Original Article

The relationship between peripheral blood inflammatory markers and diabetic macular edema in patients with severe diabetic retinopathy

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Background: Diabetic macular edema (DME) is a serious complication of diabetic retinopathy (DR). Recent studies have shown that inflammation is closely associated with the development of DME, and peripheral blood inflammatory markers [white blood cell (WBC) count and its subtypes] are relatively simple and easy to detect. Here, we investigated the relationship between peripheral blood inflammatory markers and macular edema in patients with severe DR (including both severe non-proliferative DR and proliferative DR).

Methods: A total of 42 patients with severe DR were included in this study and divided into two groups: a severe DR with DME group (DME group, n=18) and a severe DR without DME group (non-DME group, n=24). Ophthalmologic findings and hematologic results were retrospectively retrieved from hospitalization records and databases.

Results: The neutrophil percentage was significantly higher in the DME group (62.52%±8.21%) than in the non-DME group (57.30%±8.17%) (P<0.05); in contrast, the lymphocyte percentage was significantly lower in the DME group (28.09%±7.45%) than in the non-DME group (33.54%±7.29%) (P<0.05). Logistic regression analysis showed a significant correlation between lymphocyte percentage and DME [odds ratio (OR) =0.654, 95% CI: 0.436–0.851; P=0.011].

Conclusions: Lymphocyte percentage can be used as an inflammatory marker for the development of DME in patients with severe DR.

Keywords: Severe diabetic retinopathy; diabetic macular edema (DME); peripheral blood inflammatory markers; lymphocyte percentage

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Introduction

Diabetic macular edema (DME) is a serious vision-threatening complication of diabetes mellitus. According to the optical coherence tomography (OCT)-based grading of diabetic maculopathy proposed in the European School for Advanced Studies in Ophthalmology classification (1), if the inner and/or outer layers of the macula are damaged, the lesion may be irreversible and vision may not be recoverable even after anti-vascular endothelial growth factor (VEGF) therapy (2). DME can occur at any stage of diabetic retinopathy (DR) but is more common in the severe non-proliferative and proliferative stages. If left untreated,

about 50% of DME patients will lose more than 2 lines of visual acuity (VA) within 2 years (3). In contrast, most patients without DME have a more satisfactory prognosis after total retinal laser photocoagulation or vitreoretinal surgery. Previous studies have shown that the development of DME is associated with glycated hemoglobin (4); the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found that 25% of those with type 2 diabetes will develop DME after 10 years of follow-up (5). Anti-vascular endothelial growth factor (VEGF) injections are generally first-line therapy for DME a in the majority. However, clinical trials have shown that approximately 40% of patients are non-responsive to anti-VEGFs (6). While more recent research suggests that inflammatory factors play key roles in the development of DME (7,8). Increased levels of inflammatory mediators may lead to early and sustained chronic inflammation of diabetic retina, leukocyte activation, adhesion to vascular endothelium, disruption of blood retinal barrier, increased vascular permeability, and eventually macular edema. However, the sampling of intraocular fluid and measurement of inflammatory factors in intraocular fluid are exceedingly complicated. A more readily available marker source is the peripheral blood, from which white blood cell (WBC) count and its subtypes can be used a classic inflammation markers (9). Platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and neutrophil to lymphocyte ratio (NLR) are potential inflammatory markers for diabetes and its complications (10-12). The associations between PLR, NLR, and MLR with DR progression have been described in the literature (13-15); however, the relationship between peripheral blood inflammatory markers and severe DR with DME remains to be clarified.

This study therefore examined the relationship between severe DR with DME and peripheral blood inflammatory markers. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-102/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First People's Hospital of Nantong (No. 2021KT004). Individual consent for this retrospective analysis was waived. Data of patients with type 2 diabetes mellitus (T2DM) who were hospitalized in the endocrinology department of our hospital from 2015 to 2019 were retrospectively analyzed. Hypertension was confirmed through a physician diagnosis, the use of antihypertensive medication, or a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg (measured twice).

The exclusion criteria for patients were as follows: (I) with chronic diseases other than diabetes, hypertension, or hyperlipidemia (including cancer, end-stage renal failure requiring dialysis, disabling stroke, coronary artery disease, and liver disease); (II) with a history of prior ophthalmic surgery or intraocular inflammation or ischemia due to conditions other than DR; (III) having received laser therapy or intravitreal injections of anti-vascular growth factor drugs in both eyes due to DR or other conditions; and (IV) with refractive interstitial clouding that could affect fundus examination.

Examinations

Fundus photography and fluoroscopy

After pupil dilatation with tropicamide, fundus photography was performed with a scanning laser ophthalmoscope (Optos PLC, Dunfermline, Scotland) to create retinal images. Fluoroscopy (Heidelberg, HRA Spectralis) was performed by an experienced fluoroscopist to capture early, mid, and late fundus images. Ophthalmologists graded the patients according to the staging system in the Early Treatment Diabetic Retinopathy Study, and 42 eligible patients with severe DR were enrolled in the cohort.

OCT

OCT performed by the same sonographer (Heidelberg, OCT Spectralis) was used to acquire 19 ultrasound scans and 16 automated real-time scans in high-resolution mode in a 20°×15° (5.9 mm × 4.4 mm) area centered in the foveal after pupil dilatation. In total, 42 DR patients were divided into a DME group (n=24, with DME) and a non-DME group (n=18, without DME) according to OCT findings. DME was diagnosed by a foveal thickness [also known as central subfield thickness (CST)] of ≥320 μm (men) or ≥305 μm (women) on OCT (16). If macular edema was present in both eyes, data were recorded for the one with the more severe condition.

Collection of clinical data

Serum specimens were collected from diabetic patients

after 12 hours of fasting and before the administration of insulin and other drugs. A hematology analyzer (Mindray, Shenzhen) was used to make a complete blood count (CBC) that included measures of WBCs, neutrophils, monocytes, lymphocytes, red blood cells (RBC), hemoglobin, platelets, and many other parameters. A fully automated biochemical analyzer (Hitachi Ltd., Tokyo, Japan) was used to measure total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), ApoA1, ApoB, and glycated hemoglobin (HbA1c) levels. The calculation of NLR, PLR, and MLR were the division of the corresponding absolute count of blood cells, and MHR was calculated as the ratio of the absolute monocyte count divided by the HDL-C. Age, sex, disease course of T2DM, blood pressure, and body mass index (BMI) were recorded for all patients.

Statistical analysis

Dataset cleaning and statistical analysis were performed using R v. 4.0.5 software (The R Foundation of Statistical Computing). Continuous variables are presented as the means ± standard deviation, while categorical variables are expressed as numbers (percentages). A 2-sided permutation test was applied for the comparison of continuous variables among groups.

We first employed a complete model, in which the main variables considered were age, diabetes duration, BMI, WBC count and its subtypes, and various examination indexes of blood lipids. Only platelets were significant in the complete model, and we thus used stepwise regression analysis. For this, Akaike information criterion (AIC) information statistic was used as the criterion, and the selection of the optimal model was achieved by selecting the smallest AIC statistic.

In order to clarify the relationship between DME and variables, binary logistic regression was performed. Odds ratios (ORs) and 95% CIs were estimated for the association between DME and predictor variables, and a P value <0.05 was considered statistically significant.

Results

Of the 42 patients with severe DR, 18 were placed in the DME group and 24 in the non-DME group. The clinical characteristics of all participants are summarized in *Table 1*. No significant differences were observed between these two groups in relation to age, sex, disease course, BMI, blood pressure, WBC, monocytes, RBC, hemoglobin, platelets, neutrophils, lymphocytes, or lipids. The HbA1c level in the DME group (9.73%±2.02%) was lower than that in the non-DME group (10.80%±1.85%), but the difference was not statistically significant (P>0.05; *Figure 1*). The prevalence of DME was associated with the disease course of T2DM: the prevalence rate of DME was 2.8% within 5 years of the diabetes diagnosis and 22.0% within 5 years after the diagnosis (P<0.001); after 10 years, the prevalence rose prominently (17). *Figure 2* shows that DME occurred mainly around the 10th year of DR, while *Figure 3* indicates that the patients with DME were typically older than 50 years. Neutrophil percentage was significantly higher in the DME group (62.52%±8.21%) than in the non-DME group (57.30%±8.17%) (P<0.05; *Figure 4*); in contrast, lymphocyte percentage was significantly lower in the DME group (28.09%±7.45%) than in the non-DME group (33.54%±7.29%) (P<0.05; *Figure 5*).

A full model was used first, in which the predictor variables included were age, sex, disease course, BMI, blood pressure, WBC count and its subtypes, and blood lipids. Platelets were found to be a statistically significant predictor in the full model; therefore, we attempted to reclassify these variables. Stepwise regression analysis was applied, in which the AIC was used as a criterion to select the optimal model by choosing the smallest AIC. After reclassification, the modeling results were improved (degrees of freedom =4; P=3.506×0.00001), with an accuracy of 88.10%. Logistic regression analysis showed a significant correlation between lymphocyte percentage and DME (OR =0.654, 95% CI: 0.436–0.851; P=0.011; *Table 2*).

Discussion

Vision loss due to DR is mainly associated with 2 late complications: DME and proliferative DR. A report of UK about diabetic retinopathy and diabetic macular oedema pathways and management points out (18): DR is a common cause of visual loss across the world, especially in the working-age group. The latest National Health Service (NHS) spending figures from 2019 show that £14 billion is spent on the management of diabetes and its complications. Owing to the improved management of diabetes, DR patients can now undergo retinal laser treatment in a timely manner. DME is currently the leading cause of blindness and visual impairment in DR patients (19). According to OCT findings, The European School for Advanced Studies (1)

Table 1 Baseline characteristics

Clinical laboratory index	DME (n=18)	Non-DME (n=24)	P value
Sex (men/women)	4/14	9/15	
Age (years)	56.00±8.25	56.38±10.51	0.899
Diabetes duration (years)	9.38±3.64	12.17±7.23	0.142
BMI (kg/m^2)	25.77±4.70	24.37±3.22	0.254
BP (mmHg)			
SBP	137.89±25.40	140.00±18.15	0.601
DBP	80.22±9.26	79.00±11.69	0.730
Laboratory tests			
HbA1c%	9.73±2.02	10.80±1.85	0.083
White blood cells (×10^9/L)	6.76±2.01	6.48±1.86	0.639
Monocytes (×10^9/L)	0.45±0.20	0.45±0.19	0.926
Platelets (×10^9/L)	180.80±41.56	182.10±41.99	0.849
Red blood cell (×10^{12}/L)	4.31±0.62	4.48±0.55	0.351
Hemoglobin (g/L)	127.60±21.45	134.40±15.98	0.240
Neutrophils (×10^9/L)	4.21±1.27	3.73±1.20	0.215
Neutrophils%	62.52±8.21	57.30±8.17	0.048
Lymphocytes (×10^9/L)	1.91±0.83	2.16±0.75	0.318
Lymphocytes%	28.09±7.45	33.54±7.29	0.024
TG (mmol/L)	2.63±2.44	2.31±1.76	0.622
TC (mmol/L)	5.23±1.10	4.83±1.20	0.269
apoA1 (g/L)	1.18±0.19	1.12±0.27	0.462
apoB (g/L)	1.08±0.24	1.02±0.27	0.427
HDL-C (mmol/L)	1.15±0.24	1.14±0.34	0.936
LDL-C (mmol/L)	2.96±0.81	2.79±0.94	0.533
NLR	2.54±1.25	1.87±0.82	0.058
PLR	114.81±64.82	91.69±30.47	0.132
MLR	0.26±0.13	1.87±0.82	0.188
MHR	0.39±0.16	0.42±0.19	0.683
apoA1/apoB	1.14±0.30	1.17±0.41	0.768

DME, diabetic macular edema; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TG, triglycerides; TC, total cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

classifies DME into four different stages: early DME, advanced DME, severe DME, and atrophic maculopathy. Advanced DME is associated with severe discontinuity of the cystoid spaces, ellipsoid zone, and/or external limiting membrane, whereas severe DME manifests as disorder of the intraretinal layer and damage to the ellipsoid zone and/

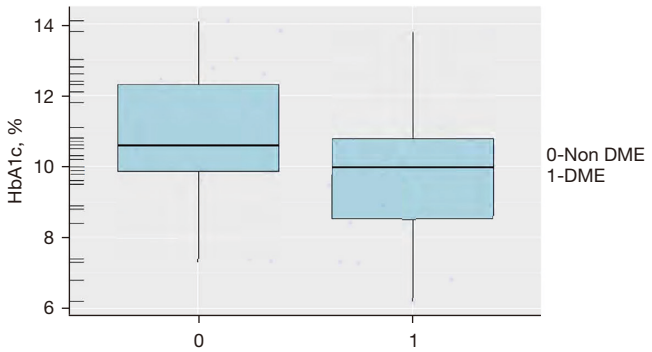

Figure 1 HbA1c levels in the DME and non-DME groups. HbA1c, glycosylated hemoglobin; DME, diabetic macular edema.

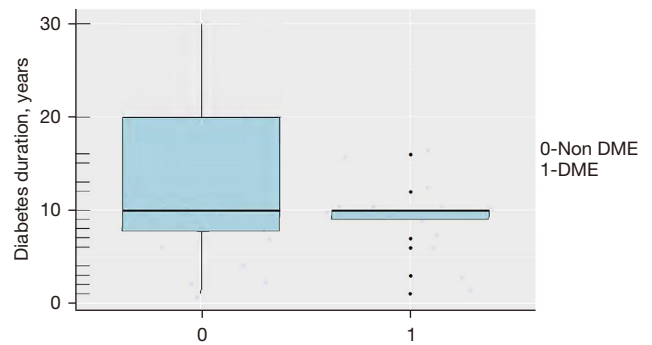

Figure 2 Diabetes duration in the DME and non-DME groups. DME, diabetic macular edema.

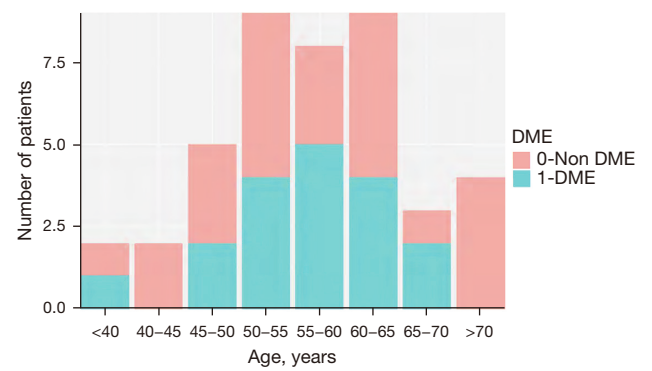

Figure 3 Age distribution map. DME, diabetic macular edema.

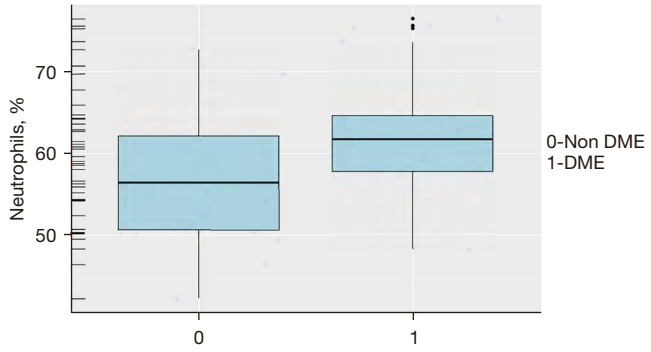

Figure 4 Neutrophils percentage in the DME and non-DME groups. DME, diabetic macular edema.

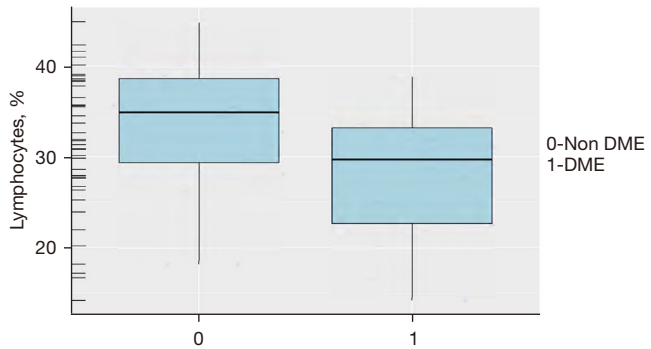

Figure 5 Lymphocytes percentage in the DME and non-DME groups. DME, diabetic macular edema.

or external limiting membrane. Even with repeated anti-VEGF therapy, some affected eyes still enter the stage of "atrophic maculopathy", and satisfactory vision cannot be recovered (20-22). Therefore, it is particularly important to treat DME in its early stage; however, early diagnosis is often difficult to achieve. Once the disease progresses to the second or third stage, dysfunction of the inner and outer retinal layers will occur, rendering DME difficult to reverse. The focus on diabetes eye care should be between prevention, early detection of complications and then managing complications.

Numerous studies have found high HbA1c level to be independently associated with DME (23-25). In our current study, 42 patients with severe DR were enrolled and divided into a DME group (n=18) and a non-DME group (n=24) based on the findings of ocular examinations including fluoroscopic angiography, OCT, and fundus photography. The HbA1c level was >7.5% in these patients, and the mean HbA1c level was higher in the non-DME group than in the DME group, but the difference was not statistically different. Thus, even with the presence of long-term hyperglycemia, other factors may also contribute to the occurrence of DME.

According to OCT findings, DME can be classified into serous retinal detachment (SRD), cystoid macular edema

Table 2 The association of the variables with DME

Comparison of a variety of risk factors	OR	95% CI	P value
Sex (women)	119.990	5.067–15,310.090	0.149
Diabetes duration (years)	0.831	0.655–0.994	0.071
HbA1c	0.616	0.313–1.043	0.098
Platelets ($\times 10^9$/L)	0.945	0.895–0.982	0.014
Lymphocytes ($\times 10^9$/L)	16.396	1.582–525.168	0.057
Lymphocyte%	0.654	0.436–0.851	0.011
TG (mmol/L)	0.649	0.345–1.087	0.120
apoB (g/L)	124.412	1.567–10,5082	0.069

DME, diabetic macular edema; OR, odds ratio; HbA1c, glycosylated hemoglobin; TG, triglycerides; apoB, apolipoprotein B.

(CME), and diffuse retinal thickening (DRT) (26). SRD has been identified as a biomarker of severe inflammation (27). The intraretinal cysts present in the CME type of DME presumably originate from the production of inflammatory cytokines (28,29). Due to inflammation and oxidative stress, DRT leads to the impairment of the outer retinal barrier, causing increased vascular permeability (30). The hyperreflective spots observed on OCT may be the activated microglia, which are associated with a severe inflammatory response (7,27). These findings all suggest a close association between DME and inflammation. It has been reported that the systemic and local expressions of proinflammatory cytokines are increased in the retina of DR patients (31,32). These proinflammatory molecules lead to structural and functional abnormalities in the retina and adversely affect endothelial cells, pericytes, Müller cells, and microglia (33). The determination of specific inflammatory factors in systemic and intraocular fluids allows for the early identification of DME; however, the high cost of the testing itself and the complex harvesting of intraocular fluid restrict the clinical application of these inflammatory factors.

Studies have shown that systemic inflammatory markers such as neutrophils, lymphocytes, monocytes, HDL-C, and apolipoprotein A-1 not only play important roles in the pathophysiology of diseases such as cardiovascular disease (34) and cancer (35), but also figure prominently in the development of ocular disorders such as retinal vein occlusion (36) and uveitis (37). NLR has become a reliable predictor of DR (10,38), while WBCs have been reported to directly cause retinal endothelial cell death and blood-retina barrier dysfunction (39,40). In Ilhan *et al.*'s study (41), NLR was found to be higher in a DME group than in two other control groups, and it was concluded that NLR is a highly sensitive and specific diagnostic indicator of DME.

In our clinical practice, we also find that some patients with severe DR eventually lose their visual function due to structural disorders in the macula even after undergoing total retinal photocoagulation, vitreous cavity injection of anti-VEGF drugs, and vitrectomy. In contrast, for some patients without DME, vision can be maintained or improved with aggressive treatment. In our current retrospective study, we collected and analyzed various clinical parameters, including measures of WBCs, neutrophils, lymphocytes, and blood lipids. Neutrophils and lymphocytes showed no significant difference between the DME group and non-DME group; however, the DME group had a significantly higher neutrophil percentage and a lower lymphocyte percentage, with the lymphocyte percentage being significantly associated with DME. Thus, inflammation may be a risk factor for DME in patients with severe DR, and lymphocyte percentage may be an important diagnostic tool in detecting the occurrence and development of DME in patients with severe DR.

Chung *et al.* (42) showed that hypertriglyceridemia might be used as a surrogate marker for DME; in our current study, however, we did not find significant differences in the blood lipids between DME group and non-DME group, which might be explained by the different DR stages. In their meta-analysis, Das *et al.* (43) concluded that no prospective randomized controlled trial had confirmed the statistical correlation between lipids and DME, which is consistent with our findings.

Diabetes, especially T2DM, occurs more often in males. Among women, postmenopausal women, who

have substantially lower circulating levels of estrogen, are more likely to develop diabetic complications (44). A cross-sectional study (17) in Turkey found that DME was significantly more frequent in men than in women although no significant correlation between gender and DME was found in the DR population with phakic eyes. Our study found that DME occurred mostly in female patients who were mostly over 50 years of age and were in a period of declining estrogen levels. Yousefi *et al.* (45) found that estrogen deficiency could cause the development of inflammation, neovascularization, and subsequent retinopathy in streptozotocin-induced diabetic ovariectomized rats. Nilsson *et al.* (46) also demonstrated that estrogen treatment attenuates the recruitment and adhesion of leukocytes to the endothelium induced by inflammation promoters, which offers a possible mechanism by which estrogens exert an anti-inflammatory effect. Thus, estrogen may play a key role in the progression of DME, although further investigations are warranted.

Our current study had a few limitations. First, only 2 inflammatory markers, WBC count and blood lipids, were studied. Second, only 42 patients were enrolled. Third, the study employed a retrospective design; thus, additional prospective studies need to be conducted among mild/moderate non-proliferative DR patients with DME patients being used as controls. Fourth, this study is a retrospective analysis, which is likely to cause some deviations in the results. It needs to be further confirmed by multi-center clinical trials. Finally, the effect of gender on DME should be examined in studies with larger sample sizes and longer follow-up periods.

In conclusion, simple and inexpensive laboratory methods can help us to assess the impact of systemic inflammatory response on DME in patients with severe DR, and decreased lymphocyte percentage may be a convenient and effective predictor of DME in this population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-102/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-102/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-102/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First People's Hospital of Nantong (No. 2021KT004). Individual consent for this retrospective analysis was waived.

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