

# The Predictive Effects of Atherogenic Indices and Remnant Cholesterol on Gestational Diabetes Mellitus Risk

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**Purpose:** This study aimed to investigate the predictive effects of atherogenic indices and remnant cholesterol on the risk of GDM.

**Patients and Methods:** This observational study was conducted based on the Hospital's clinical information system. A total of 6619 participants including 2054 GDM patients and 4565 controls were obtained. Serum lipid data, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were collected. Atherogenic indices including TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C, and remnant cholesterol were regarded as independent variables, and GDM was regarded as the dependent variable. Logistic regression analyses, nomogram analysis, decision curve analysis (DCA), and restricted cubic spline (RCS) analysis were applied to explore the impact of atherogenic indices and remnant cholesterol on GDM.

**Results:** The prevalence of GDM was 31.03% in this study. In comparison to the 1st quartile, the 4th quartile levels of atherogenic indices and remnant cholesterols were significantly associated with increased risks of gestational diabetes mellitus (GDM). The odds ratios (OR) for these associations were as follows: OR = 1.66 (95% CI: 1.41, 1.96) for TG/HDL-C; OR = 1.47 (95% CI: 1.24, 1.73) for TC/HDL-C; OR = 1.47 (95% CI: 1.24, 1.73) for LDL-C/HDL-C; and OR = 1.39 (95% CI: 1.18, 1.64) for remnant cholesterol. The DCA results confirmed the reliable clinical utility of GDM prediction by atherogenic indices and remnant cholesterol. The RCS regression analysis revealed the nonlinear relationships between the atherogenic indices, remnant cholesterol and GDM.

**Conclusion:** This study revealed the potential predictive effects of atherogenic indices and remnant cholesterol on GDM. These findings underscore the potential of routine lipid testing as a cost-effective strategy for the early identification and management of GDM in clinical settings.

**Keywords:** gestational diabetes mellitus, lipid index, atherogenic index, remnant cholesterol, dyslipidemia

## Introduction

Gestational diabetes mellitus (GDM) refers to any form of glucose intolerance with onset or first recognition in the perinatal period.<sup>1</sup> Various studies have revealed that GDM could contribute to adverse pregnancy outcomes for both mothers and their offspring. For mothers, GDM patients are at higher risks of subsequent GDM, cardiovascular disease, dysglycemia, and type 2 diabetes.<sup>2-4</sup> For their offspring, GDM could bring out neonatal macrosomia, childhood obesity and metabolic syndrome.<sup>5</sup> Moreover, the majority of pregnant women who experience GDM are young, which could affect their life for a longer time.

The prevalence of GDM is 1%–28% worldwide, with significant variations observed across different populations.<sup>6</sup> These differences can be attributed to several factors, including geographic and ethnic predisposition, screening strategies and diagnostic criteria, as well as the varying risk factors.<sup>7</sup> With improvements in living conditions and strengthened nutrition during pregnancy, the prevalence of GDM is increasing year by year.<sup>8</sup> Although there are plenty of studies have explored the risk factors of GDM on genetic, lifestyle, diet, and other factors, the pathogenesis of GDM is still unclear. Current studies emphasized placental hormone-driven insulin resistance,  $\beta$ -cell dysfunction, and low-grade inflammation may collectively contribute to GDM development.<sup>9</sup>

Population GDM risk is increasing with the high prevalence of obesity. To provide sufficient energy for fetal growth, blood lipid levels rise as pregnancy progresses.<sup>10</sup> Lipid metabolism is closely related to glycometabolism, which is regulated by insulin. Therefore, dyslipidemia has the potential to induce insulin resistance and the occurrence of GDM. Previous studies have demonstrated the relationships between lipid biomarkers and the risk of GDM. A meta-analysis based on 292 studies interpreted that blood triglyceride (TG) concentrations were significantly different between mothers with GDM and mothers without GDM.<sup>11</sup> A few studies showed that elevated serum TG levels and/or decreased high-density lipoprotein cholesterol (HDL-C) could contribute to the development of GDM.<sup>12–16</sup> These studies prompted that TG/HDL-C could be potential indicators of GDM, which is one of the atherogenic indexes.<sup>17</sup>

Currently, little information has been given to the risk of GDM derived from atherogenic indices,<sup>18</sup> which were originally calculated to evaluate the risk of atherosclerosis.<sup>19</sup> Notably, another indicator of dyslipidemia of remnant cholesterol, which refers to the cholesterol content within triglyceride-rich lipoprotein remnants (including very-low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL], and chylomicron remnants), may relate to the occurrence GDM. The connection between remnant cholesterol and the risk of type 2 diabetes has been well-documented, but evidence regarding its role in GDM risk remains insufficient.<sup>20</sup> While emerging studies have indicated a positive association between remnant cholesterol and GDM, none have specifically examined the predictive effect of remnant cholesterol on GDM risk.<sup>21–23</sup> Moreover, although dyslipidemia is a potential indicator of GDM as mentioned above, GDM patients might have abnormal atherogenic indices and remnant cholesterol but normal serum lipids at the same time. Therefore, it is still necessary to apply atherogenic indices for the assessment of GDM risk. To fill this gap, this study aimed to investigate the predictive effects of atherogenic indices and remnant cholesterol on the risk of GDM.

## Materials and Methods

### Study Population

This retrospective study was conducted at the Maternal and Child Health Hospital of Hubei Province, which is one of the largest tertiary hospitals focusing on maternal and child health care in Wuhan City, China. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province (2021IECXM005). First, the entire list of inpatients who delivered at this hospital from December 2020 to March 2022 was exported from the clinical information system. Second, patients whose outpatient examination data were complete were reviewed and selected. Complete data were defined as containing the essential independent variables of blood lipid indicators and the outcome variable of GDM diagnosis. There were a total of 6946 inpatients who underwent blood lipid examination in the 1st (0–13<sup>+6</sup> weeks) or 2nd (14–27<sup>+6</sup> weeks) trimester. Third, after removing missing maternal age (essential covariates, N = 26), missing family history of diabetes (essential covariates, N = 33), missing records of in vitro fertilization (IVF) (essential covariates, N = 4), missing body mass index (BMI) (essential covariates, N = 32), multiple pregnancies (have different risk of GDM compared to singleton pregnancies, N = 135), missing oral glucose tolerance test (OGTT) results (outcome measurement, N = 85), and type 1 or type 2 diabetes (pre-gestational dysglycemia confounders, N = 12), 6619 participants were included in this study.

### Data Collection

Clinical data were exported from the Hospital's electronic medical records from the clinical information system. General personal information was collected including maternal age, family history of diabetes (one or more clinically diagnosed diabetes patients within three generations), reproductive history, gestational weight gain, IVF, fasting plasma glucose (FPG) in the 1st

trimester of pregnancy, and pre-pregnancy BMI (calculated by self-reported pre-pregnancy weight and height). Specifically, pre-pregnancy BMI was divided into four categories according to the Chinese standard of obesity: underweight (BMI < 18.5), healthy weight (18.5–23.9), overweight (24–27.9), and obese ( $\geq 28$ ). Gestational weight gain was classified as insufficient, normal, or excessive according to the standard of recommendation for weight gain during pregnancy released by the Health Industry Standards of the People's Republic of China.<sup>24</sup>

Serum lipids, including TG, total cholesterol (TC), HDL-C, and low-density lipoprotein cholesterol (LDL-C) were obtained during the 1st or 2nd trimester of pregnancy. Atherogenic indices including TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C, and remnant cholesterol were regarded as independent variables. All of the independent variables were classified by four interquartile ranges (IQRs).

The dependent variable of GDM was diagnosed according to the recommendations of the International Association of the Diabetes and Pregnancy Study Groups Consensus Panel.<sup>25</sup> A 75 g OGTT was performed at 24–28 weeks of gestation on the following criteria: fasting plasma glucose  $\geq 5.1$  mmol/L, and/or 1-hour plasma glucose  $\geq 10.0$  mmol/L, and/or 2-hour plasma glucose  $\geq 8.5$  mmol/L. GDM is diagnosed if one or more of the following glucose values is exceeded.

## Data Analysis

The normality of continuous independent variables was examined by Shapiro–Wilk tests. Nonnormal continuous variables were classified into four categories by IQR or summarized as medium (P25, P75). The differences in the prevalence of GDM among subgroups of general personal variables and independent variables were examined by Chi-square tests for categorical variables and Wilcoxon–Mann–Whitney tests for continuous variables. Logistic regression analyses were performed to examine the associations between the independent variables and the risk of GDM. First, the risk of GDM was assessed by several unadjusted logistic regression models for the independent variables, including TC, TG, HDL-C, LDL-C, TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. Second, based on unadjusted logistic regression analysis, the associations between serum lipids and GDM were further adjusted for general personal variables including maternal age, family history of diabetes, parity history, pre-pregnancy BMI, IVF, FPG, and gestational weight gain. To explore the causal relationship between atherogenic indices, remnant cholesterol, and the risk of GDM, stratified analysis of 1st trimester and 2nd trimester were conducted in this study. The normality examinations, Chi-square tests, Wilcoxon–Mann–Whitney tests, and logistic regression analysis were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Furthermore, the risk of GDM was predicted by nomogram analysis and decision curve analysis (DCA) to gauge the net benefit of identifying high-risk patients that ought to have intervention and the net reduction of unnecessary interventions. The potential nonlinear relationships between the atherogenic indices, remnant cholesterol and the risk of GDM were examined by the restricted cubic splines (RCS). We adopted an RCS with 4 knots, and the media of the atherogenic indices and remnant cholesterols were used as references to obtain the ORs. Nomogram analysis, DCA, and RCS regression analysis were performed with R 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided  $P < 0.05$  was regarded as statistically significant.

## Results

The results showed that the prevalence of GDM was 31.03% (Table 1). Nearly half of the participants were mothers aged 30–34 years (45.34%), and the median age of the participants was 31 years. The prevalence of GDM among the subgroups stratified by age was significantly different ( $P < 0.0001$ ). Compared with mothers without a family history of diabetes, women with a family history of diabetes had a significantly higher prevalence of GDM (52.58% vs 29.91%,  $P < 0.0001$ ). Compared with primiparous women, multiparas had a higher prevalence of GDM (34.06% vs 29.53%,  $P = 0.0002$ ). The prevalence of GDM was higher among mothers who were fertilized by IVF (42.52% vs 30.57%,  $P < 0.0001$ ). The higher the pre-pregnancy BMI of participants was, the greater the corresponding prevalence of GDM as well ( $P < 0.0001$ ). Furthermore, the prevalence of GDM was higher among mothers with insufficient gestational weight gain than those with excessive gestational weight gain (52.00% vs 23.42%,  $P < 0.0001$ ).

The serum atherogenic indices and remnant cholesterols were classified into four categories by IQR, and the differences in the continuity indicators were examined between the GDM group and the control group (Table 2). The prevalence of GDM among the Q4 group in terms of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol

**Table 1** General Personal Characteristics Between Gestational Diabetes Mellitus and Control Group

Variables	GDM	Control Group	Total	$\chi^2$	P
<b>Age (years)</b>				145.25	<0.0001
<30	590(23.38)	1934(76.62)	2524(38.13)		
30~34	997(33.22)	2004(66.78)	3001(45.34)		
≥34	467(42.69)	627(57.31)	1094(16.53)		
Median (P25, P75)	32(29,34)	30(28,33)	31(28,33)	–	<0.0001
<b>Family history of diabetes</b>				75.09	<0.0001
No	1881(29.91)	4409(70.09)	6290(95.03)		
Yes	173(52.58)	156(47.42)	329(4.97)		
<b>Parity history</b>				14.08	0.0002
I	1307(29.53)	3119(70.47)	4426(66.87)		
>I	747(34.06)	1446(65.94)	2193(33.13)		
<b>IVF</b>				16.28	<0.0001
NO	1946(30.57)	4419(69.43)	6365(96.16)		
Yes	108(42.52)	146(57.48)	254(3.84)		
<b>Pre-pregnancy BMI</b>				223.64	<0.0001
<18.5	185(18.76)	801(81.24)	986(14.90)		
18.5~23.9	1321(29.39)	3173(70.61)	4494(67.90)		
24.0~27.9	433(46.96)	489(53.04)	922(13.93)		
≥28	115(53.00)	102(47.00)	217(3.28)		
Median (P25, P75)	21.77(19.92,24.06)	20.55(19.05,22.31)	20.89(19.23,22.86)	–	<0.0001
<b>Gestational weight gain</b>				68.78	<0.0001
Insufficient	429(52.00)	396(48.00)	825(12.48)		
Normal	999(31.97)	2126(68.03)	3125(47.28)		
Excessive	623(23.42)	2037(76.58)	2660(40.24)		
Median (P25, P75)	11.00(8.0,14.50)	14.00(11.00,17.00)	13.00(10.00,16.00)	–	<0.0001
<b>Fasting plasma glucose</b>				408.52	<0.0001
Low	4(80.00)	1(20.00)	5(0.08)		
Normal	1180(24.19)	3699(75.81)	4879(73.71)		
High	870(50.14)	865(49.86)	1735(26.21)		
Median (P25, P75)	5.02(4.84,5.28)	4.87(4.65,5.04)	4.90(4.69,5.12)	–	<0.0001
<b>Total</b>	2054(31.03)	4565(68.97)	6619(100)	–	–

**Table 2** Atherogenic Indices and Remnant Cholesterol Between Gestational Diabetes Mellitus and Control Group

Variables	GDM	Control Group	$\chi^2$	P
<b>TG/HDL-C ratio</b>			141.93	<0.0001
Q1 (0–0.61)	396(23.90)	1261(76.10)		
Q2 (0.62–0.82)	434(26.22)	1221(73.78)		
Q3 (0.83–1.10)	526(31.78)	1129(68.22)		
Q4 (>1.10)	698(42.25)	954(57.75)		
Median (P25, P75)	0.90(0.67,1.26)	0.78(0.59,1.04)	–	<0.0001
<b>TC/HDL-C ratio</b>			96.80	<0.0001
Q1 (0–2.38)	390(23.65)	1259(76.35)		
Q2 (2.39–2.70)	482(29.00)	1180(71.00)		
Q3 (2.71–3.08)	535(32.37)	1118(67.63)		
Q4 (>3.08)	647(39.09)	1008(60.91)		
Median (P25, P75)	2.79(2.46,3.22)	2.65(2.34,3.03)	–	<0.0001

(Continued)

**Table 2** (Continued).

Variables	GDM	Control Group	$\chi^2$	P
<b>LDL-C/HDL-C ratio</b>			84.29	<0.0001
Q1 (0–1.23)	394(23.86)	1257(76.14)		
Q2 (1.24–1.50)	491(29.54)	1171(70.46)		
Q3 (1.51–1.80)	534(32.34)	1117(67.66)		
Q4 (>1.80)	635(38.37)	1020(61.63)		
Median (P25, P75)	1.57(1.31,1.90)	1.47(1.20,1.76)	–	<0.0001
<b>Remnant cholesterol</b>			56.10	<0.0001
Q1 (0–0.17)	405(24.62)	1240(75.38)		
Q2 (0.18–0.30)	489(30.26)	1127(69.74)		
Q3 (0.31–0.47)	571(32.87)	1166(67.13)		
Q4 (>0.47)	589(36.34)	1032(63.66)		
Median (P25, P75)	0.33(0.20,0.50)	0.29(0.16,0.45)	–	<0.0001

**Notes:** continuous variables were presented as medium (P25, P75); categorical variables were presented with count (percentage).

**Abbreviations:** TG, total triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

was significantly higher than that among the Q1 group (42.25% vs 23.90%,  $P < 0.0001$ ; 39.09% vs 23.65%,  $P < 0.0001$ ; 38.37% vs 23.86%,  $P < 0.0001$ ; 36.34% vs 24.62%,  $P < 0.0001$ ; respectively). In line with the Chi-square analysis, the corresponding continuity indicators also showed significant differences between the GDM group and the control group. The results of the univariate analysis between the serum lipid indexes and GDM are provided in [Table S1](#).

**Table 3** shows the effects of serum atherogenic indices and remnant cholesterol on the risk of GDM. Both adjusted and unadjusted logistic regression analyses presented that atherogenic indices and remnant cholesterol were significantly related to the risk of GDM. Compared to those of the lowest quartile, mothers in the highest quartile of TG/HDL-C had a 66% higher risk of GDM (adjusted OR = 1.66, 95% CI: 1.41, 1.96). Mothers in the highest quartile of TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol demonstrated significantly elevated GDM risk compared to those in the lowest

**Table 3** Multivariable Analysis Between Atherogenic Indices, Remnant Cholesterol and Gestational Diabetes Mellitus

Variables	Unadjusted Model OR (95% CI)	Adjusted Model <sup>a</sup> OR (95% CI)
<b>TG/HDL-C ratio</b>		
Q1	1.00	1.00
Q2	1.13(0.97,1.32)	1.06(0.90,1.26)
Q3	<b>1.48(1.27,1.73)</b>	<b>1.24(1.05,1.46)</b>
Q4	<b>2.33(2.01,2.71)</b>	<b>1.66(1.41,1.96)</b>
P for trend	<0.0001	<0.0001
<b>TC/HDL-C ratio</b>		
Q1	1.00	1.00
Q2	<b>1.32(1.13,1.54)</b>	<b>1.24(1.05,1.47)</b>
Q3	<b>1.54(1.33,1.80)</b>	<b>1.30(1.10,1.54)</b>
Q4	<b>2.07(1.78,2.41)</b>	<b>1.47(1.24,1.73)</b>
P for trend	<0.0001	<0.0001
<b>LDL-C/HDL-C ratio</b>		
Q1	1.00	1.00
Q2	<b>1.34(1.15,1.56)</b>	<b>1.28(1.09,1.51)</b>
Q3	<b>1.53(1.31,1.78)</b>	<b>1.36(1.15,1.60)</b>
Q4	<b>1.99(1.71,2.31)</b>	<b>1.47(1.24,1.73)</b>
P for trend	<0.0001	<0.0001

(Continued)

**Table 3** (Continued).

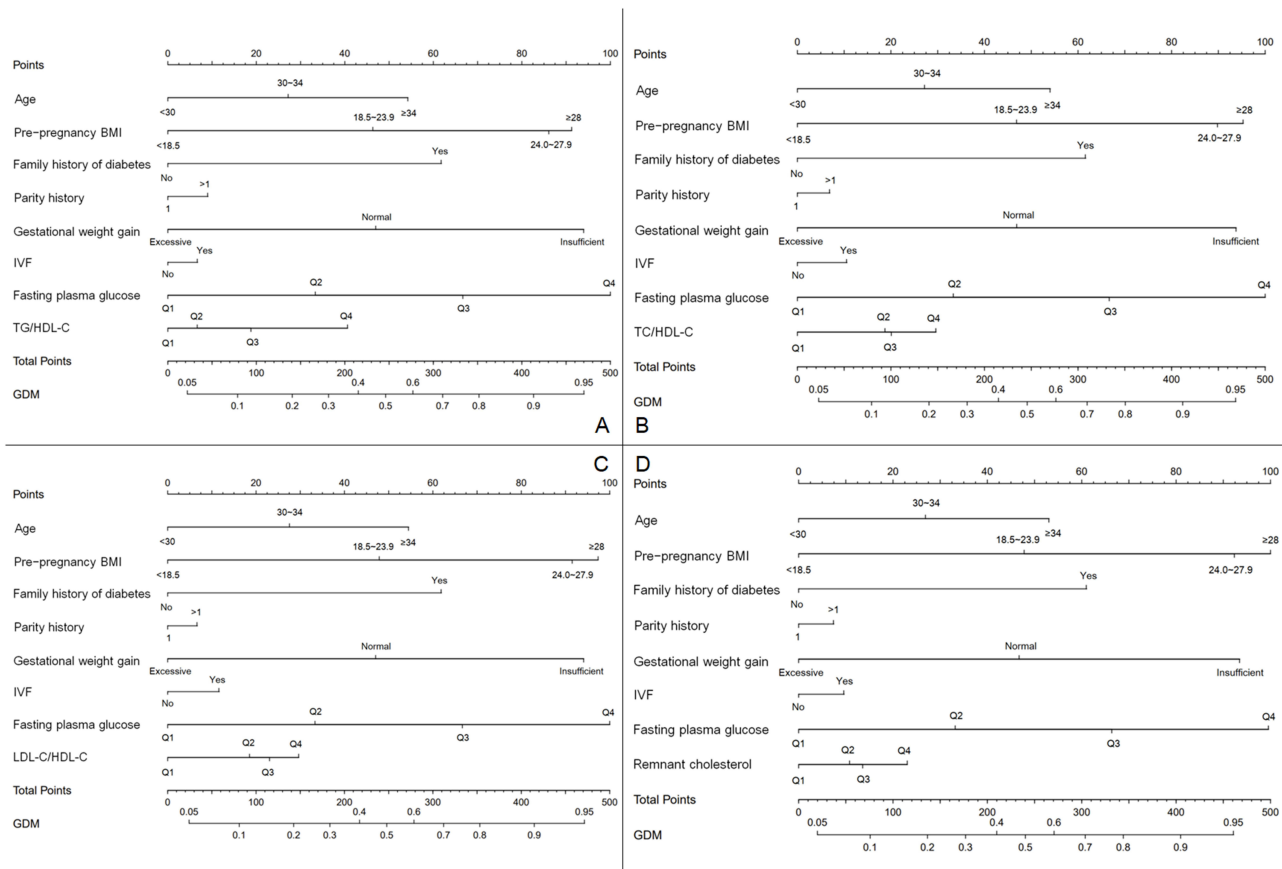
Variables	Unadjusted Model OR (95% CI)	Adjusted Model <sup>a</sup> OR (95% CI)
<b>Remnant cholesterol</b>		
Q1	1.00	1.00
Q2	<b>1.33(1.14,1.55)</b>	<b>1.22(1.03,1.43)</b>
Q3	<b>1.50(1.29,1.74)</b>	<b>1.24(1.06,1.46)</b>
Q4	<b>1.75(1.50,2.03)</b>	<b>1.39(1.18,1.64)</b>
P for trend	<0.0001	0.0002

**Notes:** <sup>a</sup>Adjusted for age, pre-pregnancy BMI, gestational weight gain, family history of diabetes, IVF, FPG, and parity history. Bold represent for  $P < 0.05$ .

**Abbreviations:** TG, total triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

quartile, with adjusted ORs of 1.47 (95% CI: 1.24–1.73), 1.47 (95% CI: 1.24–1.73), and 1.39 (95% CI: 1.18–1.64), respectively. Moreover, [Table S2](#) presented the results of multivariable analysis between serum lipid indexes and GDM stratified by stages of pregnancy. Groups in the highest quartiles of TG, TC, and LDL-C showed higher risks of GDM than did those in the lowest quartile. Furthermore, consistent with [Table 3](#), all atherogenic indices and remnant cholesterol significantly predicted GDM risk stratified by pregnancy stage ([Table S3](#)).

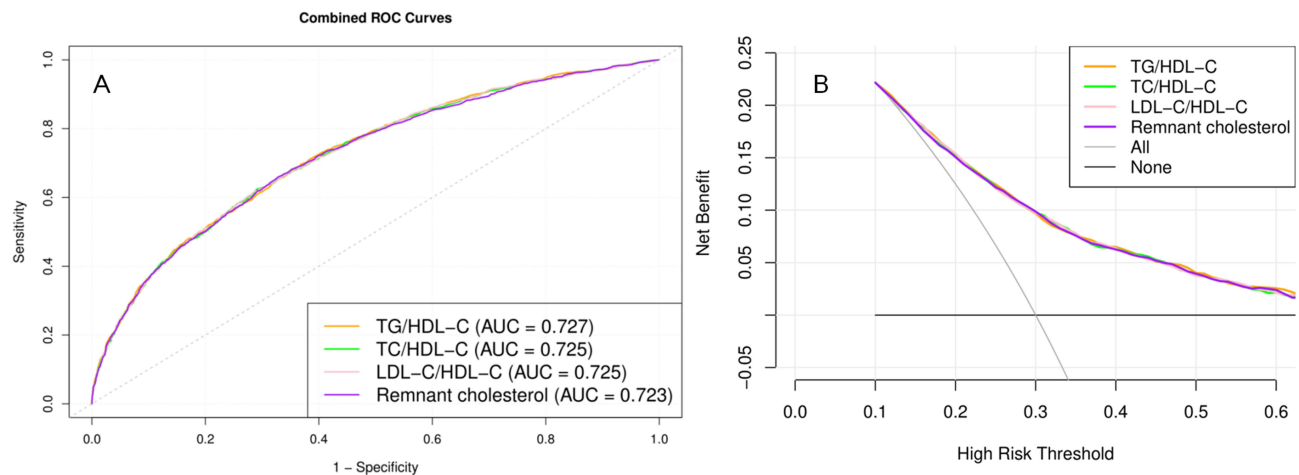
To better visualize the predictive outcomes of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol, the results of the nomogram analyses are provided in [Figure 1](#). The Hosmer and Lemeshow goodness of fit test results for



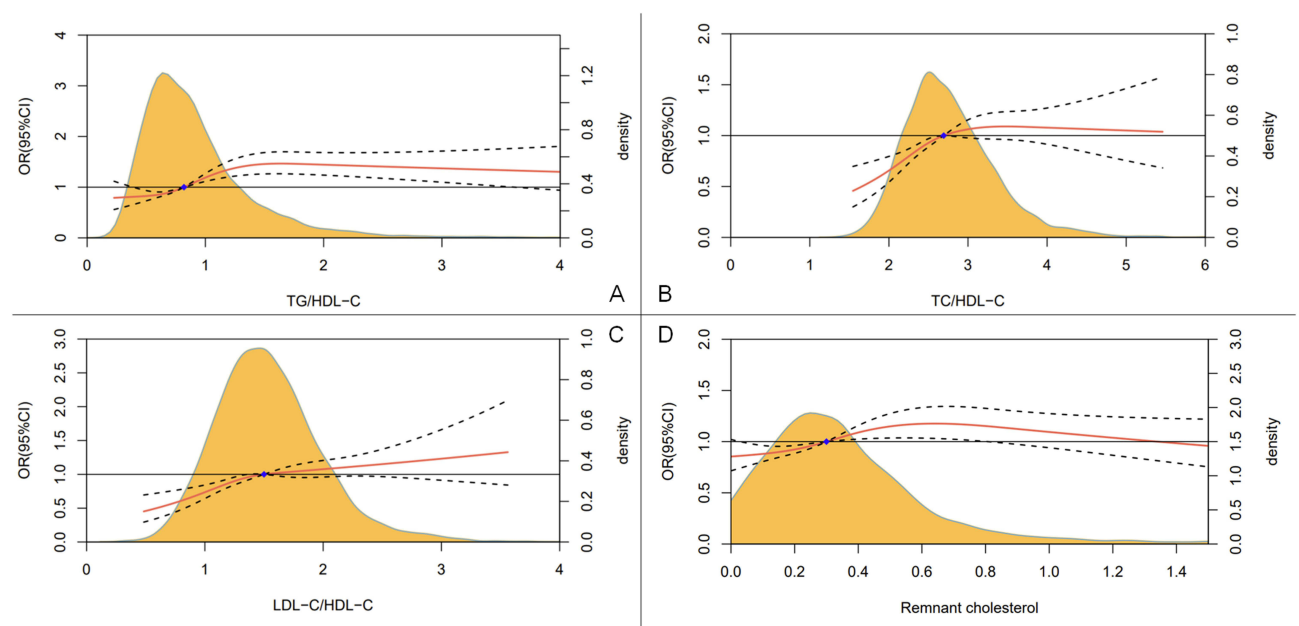
**Figure 1** The nomogram prediction of gestational diabetes mellitus by atherogenic indices and remnant cholesterol (A) the nomogram prediction of GDM by TG/HDL-C; (B) the nomogram prediction of GDM by TC/HDL-C; (C) the nomogram prediction of GDM by LDL-C/HDL-C; (D) the nomogram prediction of GDM by remnant cholesterol.

the four groups showed that all of the prediction models were significant ( $P > 0.05$ ). The AUCs for the TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol predictive models were 0.73 (95% CI: 0.71, 0.74), 0.73 (95% CI: 0.71, 0.74), 0.73 (95% CI: 0.71, 0.74), and 0.72 (95% CI: 0.71, 0.74), respectively. The result of DCA analysis showed that all indicators demonstrated high net benefit (approximately 0.22), excellent sensitivity (>97%), and good negative predictive value (>88%) at a threshold of 0.1 (Figure 2).

The nonlinear associations between atherogenic indices, remnant cholesterol and GDM are presented in Figure 3. All of the atherogenic indices and remnant cholesterol exhibited unimodal distributions. A nonlinear relationship was detected between atherogenic indices, remnant cholesterol, and the risk of GDM ( $\chi^2 = 30.91$ ,  $P < 0.0001$ ;  $\chi^2 = 13.08$ ,  $P = 0.0014$ ;  $\chi^2 = 6.95$ ,  $P = 0.0309$ ;  $\chi^2 = 12.52$ ,  $P = 0.0019$ ; respectively). First, the risk of GDM showed an upward trend with the increasing of TG/HDL-C. But after TG/HDL-C reached 1.64, the risk of GDM started to decline. Similar



**Figure 2** The receiver operating characteristic curves and the decision curve analysis of the nomogram predictions (A) the receiver operating characteristic curves of the predictive outcomes of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol; (B) the decision curve analysis of the predictive outcomes of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol.



**Figure 3** The associations between atherogenic indices and gestational diabetes mellitus risk by RCS regression analysis (A) The associations between TG/HDL-C and GDM; (B) The associations between TC/HDL-C and GDM; (C) The associations between LDL-C/HDL-C and GDM; (D) The associations between remnant cholesterol and GDM. Adjusted for age, pre-pregnancy BMI, gestational weight gain, family history of diabetes, and parity history.

nonlinear patterns were observed in the relationships between TC/HDL-C, remnant cholesterol, and GDM, with inflection points at 3.47 and 0.65, respectively. Although the LDL-C/HDL-C ratio showed a significant nonlinear relationship with GDM risk, the risk of GDM continued to rise with increasing levels of LDL-C/HDL-C. However, the rising pace decelerated once the ratio exceeded 1.54.

## Discussion

The results of this study showed that atherogenic indexes and remnant cholesterol were closely related to the risk of GDM. Higher values of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol were significantly associated with elevated risks of GDM, and the results of the nomogram analysis showed that these indicators exhibited similar predictive performance, suggesting that all of them may serve as strong predictors for GDM.

In line with this study, previous studies have showed the positive associations between atherogenic indexes and GDM, but little of them examined the predictive ability. A cross-sectional study conducted by Khosrowbeygi et al among Iranian reported that LDL-C/HDL-C, TG/HDL-C, and TC/HDL-C levels were significantly higher in the GDM group than in the control group.<sup>18</sup> Wang et al analyzed data from 15 hospitals in Beijing, China demonstrated that elevated TG/HDL-C and LDL-C/HDL-C in the 1st trimester of pregnancy were related to increased risks of GDM.<sup>17</sup> Pazhohan et al reported that mothers in Iran with the highest tertile of TG/HDL-C in the 1st trimester of pregnancy contributed to a 3.9-fold of the risk of GDM compared with the lowest tertile.<sup>26</sup> Cross-sectional studies conducted by Barat et al and Wang et al also revealed that TG/HDL-C was sensitive to GDM diagnosis,<sup>14,27,28</sup> and a retrospective cohort study with a TG/HDL-C ratio cutoff of 3 reported that higher pre-gestational TG/HDL-C was associated with higher rates of GDM (13.1% vs 5.2%).<sup>29</sup> Zhang et al conducted a prospective cohort study in the Korean population and suggested that a log<sub>10</sub> (TG/HDL) below 0.36 might be beneficial for GDM control.<sup>30</sup> Besides, Yue et al investigated serum lipids during the 2nd trimester and found that TG/HDL-C was related to the risk of GDM, but no significant difference was detected for LDL-C/HDL-C.<sup>31</sup> Liu et al reported that Beijing mothers in the top tertile of TG/HDL-C before 12 weeks' gestation had a significantly greater risk of GDM (OR = 2.388), but this relationship was not observed in TC/HDL-C.<sup>32</sup> Based on the above findings, it was reconfirmed that TG/HDL-C has a positive effect on the risk of GDM, but discrepancies were noted in the relationships between TC/HDL-C and LDL-C/HDL-C and GDM. These gaps could be explained by the different study designs, populations, and gestational weeks of lipid-data collection.

The positive associations between atherogenic indexes and GDM could be explained by insulin resistance regulated by atherogenic indexes. Case-control studies conducted by Xiang et al and Kimm et al aimed to clarify the associations between atherogenic indexes and insulin resistance and revealed that all of the atherogenic indexes were significantly correlated with insulin resistance.<sup>33,34</sup> Specifically, previous studies have confirmed that TG/HDL-C is a reliable biomarker of insulin resistance.<sup>35,36</sup> Moreover, increased TC or decreased HDL-C concentrations could contribute to insulin resistance, glucose intolerance, and hyperinsulinemia,<sup>37</sup> and these factors are leading hazards for GDM.

Consistent with our findings, elevated remnant cholesterol levels were significantly associated with an increased risk of GDM. Our study further highlights the promising predictive effect of remnant cholesterol on the risk of GDM. A high concentration of remnant cholesterol was reported to have a higher risk of GDM, even among pregnancies with low TC.<sup>21</sup> Another prospective cohort study conducted in Korea confirmed the independent association between remnant cholesterol and GDM.<sup>22</sup> Su et al reported a significant dose-response relationship that the risk of GDM elevated along with the increasing of remnant cholesterol.<sup>23</sup> Although the exact mechanistic link between remnant cholesterol and GDM remains to be fully elucidated, it was hypothesized that remnant cholesterol may contribute to GDM pathogenesis through dual pathways similar to those observed in type 2 diabetes: The direct effects of remnant cholesterol-induced insulin resistance or  $\beta$ -cell dysfunction,<sup>38</sup> and the indirect effects of low-grade inflammation triggered by remnant cholesterol promote insulin resistance.<sup>39,40</sup> Further studies are warranted to validate these mechanisms.

The present study novelly revealed intuitive changes in GDM risk with respect to atherogenic indexes and remnant cholesterol and warned the elevated risk of GDM under high values of atherogenic indexes and remnant cholesterol. However, certain limitations should be addressed. First, the causal correlations between atherogenic indexes and remnant cholesterol and GDM in this study might be undermined. Second, this study obtained clinical data from a single hospital of Chinese population; caution should be taken when generalizing this study to other populations. Third, other

confounding factors that might interfere with the relationship between atherogenic indexes and remnant cholesterol and GDM, such as insulin resistance, gestational weight gain before the diagnosis of GDM, liver function indexes, lifestyle behavior factors, and socioeconomic status et al were not considered in this study because they were not routine examined in the clinical practice. Fourth, this study included only one serum lipid data point per person, and the effects of dynamic changes in lipid ratios on the risk of GDM were failed to examine. Future studies focused on the dynamic changes in lipid indicators on the risk of GDM prediction are highly promoted.

## Conclusion

Notably, our findings highlight the promising role of atherogenic indices and remnant cholesterol as potential predictive biomarkers for GDM risk assessment, which has not been fully explored in previous studies. Elevated levels of blood TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol are linked to a significant increase in the risk of developing GDM. Therefore, it is essential to maintain atherogenic indexes and remnant cholesterols at low levels in order to reduce the risk of GDM. Specially, the turning points (TG/HDL-C = 1.64, TC/HDL-C = 3.47, LDL-C/HDL-C = 1.54, and remnant cholesterol = 0.65) identified by the nonlinear relationships could serve as potential warning thresholds for clinical interventions to optimize GDM risk assessment. These findings underscore the potential of routine lipid testing as a cost-effective strategy for the early identification and management of GDM in clinical settings.

## Abbreviations

GDM, gestational diabetes mellitus; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

## Data Sharing Statement

The datasets used during the current study are available from the corresponding author on reasonable request, which should be approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province.

## Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province (2021IECXM005).

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## Disclosure

The authors report no conflicts of interest in this work.

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