both the risk factors for cancer. This study aimed to explore the prognostic value of fasting blood glucose (FBG) and hypertension in type 2 DM (T2DM) patients with advanced non-small cell lung cancer (NSCLC) who had received chemotherapy treatment.

Material/Methods: There were 181 advanced NSCLC patients with T2DM between 2010 and 2019 included in this study. Their laboratory and clinical data were retrospectively analyzed. The predictive value of FBG and hypertension was evaluated. The Kaplan-Meier method was used to evaluate progression-free survival (PFS).

Results: The median PFS was 168.0 days (95% CI: 137.9–198.7 days) in patients with FBG ≥7 mmol/L compared to 154.0 days (95% CI: 126.7–181.3 days) for patients with FBG <7 mmol/L (hazard ratio [HR]=1.054; 95% CI: 0.7669–1.452; P=0.7447). Median PFS was longer in non-hypertensive patients than in hypertensive patients [179.0 days (95% CI: 137.3–220.7 days) versus 128.0 days (95% CI: 96.3–159.7 days); P=0.0189]. The existence of hypertension (HR=1.478; 95% CI: 1.063–2.055; P=0.020) was an independent predictor for shorter PFS in the multivariate analysis. Decreased hemoglobin was the major adverse event (over 95% patients). The incidence of all grades of adverse reactions was similar between hypertensive and non-hypertensive patients (all P>0.05) except diarrhea (P=0.020).

Conclusions: Complication of hypertension might confer a poor survival for advanced NSCLC patients with T2DM. Further prospective research is needed to confirm these findings.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung · Diabetes Mellitus, Type 2 • Disease-Free Survival • Fasting • Hypertension

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Background

Non-small cell lung cancer (NSCLC) has caused growing public health concern worldwide, including in China. Epidemiological studies have suggested that individuals with diabetes mellitus (DM) are at higher risk for lung cancer [1–3]. It is estimated that 8% to 18% of NSCLC patients have diabetes [4]. Diabetes may promote lung cancer progression through the mechanisms of hyper-insulin anemia, hyperglycemia and chronic inflammation, which have been associated with cell proliferation and cancer progression [3]. However, although many researchers have focused on the prognostic value of diabetic state or fasting blood glucose (FBG) in NSCLC patients with DM, these studies have yielded equivocal results [5].

Hypertension, another risk factor for cancers, has also been found to be more prevalent in patients with DM, especially middle-age and older-age diabetic patients [6]. In China, the presence of coexisting diabetes and hypertension was observed in approximately 30% of hypertensive patients, and in approximately 60% of diabetic patients [7]. The potential relevance between hypertension and cancer risk was first investigated in 1974, and subsequent studies revealed that blood pressure was positively associated with risk for all-cancer overall including lung cancer [8–10]. However, the prognostic significance of preexisting hypertension in NSCLC patients with type 2 DM (T2DM) undergoing platinum-based chemotherapy is still unknown.

In this study, we retrospectively enrolled advanced NSCLC patients with T2DM treated with platinum-based doublets to explore the predictive factors of their survival, especially baseline FBG and blood pressure.

Material and Methods

Patients

This retrospective study included 181 consecutive advanced NSCLC patients with T2DM, who visited Xinqiao Hospital, Chongqing, China between January 2010 and May 2019. Each eligible participant was histologically diagnosed with advanced-stage (III or IV) disease and had received no less than 2 cycles of chemotherapy (platinum-based doublets) after inclusion. Patients were not eligible for inclusion if they met either of the following requirements: 1) they had other cancers concurrently; 2) they received other anti-tumor treatment except chemotherapy; 3) they had no FBG test before their first chemotherapy treatment; 4) they lacked blood pressure monitoring before treatment.

Patients' characteristics and clinical examination results were extracted for analysis, including age, sex, prechemotherapy body mass index (BMI), tumor stage (TNM), pathologic type, alcohol intake, smoking history, performance status (PS), baseline FBG, hypertension grade, and chemotherapy protocols. Moreover, laboratory test results (leukocyte count, platelet count, hemoglobin, neutrophil count, creatinine, alanine aminotransferase and aspartate aminotransferase), and also clinical symptoms during first-line therapy (including constipation, diarrhea, fatigue, nausea and vomiting) were collected to analyze the side effects of chemotherapy.

The study adhered to the ethical guidelines issued by the Ethics Committee of Xinqiao Hospital, Third Military Medical University (Chongqing, China) and was performed in accordance with the Declaration of Helsinki. Anonymous analyses were performed with the recorded data.

Measurements

The diagnosis of T2DM was mainly based on an elevated FBG level (>7 mmol/L) or random blood glucose (>11.1 mmol/L), or a history of diabetes [11]. Hypertension and hypertension grade were determined according to the 2010 Chinese Guidelines for the Management of Hypertension [12].

The progression-free survival (PFS) was calculated from the date of the most recent examination of chest computed tomography (CT) prior to the first treatment (interval between chest CT and treatment less than 2 weeks) to the time of tumor progression, death or last follow-up upon imaging findings on the basis of the response evaluation criteria in solid tumors (RECIST) guidelines [13].

Chemotherapy-induced adverse events, involving constitutional symptoms, gastrointestinal symptoms, and laboratory results (hematological toxicities) were stratified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [14].

Statistical analysis

GraphPad Prism version 7 (San Diego, CA, USA) and SPSS 20.0 software (Inc., Chicago, IL, USA) were used for statistical analysis. The differences for data related to baseline characteristics and adverse reactions were calculated by Student's t-test or a chi-square test. PFS was computed by Kaplan-Meier methods. Cox regression analysis was generated for multivariate survival analysis. Statistically significant differences were set at a $P<0.05$.

Results

Baseline characteristics

A total of 181 advanced NSCLC patients with T2DM were ultimately included in the final analysis. The baseline characteristics of all participants are summarized in Table 1. Overall, our study cohort consisted of 155 males (85.6%) and 26 females (14.4%). The mean age of the patients was 61.7±8.2 years, with a mean body mass index (BMI) of 23.8±3.0 kg/m². The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (87.3%). Metastatic lesions were found in approximately two-thirds of patients (61.9%). Nearly 40% of the patients had concomitant hypertension, including 8 patients (4.4%) with grade 1, 32 patients (17.7%) with grade 2 and 29 patients (16.0%) with grade 3 hypertension.

Survival

In the study, the median PFS of all patients was 155.0 days (95% CI: 129.7–180.3 days). Considering that the potential confounding variables such as sex, age, BMI, tumor stage, pathological type, ECOG PS, smoking history, alcohol intake, baseline FBG and complications of hypertension may affect the survival, univariate analysis was performed to assess the predictive value of the candidate variables aforementioned on the outcome, as listed in Table 2 and Figure 1. Median PFS was similar between patients with a higher baseline FBG ≥7.0 mmol/L and those with a lower baseline FBG <7.0 mmol/L [154.0 days (95% CI: 126.7–181.3 days) versus 168.0 (95% CI: 137.3–198.7) days; P=0.745]. The same findings were also obtained for other potential factors except hypertension (P=0.019), as showed in Table 2.

Patients complicated with hypertension had a worse survival than those without hypertension [128.0 days (95% CI: 96.3–159.7 days) versus 179.0 days (95% CI: 137.3–220.7 days); P=0.0189; Figure 2)], but with a nonsignificant baseline FBG (P=0.986). A comparison of the baseline characteristics of the patients between the 2 groups is shown in Table 3. There were marginally significant differences between patients with hypertension and those without hypertension in terms of sex (P=0.074) and age (P=0.069). Furthermore, we introduced the possible prognostic factors (age, sex, and hypertension) and then performed a multivariate Cox regression analysis. After adjustment, the presence of hypertension in NSCLC with T2DM remained an independent and significant predictor of PFS (hazard ratio [HR]=1.705; 95% CI: 1.200–2.422; P=0.022).

Stratified analyses were performed according to hypertension grade (grade 1–2 versus grade 3) to further assess the potential effect modification by hypertension in our study, as presented

**Table 1.** Baseline Characteristics of T2DM Patients with NSCLC.

Characteristics	Values
Age, mean years ±SD	61.7±8.2
Sex	
Female, n (%)	26 (14.4%)
Male, n (%)	155 (85.6%)
Body mass index (kg/m²)	23.8±3.0
TNM stages	
III, n (%)	69 (38.1%)
IV, n (%)	112 (61.9%)
Pathological type	
Adenocarcinoma, n (%)	99 (54.7%)
Squamous cell carcinoma, n (%)	82 (45.3%)
ECOG PS	
0–1, n (%)	158 (87.3%)
2, n (%)	23 (12.7%)
Fasting blood glucose (mmol/l)	
<7.0	82 (45.3%)
≥7.0	99 (54.7%)
Complication-hypertension	
No	112 (61.9%)
Yes	69 (38.1%)
Hypertension grade	
0	112 (61.9%)
1–2	40 (22.1%)
3	29 (16.0%)
Smoking history	
Never, n (%)	54 (29.8%)
Once, n (%)	99 (54.7%)
Current, n (%)	28 (15.5%)
Drinking status	
Never, n (%)	125 (69.1%)
Once, n (%)	37 (20.4%)
Current, n (%)	19 (23.5%)

NSCLC – non-small cell lung cancer; T2DM – type 2 diabetes mellitus; SD – standard deviation; ECOG PS – Eastern Cooperative Oncology Group performance status.

Table 2. Univariate analyses of potential prognostic variables for survival in NSCLC patients with T2DM.

Univariate analyses			
Variables	**Reference**	**P-value**	**HR (95% CI)**
Age (≥60)	Age (<60)	0.742	0.945 (0.673–1.326)
Male	Female	0.323	1.248 (0.804–1.936)
BMI (≥25)	BMI (<25)	0.857	1.033 (0.728–1.465)
TNM: IV	TNM: III	0.154	1.273 (0.913–1.773)
Squamous cell carcinoma	Adenocarcinoma	0.877	1.026 (0.743–1.417)
ECOG PS: 2	ECOG PS: 0–1	0.380	1.267 (0.747–2.215)
Tobacco use	No use	0.465	1.198 (0.738–1.943)
Alcohol use	No use	0.951	1.017 (0.602–1.718)
FBG (≥7.0)	FBG (<7.0)	0.745	0.919 (0.665–1.270)
Hypertension	None	0.019	1.517 (1.071–2.148)

NSCLC – non-small cell lung cancer; T2DM – type 2 diabetes mellitus; BMI – body mass index; ECOG PS – Eastern Cooperative Oncology Group performance status; FBG – fasting blood glucose; HR – hazard ratio; CI – confidence interval.
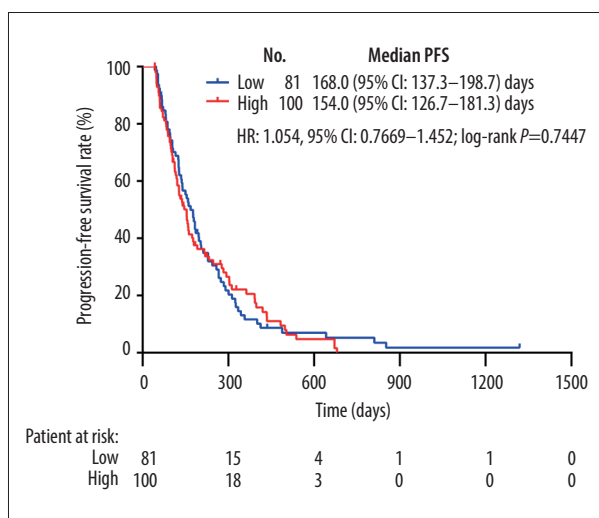
Figure 1. Kaplan-Meier plots of PFS in non-small-cell lung cancer patients with TSDM between lower (<7.0) and higher (≥7.0) baseline FBG. PFS – progression-free survival; T2DM – type 2 diabetes mellitus; FBG – fasting blood glucose; HR – hazard ratio; CI – confidence intervals.
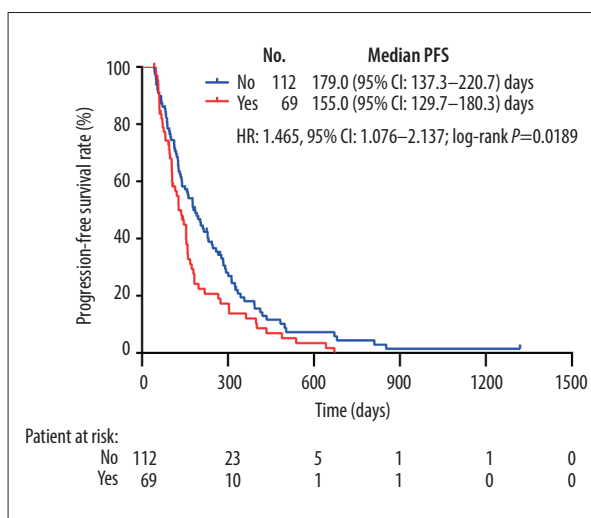
Figure 2. Kaplan-Meier plots of PFS in NSCLC with T2DM with hypertension and those without hypertension. PFS – progression-free survival; NSCLC – non-small cell lung cancer patients; T2DM – type 2 diabetes mellitus; HR – hazard ratio; CI – confidence intervals.

in Figure 3. Patients without hypertension had a longer median PFS than patients with grade 1–2 hypertension, but had a nonsignificant median PFS when compared patients with grade 3 hypertension [179.0 days (95% CI: 137.3–220.7 days) versus 121.0 days (95% CI: 78.0–164.0 days, P=0.023; 179.0 days (95% CI: 137.3–220.7 days) versus 154.0 days (95% CI: 106.3–201.7 days) P=0.0183; respectively]. Additionally, no difference was found in median PFS here between patients with grade 1-2 hypertension and those with grade 3 hypertension [154.0 days (95% CI: 106.3–201.7 days) versus 121.0 days (95% CI: 78.0–164.0 days), P=0.649].

Adverse events

All 181 participants were included in the safety evaluations, as listed in Table 4. Decreased hemoglobin was the major adverse event (over 95% patients in both groups). The incidence of all grades of adverse reactions was not significantly different between patients with and without hypertension, except diarrhea (P = 0.020). Diarrhea occurred in 5 patients (7.2%) with hypertension and only 1 patient (0.8%) without hypertension. Severe side effects (grade 3 or more) that occurred in all patients were mainly hematotoxicity, including

Table 3. Comparison of patients with hypertension (Yes) and without hypertension (No) in T2DM patients with NSCLC.

| Characteristics	No (112)		Yes (69)		*P*-value
Age, mean years ±SD	60.7±8.4		63.4±7.5		0.069
Sex					0.074
Male, n (%)	100	(89.3%)	55	(79.7%)	
Female, n (%)	12	(10.7%)	14	(20.3%)	
Body mass index (kg/m²)	23.7±3.0		24.1±3.2		0.447
Baseline FBG	8.2±3.2		8.0±2.9		0.986
TNM stages					0.924
III, n (%)	43	(38.4%)	26	(37.7%)	
IV, n (%)	69	(61.6%)	43	(62.3%)	
Pathological type					0.316
Adenocarcinoma, n (%)	58	(51.8%)	41	(59.4%)	
Squamous cell carcinoma, n (%)	54	(48.2%)	28	(40.6%)	
ECOG PS					0.571
0–1, n (%)	99	(88.4%)	59	(85.5%)	
2, n (%)	13	(11.6%)	10	(14.5%)	
Hypertension grade					<0.001
0	112	(100%)	0		
1–2	0		40	(58.0%)	
3	0		29	(42.0%)	
Smoking history					0.720
Never, n (%)	31	(27.7%)	23	(33.3%)	
Once, n (%)	63	(56.3%)	36	(52.2%)	
Current, n (%)	18	(16.0%)	10	(14.5%)	
Drinking status					0.246
Never, n (%)	77	(68.8%)	48	(69.6%)	
Once, n (%)	26	(23.2%)	11	(15.9%)	
Current, n (%)	9	(8.0%)	10	(14.5%)	

NSCLC – non-small cell lung cancer; SD – standard deviation; T2DM – type 2 diabetes mellitus; SD – standard deviation;
ECOG PS – Eastern Cooperative Oncology Group performance status; FBG – fasting blood glucose.

agranulocytosis, neutropenia, anemia, and thrombocytopenia None of the patients suffered from grade 3 or worse toxicity of systemic symptoms. None of the patients died from treatment-related side effects.

Discussion

There is an increasing number of NSCLC patients with T2DM worldwide. Studies have been conducted exhaustively to reveal the correlations between DM and survival in a population with NSCLC, but the results remain ambiguous [15,16]. The equivocal results of these studies might be due to the difference in the confounding factors caused by cohort studies. Many other potential factors, including sex, age, TNM stage, PS, complications, and chemotherapy, can affect the PFS of NSCLC patients with T2DM. In this regard, our present study aimed to illuminate proper prognostic factors for NSCLC patients with T2DM who are undergoing platinum-based therapy.
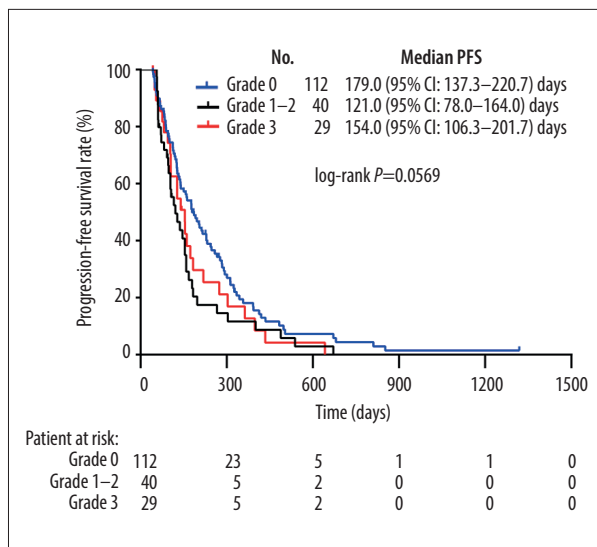
Figure 3. Kaplan-Meier plots of PFS in NSCLC with T2DM according to hypertension grades. PFS – progression-free survival; NSCLC – non-small cell lung cancer patients; T2DM – type 2 diabetes mellitus; HR – hazard ratio; CI – confidence intervals.

First of all, we found no significant difference existed in PFS between patients with lower baseline FBG (<7.0 mmol/L) and those with higher baseline FBG (≥7.0 mmol/L). Thus, FBG at baseline could not independently predict survival in NSCLC patients with T2DM during chemotherapy. This finding was consistent with the findings of another matched case-control study [17].

Next, we investigated the value of several conventional and potential confounding factors in predicting the outcome of NSCLC patients with T2DM. We found that among the confounding variables, hypertensive patients had significantly inferior PFS as compared to patients without hypertension (HR=1.465; 95% CI: 1.076–2.137; P=0.0189). After adjustment for other factors, the presence of hypertension was still an unfavorable predictive index independent of other prognostic factors. However, no positive correlation existed between the severity of hypertension and PFS (P=0.0569 overall). The small sample size in hypertension grade 3 might lead to the statistical bias.

Hypertension tends to occur in clusters with T2DM; between 20% to 60% of individuals with T2DM will have concomitant hypertension [18]. T2DM patients have a 2-fold risk of developing hypertension compared to nondiabetic individuals. Blood glucose has been shown to exhibit a positive and independent correlation with new development of hypertension,

Table 4. Common adverse events related to chemotherapy.

Events (n,%)	No (n=112)		Yes (n=69)		*P* value*
	All grades	Grade ≥3	All grades	Grade ≥3	
Laboratory results					
Leukocytes	43 (38.4%)	14 (12.5%)	31 (44.9%)	3 (4.3%)	0.385
Neutrophils	41 (36.6%)	16 (14.3%)	30 (43.5%)	8 (11.6%)	0.175
Hemoglobin	110 (98.2%)	13 (11.6%)	66 (95.7%)	3 (4.3%)	0.307
Platelets	61 (54.5%)	6 (5.4%)	37 (53.6%)	3 (4.3%)	0.912
ALT	35 (31.3%)	0	24 (34.8%)	0	0.622
AST	21 (18.8%)	0	12 (17.4%)	0	0.818
Creatinine	4 (3.6%)	0	6 (8.7%)	0	0.143
Clinical symptoms					
Fatigue	34 (30.4%)	0	19 (17.0%)	0	0.685
Anorexia	32 (28.6%)	0	14 (20.3%)	0	0.214
Nausea	54 (48.2%)	0	31 (44.9%)	0	0.667
Vomiting	15 (13.4%)	0	10 (14.5%)	0	0.969
Diarrhea	1 (0.8%)	0	5 (7.2%)	0	0.020
Constipation	22 (19.6%)	0	16 (23.2%)	0	0.569

ALT – aspartate aminotransferase; AST – alanine aminotransferase. * *P* value meant the difference of all grades of adverse events in patients between patients with hypertension (Yes) and without hypertension (No).

with a cumulative incidence approaching up to 10.2% over 5 years [19].

Regarding the potential associations of hypertension with cancer, hypertension has been reported to be a higher risk factor for cancer morbidity and mortality, including renal, endometrial, prostate, postmenopausal breast, and colorectal cancer, as well as esophageal squamous cell carcinoma and gastric adenocarcinoma [20,21]. The biological mechanism underlying the role of hypertension in inducing carcinogenesis has not yet been elucidated but is presumably related to reactive oxygen species caused by chronic hypoxia and maladaptive lipid peroxidation [22]. Additionally, in the hypertensive state, elevation of angiogenic and hypoxia-inducible factors (such as HIF-1α), might also contribute to the increased risk of cancer [9,23,24]. Few studies have investigated the relationship between blood pressure and lung cancer. Christakoudi et al. found that among 3229 lung cancer patients there was no positive correlation between blood pressure and the risk of adenocarcinoma, squamous cell carcinoma, or small cell carcinoma morphologies, except for other morphologies (unclassified or large cell, HR=1.06) [9]. As for the impact of hypertension on survival, one study found that of 673 patients during a median follow-up period of 19 years, that the patients with hypertension experienced a higher risk of mortality from lung cancer (HR 2.50, 95% CI 1.37–4.59) [25]. A statistically significant positive association was similarly observed between blood pressure and cancer mortality in other previous studies [26,27]. Based on a large clinical database at the University of Texas MD Anderson Cancer Center, hypertension was also found to be an independent risk factor for disease-free survival in patients who had received definitive radiotherapy for advanced NSCLC [1.03 (95% CI: 1.01–1.05), P=0.01] [28]. Lung cancer-related mortality also tended to be correlated to systolic blood pressure but the relationship was not consistent in the highest blood pressure group and was not statistically significant in a 13.5 years follow-up of 855 male participants [29], which was similar to our findings that survival was poorer in hypertensive patients but not associated with the grades of hypertension. However, another large study found that the incidence of lung cancer was reduced among hypertensive participants and was not correlated with blood pressure levels [20]. It was even reported that the new onset of apatinib and bevacizumab-related events – hypertension might imply an improved clinical outcome for patients with NSCLC who had undergone longer-term apatinib or bevacizumab therapy [30,31]. In our study, we focused on the relationship between hypertension and the prognosis of NSCLC participants with T2DM after platinum-based chemotherapy, which has not yet been reported, and determined that hypertension might compromise the efficacy of chemotherapy in NSCLC patients with T2DM, and induce an increased risk of chemotherapy-related diarrhea.

This study had several inevitable limitations. First, it was a retrospective and single center clinical study, which might introduce a selective bias and also affect the generalizability of our findings. Moreover, some morphologies of lung cancer (predominantly unclassified or large cells), which were reported to be closely related to hypertension in another study, were not included in this study [9]. Ultimately, we did not take overall survival into account, because overall survival rates were significantly affected by the choice of subsequent treatment significantly [32].

Conclusions

In conclusion, our data suggests that it is not baseline FBG levels but the complication of hypertension that might confer a poor prognostic factor for outcomes in NSCLC patients with T2DM. Additional studies are still needed to verify our findings.

Acknowledgments

Ethical statement

The study was approved by the Ethics Committee of Xinqiao Hospital, Third Military Medical University (Chongqing, China).

Conflict of interest

None.

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