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Combining the triglyceride-glucose index and glycated hemoglobin A1c to assess the risk of preeclampsia in women with normal glucose tolerance: a cross-sectional study

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Abstract. – OBJECTIVE: This study aimed to explore the relationship between the triglyceride-glucose (TyG) index, glycated hemoglobin A1c (HbA1c), and preeclampsia in pregnant women without gestational diabetes mellitus (GDM).

PATIENTS AND METHODS: This retrospective study included pregnancies with normal oral glucose tolerance tests (OGTTs) from March 2018 to February 2019. During the second trimester, serum lipids, fasting plasma glucose (FPG), and HbA1c were measured, and OGTTs were performed. Participants were classified into four groups based on their TyG index and HbA1c levels. Logistic regression analysis was done to determine the odds ratios (ORs), and receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of the TyG index and HbA1c to predict the risks of preeclampsia.

RESULTS: Patients with preeclampsia exhibited higher TyG index and HbA1c levels (all $p < 0.001$). The incidence of preeclampsia increased with elevated TyG index and HbA1c levels individually. Furthermore, the highest incidence of preeclampsia was observed when both the TyG index and HbA1c levels were elevated. ROC curve analysis revealed that the combined TyG index and HbA1c displayed an area under the curve (AUC) of 0.689 in predicting the risk of preeclampsia. Even after adjusting for potential confounding factors, the risk of developing preeclampsia remained significantly higher. These associations were especially prominent in women aged ≥ 35 years or those with a normal BMI.

CONCLUSIONS: The findings of this study indicate that increased TyG index and HbA1c levels are associated with a higher incidence and risk of preeclampsia in women with normal glucose tolerance during pregnancy. The TyG index and HbA1c levels may serve as potential markers for preeclampsia in individuals with normal OGTT results.

Key Words:
Triglyceride-glucose index, Glycated hemoglobin A1c, Insulin resistance, Preeclampsia, Risk, Gestational diabetes mellitus.

Introduction

Preeclampsia is a pregnancy-specific disease that affects 2-4% of all pregnancies[1]. It remains a leading cause of short- and long-term neonatal and maternal morbidity and mortality[2,3]. Statistics indicated an estimated annual toll of around 46,000 maternal deaths and approximately 500,000 fetal and newborn death[4,5]. All women with preeclampsia are at risk of rapid progression and severe disease, regardless of the timing of onset. In recent years, significant research[6] efforts have been directed toward understanding the disorder's pathophysiology, identifying women at risk through predictive models, and developing preventive strategies to reduce the incidence of preeclampsia. However, despite all these efforts, the prevalence of preeclampsia has remained relatively unchanged in recent decades.

Epidemiological research[7] suggests that insulin resistance (IR) is an initiation factor for preeclampsia. While physiological IR during pregnancy benefits fetal growth and nutrient supply[8], the degree of IR is significantly higher during pregnancy than in normal circumstances, which can have multiple adverse effects on both the mother and fetus, including the development of preeclampsia[9]. Recently, the triglyceride-glucose (TyG) index, derived from fasting plasma triglyceride and glucose levels, has been identified as a reliable indicator of IR[10]. This index can be

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conveniently and effortlessly employed in clinical practice[11]. However, no correlation between the TyG index and preeclampsia has been reported. On the other hand, glycated hemoglobin A1c (HbA1c) reflects average blood glucose levels in the preceding 8-12 weeks and is widely used to monitor blood glucose in people with diabetes. Elevated levels of HbA1c are closely associated with adverse pregnancy outcomes[12,13].

Gestational diabetes mellitus (GDM) is a widespread and complex condition, occurring in approximately 7.5-27% of all pregnancies[14]. Research[15-17] has shown that GDM is an independent risk factor for preeclampsia, even after adjusting for confounders. However, most women are not diagnosed with GDM, and the healthcare system and pregnant women may overlook those who go undiagnosed. Therefore, it is crucial to identify women at higher risk for preeclampsia, even among those not diagnosed with GDM. Although significant evidence links GDM to preeclampsia, studies exploring the associations between various degrees of maternal TyG index and HbA1c levels outside the range of GDM with preeclampsia are limited. Consequently, we aimed to retrospectively evaluate the associations between the TyG index and HbA1c in women with preeclampsia and further explore risk factors for the disease in women with normal oral glucose tolerance tests (OGTTs). Thus, early detection of high-risk individuals could aid in managing preeclampsia and improve maternal and fetal outcomes.

Patients and Methods

Study Participants

This retrospective cohort study was conducted at Women's Hospital, Zhejiang University School of Medicine, from March 2018 to February 2019. The study population consisted of pregnant women receiving routine prenatal care and delivery at the hospital. The study received approval from the hospital's Ethics Committee (approval number: IRB-20220357-R), and informed consent was waived as anonymous patient records were used. Nevertheless, individuals who met any of the following criteria were excluded from the study: (1) aged < 18 years, (2) had missing data on the TyG index (fasting plasma triglyceride and glucose) and HbA1c, (3) had diseases affecting blood glucose levels such as hyperthyroidism, Cushing's syndrome, polycystic ovary syndrome, and pancreatitis, (4) had multiple pregnancies, (5) delivered before 28 weeks of gestation, (6) experienced abortion or stillbirth, (7) had diabetes mellitus or chronic hypertension before pregnancy, (8) had severe heart, liver, and kidney diseases, (9) had diseases related to autoimmune or malignancy, (10) had abnormal OGTT results, defined as one or more values equal to or above the following thresholds: fasting plasma glucose (FPG) 5.1 mmol/L; 1-h plasma glucose 10.0 mmol/L, and 2-h plasma glucose 8.5 mmol/L at 24-28 weeks of gestation, or (11) had an HbA1c level ≥ 6.5%. From electronic medical databases, 9,041 delivery records were retrieved without missing or duplicate medical data. After applying the exclusion criteria, the final analysis included 6,798 individuals (Figure 1).

Data Collection and Measurements

From the hospital's electronic medical databases, we gathered demographic information from participants, including age, height, preconception weight, educational background, gestational weight gain (GWG), birth weight, gravidity, parity, and maternal and neonatal events. The medical staff recorded this information. We obtained data from the laboratory information system, including fasting plasma glucose (FPG), 1-h plasma glucose, 2-h plasma glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), glycated hemoglobin A1c (HbA1c), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), creatinine (Cre), blood urea nitrogen (BUN), and uric acid (UA). Maternal laboratory tests were analyzed using the Architect c16000 chemistry analyzer (Abbott, IL, USA), while HbA1c was performed using the HLC-723-G8 (Tosoh, Japan) by the hospital's clinical laboratory department. The laboratory performs daily internal quality controls (IQC) and conducts annual instrument calibrations. Throughout this period, the coefficient of variation (CV) for TG, glucose, and HA1c at low-level IQC was 2.58%, 1.14%, and 2.02%, respectively. Furthermore, the CV at high-level IQC was 2.64%, 1.21%, and 1.79%, all falling comfortably below the industry standards. Additionally, the laboratory participated in external quality assessment (EQA) programs organized by national and provincial authorities to ensure the accuracy of laboratory test results. The laboratory used the Westgard multi-rule quality control method throughout the testing process to ensure result stability. All operations strictly adhered to the standard operating procedures of the instruments.

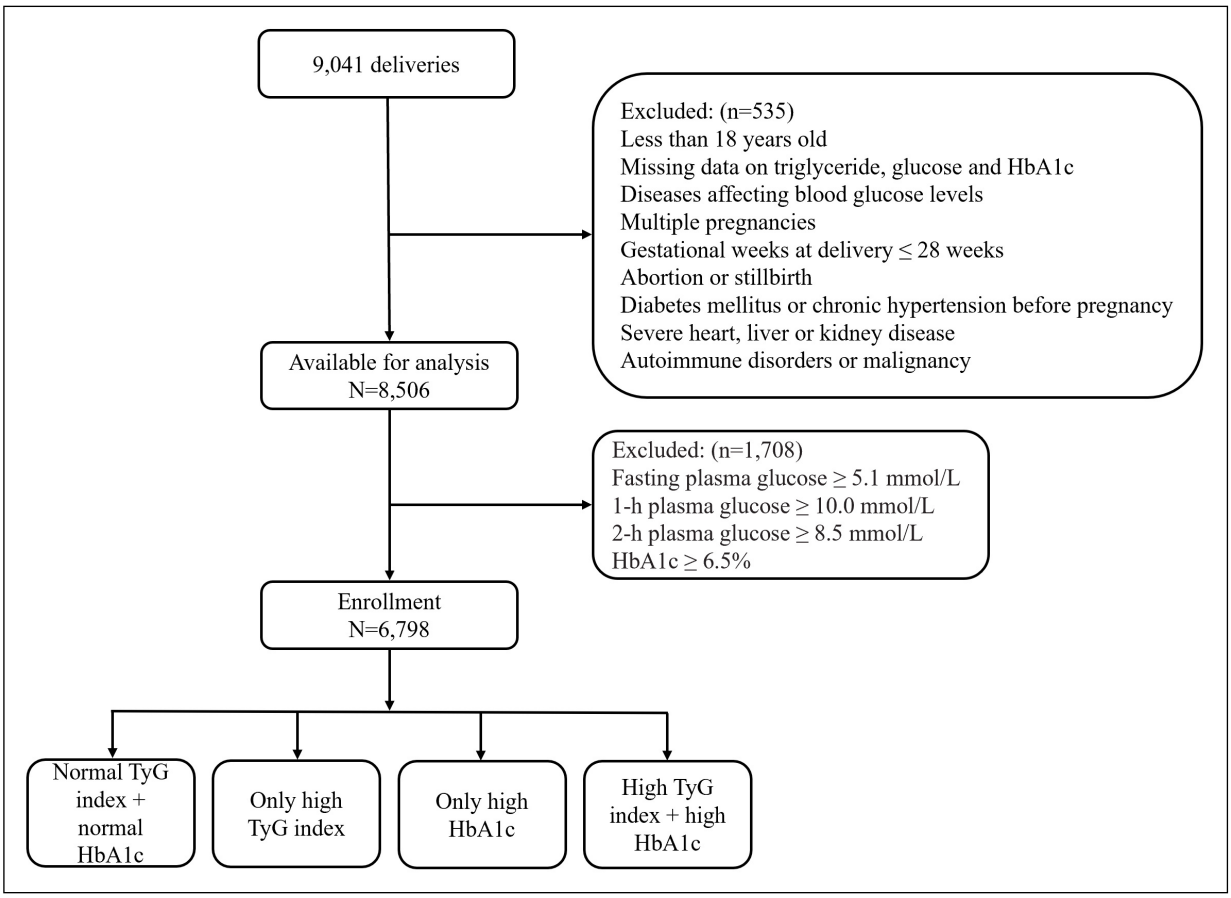

Figure 1. Flowchart of participants' enrollment and group assignment.

Sample Collection

All participants were subjected to routine screening for GDM at 24-28 weeks of gestation using a 75-g OGTT[18]. Peripheral venous blood samples were collected from participants after an overnight fasting period of 8-12 hours. The blood sample testing items included FPG, 1-h plasma glucose, 2-h plasma glucose, TC, TG, HDL-c, LDL-c, HbA1c levels, ALT, AST, TBIL, Cre, BUN and UA.

Definitions

Preeclampsia was defined as gestational hypertension, indicated by systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or both, based on two measurements taken four hours apart. Additionally, the presence of proteinuria of at least 300 mg/24 hours or a 1+ level or higher with dipstick testing in a random urine sample was required for diagnosis[19]. A diagnosis of GDM was established if any of the following values were met or exceeded during the 75-g OGTT: 0 hours (fasting) ≥ 5.1 mmol/L, 1-hour plasma glucose ≥ 10.0 mmol/L, or 2-hour plasma glucose ≥ 8.5 mmol/L[15]. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height in meters[20]. Preconception BMI categories were determined as follows: underweight (< 18.5 kg/m^2), normal (18.5-23.9 kg/m^2), overweight (24.0-27.9 kg/m^2), and obese (≥ 28.0 kg/m^2)[21]. The TyG index was calculated using the formula: TyG = Ln [TG (mg/dl) × FPG (mg/dl) /2][22].

There is no standard reference value for HbA1c and TyG index in pregnant women. A previous study[23] suggests that an HbA1c value greater than 5.4% during the second trimester could indicate a high HbA1c level. However, the literature has not reported reference intervals for the TyG index in pregnant women. Consequently, the participants were divided into three tertiles based on their TyG index levels: Tertile 1 (< 8.70), Tertile 2 (8.70-8.97), and Tertile 3 (≥ 8.98). A TyG index value lower than 8.98 was considered normal, while a value of 8.98 or greater was considered high. The patients

were categorized into four groups based on the presence or absence of elevated TyG index and HbA1c levels: Group 1 consisted of participants with both normal TyG index and normal HbA1c; Group 2 had a high TyG index only; Group 3 had a high HbA1c only, and Group 4 consisted of participants with both high TyG index and high HbA1c.

GWG was categorized according to the guidelines of the Institute of Medicine (IOM)[24]. The insufficient GWG group was defined as weight gain during the gestation of less than 12.5 kg in underweight women (< 18.5 kg/m^2), less than 11.5 kg in normal-weight women (18.5-24.9 kg/m^2), less than 7 kg in overweight women (BMI 25.0-30.0 kg/m^2), and less than 5 kg in obese women (≥ 30.0 kg/m^2). The excessive GWG group was defined as weight gain during gestation exceeding 18 kg in underweight women, exceeding 16 kg in normal-weight women, exceeding 11.5 kg in overweight women, and exceeding 9 kg in obese women. All other women were classified as having sufficient GWG.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA), and graphs were created using GraphPad Prism 8.0 (San Diego, CA, USA) and MedCalc 20.1 (Ostend, Belgium). Continuous variables were reported as means ± standard deviations (SD), while categorical variables were presented as frequencies and proportions (n, %). An independent sample *t*-test was employed to compare continuous variables between two groups, and the Chi-square test was used to compare categorical variables between groups. Receiver operating characteristic (ROC) curves were utilized to calculate the area under the curve (AUC) to evaluate the diagnostic value and accuracy of different parameters and determine the sensitivity and specificity for specific cut-off values. Logistic regression analyses were performed with or without adjustments for potential covariates to determine the odds ratios (ORs) and 95% confidence intervals (CIs). $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Table I summarizes the baseline characteristics of the study participants (n = 6,798), who ranged in age from 18 to 47 years, with an average age of 30.60 ± 4.15 years. Their preconception BMI ranged from 12.7 to 42.7 kg/m^2, averaging 20.66 ± 2.63 kg/m^2. The participants were divided into four groups based on their TyG index and HbA1c levels: the normal TyG index + normal HbA1c group (G1), the high TyG index only group (G2), the high HbA1c only group (G3), and the high TyG index + high HbA1c group (G4). Significant differences were observed in maternal age ($p < 0.001$), preconception BMI ($p < 0.001$), GWG ($p < 0.001$), birth weight ($p < 0.001$), gravidity ($p < 0.001$), parity ($p < 0.001$), systolic pressure ($p < 0.001$) and diastolic pressure ($p < 0.001$) among the four groups (Table I). The laboratory test results also revealed significant differences in FPG, 1-h plasma glucose, 2-h plasma glucose, TC, TG, HDL-c, LDL-c, TyG index, HbA1c, ALT, AST, TBIL, Cre, BUN and UA among the four groups (all $p < 0.05$). There was no significant difference in educational background among the four groups ($p > 0.05$).

Differences Between Pregnant Women Who Have Developed and Not Developed Preeclampsia

Table II indicates that individuals with preeclampsia exhibited higher preconception BMI and GWG and lower birth weight (all $p < 0.001$). Furthermore, the two groups observed significant differences in gravidity and parity (all $p < 0.01$). No significant disparities were found in other baseline characteristics (Table II).

Additionally, we compared the levels of the TyG index and HbA1c between the preeclampsia and non-preeclampsia groups to assess their contributions. The analysis revealed elevated TyG index (9.01 ± 0.38 *vs.* 8.85 ± 0.33) and HbA1c levels (5.1 ± 0.3 *vs.* 4.9 ± 0.3) in the preeclampsia group compared to the non-preeclampsia group (Table II) (all $p < 0.001$).

The Relationship Between the TyG Index and HbA1c and the Incidence of Preeclampsia

The incidence of preeclampsia among the pregnant women included in the study was 1.56% (106/6,798). It demonstrated a progressive increase across the three tertiles. Specifically, Tertile 1 had an incidence of 0.92% (21 out of 2,281), Tertile 2 had an incidence of 1.19% (27 out of 2,269), and Tertile 3 had the highest incidence of 2.58% (58 out of 2,248) (data not shown). Similarly, pregnant women with high HbA1c levels (> 5.4%) had a significantly higher incidence (12/183, 6.56%) of preeclampsia compared to those with normal HbA1c levels (94/6,615, 1.42%) at 24-28 weeks of gestation (data not shown, $p < 0.001$).

Table I. The baseline characteristics of the population in the cohort study after grouping according to the TyG index and HbA1c.

	All	Normal TyG index + HbA1c, G1	Only high TyG index, G2	Only high HbA1c, G3	High TyG index + HbA1c, G4	*p*-value
Total, n (%)	6,798	4,459 (65.59)	2,156 (31.72)	91 (1.34)	92 (1.35)	
Maternal age (years)	30.60 ± 4.15	30.31 ± 4.04	31.06 ± 4.25	32.40 ± 4.93	32.64 ± 4.85	< 0.001
Maternal age category, n (%)						< 0.001
< 35	5,509 (81.04)	3,279 (73.54)	1,665 (77.23)	56 (61.54)	59 (64.13)	
≥ 35	1,289 (18.96)	730 (16.37)	491 (22.77)	35 (38.46)	33 (35.87)	
Preconception BMI (kg/m^2)	20.66 ± 2.63	20.26 ± 2.43	21.33 ± 2.81	21.90 ± 2.92	23.18 ± 2.67	< 0.001
Preconception BMI category, n (%)						< 0.001
Underweight	1,299 (19.11)	1,006 (22.56)	280 (12.99)	10 (10.99)	3 (3.26)	
Normal	5,079 (74.71)	3,279 (73.54)	1,670 (77.46)	64 (70.33)	66 (71.74)	
Overweight	386 (5.68)	156 (3.50)	192 (8.91)	16 (17.58)	22 (23.91)	
Obese	34 (0.50)	18 (0.40)	14 (0.64)	1 (1.10)	1 (1.09)	
Education, n (%)						0.338
Primary or below	22 (0.32)	15 (0.34)	6 (0.28)	0 (0.00)	1 (1.09)	
Middle school	945 (13.90)	591 (13.25)	326 (15.12)	15 (16.48)	13 (14.13)	
College or above	5,831 (85.78)	3,853 (86.41)	1,824 (84.60)	76 (83.52)	78 (84.78)	
GWG, n (%)						< 0.001
Inadequate	1,543 (22.70)	1,044 (23.41)	468 (21.71)	15 (16.48)	16 (17.39)	
Adequate	3,168 (46.60)	2,145 (48.11)	947 (43.92)	39 (42.86)	37 (40.22)	
Excess	2,087 (30.70)	1,270 (28.48)	741 (34.37)	37 (40.66)	39 (42.39)	
Birth weight (g)	3,312 ± 433	3,288 ± 419	3,361 ± 440	3,304 ± 597	3,311 ± 625	< 0.001
Gravidity, n (%)						< 0.001
1	2,694 (39.63)	1,887 (42.32)	747 (34.65)	28 (30.77)	32 (34.78)	
2	2,051 (30.17)	1,298 (29.11)	699 (32.42)	30 (32.97)	24 (26.09)	
≥ 3	2,053 (30.20)	1,274 (28.57)	710 (32.93)	33 (36.26)	36 (39.13)	

Continued

Table I *(Continued)*. The baseline characteristics of the population in the cohort study after grouping according to the TyG index and HbA1c.

	All	Normal TyG index + HbA1c, G1	Only high TyG index, G2	Only high HbA1c, G3	High TyG index + HbA1c, G4	*p*-value
Parity, n (%)						< 0.001
Nullipara	4,178 (61.46)	2,856 (64.05)	1,234 (57.24)	41 (45.05)	47 (51.09)	
Multipara	2,620 (38.54)	1,603 (35.95)	922 (42.76)	50 (54.95)	45 (48.91)	
Systolic pressure (mm Hg)	110 ± 12	109 ± 11	112 ± 12	111 ± 11	118 ± 12	< 0.001
Diastolic pressure (mm Hg)	64 ± 9	63 ± 9	65 ± 9	66 ± 9	69 ± 9	< 0.001
Laboratory test at 24-28 weeks						
FPG (mmol/L)	4.33 ± 0.29	4.28 ± 0.28	4.41 ± 0.29	4.47 ± 0.34	4.57 ± 0.30	< 0.001
1-h PG (mmol/L)	7.60 ± 1.29	7.51 ± 1.31	7.76 ± 1.24	7.99 ± 1.12	8.29 ± 1.06	< 0.001
2-h PG (mmol/L)	6.59 ± 0.97	6.50 ± 0.98	6.75 ± 0.94	6.89 ± 0.91	7.11 ± 0.77	< 0.001
TC (mmol/L)	5.91 ± 0.98	5.82 ± 0.94	6.11 ± 1.05	5.94 ± 0.97	5.94 ± 1.02	< 0.001
TG (mmol/L)	2.14 ± 0.75	1.74 ± 0.36	2.93 ± 0.69	1.79 ± 0.34	3.05 ± 0.88	< 0.001
HDL-c (mmol/L)	1.93 ± 0.36	1.99 ± 0.36	1.81 ± 0.34	1.95 ± 0.35	1.80 ± 0.31	< 0.001
LDL-c (mmol/L)	2.83 ± 0.75	2.81 ± 0.71	2.87 ± 0.82	2.85 ± 0.67	2.80 ± 0.84	0.016
TyG index	8.85 ± 0.33	8.67 ± 0.21	9.22 ± 0.20	8.74 ± 0.18	9.28 ± 0.26	< 0.001
HbA1c (%)	4.9 ± 0.3	4.9 ± 0.2	4.9 ± 0.3	5.6 ± 0.1	5.6 ± 0.1	< 0.001
ALT (U/L)	20 ± 18	22 ± 19	18 ± 15	20 ± 22	20 ± 13	< 0.001
AST (U/L)	20 ± 9	21 ± 9	19 ± 7	20 ± 11	19 ± 8	< 0.001
TBIL (μmol/L)	7.3 ± 3.1	7.4 ± 3.1	7.2 ± 3.0	6.6 ± 2.3	6.3 ± 2.3	< 0.001
Cre (μmol/L)	51 ± 6	51 ± 6	51 ± 6	51 ± 6	53 ± 8	0.070
BUN (mmol/L)	2.8 ± 0.6	2.8 ± 0.7	2.7 ± 0.6	2.7 ± 0.7	2.7 ± 0.6	< 0.001
UA (μmol/L)	234 ± 46	230 ± 44	242 ± 47	227 ± 44	246 ± 55	< 0.001

Values were expressed as mean ± standard deviation (SD) or n (%). TyG: triglyceride-glucose; HbA1c: glycated hemoglobin A1c; BMI: body mass index; GWG: gestational weight gain; FPG: fasting plasma glucose; PG: plasma glucose; TC: total cholesterol; TG: triglyceride; HDL-c: high-density lipoprotein-cholesterol; LDL-c: low-density lipoprotein-cholesterol; ALT: alanine transaminase; AST: aspartate transaminase; TBIL: total bilirubin; Cre: creatinine; Urea: blood urea nitrogen; UA: uric acid.

Table II. Demographic characteristics of pregnant women with and without preeclampsia.

Characteristic	Preeclampsia	Non-preeclampsia	*p*-value
N	106	6,692	
Maternal age (years)	30.87 ± 4.30	30.60 ± 4.15	0.510
Preconception BMI (kg/m^2)	22.38 ± 3.11	20.64 ± 2.62	< 0.001
Education, n (%)			0.791
Primary or below	0 (0.00)	22 (0.33)	
Middle school	16 (15.09)	929 (13.88)	
College or above	90 (84.91)	5,741 (85.79)	
GWG (kg)	16.29 ± 5.17	14.30 ± 4.47	< 0.001
Birth weight (g)	2,958 ± 684	3,317 ± 425	< 0.001
Gravidity, n (%)			0.001
1	60 (56.61)	2,634 (39.36)	
2	25 (23.58)	2,026 (30.27)	
≥ 3	21 (19.81)	2,032 (30.37)	
Parity, n (%)			< 0.001
Nullipara	87 (82.08)	4,091 (61.13)	
Multipara	19 (17.92)	2,601 (38.87)	
TyG index	9.01 ± 0.38	8.85 ± 0.33	< 0.001
HbA1c (%)	5.1 ± 0.3	4.9 ± 0.3	< 0.001

Values were expressed as mean ± standard deviation (SD) or n (%). BMI: body mass index; GWG: gestational weight gain; TyG: triglyceride-glucose index; HbA1c: glycated hemoglobin A1c.

Upon examining the combined effects of the TyG index and HbA1c, it was observed that the normal TyG index + HbA1c group (G1) displayed the lowest preeclampsia incidence (43/4,459, 0.96%). In contrast, the high TyG index + high HbA1c group (G4) exhibited the highest incidence (7/92, 7.61%) (Figure 2). The difference in preeclampsia incidence between G1 and G4 was statistically significant ($p < 0.001$).

ROC Curve Analyses of the TyG Index and HbA1c to Predict Preeclampsia

To assess the predictive value of the TyG index and HbA1c levels, we analyzed sensitivity and specificity using ROC curves. The AUC for the TyG index in predicting preeclampsia was 0.628 (0.616, 0.639), while the AUC for HbA1c was 0.662 (0.650, 0.673), both of which demonstrated significant areas under the curve ($p < 0.001$). Furthermore, when combining the TyG index with HbA1c, the AUC reached its highest value of 0.689 (0.677, 0.700), surpassing the individual AUCs for the TyG index or HbA1c alone. The AUCs suggest satisfactory accuracy and specificity, as depicted in Figure 3 and Table III. Using an HbA1c cut-off of 5.4, the sensitivity and specificity for predicting preeclampsia were 11.32% and 97.44%, respectively. Employing a TyG index cut-off of 8.98 resulted in a sensitivity of 54.72% and specificity of 67.27% for predicting preeclampsia. When the TyG index and HbA1c were combined, the sensitivity reached 59.43%, while the specificity reached 65.99%. Table III and Figure 3 present the results of the ROC curve analysis and the selected cut-off points for predicting preeclampsia.

Association Between the TyG Index and HbA1c and the Risk of Developing Preeclampsia

On univariate analysis, pregnant women with a higher TyG index alone demonstrated a significant association with preeclampsia [OR: 2.488 (1.653, 3.746)] ($p < 0.001$) compared to those with a normal TyG index + normal HbA1c. Similarly, a higher HbA1c alone was also significantly associated with preeclampsia [OR: 5.971 (2.308, 15.444)] ($p < 0.001$). Interestingly, pregnant women with both high TyG index and high HbA1c had the highest significantly increased risk of developing preeclampsia [OR: 8.547 (3.698, 19.340)] ($p < 0.001$) compared to those with a normal TyG index + normal HbA1c, as presented in Table IV.

To ascertain the stability of this relationship across various conditions, we constructed two additional models for verification. In model 1, the only variables adjusted for were basic characteristics, in-

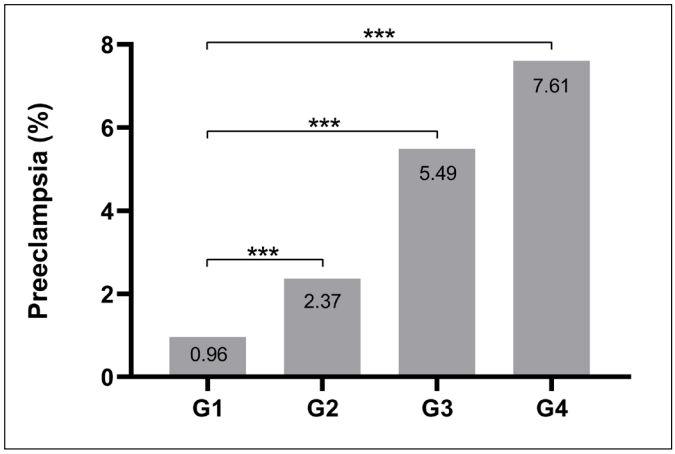

Figure 2. Incidence of preeclampsia in four groups based on the TyG index and HbA1c level. G1: normal TyG index + normal HbA1c; G2: only high TyG index; G3: only high HbA1c; G4: high TyG index + high HbA1c. (***$p < 0.001$).

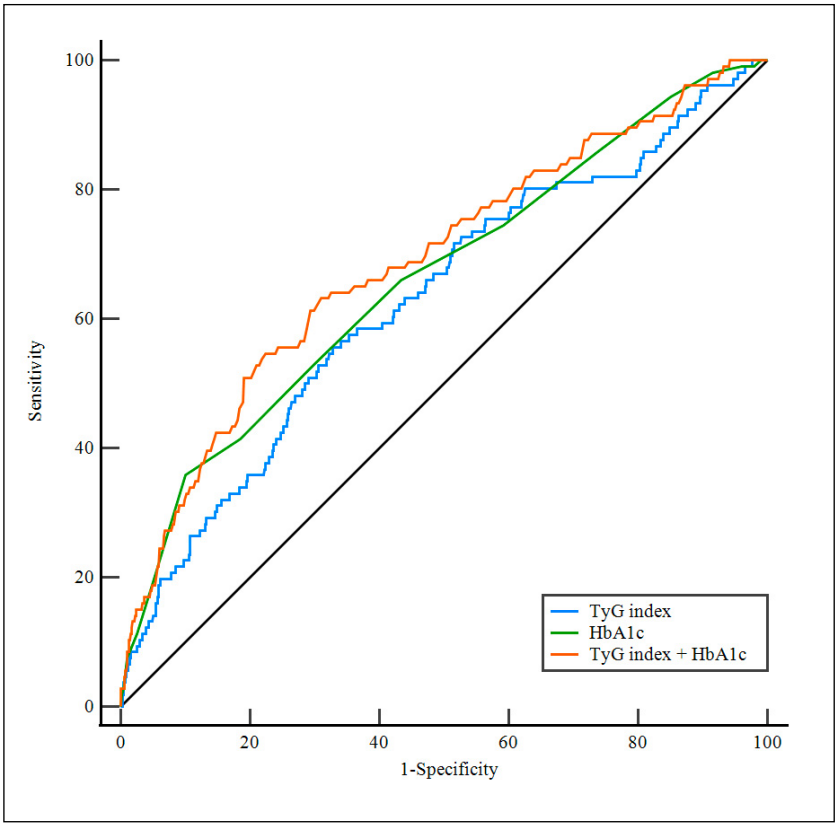

Figure 3. ROC curve analyses of the TyG index and HbA1c to predict preeclampsia.

cluding maternal age and preconception BMI. This logistic regression analysis showed that a higher TyG index alone, a higher HbA1c alone, or both a high TyG index and HbA1c significantly correlated with the risk of preeclampsia (all $p < 0.001$). Then, in model 2, education, GWG, gravidity, and parity were added as covariates, alongside maternal age and preconception BMI. Similar results were obtained for this model, showing that pregnant women with either a higher TyG index [adjusted OR: 2.216 (1.458, 3.368), $p < 0.001$], a higher HbA1c [adjusted OR: 4.528 (1.667, 12.301), $p = 0.003$], or both high TyG index and HbA1c had higher adjusted OR [5.601 (2.308, 13.593), $p < 0.001$] for developing preeclampsia compared to the reference group with normal TyG index and normal HbA1c.

Table III. Performance of the TyG index and HbA1c to predict preeclampsia.

Subsets	AUC (95% CI)	*p*-value	Sensitivity	Specificity	Cut-off point
TyG index	0.628 (0.616, 0.639)	< 0.001	54.72	67.27	8.98
HbA1c	0.662 (0.650, 0.673)	< 0.001	11.32	97.44	5.4
HbA1c + TyG index	0.689 (0.677, 0.700)	< 0.001	59.43	65.99	-

AUC: the area under the curve; TyG: triglyceride-glucose index; HbA1c: glycated hemoglobin A1c.

Association Between the TyG Index and HbA1c and Preeclampsia in Different Maternal Age and Preconception BMI

Advanced maternal age and being overweight are two well-recognized risk factors associated with preeclampsia. To investigate their impact further, subgroup analyses by maternal age and preconception BMI were conducted, as presented in Figure 4. The findings reveal that women aged < 35 years or ≥ 35 years with high TyG index + high HbA1c had significantly positive associations with developing preeclampsia [adjusted OR 7.234, 95% CI 2.647-19.772, $p < 0.001$; adjusted OR 8.245, 95% CI 1.387-49.021, $p < 0.001$] compared to their counterparts with a normal TyG index + normal HbA1c. Notably, a more pronounced association was observed in women aged ≥ 35 years. Furthermore, preconception BMI with a high TyG index + high HbA1c was significantly associated with an increased risk of developing preeclampsia in women with a normal preconception BMI. It is worth noting that these associations were not observed in overweight and obese women.

Discussion

This retrospective study first demonstrated a strong relationship between the TyG index, HbA1c, and preeclampsia in Chinese women with normal glucose tolerance. A total of 6,798 women was included, with a preeclampsia incidence of 1.56%. The study found that patients with preeclampsia had higher TyG index and HbA1c levels, and the incidence was higher when both factors were elevated. The combined TyG index and HbA1c had an AUC of 0.689 in predicting preeclampsia, with a sensitivity of 59.43% and specificity of 65.99%. Even after adjusting for potential confounding factors, the rate of preeclampsia remained significantly higher. These findings suggest that the TyG index and HbA1c assessments are simple yet valuable indicators of preeclampsia, and their combination has a more significant impact on the likelihood of developing preeclampsia than each factor alone.

GDM is a frequently encountered complication during pregnancy, and its prevalence is increasing day by day worldwide[25]. It poses severe neonatal and maternal health risks, with short- and long-term adverse complications. Preeclampsia, which GDM can induce, is a common pregnancy-related complication. Studies[16,17] have shown that GDM is an independent risk factor for preeclampsia, even after adjusting for confounding factors. In a retrospective study[17] of 647,392 pregnancies, women with GDM had an increased risk of preeclampsia (adjusted OR 1.29; 95% CI 1.19-1.41). A retrospective population-based Cohort study[26-28] in multiple countries also supports the independent association between GDM and the occurrence of preeclampsia. Preeclampsia remains a significant cause of maternal mortality and morbidity, leading to acute kidney injury, liver injury, neurologic complications, pulmonary edema, hematologic complications, and uteroplacental dysfunction[1]. Furthermore, preeclampsia is associated with an increased risk of adverse pregnancy outcomes in the short-term and long-arching. Women who survive preeclampsia have reduced life expectancy, with increased risks of cardiovascular and cerebrovascular disease, stroke, and diabetes[3,29,30]. Offspring from preeclamptic pregnancies also face higher risks of perinatal death, preterm birth, metabolic disease, cardiovascular disease, and neurodevelopmental delay later in life[3,29], leading to lifelong consequences for the child[31,32]. Currently, the only cure for preeclampsia is the delivery of the placenta and fetus[33].

In China, the prevalence of preeclampsia was reported to be 2.2%[34], slightly higher than the incidence rate (1.56%) observed in our study. This discrepancy may be due to our exclusion of certain risk factors, such as GDM, chronic hypertension, pregestational diabetes mellitus, multiple gestations, polycystic ovary syndrome, and autoimmune diseases like antiphospholipid syndrome and systemic lupus erythematosus[16,35,36].

Table IV. Association between the TyG index and HbA1c and the risk of developing preeclampsia.

	Normal TyG index + HbA1c, G1	Only high TyG index, G2	Only high HbA1c, G3	High Tyg index + HbA1c, G4	*p*-value#	*p*-value*	*p*-value**
N	43	51	5	7			
Model 0, OR (95% CI)	1.00 (Ref.)	2.488 (1.653, 3.746)	5.971 (2.308, 15.444)	8.547 (3.698, 19.340)	< 0.001	< 0.001	< 0.001
Model 1, OR (95% CI)	1.00 (Ref.)	2.196 (1.448, 3.330)	4.556 (1.724, 12.040)	5.885 (2.495, 13.878)	< 0.001	0.002	< 0.001
Model 2, OR (95% CI)	1.00 (Ref.)	2.216 (1.458, 3.368)	4.528 (1.667, 12.301)	5.601 (2.308, 13.593)	< 0.001	0.003	< 0.001

Model 0: unadjusted; Model 1: adjusted for maternal age and BMI; Model 2: adjusted for maternal age, preconception BMI, education, gestational weight gain, gravidity, parity. *p*-value#: G2 *vs.* G1; *p*-value*: G3 *vs.* G1; *p*-value**: G4 *vs.* G1. TyG: triglyceride-glucose index; HbA1c: glycated hemoglobin A1c; OR: odds ratio.

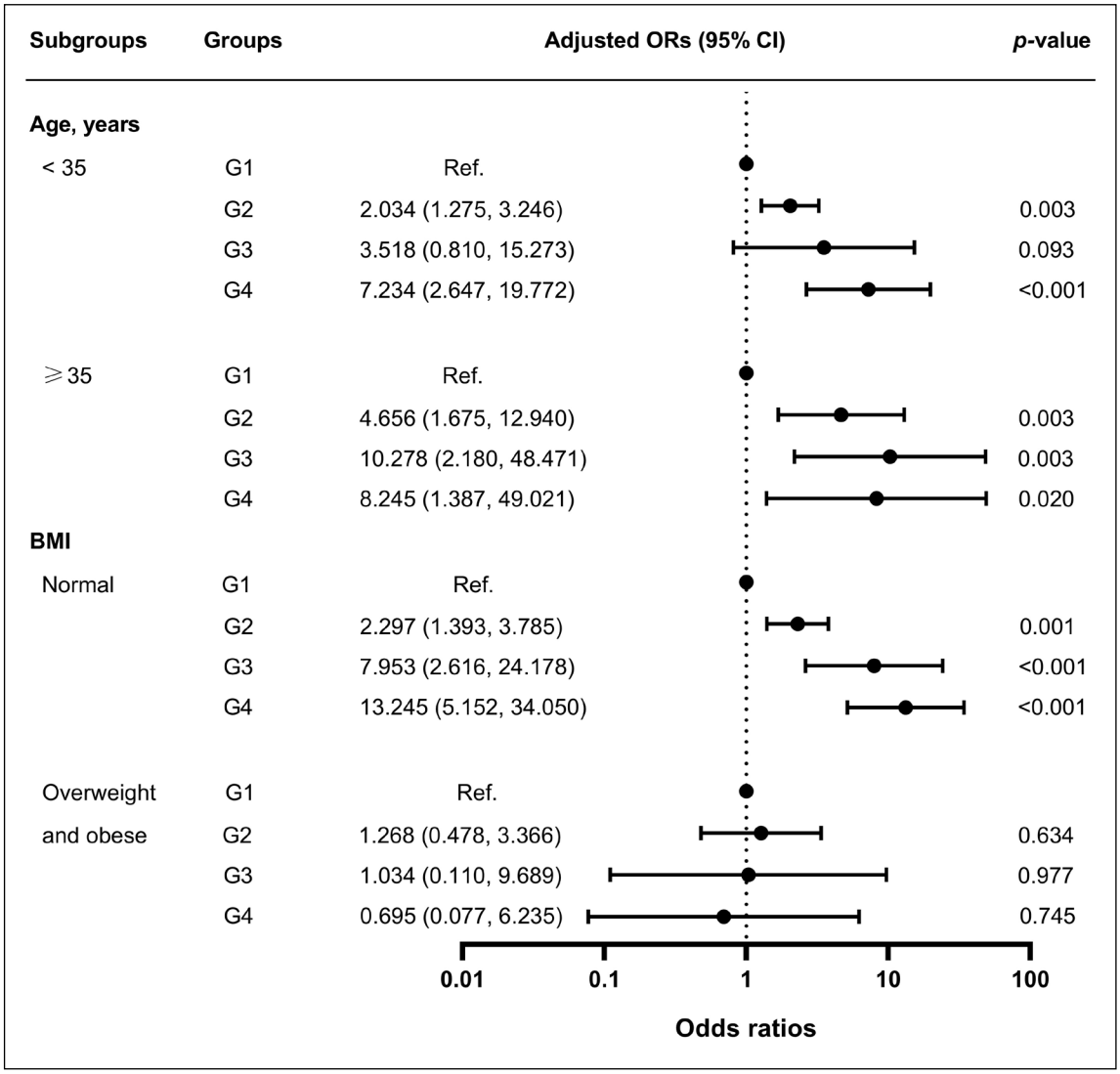

Figure 4. Subgroup analysis exploring the association between TyG index and HbA1c with the risk of preeclampsia. Models were adjusted for maternal age, preconception BMI, education, gestational weight gain, gravidity, and parity.

It is worth noting that previous research[37] has demonstrated a significant reduction in the incidence of severe perinatal complications and preeclampsia through the treatment and management of GDM. Unfortunately, a meta-analysis[38] unveiled that GDM affected up to 14.8% of the Chinese population, indicating that China, with its vast population, likely has the highest number of GDM patients globally. Furthermore, there has been an upward trend in GDM incidence in China, resulting in increased GDM complications, including preeclampsia. Nevertheless, with increased awareness of prenatal health, robust medical service systems, and lifestyle adjustments, doctors consistently develop personalized treatment plans for GDM patients, incorporating measures like dietary control, regular exercise, and insulin intervention. Consequently, this approach effectively manages GDM-related complications, including preeclampsia. However, non-GDM patients, who constitute a larger population, are often overlooked, with over 300 million women of childbearing age reported in China's seventh national population census. Hence, identifying non-GDM women at higher risk holds significant clinical value since appropriate management can positively impact maternal and fetal outcomes.

It has been observed[7,39] that insulin resistance may increase the risk of developing preeclampsia. Furthermore, poor glycemic control has been found[40,41] to play a crucial role in the development of preeclampsia, as demonstrated by the strong correlation between HbA1c levels and the risk of preeclampsia. Therefore, insulin resistance and hyperglycemia are significant contributing factors in the development of preeclampsia. The association between these factors is likely due to the over-activation of insulin resistance during pregnancy, leading to placental hypoxia and ischemia, damage to vascular endothelial cells, promotion of endothelial dysfunction, disruption of lipid metabolism, increased oxidative stress, and ultimately resulting in the distinct symptoms of preeclampsia[42,43]. Moreover, hyperglycemia can escalate the risk of preeclampsia by fostering a pro-inflammatory environment. This is achieved through two key mechanisms: the formation of advanced glycation end products and the metabolism of immune cells with a pro-inflammatory phenotype. Both of these mechanisms are influenced by elevated serum glucose levels[39,44].

The TyG index, derived from fasting triglyceride levels and plasma glucose, has emerged as a novel marker for identifying insulin resistance. Compared to the gold standard for IR assessment, the hyperinsulinemic-euglycemic clamp (HIEC)[45], using the TyG index, solves the problem of being time-consuming, costly, and technically demanding. Furthermore, research[46] has reported that the TyG index correlated better with the HIEC than the homeostasis model assessment of insulin resistance (HOMA-IR), the most commonly used measure in clinical settings. Several studies[47-49] have also shown that the TyG index outperforms other measures in identifying insulin resistance. Our study revealed a significantly higher TyG index in the preeclampsia group than in the non-preeclampsia group ($p < 0.001$). Additionally, the incidence of preeclampsia among pregnant women in the study was 1.56% (106/6,798) and increased progressively from Tertile 1 to Tertile 3, with an incidence of 0.92%, 1.19%, and 2.58%, respectively. The above findings suggest that a higher TyG index may be a potentially useful biomarker for predicting preeclampsia.

HbA1c summarized glycemic levels over the past 2-3 months. It has become the standard for assessing glycemic control in patients with diabetes after the American Diabetes Association (ADA)[50] recommended its use in 1988. For several decades, the diagnosis of diabetes relied on glucose criteria using fasting glucose, random glucose, or the 75-g OGTT. Although initially not endorsed for the diagnosis of diabetes, improved assays led to the ADA validating the use of HbA1c as a diagnostic criterion for diabetes in 2010 at a cut-off of $\geq 6.5\%$[51]. Consequently, our study excluded pregnant women with abnormal OGTT results and those with HbA1c levels exceeding 6.5%. Additionally, measuring HbA1c offers several advantages, including convenience without pre-test preparation, sample stability upon collection, and reduced day-to-day variability. However, various factors can influence its accuracy, resulting in increased cost and low sensitivity[51]. HbA1c is not sensitive to glucose level variations and can be affected by diseases that impact glucose metabolism, such as hyperthyroidism, Cushing's syndrome, polycystic ovary syndrome, and pancreatitis. To address these concerns, we excluded common glucose-affecting diseases from the study. In addition, our research found that HbA1c levels were significantly higher in the preeclampsia group than in the non-preeclampsia group ($p < 0.001$), and the incidence of preeclampsia increased with rising HbA1c ($p < 0.001$). However, physiological changes during pregnancy, such as high erythrocyte turnover and hemodilution[52], and HbA1c levels in pregnant women were lower than in non-pregnant women. For instance, our study revealed that only 2.69% (183/6,798) of pregnant women had an HbA1c level of > 5.4%, with over 90% of the data falling between 4.5% and 5.4% (data not shown). The above results indirectly suggest that HbA1c alone is unsuitable due to its limited sensitivity and specificity. In summary, while an increase in HbA1c levels may hold clinical value in detecting preeclampsia in pregnant women, it needs to be combined with other indicators to improve the overall detection rate of preeclampsia.

Given the significant impact of preeclampsia on maternal and perinatal morbidity and mortality worldwide, developing practical predictive test for preeclampsia is urgently needed to enable early diagnosis, targeted surveillance, and timely intervention. However, currently, available options are limited. Various biochemical markers, such as C-reactive protein (CRP), interleukin (IL)-6, Tumor necrosis factor (TNF)-α, and B-type natriuretic peptides, have been studied[37] as potential predictors of preeclampsia, but none have been adopted as practical clinical markers. Although soluble fms-like tyrosine kinase 1 (sFLT-1) and placental growth factor (PlGF) are now being used

clinically in cases of suspected preeclampsia, their sensitivity is modest despite having a high negative predictive value. As a result, there has been a concerted effort to identify novel biomarkers that could improve prediction[53]. We performed ROC analysis for the TyG index and HbA1c in the present study. The results demonstrated that the AUC for the TyG index in predicting preeclampsia is 0.628 (0.616, 0.639), while the AUC for HbA1c is 0.662 (0.650, 0.673), both of which indicate significant areas under the curve ($p < 0.001$). Moreover, when the TyG index and HbA1c were combined, the maximum AUC value reached 0.689 with a confidence interval of 0.677 to 0.700 ($p < 0.001$). This combined value was higher than the individual AUCs for the TyG index and HbA1c. Additionally, among these indexes, the combined TyG index + HbA1c achieved a maximum sensitivity of 59.43%, followed by the TyG index at 54.72% and HbA1c at 11.32%. These results indicate that the combined TyG index and HbA1c demonstrate significant clinical value in accurately and specifically predicting preeclampsia.

As we all know, knowing the optimal time to intervene and identifying risk factors that predispose women to preeclampsia would greatly benefit the diagnostic work-up and potential prevention efforts in these cases. MacDonald et al[53] have pointed out several significant issues with current markers of preeclampsia, such as uncertainty regarding the optimal time point in the pregnancy for screening. Considering this issue, our study offers an advantage by utilizing the TyG index and HbA1c as indicators at 24-28 weeks gestation. This timeframe aligns with the typical timing of glucose tolerance tests and is closer to when preeclampsia is likely to develop. Since both indicators are already used in pregnancy testing, there is no additional financial burden for pregnant women. Therefore, our study holds clinical value as one of its advantages, but further validation is required to confirm the accuracy of our findings' extrapolation.

While our understanding of the complex pathophysiology of preeclampsia is improving, accurate prediction and uniform prevention continue to elude us. The prospect of effectively predicting preeclampsia is driven by the desire to identify women at high risk of developing the condition so that necessary measures can be initiated early to improve placentation and reduce the prevalence of the disease. Moreover, identifying an "at-risk" group will facilitate tailored prenatal surveillance to anticipate and recognize the onset of the clinical syndrome and manage it promptly. In our study, logistic regression analysis revealed that the TyG index and HbA1c were independently and positively correlated with preeclampsia after adjusting for potential confounders. Moreover, our study indicates that pregnant women meeting the criteria for both a high TyG index and high HbA1c face the highest risk of preeclampsia compared to women with normal TyG index and HbA1c values. This observation holds whether in model 0 (unadjusted, OR: 8.547, $p < 0.001$), in model 1 (adjusted for maternal age and BMI, OR: 5.885, $p < 0.001$), or in model 2 (adjusted for maternal age, preconception BMI, education, gestational weight gain, gravidity, parity, OR: 5.601, $p < 0.001$). To our knowledge, there have been no previous studies on the combined use of the TyG index and HbA1c to assess the risk of preeclampsia in pregnant women. However, this approach may provide a novel direction for further investigations into preeclampsia.

In addition, advanced maternal age and obesity are two common risk factors associated with developing preeclampsia and have been extensively studied. Therefore, we stratified the analysis based on maternal age and preconception BMI. Regarding maternal age, we found that the risk of preeclampsia in the high TyG index + high HbA1c group was significantly higher compared to the normal HbA1c + normal group, regardless of whether the pregnant women were younger (aged < 35) or of advanced maternal age (aged ≥ 35) ($p < 0.001$). Notably, these associations were more pronounced in women aged ≥ 35 years. These results suggest that having a high TyG index + high HbA1c indicates a high risk of preeclampsia regardless of age and should be taken seriously. Due to the limited number of overweight and obese women before pregnancy in this study, we combined them for analysis. Interestingly, in the normal preconception BMI group, the risk of preeclampsia in the high TyG index + high HbA1c group was significantly higher compared to the normal HbA1c + normal group. However, we did not observe these associations in overweight and obese women. Further research is needed to confirm whether the small number of overweight/obese individuals led to biased results.

To the best of our knowledge, the present study appears to be the first to comprehensively report that the TyG index and HbA1c are independently associated with an increased likelihood of preeclampsia. Moreover, our findings indicate that combining the TyG index and HbA1c can en-

hance preeclampsia detection rate and risk assessment in GDM-negative women. However, several limitations of our study must be considered. Firstly, we need to collect adequate information about our participants, such as their dietary and physical activity factors, medical interventions, or other unknown and complex factors that could act as confounders. Secondly, our analysis was based on a small sample size from a single center, which may have introduced selection bias and limited the generalizability of the results. Therefore, further multicenter and future research is required to investigate the utility of the TyG index and HbA1c in predicting preeclampsia in different ethnicities and gestational ages. Thirdly, due to the retrospective nature of our study design, we could not compare the TyG index and HbA1c with existing markers such as sFlt-1 and PlGF, as these tests are not typically included in routine pregnancy examinations.

Conclusions

Pregnant women without GDM constitute a larger population often overlooked by the healthcare system and even the women themselves. The present study focused on this specific population and discovered that the incidence of preeclampsia increased in correlation with the TyG index and HbA1c levels. Moreover, when both the TyG index and HbA1c were elevated, the incidence and risk of preeclampsia were significantly higher. These findings offer valuable insights to healthcare providers, enabling them to identify women in the "at-risk" groups and implement tailored prenatal surveillance, facilitating early recognition and prompt management of preeclampsia.

Conflict of Interest
The authors declare that they have no conflict of interest.

Data Availability
The data are available from the corresponding author upon reasonable request.

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Authors' Contributions
All authors contributed to data collection, analysis, and participated in drafting or revising articles.

Ethical Approval
This research was reviewed and approved by the Ethics Committee of Women's Hospital, Zhejiang University School of Medicine (with the approval number: IRB-20220357-R).

Informed Consent
The Ethics Committee of Women's Hospital, Zhejiang University School of Medicine approved the informed consent exemption due to anonymous patient records.

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