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Study on the levels of 25(OH)D, inflammation markers and glucose and fat metabolism indexes in pregnant women of Han nationality in Jiangsu province with gestational diabetes mellitus

Liu Yaqiong, MD, Wang Guohua, PhD*, Yang Fuyan, MD, Lu Wei, BD, Shi Dan, BD, Zhang Yi, MD

Abstract

The aim of this study is to investigate the levels of 25(OH)D, inflammation markers and glucose and fat metabolism indexes in pregnant women with Gestational diabetes mellitus (GDM).

One hundred and ten cases GDM and 100 cases healthy pregnant women in the First People's Hospital of Lianyungang City from October 2016 to December 2018 were recruited for this observational cross-sectional study. Each participant's anthropometric and demographic data was recorded. Blood samples were collected and analyzed to determine the levels of 25(OH)D, high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), fasting blood glucose, fasting blood insulin, hemoglobin A1c (HbA1c), homeostasis model assessment of insulin resistance (HOMA-IR), cholesterol and triglycerides.

Inflammatory markers and glucose and fat metabolism indexes were all significantly higher in the GDM group than that in the control group, while Serum 25(OH)D level in the GDM group was significantly lower. Serum 25(OH)D levels were negatively correlated with hs-CRP, while not with TNF-α. Furthermore, Serum 25(OH)D, hs-CRP and TNF-α levels were all associated with increased risk of developing GDM.

Nowadays, the reports on the association between 25(OH)D level and GDM were controversial. Our results are consistent with the view that there was association between 25(OH)D level and GDM, and expand the literature by showing the roles of 25(OH)D, inflammation markers as well as glucose and fat metabolism indexes in the risk of developing GDM in the pregnant women with the low overall levels of 25(OH)D before delivery. This broadens our knowledge on the pathophysiology of GDM, which may be helpful in prevention and treatment of GDM.

Abbreviations: GDM = gestational diabetes mellitus, hs-CRP = high sensitivity C-reactive protein, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha, HbA1c = Hemoglobin A1c, HOMA-IR = homeostasis model assessment of insulin resistance, OGTT = Oral Glucose Tolerance Test, BMI = Body mass index, EDTA = Ethylene Diamine Tetraacetic Acid, Institute of Medicine (IoM), ELISA = enzyme-linked immunosorbent assay, SD = standard deviation, SPSS = Statistical Package for the Social Sciences.

Keywords: 25-dihydroxyvitamin D, gestational diabetes mellitus, high sensitivity C-reactive protein, tumor necrosis factor-alpha

1. Introduction

Gestational diabetes mellitus (GDM) is defined as hyperglycemia diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes.[1] The prevalence of GDM varies from 1% to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed.[2] The prevalence of GDM in high risk population is even higher, 25% in midtrimester pregnancies[3] and 33% in third trimester pregnancies.[4] According to the medical records of 17,186 pregnant women who received care at the GDM centers established in 13 hospitals in China, 17.5% women were diagnosed with GDM.[5] GDM has both short-term and long-term complications for mothers and their children.[6] Thus, it is valuable to investigate the pathophysiology and identify potential risk factors of GDM.

Beta β-cell dysfunction and insulin resistance play important roles in the pathophysiology of GDM.[6] It is well known that some risk factors such as advanced maternal age, ethnicity and overweight/obesity are associated with development of GDM.[7] Vitamin D plays an important role in bone mineralization and calcium/phosphorus homeostasis.[8] Recently, more and more evidence has shown that Vitamin D also involves in many aspects for human health especially in chronic diseases.[9–11] Vitamin D deficiency may relate to glucose intolerance, altered insulin secretion and type 2 diabetes.[12] However, the reports on the association between vitamin D level and GDM were controversial.

Inflammation, especially chronic inflammation, is a state of persistent secretion of cytokines and chemokines, which

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Department of Obstetrics, the First People's Hospital of Lianyungang City, China.

* Correspondence: Wang Guohua, Department of Obstetrics, the First People's Hospital of Lianyungang City, No. 182 Tongguan North Road, Haizhou District, Lianyungang City 222000, Jiangsu Province, China (e-mail: wghua625@126.com).

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interferes with normal metabolism including disrupting insulin signaling.[12] Chronic low-grade inflammation is linked to many risk factors of GDM.[6] Vitamin D is converted to 25(OH)D in the liver, which is further converted to $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$, the active form of Vitamin D with biological activity, in the kidney. Interestingly, $1,25(OH)_2D_3$ reduces inflammation through multiple mechanism and serum 25(OH)D has been found to have cross sectional relationships with some inflammation markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[13] We wonder what is the relationship between 25(OH)D and inflammation in GDM. However, such reports are limited.

In this study, we performed an observational cross-sectional study including 210 pregnant women (110 cases GDM and 100 cases normoglycemic women) and investigated the levels of 25 (OH)D, inflammation markers and glucose and fat metabolism indexes in these participants. Our results confirmed the association between 25(OH)D level and GDM and further expanding the literature by showing the roles of 25(OH)D, inflammation markers as well as glucose & fat metabolism indexes in the risk of developing GDM.

2. Materials and methods

2.1. Study participants

This is an observational cross-sectional study. It was performed among the pregnant women who underwent routine prenatal examination and delivered in the First People's Hospital of Lianyungang City, which is a tertiary hospital, from October 2016 to December 2018. The inclusion criteria were Han nationality, singleton pregnancy, aged 18 to 40 years, showing normal results of routine blood tests, routine urine tests, coagulation tests, liver & kidney function check (blood test) and electrocardiogram test. The exclusion criteria were history of diabetes, hypertension during pregnancy, thyroid disease, premature rupture of membranes, autoimmune disease and taking hormone therapy. For the diagnosis of GDM, 75 g Oral Glucose Tolerance Test (OGTT) is performed in the morning after overnight fast of >8 hours in the pregnant women after 24 weeks of gestation. GDM was confirmed if at least one of the three glucose level results exceeded the following: fasting $<$ 5.1 mmol/L, 1 h $<$ 10.0 mmol/L and 2 h $<$ 8.5 mmol/L.

The participants were included in this study after their admittance to maternity ward in the First People's Hospital of Lianyungang City. One hundred ten pregnant women with GDM who met all the inclusion criteria and did not meet any item of the exclusion criteria were included in the study group (GDM group). These women did not receive insulin therapy during pregnancy. One hundred healthy pregnant women without GDM were randomly selected as the control. A written informed consent was obtained from each participant after explaining the procedure of the study. This study was approved by the local ethics committee (No. YJ-20160926001).

2.2. Anthropometric measurements

Each participant's anthropometric and demographic data was recorded. We obtained the information on the age, gestational age, pregnancy and birth history, pre-pregnancy weights, history of pregestational diabetes mellitus, family history of diabetes and education through face to face interview. Weight was measured with light clothing and without shoes, while height was measured using pointer body weight scale with height meter (RGZ-120-RT, Wuxi Xiheng). Body mass index (BMI) was calculated as Weight (kg) / [Height (m) × Height (m)]. The amount of weight gain during pregnancy was calculated as current weight (kg) − pre-pregnancy weight (kg).

2.3. Blood collection

We collected blood samples from all participants at indicated time points after overnight fasting. The blood samples were centrifuged. Then serum was separated and stored at -80°C until analysis. Hemoglobin A1c (HbA1c) was measured in whole blood collected in an Ethylene Diamine Tetraacetic Acid (EDTA)-2K tube.

2.4. Blood sampling analyses

Serum 25(OH)D concentration was determined using electrochemiluminescence binding assay in Cobas E601 mass analyzer (Roche Diagnostics). The method had a sensitivity below 3.0 ng/ml and an analytic range to 70.0 ng/ml. Based on Institute of Medicine (IoM) criteria, Vitamin D status was categorized as sever deficiency ($<$ 10 ng/ml), deficiency (10–20 ng/ml) and insufficiency (20–30 ng/ml).[14] Serum Hs-CRP, cholesterol and triglycerides concentrations were measured by immunoturbidimetry on the IMMAGE 800 System (Beckman Coulter, Brea, CA). The method had a sensitivity below 0.1 mg/l and an analytic range to 8.0 mg/l for Hs-CRP, an analytic range from 0 to 12.9 mmol/l for cholesterol and an analytic range from 0 to 0∼11.3mmol/l for triglycerides. Serum TNF-α concentration was detected with Human TNF-α enzyme-linked immunosorbent assay (ELISA) Kit (Absin (Shanghai) Biotechnology Co., Ltd, China). The method had a sensitivity below 0.68 pg/ml. Blood glucose level was monitored using Glucose oxidase method on VITROS 350 Chemistry System (Johnson & Johnson, USA), which had an analytic range from 1.00 mmol/l to 34.69 mmol/l. Serum insulin was determined using electrochemiluminescence binding assay in Cobas E601 mass analyzer (Roche Diagnostics). The method had sensitivity below 0.2 uIU/ml and an analytic range to 1000.0uIU/ml. HbA1c level was detected using electrochemiluminescence assay on D-10 Hemoglobin Testing System (Bio-Rad, USA). The method had sensitivity below 3.8% and an analytic range to 18.5%. Homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as fasting plasma glucose level (mmol/L) × fasting serum insulin (mIU/L)/22.5.

2.5. Statistical analysis

Normally distributed quantitative data were presented as mean ± standard deviation (SD) and compared using independent sample T-test. If the variances were unequal, T'-test was applied. Non-normally distributed quantitative data were presented as median and interquartile range (quartile 1-quartile 3) and compared with nonparametric Mann-Whitney U test. Qualitative data were expressed as numbers & proportions and compared with χ^2 or Fisher exact probability methods. As to pairwise comparison, P value was corrected by Bonferroni method. The Spearman rank correlation test was performed to test the correlation of 25(OH) D, Hs-CRP or TNF-α level with other Variables. Risk factors of GDM were analyzed using binary logistic regression model. SPSS (Statistical Package for the Social Sciences) version 25.0 was used

Table 1

Anthropometric and demographic data of GDM group and the control group.

Variables	GDM Group (n = 110)	Control Group (n = 100)	P
Age (yr)	30.44 ± 4.20	29.68 ± 3.93	.181
Pre-pregnancy weights (Kg)	60.15 ± 7.30	59.61 ± 7.40	.595
Pre-pregnancy BMI (Kg/m^2)	22.89 ± 2.48	22.55 ± 2.69	.337
Weight gain during pregnancy (Kg)	16.30 ± 4.44	15.22 ± 3.40	.047
Pre-pregnancy BMI ≥ 25 Kg/m^2(N)	24 (21.8%)	18 (18.0%)	.490
Positive GDM history in previous pregnancies (N)	7 (6.4%)	3 (3.0%)	.253
Positive family history of diabetes (N)	14 (12.7%)	10 (10.0%)	.535
Without birth history (N)	70 (63.6%)	62 (62.0%)	.806
High school education or above (N)	103 (93.6%)	90 (90.0%)	.335

Quantitative data were expressed as mean ± SD and compared with Student t-test. Qualitative data were expressed as proportions and compared with χ^2 or Fisher exact probability methods. $P < .05$ was considered statistically significant. GDM = Gestational diabetes mellitus, BMI = body mass index.

Table 2

25(OH)D level, inflammatory markers and glucose & fat metabolism indexes of GDM group and the control group.

Variables	GDM Group	Control Group	P
25(OH)D (ng/ml)	13.90 (9.06-18.64)	17.50 (12.64-22.78)	<.001
Hs-CRP (mg/l)	5.55 (3.94-7.56)	3.82 (3.25-4.71)	<.001
TNF-α (pg/ml)	7.94 (6.30–10.91)	6.30 (4.62–8.27)	<.001
Fasting Blood glucose (mmol/l)	5.04 ± 0.56	4.31 ± 0.41	<.001
Fasting Blood Insulin (ulU/ml)	19.71 ± 6.90	14.21 ± 5.63	<.001
HOMA-IR	4.40 ± 1.63	2.73 ± 1.14	<.001
HbA1c (%)	5.52 ± 0.54	4.87 ± 0.45	<.001
Cholesterol (mmol/l)	6.436 ± 1.07	3.33 ± 0.94	<.001
Triglycerides (mmol/l)	3.26 (2.50–4.08)	1.66 (1.48–2.15)	< .001

Parametric variables were expressed as mean ± SD and compared with Student t-test. Nonparametric variables were expressed as interquartile range (quartile 1-quartile 3) and compared with nonparametric Mann-Whitney U test. $P < .05$ was considered statistically significant.
GDM = gestational diabetes mellitus, HOMA-IR = homeostasis model assessment of insulin resistance.

for statistical analyses and $P < .05$ was considered statistically significant.

3. Results

3.1. Anthropometric and demographic data

This study included 210 pregnant women (GDM group, 110 women; control group, 100 women). Anthropometric and demographic data of all the participants were shown in Table 1. There were no significant differences in age, pre-pregnancy weights, pre-pregnancy BMI, pregnancy & birth history, history of pregestational diabetes mellitus, family history of diabetes and education between GDM group and the control group. The amount of weight gain during pregnancy was significantly higher in the GDM group than that in the control group (16.30 ± 4.44 kg vs 15.22 ± 3.40 kg, $P < .05$).

3.2. Characteristics of 25(OH)D level, inflammatory markers and glucose and fat metabolism indexes

Data for 25(OH)D level, inflammatory markers and glucose & fat metabolism indexes of the GDM group and the control group were shown in Table 2. Inflammatory markers and glucose and fat metabolism indexes, including hs-CRP, TNF-α, fasting blood glucose, fasting blood insulin, HbA1c, HOMA-IR, cholesterol and triglycerides were all significantly higher in the GDM group than that in the control group. Serum median (quartile 1-quartile 3) 25(OH)D level in the GDM group was 13.90 (9.06–18.64) ng/ml, which was significantly lower than that in the control group (17.50 (12.64–22.78) ng/ml, $P < .001$). According to Institute of Medicine (IoM) criteria, serum 25(OH)D levels were categorized as sever deficiency (< 10 ng/ml), deficiency (10–20 ng/ml) and insufficiency (20–30 ng/ml).[14] In this study, serum 25(OH)D levels in most majorities of the participants in both the GDM group (48.20%) and the control group (61.00%) were 10 to 20 ng/ml. Furthermore, there was a 31.80% prevalence of sever deficiency of serum 25(OH)D level (<10 ng/ml) in the GDM group, while only 8.00% prevalence in the control group (Table 3).

3.3. Correlation of 25(OH)D and inflammatory markers with other variables

We investigated the correlation of 25(OH)D and inflammatory markers with other variables. As shown in Table 4, serum 25 (OH)D levels were negatively correlated with hs-CRP, while not with TNF-α. The correlation of TNF-α with neither 25(OH)D nor hs-CRP was significant. As to glucose & fat metabolism indexes, both hs-CRP and TNF-α were positively correlated with all the glucose & fat metabolism indexes detected. Serum 25(OH) D levels were negatively correlated with fasting blood glucose, HbA1c, HOMA-IR, Cholesterol and triglycerides, while not with fasting blood insulin.

3.4. Effects of 25(OH)D and inflammatory markers on the risk of developing GDM

We investigated the effects of 25(OH)D and inflammatory markers on the risk of developing GDM. First, univariate binary logistic regression analysis of 25(OH)D, hs-CRP or TNF-α alone was conducted. The results showed that lower 25(OH)D levels

Table 3

Distribution of 25(OH)D level.

25(OH)D status	GDM Group (n = 110)	Control Group (n = 100)	Total (n = 210)	P
< 10 ng/mL	35 (31.80%)	8 (8.00%)	43 (20.48%)	<.001
10–19.99 ng/mL	53 (48.20%)	61 (61.00%)	114 (54.29%)	.252
20–29.99 ng/mL	17 (15.50%)	28 (28.00%)	45 (21.43%)	.108
> = 30 ng/mL	5 (4.50%)	3 (3.00%)	8 (3.80%)	1.000

X^2 test and Fisher exact probability methods was performed. P value was corrected by Bonferroni method and $P < .05$ was considered statistically significant. GDM = gestational diabetes mellitus.

Table 4

Correlation of 25(OH)D, Hs-CRP or TNF-α level with other Variables.

Variables	25(OH)D		Hs-CRP		TNF-α	
	r	*P*	*r*	*P*	*r*	*P*
25(OH)D			−0.245	.000	−0.003	.970
hs-CRP	−0.245	.000			0.023	.742
TNF-α	−0.003	.970	−0.023	.742		
Fasting Blood Insulin	−0.109	.116	0.572	.000	0.358	.000
HOMA-IR	−0.158	.022	0.579	.000	0.386	.000
HbA1c	−0.245	.000	0.329	.000	0.297	.000
Fasting Blood glucose	−0.191	.006	0.275	.000	0.259	.000
Cholesterol	−0.206	.003	0.324	.000	0.311	.000
Triglycerides	−0.184	.008	0.343	.000	0.207	.003

The Spearman rank correlation test was performed. $P < .05$ was considered statistically significant. GDM = gestational diabetes mellitus, HOMA-IR = homeostasis model assessment of insulin resistance.

were associated with increased risk of developing GDM (OR = 0.934; 95% CI 0.896–0.974; $P = .001$), higher hs-CRP levels were associated with increased risk of developing GDM (OR = 1.627; 95% CI 1.357–1.951; $P < .001$) and higher TNF-α levels were associated with increased risk of developing GDM (OR = 1.259; 95% CI 1.134–1.398; $P < .001$).

Then we established the multivariable binary logistic regression models with multiple variables including 25(OH)D, hs-CRP, TNF-α, HOMA-IR, weight gain during pregnancy and age. As shown in Table 5, lower 25(OH)D levels were associated with increased risk of developing GDM in the unadjusted model (OR = 0.948; 95% CI 0.900–0.998; $P = .042$). While the association was not statistically significant after adjustment for age, body mass index, GDM history in previous pregnancies, family history of diabetes, birth history and education (OR = 0.949; 95% CI 0.899–1.002; $P = .059$). Furthermore, higher hs-CRP, TNF-α and HOMA-IR levels were associated with increased risk of developing GDM in both the unadjusted model and the adjusted model. As to weight gain during pregnancy, the association was not statistically significant.

Table 5

Multivariable logistic regression models using 25(OH)D and other variables.

Variables	OR	95% CI	*P*
25(OH)D			
Unadjusted model	0.948	0.900–0.998	.042
Adjusted model	0.949	0.899–1.002	.059
Hs-CRP			
Unadjusted model	1.357	1.069–1.721	.012
Adjusted model	1.404	1.094–1.801	.008
TNF-α			
Unadjusted model	1.228	1.073–1.404	.003
Adjusted model	1.228	1.070–1.410	.004
HOMA-IR			
Unadjusted model	1.690	1.206–2.367	.002
Adjusted model	1.729	1.225–2.439	.002
Weight gain during pregnancy			
Unadjusted model	1.032	0.945–1.127	.478
Adjusted model	1.056	0.960–1.160	.262
Age	1.107	1.002–1.223	.046

Binary logistic regression analysis was performed. $P < .05$ was considered statistically significant. Adjusted model, adjusted for age, body mass index, GDM history in previous pregnancies, family history of diabetes, birth history and education. GDM = gestational diabetes mellitus, HOMA-IR = homeostasis model assessment of insulin resistance.

4. Discussion

In this study, we compared the levels of 25(OH)D and inflammatory markers (hs-CRP and TNF-α) between the GDM group and the control group. Our results indicated that both hs-CRP and TNF-α were significantly higher in the GDM group than that in the control group, while 25(OH)D level was significantly lower in the GDM group. Serum 25(OH)D and hs-CRP levels were negatively correlated with each other. However, the correlation of TNF-α with neither 25(OH)D nor hs-CRP was significant. Furthermore, lower 25(OH)D levels were associated with increased risk of developing GDM, and higher hs-CRP or TNF-α levels were associated with increased risk of developing GDM.

Nowadays, the association between vitamin D level and GDM has aroused much attention. However, the conclusions are inconsistent. Some studies reported that lower 25(OH)D level was associated with elevated risk of GDM.[15–19] But some studies reported that 25(OH)D deficiency was not associated with GDM.[20–23] In a case-sectional study of 723 pregnant women, of which 97% were vitamin D sufficient [25(OH)D ≥50 nmol/L], there was no difference in 25(OH)D concentration between GDM and non-GDM group.[21] Baker et al also reported that in a cohort of pregnant women with mostly sufficient levels of serum25 (OH)D, vitamin D deficiency was not associated with GDM.[24] In this study, we found that 25(OH)D level was significantly lower in the GDM group than that in the control group and lower 25(OH)D levels were associated with increased risk of developing GDM. It should be noticed that in our study, serum median 25(OH)D levels in the GDM group and the control group were 13.90 ng/ml and 17.50 ng/ml respectively, which were categorized as deficiency (10–20 ng/ml) according to Institute of Medicine (IoM) criteria. This result reflected the low overall levels of 25(OH)D in the pregnant women enrolled in this study. It seems that as to the effects of 25(OH)D on the risk of GDM, more attention will be needed in populations with lower levels of 25(OH)D.

GDM is a metabolic disease and characterized as high blood glucose level. Accordingly, we observed increased fasting blood glucose and HbA1c in the GDM group. One of the key factors in the pathophysiology of GDM is insulin resistance. In this study, both fasting blood insulin level and HOMA-IR were significantly higher in the GDM group. It seems that increased secretion of insulin in the GDM group cannot compensate for the impaired function of insulin. It has been known that altered lipid metabolism during pregnancy is one of the causes of insulin

resistance.[25] Alyas et al reported significantly higher levels of total plasma cholesterol and triglycerides in the GDM group during both the second and the third trimester.[26] In this study, we also observed increased levels of cholesterol and triglycerides in the pregnant women with GDM before delivery.

The role of inflammation in the development of GDM also aroused much attention.[6] The obesity-associated chronic inflammation plays an important role in the pathogenesis of insulin resistance, in which process, TNF-α is one of the key factors.[27,28] CRP is synthesized in response to inflammation cytokines and can be used as indicator of systematic inflammation.[29] In women with GDM, elevated TNF-α or hs-CRP levels have been reported by several studies.[26,30–33] In this study, we observed that both hs-CRP and TNF-α levels were significantly higher in the GDM group than that in the control group and they were positively correlated with all the glucose & fat metabolism indexes detected. Higher hs-CRP and TNF-α levels were associated with increased risk of developing GDM, further supporting the association of inflammation with GDM.

In general, 25(OH)D reduces inflammation through switching the immune system from more inflammatory response to the less inflammatory status.[13,34] CRP is one of the mostly used inflammatory markers to determine the inflammatory status in clinical practice.[35] In this study, lower 25(OH)D levels were associated with increased risk of developing GDM and serum 25 (OH)D levels were negatively correlated with hs-CRP. It seems that the role of 25(OH)D in GDM may associate with its correlation with inflammatory status, which deserves further investigation. At a cellular level, 25(OH)D inhibits production of TNF-α in monocyte.[36] Bellia et al reported that serum 25(OH)D was inversely correlated with TNF-α in 147 morbidly obese subjects.[37] However, the study on the correlation of 25(OH)D with TNF-α in GDM was rare. In this study, we observed that serum 25 (OH)D levels were not correlated with TNF-α. Fatemeh et al also reported that the relationship between 25(OH)D levels and TNF-α were not significant.[38] Thus, 25(OH)D and TNF-α may affect the risk of developing GDM through different mechanism.

There are some limitations concerning this study. First, we only collected blood samples of the participants before delivery, which could not reflect the changes throughout the pregnancy. Second, we examined the correlation of 25(OH)D levels with TNF-α and hs-CRP. More inflammation markers should be detected in the future work.

In conclusion, in this study we investigated the levels and correlation of 25(OH)D, inflammation markers as well as glucose & fat metabolism indexes in GDM in the population with the low overall levels of 25(OH)D before delivery. This broadens our knowledge on the pathophysiology of GDM, which may be helpful in prevention and treatment of GDM.

Author contributions

Conceptualization: Yaqiong Liu, Guohua Wang.
Methodology: Yaqiong Liu.
Project Administration: Wei Lu.
Formal analysis: Yaqiong Liu.
Investigation: Yaqiong Liu, Dan Shi, Yi Zhang.
Funding Acquisition: Yaqiong Liu.
Resources: Fuyan Yang, Dan Shi, Yi Zhang.
Data Curation: Fuyan Yang, Dan Shi, Yi Zhang.
Supervision: Guohua Wang, Wei Lu.
Validation: Guohua Wang.
Visualization: Guohua Wang.
Writing-Original Draft: Yaqiong Liu.
Writing-Review & Editing: Guohua Wang, Fuyan Yang, Wei Lu.

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