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Model for Risk-Based Screening of Diabetic Retinopathy in People With Newly-Diagnosed Type 2 Diabetes Mellitus

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Purpose. The purpose of this study was to evaluate the role of inflammatory/lipid markers and potential risk factors for diabetic retinopathy (DR) development in newly diagnosed patients with type 2 diabetes mellitus (T2DM).

Methods. Participants in this study were 1062 patients with newly diagnosed T2DM. Demographic and clinical data of patients were collected. Assessment of DR status was performed using digital two-field photography. In addition, HbA_{1c} (%), lipid profile, and urinary albumin were measured at recruitment. The following inflammatory markers were also measured: serum C-reactive protein, white blood cells, platelet, adiponectin, IL-4, IL-6, IL-10, vascular endothelial growth factor, tumor necrosis factor-α (TNF-α), IL-1b, IL-1 receptor antagonist (IL-1RA), and monocyte chemotactic protein-1. Univariate and multivariate analyses of the association of various potential risk factors and DR were conducted.

Results. Univariate analysis showed that male sex, any cardiovascular event, and HbA_{1c} were positively associated with DR, while IL-1RA, IL-1b, IL-6, and TNF-α were significantly negatively associated with presence of DR in the cohort. Risk factors that remained significantly associated with DR presence at the multivariate analysis were male sex, any cardiovascular event, HbA_{1c}, and IL-1RA.

Conclusions. Our study demonstrated that HbA_{1c} levels, male sex, and previous cardiovascular events were risk factors for presence of DR in people with newly diagnosed T2DM, while IL-1RA seemed to have a protective role. The prevalence of DR in our population was 20.2%, reflecting current practice. Our findings may contribute to future risk-based modelling of screening for DR.

Keywords: diabetes, inflammatory, lipid, biomarkers, model, risk factors

Diabetes mellitus (DM) affects over 400 million people worldwide and it is expected to affect 642 million by 2040.[1] Diabetic retinopathy (DR) is one of the most common complications of DM and is the leading cause of blindness among adults under 45 years old in the industrialized world.[1–3] Early stages of DR (nonproliferative DR) are characterized by microaneurysms, dot and blot hemorrhages, and exudates, while in the later stages retinal neovascularization and its complications (proliferative DR) are evident.[4,5] Diabetic macular edema (DME) may occur at any stage of DR and is caused by increased vascular permeability and resultant leakage of proteins and lipid exudation in the macula.[4,5] The United Kingdom Prospective Diabetes Study (UKPDS) reported 20 years before that 30% of participants had microvascular complications at diagnosis.[6] However, this observation may not be applicable in patients with type 2 DM (T2DM) today because of early diagnosis and better management of DM, as well as robust screening of DR in primary care. It is worth mentioning that studies examining prevalence of DR in people with new-onset DM are scanty.[7–9]

The pathogenesis of DR is multifactorial, but increasing evidence points to the involvement of inflammation in DR pathophysiology.[10–20] Specifically, previous studies have shown that low-grade subclinical inflammation can damage retinal vasculature, leading to neovascularization or macular edema, and pro- and anti-inflammatory markers in the serum and ocular fluids have been shown to be related to DR.[10–20] The role of dyslipidemia in the pathogenesis of DR is poorly understood. Studies on various lipid markers, such as serum total cholesterol, triglycerides, low density lipoproteins (LDLs), and high density lipoproteins (HDLs) in DR have reported conflicting results.[21,22]

Apart from inflammation and dyslipidemia, several other risk factors have been described in DR. In a recent meta-analysis, diabetes duration and ethnicity have been substantiated as nonmodifiable risk factors and raised HbA_{1c} and blood pressure as risk factors that are amendable to modification.[1] Nevertheless, a recently published Cochrane Systematic Review reported that there is lack of evidence to support that control of hypertension leads to prevention of DR progression.[23] Obesity, smoking, pregnancy, genetic factors, and diabetic

kidney disease have been previously evaluated as potential risk factors for DR, but these associations remain controversial.[2,24–27]

One study reported DR and macrovascular complications each in one-third of people with T2DM of mean duration of 9 years.[28] Another described 20% to 30% microvascular and 40% macrovascular complications in patients with mean duration of 4 years.[29] However, it is important to understand the profile of patients with DR in newly diagnosed T2DM, especially in countries where there is robust DR screening because it will enable us to identify patients at risk of DR progression earlier in the course of their disease. The purpose of this study was to evaluate the role of inflammatory/lipid markers and potential risk factors for DR development in newly diagnosed patients with T2DM.

Methods

Design

This is a population-based, cross-sectional study based on the baseline data from participants of the South London-Diabetes (SOUL-D) study. SOUL-D is a prospective cohort of people newly diagnosed with T2DM, aiming to investigate the role of various biopsychosocial factors on biomedical outcomes over a period of 2 years.[30] Ethical approval was granted by the King's College Hospital Research Ethics Committee (reference 08/H0808/1) and by Lambeth, Southwark, and Lewisham Primary Care Trusts (reference RDLSLB 410). The study was conducted according to the tenets of the Declaration of Helsinki and written informed consent was obtained from all the participants.

Setting and Sampling Frame

Three adjacent inner-city boroughs (Lambeth, Southwark, and Lewisham) in South London, which serve a multiethnic and socioeconomically diverse population of approximately 0.75 million UK residents, participated in the study. The sampling frame included 96 of the 138 general practices (primary care clinics in the UK's Government-funded National Health Service) in these boroughs.[30] Every 6 months, each practice's diabetes register was searched to identify patients with a new diagnosis of T2DM.

Inclusion-Exclusion Criteria

T2DM was diagnosed according to World Health Organization (WHO) guidelines[31] and the diagnosis validated at recruitment by patient's history and review of the medical records. The inclusion criteria were: age 18 to 75 years at diagnosis and diagnosis of T2DM not more than 6 months before recruitment to the study. The exclusion criteria were: DM other than T2DM (such as gestational diabetes); patient not fluent in English; known severe mental illness; a separate advanced or terminal condition; and severe advanced diabetic complications defined as being registered blind, requiring dialysis, or having had an above-the-knee amputation. Recruitment was conducted between May 2008 and September 2012. In this study, we have only included patients with full data set including serum markers.

Measurements

The following data were recorded and coded: age (years), sex, employment status, legal partnership status, self-reported ethnicity based on 2001 UK Census methods.[32] Height, weight, body mass index (kg/m^2), and systolic and diastolic blood pressure (mm Hg) at diagnosis were taken from the medical record and measured by the study team at recruitment, with systolic blood pressure (SBP) and diastolic blood pressure (DBP) taken after 15 minutes of rest in the sitting position by using a mercury sphygmomanometer.

History of macrovascular disease (myocardial infarction [MI], coronary artery bypass graft [CABG], cerebrovascular accident [CVA], carotid or limb revascularization, and amputation) or microvascular one (erectile dysfunction), smoking status, as well as current prescribed medications including diabetes tablets, insulin, cholesterol lowering agents, antihypertensives, diuretics, and medications with a possible anti-inflammatory action (statins, fibrates, systemic steroids, nonsteroidal anti-inflammatory drugs, and COX-2 inhibitors) were also recorded. They were assessed by self-report and validated by medical records review. If there were several macrovascular complications, the date of the first presentation of each complication was recorded.

Retinopathy was assessed from the patient's first retinal eye screen. For all patients, this was performed by the local Diabetes Eye Complication Screening (DECS) service, using digital two-field photography, according to national guidelines.[33] Images were coded by trained graders, using the English Retinopathy Minimum grading system.[34] Retinopathy was coded as any retinopathy present or absent in at least one eye. The worst eye defined the level of retinopathy. Moreover, history of previous laser photocoagulation or presence of cataract were recorded.

Additionally, HbA_{1c} (%), lipid profile (mM), and urinary albumin were measured at recruitment. The laboratory tests were analyzed at the one of the three accredited laboratories used by the participants' general practice: HbA_{1c} using affinity chromatography in the Primus Ultra 2 analyzer (Primus Corporation, Kansas City, MO, USA); lipid profile using Siemens Advia 2400 analyzer; and glucose using hexokinase, plasma measurement (Siemens Diagnostics, Frimley, UK). The detection limits of the assays were as follows: triglyceride (T) 0.01 mM, total cholesterol 0.01 mM, and HDL cholesterol 0.01 mM; LDL cholesterol was calculated using the Friedewald formula. Urinary albumin to creatinine ratio (ACR) was measured at diagnosis using Siemens Advia 2400, the polyethylene glycol-enhanced immunoturbidimetric assay for urinary albumin, and the Jaffe reaction for urinary creatinine. Participants were considered positive for microalbuminuria for ratios ≥ 3 and negative for ratios <3. Single random assessment of ACR is the norm for excluding microalbuminuria during annual review in primary care owing to the convenience of acquiring the sample.[35]

The following inflammatory markers were also measured: serum C-reactive protein (CRP) by a high-sensitivity CRP (hs-CRP) using an Advia 2400 analyzer, with an assay detection limit of 0.1 mg/L; white blood cells (WBCs) and platelet (PLT) using an Advia 2100 analyzer and adiponectin using ELISA kits (R&D Systems Europe, Oxon, UK), with a detection limit of 0.246 mg/L. IL-4, IL-6, IL-10, vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), IL-1b, IL-1 receptor antagonist (IL-1RA), and monocyte chemotactic protein-1 (MCP-1) were all measured from serum samples centrifuged from venous blood samples taken after an overnight fast and stored between −40 and −80°C using cytokine-array biochip kits (Randox, Belfast, UK) and analyzed using the Randox Evidence Investigator. The inter- and intraassay coefficients of variation for all analytes measured using these kits are $<15\%$ and $<10\%$, respectively.

Statistical Analysis

The main characteristics of the cohort are presented as mean ± standard deviation or as proportion (percentage) of patients.

Table 1. Demographic and Clinical Characteristics, as well as Laboratory Results of Our Study Sample

	N (%)
Age, mean ± SD, y	56.0 ± 10.9
Sex	
Male	585 (55.1)
Female	477 (44.9)
Race	
White	565 (53.2)
Black	360 (33.9)
Asian	70 (6.6)
Mixed	67 (6.3)
Legal partnership	
Married	569 (53.6)
Single/divorced/widowed	493 (46.4)
Current employment	
Yes	527 (49.6)
No	535 (50.4)
Smoking	
Current	208 (19.6)
Former	466 (43.9)
Never	388 (36.5)
Duration of diabetes	
<6 mo	720 (67.8)
≥6 mo	342 (32.2)
HbA1c (%)	
<7.5	249 (23.4)
≥7.5	813 (76.6)
Cataract	
Yes	105 (9.9)
No	957 (90.1)
Body mass index	
<25	744 (70.1)
≥25	318 (29.9)
Central obesity	
Yes	940 (88.5)
No	122 (11.5)
Hypertension	
Yes	506 (47.7)
No	556 (52.4)
Medications, yes	
Tablets	582 (54.8)
Insulin	34 (3.2)
Statins/fibrates	644 (60.6)
Antihypertensives	566 (53.3)
Any cardiovascular event	
Yes	95 (8.9)
No	967 (91.1)
DR	
Yes	214 (20.2)
No	848 (79.8)
Erectile dysfunction*	
Yes	332 (56.8)
No	253 (43.2)
Microalbuminuria	
Positive	160 (15.1)
Negative	902 (84.9)
HbA1c, %	6.96 ± 1.38
Creatinine, μM	81.5 ± 25.6
CRP, mg/L	5.04 ± 7.69
IL-1ra, pg/mL	526.7 ± 342.2
IL-1b, pg/mL	2.23 ± 3.99
IL-4, pg/mL	1.50 ± 0.90
IL-6, pg/mL	8.74 ± 27.88
IL-10, pg/mL	0.63 ± 0.87
VEGF, pg/mL	90.9 ± 66.7
Adiponectin, ng/mL	6067.3 ± 3982.0
TNF-α, pg/mL	2.41 ± 5.09
MCP-1, pg/mL	111.7 ± 63.5
Cholesterol, mM	4.59 ± 1.05
LDL, mM	2.66 ± 0.88
HDL, mM	1.21 ± 0.34
Triglycerides, mM	1.67 ± 1.11
WBC, $\times 10^6$	6.82 ± 2.03
PLT, $\times 10^3$	269.9 ± 76.9

* The percentage was based only on male patients.

Univariate and multivariate analyses of the association of various potential risk factors and DR were conducted. Subjects with missing values for the outcome variables (presence or absence of DR) were excluded from the analysis. At the univariate analysis, ordinal logistic regression was performed; the dependent variable was converted to an ordinal variable with four levels (1: minimum value-25th percentile; 2: 25th percentile-median; 3: median-75th percentile; and 4: 75th percentile-maximum value), where applicable. Nevertheless, when the median was equal to the maximum value of the variable due to markedly skewed distribution, as well as to the presence of numerous ties, the ordinal logistic regression model was obligatorily degenerated to logistic regression model (0: values below median; 1: values equal to median-maximum value). The odds ratios (ORs) with the respective 95% confidence intervals (CIs) are indicated in the text. At the multivariate analysis, only factors proven significant ($P < 0.05$) at the univariate analysis were tested in the stepwise multivariate model as independent variables; in the final model, only the statistically significant variables were retained (i.e., backward-selection statistical procedure). Statistical analysis was performed using STATA/SE 13 statistical software (Stata Corporation, College Station, TX, USA). A P value <0.05 was considered as statistically significant.

Results

Table 1 shows the demographic and clinical characteristics, as well as the laboratory findings of our study sample, comprising of 1062 patients with newly diagnosed T2DM. Their mean age was 56.0 ± 10.9 years. 55.1% were male. As far as ethnicity is concerned, 53.2%, 33.9%, 6.6%, and 6.3% were white, black, Asian, or mixed, respectively. The mean HbA_{1c} at recruitment was 6.9% (52 mmol/mol), with 76.6% of patients having HbA_{1c} ≥7.5%. Regarding complications of DM, 8.9% of patients reported any cardiovascular event (macrovascular complications), 15.1% had microalbuminuria, 56.8% of male patients reported erectile dysfunction), and 20.2% of patients had any severity grade of DR (microvascular complications).

Table 2 shows the results of the univariate analysis. Male sex (OR = 1.58; 95% CI = 1.16–2.14, $P = 0.004$), any cardiovascular event (OR = 1.65; 95% CI = 1.03–2.65, $P = 0.039$), and HbA_{1c} (OR = 1.62; 95% CI = 1.16–2.25, $P = 0.005$) were positively

Table 2. Results of the Univariate Analysis Regarding Factors Potentially Associated With DR Presence

Variable	Category or Increment	OR (95% CI)	*P* Value
Age	One quartile increase	0.99 (0.87–1.13)	0.873
Sex	Male vs. female	1.58 (1.16–2.14)	**0.004**
Race	Black vs. white	1.11 (0.80–1.53)	0.542
	Asian vs. white	1.00 (0.54–1.86)	>0.999
	Mixed vs. white	1.25 (0.69–2.28)	0.457
Legal partnership	Single/widowed/divorced vs. married/cohabiting	0.96 (0.72–1.30)	0.809
Current employment	Yes vs. no	0.84 (0.62–1.13)	0.247
Smoking	Current vs. never	0.99 (0.66–1.49)	0.978
	Former vs. never	0.77 (0.54–1.06)	0.106
DM duration	≥6 mo vs. <6 mo	1.13 (0.83–1.55)	0.441
Cataract	Yes vs. no	0.90 (0.54–1.50)	0.675
Any cardiovascular event	Yes vs. no	1.65 (1.03–2.65)	**0.039**
Any microvascular*	Yes vs. no	1.26 (0.70–2.27)	0.432
Erectile dysfunction*	Yes vs. no	1.26 (0.83–1.91)	0.274
Body mass index	≥25 vs. <25	0.95 (0.69–1.32)	0.767
Central obesity	Yes vs. no	1.02 (0.64–1.62)	0.945
Hypertension	Yes vs. no	1.04 (0.77–1.40)	0.817
Medications			
Antidiabetic tablets	Yes vs. no	1.20 (0.89–1.63)	0.226
Insulin	Yes vs. no	0.82 (0.33–2.00)	0.657
Statins/fibrates	Yes vs. no	1.29 (0.95–1.76)	0.108
Antihypertensives	Yes vs. no	0.92 (0.68–1.24)	0.578
HbA1c, %	≥7.5 vs. <7.5	1.62 (1.16–2.25)	**0.005**
Triglycerides, mM	≥2.0 vs. <2.0	0.95 (0.67–1.33)	0.751
Total cholesterol, mM	≥5.0 vs. <5.0	1.11 (0.81–1.52)	0.525
HDL, mM	≥1.2 vs. <1.2	0.86 (0.63–1.17)	0.333
LDL, mM	≥3.0 vs. <3.0	1.10 (0.79–1.53)	0.577
WBC, $\times 10^6$	≥11 vs. <11	1.05 (0.48–2.34)	0.896
PLT, $\times 10^3$	≥450 vs. normal	0.76 (0.26–2.24)	0.614
	≤150 vs. normal	0.99 (0.40–2.46)	0.977
Creatinine, μM	≥120 vs. <120	1.37 (0.53–3.51)	0.516
Microalbuminuria	Positive vs. negative	1.56 (0.78–2.73)	0.129
CRP, mg/L	≥5.0 vs. <5.0	0.80 (0.58–1.11)	0.188
IL-1ra, pg/mL	One quartile increase	0.84 (0.73–0.96)	**0.009**
IL-1b, pg/mL	One quartile increase	0.86 (0.75–0.98)	**0.023**
IL-4, pg/mL	One quartile increase	0.91 (0.79–1.03)	0.124
IL-6, pg/mL	One quartile increase	0.80 (0.70–0.92)	**0.001**
IL-10, pg/mL	One quartile increase	0.91 (0.79–1.04)	0.145
VEGF, pg/mL	One quartile increase	1.01 (0.89–1.15)	0.866
Adiponectin, ng/mL	One quartile increase	0.92 (0.80–1.05)	0.209
TNF-α, pg/mL	One quartile increase	0.84 (0.73–0.96)	**0.009**
MCP-1, pg/mL	One quartile increase	1.00 (0.87–1.14)	0.946

Bold values denote statistical significance.
* The OR was derived based only on male patients.

associated with DR. IL-1RA (OR = 0.84; 95% CI = 0.73–0.96, P = 0.009), IL-1b (OR = 0.86; 95% CI = 0.75–0.98, P = 0.023), IL-6 (OR = 0.80; 95% CI = 0.70–0.92, P = 0.001), and TNF-α (OR = 0.84; 95% CI = 0.73–0.96, P = 0.009) were significantly negatively associated with presence of DR in the cohort.

Table 3 shows the results of the multivariate analysis. Risk factors that remained associated significantly with DR presence were male sex (OR = 1.44; 95% CI = 1.05–1.99, P = 0.024), any cardiovascular event (OR = 1.77; 95% CI = 1.09–2.88, P = 0.022), HbA_{1c} (OR = 1.60; 95% CI = 1.13–2.25, P = 0.007), and IL-1RA (OR = 0.81; 95% CI = 0.71–0.93, P = 0.004), while IL-1b, IL-6, and TNF-α lost their significance.

Discussion

In our study of people with newly diagnosed T2DM, recruited between 2008 and 2012, DR remains a significant microvascular complication, with a prevalence of 20.2%. Presence of DR was significantly associated with male sex, HbA_{1c} levels, and any previous cardiovascular event, while IL-1RA levels were found to be protective, surviving multivariate analysis.

Table 3. Results of the Multivariate Analysis, Showing Factors Significantly Associated With DR Presence

Variable	Category or Increment	OR (95% CI)	*P* Value
Sex	Male vs. female	1.44 (1.05–1.99)	**0.024**
Any cardiovascular event	Yes vs. no	1.77 (1.09–2.88)	**0.022**
HbA1c, %	≥7.5 vs. <7.5	1.60 (1.13–2.25)	**0.007**
IL-1RA, pg/mL	One quartile increase	0.81 (0.71–0.93)	**0.004**

Bold values denote statistical significance.

Therefore, these four variables should be incorporated into any risk-based model for screening of DR.

The SOUL-D patients have a lower incidence of retinopathy compared to UKPDS patients (20.2% vs. 36%).[26] The observed differences in complication status between SOUL-D and UKPDS reflect a change in the risk of microvascular disease prevalence, probably driven by earlier diagnosis from screening for diabetes and better management of all long-term conditions, including hypertension and hyperlipidemia in primary care in the UK.[30] This is in line with a recent population-based study, in which the prevalence of DR in screening-detected patients with T2DM was estimated to be 13%.[36] The SOUL-D patients were identified by a variety of pathways, including screening.

The pathogenesis of DR is multifactorial and identification of the major risk factors for DR presence remains challenging. Previous studies have found that the duration of DM was a strong risk factor for the development of DR. The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported the prevalence of any retinopathy to be 8% in patients with 3 years of DM, 25% at duration of 5 years, 60% at duration of 10 years, and 80% at duration of 15 years.[37] The incidence of DR in our study was relatively high, given that only newly diagnosed patients were included. This could be possibly explained by the hospital-based sample in our study. In addition, since South East London has highly mobile and migrant population, late diagnosis of diabetes in this population may explain the higher incidence of DR in our study cohort. Prediagnosis duration of diabetes is of course unknown, but another contributing factor may be that the patients included in this study are of multiethnic origin. We have reported previously that DR is more prevalent and severe in people with T2DM with Black and South Asian origin.[38] In addition, the advances in better retinal imaging systems may explain the higher detection rate of DR in our cohort.

Diabetes control, as reflected by the level of HbA_{1c}, has been previously reported as an independent factor for the incidence of DR. In one study, 1% reduction in HbA_{1c} leads to a 35% reduction in microvascular complications of DM.[39] Overall glycemic control, as expressed by HbA_{1c}, and/or glycemic variability are important associations of DR development.[40] Therefore, HbA_{1c} should be definitely included in any risk-based model for DR screening.

Male sex was also found to be associated with the presence of DR. Similar observations were made by Pradeepa et al.[41] and in the Los Angeles Latino Eye Study[42] and may be related to life style differences, other comorbidities, or genetic implication. Furthermore, local neuroretinal function in T2DM, which can be used to predict retinopathy, has been reported to be more abnormal in adult males compared with adult females.[43] It is also interesting to note that all these studies included patients of Black and South Asian origin.[41,42]

Our study found an association with previous cardiovascular events and presence of DR. In fact, the strength of relation between DR and macrovascular complications, such as cardiovascular disease in this study, is as strong as in nephropathy.[44] An 8-year cohort study found that patients who had mild DR were already at higher risk of coronary heart disease or stroke, in accordance with the Chennai Urban Rural Epidemiology Study.[45,46] In contrast, although previous macrovascular complications were predictive factors for presence of DR in newly diagnosed patients with T2DM, our study did not show any association between the presence of microalbuminuria and DR. This interesting finding in this study suggests that the link between retinopathy and macrovascular complications may be better explained by shared risk factors of obesity, hyperlipidemia, and blood pressure. In contrast, an inflammatory link may better explain the association of microalbuminuria and retinopathy as studies have shown that microalbuminuria may not manifest itself initially and may precede the onset of sight threatening complications.[47,48]

It is also worthy to note that the majority of inflammatory and lipid markers, except for IL-1RA, were found not to be predictive risk factors for the detection of DR at early stages. This could be explained by the fact that our study sample included only patients with newly diagnosed DM with mild retinopathy, where potentially events related to chronicity had not set in. Studies investigating inflammatory markers to date have shown an association of proinflammatory cytokines with sight threatening retinopathy.[19,49] IL-1RA is an early inhibitory cytokine, which suppresses proinflammatory cytokines and T lymphocyte responses. It is plausible that a decrease in IL-1ra is an early sign in DR.[50] Lacraz et al.[51] have shown the beneficial effect of IL-1Ra on islet endothelial/immune cells and fibrosis parameters in diabetic rats. Therefore, longer term follow-up is needed to establish the predictive value of this marker on sight threatening retinopathy, as well as the potential therapeutic effect of IL-1RA in patients with DR.

Limitations of this study were that people who were housebound and not able to visit the general practitioner were excluded. The strengths of the study were the high participation rate and the comprehensiveness of the setting.

In conclusion, our study demonstrated that HbA_{1c} levels, male sex, and previous cardiovascular events were risk factors for presence of DR in people with newly diagnosed T2DM, while IL-1RA seemed to have a protective role. The prevalence of DR in our population was 20.2%, reflecting current practice. Our findings may contribute to future risk-based modelling of screening for DR.

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