Predictive Value of the Triglyceride to High-Density Lipoprotein Cholesterol Ratio for All-Cause Mortality and Cardiovascular Death in Diabetic Patients With Coronary Artery Disease Treated With Statins

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Background and Aims: Studies have highlighted the role of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio on subsequent cardiovascular events. However, the association of the TG/HDL-C ratio with survival outcomes in diabetic patients with coronary artery disease (CAD) treated with statins remains unknown. This study aimed to assess the predictive value of the TG/HDL-C ratio for all-cause mortality and cardiovascular death in diabetic patients with CAD treated with statins.

Methods: The data of patients with type 2 diabetes and angiographically-confirmed CAD who were undergoing statin therapy and visited Tianjin Chest Hospital between January 2016 and September 2016 were retrospectively collected. The patients were categorized based on the baseline TG/HDL-C ratio tertile. Kaplan-Meier analysis and multivariate Cox proportional hazard regression were applied to assess the role of the TG/HDL-C ratio in predicting all-cause mortality and cardiovascular death.

Results: A total of 2,080 patients were included. During the 4-year follow-up, 209 patients died, 136 of whom from cardiovascular death. The Kaplan-Meier analyses showed that an increased TG/HDL-C ratio was associated with an increased risk of all-cause mortality ($P < 0.001$) and cardiovascular death ($P < 0.001$). The multivariate cox hazard regression analysis revealed a similar effect of the TG/HDL-C ratio tertile. Kaplan-Meier analysis and multivariate Cox proportional hazard regression were applied to assess the role of the TG/HDL-C ratio in predicting all-cause mortality and cardiovascular death.
artery disease (CAD) is well-illustrated (1), and studies have demonstrated that the use of statins could reduce the risk of major cardiovascular events (MACEs) in diabetic patients (2–5). However, patients with CAD have a higher prevalence of type 2 DM, and the risk of mortality remains high even in those treated with statins. The residual risk could be attributed to abnormal lipoprotein and lipid levels (6). Therefore, it is necessary that the lipid status be re-evaluated in diabetic patients with CAD treated with statins to identify those with higher residual risk such that tailored risk reduction strategies can be developed.

Dyslipidemia is characterized by elevated triglyceride (TG) and reduced high-density lipoprotein cholesterol particles levels, and lower high-density lipoprotein cholesterol (HDL-C) levels in diabetic patients (7, 8). Elevated TG and lower HDL-C are associated with poor prognosis in diabetic patients (9–12), but the use TG or HDL-C alone does not reflect the risk of atherosclerosis and cardiovascular disease (CVD) (13). The TG/HDL-C ratio may reflect the actual lipid profiles, and is considered an important marker of plasma atherosclerosis (14). Moreover, studies found that the TG/HDL-C ratio was an important predictor of insulin resistance and could evaluate the degree of abnormal glucose metabolism (15–17).

Numerous studies have reported a positive relationship between the TG/HDL-C ratio and hypertension (18–20), obesity (21), metabolic syndrome (22–24), hyperuricemia (25), and non-alcoholic fatty liver disease (26, 27). Moreover, an elevated TG/HDL-C ratio plays an important role on heart rate recovery after exercise (28), increased arterial stiffness (29, 30) and increased carotid atherosclerosis (31). Studies have indicated that the TG/HDL-C ratio should be considered as an important primary prevention cardiovascular risk factor, while the strength of the predictive value differs for patients undergoing various status (32–43). Furthermore, the predictive value of the TG/HDL-C ratio for all-cause mortality and cardiovascular death in diabetic patients with CAD treated with statins is unknown. This retrospective cohort study was therefore performed to assess the potential role of the TG/HDL-C ratio in the prediction of all-cause mortality and cardiovascular death in diabetic patients with CAD who were treated with statins.

INTRODUCTION

The role of diabetes mellitus (DM) on subsequent coronary artery disease (CAD) is well-illustrated (1), and studies have demonstrated that the use of statins could reduce the risk of major cardiovascular events (MACEs) in diabetic patients (2–5). However, patients with CAD have a higher prevalence of type 2 DM, and the risk of mortality remains high even in those treated with statins. The residual risk could be attributed to abnormal lipoprotein and lipid levels (6). Therefore, it is necessary that the lipid status be re-evaluated in diabetic patients with CAD treated with statins to identify those with higher residual risk such that tailored risk reduction strategies can be developed.

Dyslipidemia is characterized by elevated triglyceride (TG) and reduced high-density lipoprotein cholesterol particles levels, and lower high-density lipoprotein cholesterol (HDL-C) levels in diabetic patients (7, 8). Elevated TG and lower HDL-C are associated with poor prognosis in diabetic patients (9–12), but the use TG or HDL-C alone does not reflect the risk of atherosclerosis and cardiovascular disease (CVD) (13). The TG/HDL-C ratio may reflect the actual lipid profiles, and is considered an important marker of plasma atherosclerosis (14). Moreover, studies found that the TG/HDL-C ratio was an important predictor of insulin resistance and could evaluate the degree of abnormal glucose metabolism (15–17).

Numerous studies have reported a positive relationship between the TG/HDL-C ratio and hypertension (18–20), obesity (21), metabolic syndrome (22–24), hyperuricemia (25), and non-alcoholic fatty liver disease (26, 27). Moreover, an elevated TG/HDL-C ratio plays an important role on heart rate recovery after exercise (28), increased arterial stiffness (29, 30) and increased carotid atherosclerosis (31). Studies have indicated that the TG/HDL-C ratio should be considered as an important primary prevention cardiovascular risk factor, while the strength of the predictive value differs for patients undergoing various status (32–43). Furthermore, the predictive value of the TG/HDL-C ratio for all-cause mortality and cardiovascular death in diabetic patients with CAD treated with statins is unknown. This retrospective cohort study was therefore performed to assess the potential role of the TG/HDL-C ratio in the prediction of all-cause mortality and cardiovascular death in diabetic patients with CAD who were treated with statins.

METHODS

Study Population

Patients who were admitted to Tianjin Chest Hospital between January 2016 and September 2016 were recruited in this retrospective cohort study. A total of 2,678 patients with T2DM and angiographically-confirmed CAD were included. CAD comprised stable angina pectoris (SAP) and acute coronary syndrome (ACS). ACS included unstable angina pectoris, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction (STEMI). Patients were excluded if they met any of the following criteria: (1) aged < 18.0 or >80.0 years (n = 72), (2) severe valvular heart disease or congenital heart disease (n = 34), (3) alanine aminotransferase level > 3-fold greater than the normal upper limit (n = 15), (4) serum creatinine level > 1.5-fold greater than the normal upper limit (n = 96), (5) hyperthyroidism or hypothyroidism (n = 16), (6) incomplete clinical data (n = 75), and (7) not treated with statins (n = 99). The remaining 2,271 patients were recruited, and 2,080 patients with full clinical data after 4-year follow-up were included in the final analysis. The patients were categorized based on the tertiles of the baseline TG/HDL-C ratio, as follows: tertile 1 (n = 693, TG/HDL-C ratio ≤ 1.20), tertile 2 (n = 693, 1.20 < TG/HDL-C ratio ≤ 1.92), and tertile 3 (n = 694, TG/HDL-C ratio > 1.92). The study was approved by the Ethical Committee of Tianjin Chest Hospital (NO:2021LW-006), and the need to obtain informed consent requirement was waived as the study comprised a retrospective analysis of clinical data.

Data Collection and Definitions

Baseline demographic characteristics, clinical presentation, cardiac function, extent of lesion, treatment strategy, laboratory findings at fasting status, and medication data at discharge were collected from medical records and the data managers were blinded to the study purpose. The demographic characteristics included age; sex ratio; duration of diabetes; smoker proportion; hypertension; prior myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or stroke; and body mass index (BMI). The cardiac function included left ventricle ejection fraction (LVEF). The medications at discharge included aspirin, clopidogrel/ticagrelor, ß-blocker, angiotensin II coenzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), calcium channel blocker (CCB), nitrate, and insulin.
Endpoints and Follow-Up Data
The investigated endpoints included all-cause mortality and cardiovascular death. All-cause mortality was defined as death from any cause, and cardiovascular death was defined as death caused by acute MI, heart failure, cardiac arrhythmia, or stroke. The follow-up information was collected by telephone or electronic medical record review.

Statistical Analysis
Continuous variables are presented as the mean [standard deviation (SD)] and median (interquartile) based on data.
distribution, and the differences among groups were compared using an analysis of variance or the Kruskal-Wallis test. Categorical variables are presented as frequencies and proportions, and the differences among groups were compared using the Chi-square or Fisher’s exact tests. The association between the TG/HDL-C ratio and subsequent all-cause mortality and cardiovascular death were assessed using Kaplan-Meier analysis and the log-rank test. Multivariate Cox regression analysis was performed to identify the independent predictors of all-cause mortality and cardiovascular death. All the variables in Table 1 were listed in univariate model and then were introduced into the multivariate model if the \( P \)-value was <0.10. The possible factors included age, duration of diabetes, hypertension, previous MI, previous PCI, previous stroke, LVEF, left main disease, multi-vessel disease, FPG, TC, LDL-C, uric acid, hs-CRP, and eGFR. Sensitivity analyses were performed for all-cause mortality and cardiovascular death by sequential adjustment of potential confounders. The C-statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were applied to assess the incremental predictive value of the TG/HDL-C ratio over the established model (including age, duration of diabetes, previous PCI, LVEF, left main disease, multi-vessel disease, FPG, and eGFR). The optimal cut-off values of the TG/HDL-C ratio for predicting all-cause mortality and cardiovascular death were determined using receiver operating characteristic (ROC) curves. Subgroup analyses for all-cause mortality and cardiovascular death were conducted according to sex (male or female), smoker (yes or no), BMI (≤28 or >28 kg/m²), duration of DM (≤10 or >10 years), ACS (yes or no), HbA1c (≤7.0 or >7.0%), LDL-C (≤1.8 or >1.8 mmol/L), insulin treatment (yes or no), and revascularization (yes or no). The differences between subgroup analyses were also compared using the interaction \( t \)-test. All \( P \)-values are two-sided, and the inspection level was 0.050. The statistical analyses in this study were performed using SPSS version 20.0 (IBM Corp, Armonk, New York) and SAS version 9.1.3 (Cary, NC, USA).

RESULTS

Baseline Characteristics

A total of 2,080 diabetic patients with CAD who were treated with statins were selected for analysis. The baseline characteristics of the patients in the three TG/HDL-C ratio categories are summarized in Table 1. Most variables did not significantly differ among the groups, including age; sex ratio; duration of diabetes; smoker proportion; hypertension; prior MI, PCI, CAGB, or stroke; LVEF; clinical presentation; left main disease; multi-vessel disease; treatment strategy; FPG; LDL-C; aspirin; clopidogrel/ticagrelor; β-blocker; ACEI or ARB; CCB; nitrate; and insulin (\( P > 0.050 \)). However, there were significant differences among the three groups in BMI (\( P = 0.020 \)), HbA1c (\( P = 0.002 \)), TC (\( P < 0.001 \)), TG (\( P < 0.001 \)), HDL-C (\( P < 0.001 \)), TG/HDL-C ratio (\( P < 0.001 \)), serum uric acid (\( P < 0.001 \)), hs-CRP (\( P < 0.001 \)), and eGFR (\( P = 0.003 \)).

### TG/HDL-C Ratio and All-Cause Mortality

A total of 209 patients died during the 4-year follow-up, and the proportions of all-cause mortality in tertiles 1, 2, and 3 were applied to assess the incremental predictive value of the TG/HDL-C ratio over the established model (including age, duration of diabetes, previous PCI, LVEF, left main disease, multi-vessel disease, FPG, and eGFR). The optimal cut-off values of the TG/HDL-C ratio for predicting all-cause mortality and cardiovascular death were determined using receiver operating characteristic (ROC) curves. Subgroup analyses for all-cause mortality and cardiovascular death were conducted according to sex (male or female), smoker (yes or no), BMI (≤28 or >28 kg/m²), duration of DM (≤10 or >10 years), ACS (yes or no), HbA1c (≤7.0 or >7.0%), LDL-C (≤1.8 or >1.8 mmol/L), insulin treatment (yes or no), and revascularization (yes or no). The differences between subgroup analyses were also compared using the interaction \( t \)-test. All \( P \)-values are two-sided, and the inspection level was 0.050. The statistical analyses in this study were performed using SPSS version 20.0 (IBM Corp, Armonk, New York) and SAS version 9.1.3 (Cary, NC, USA).

#### Table 2

Cox regression models in the prediction of all-cause mortality and cardiovascular death according to the triglyceride to high density lipoprotein-C ratio at baseline.

| Endpoint                      | Events, n/total (%) | Crude HR (95% CI) | Crude P-value | Adjusted HR (95% CI) | Adjusted P-value |
|-------------------------------|---------------------|-------------------|---------------|----------------------|------------------|
| All-cause mortality           |                     |                   |               |                      |                  |
| Tertile 1                     | 46/693 (6.6)        | 1.00 (reference)  | <0.001        | 1.00 (reference)     | 0.046            |
| Tertile 2                     | 70/693 (10.1)       | 1.54 (1.06–2.23)  | 1.19 (0.81–1.75) | 1.52 (1.06–2.19) | <0.001           |
| Tertile 3                     | 93/694 (13.4)       | 2.09 (1.47–2.96)  | 1.17 (1.10–1.24) | 1.20 (1.11–1.30) | <0.001           |
| Per 1-SD                      |                     |                   |               |                      |                  |
| Cardiovascular death          |                     |                   |               |                      |                  |
| Tertile 1                     | 27/693 (3.9)        | 1.00 (reference)  | <0.001        | 1.00 (reference)     | 0.009            |
| Tertile 2                     | 43/693 (6.2)        | 1.66 (1.02–2.67)  | 1.17 (1.10–1.24) | 1.20 (1.11–1.30) | <0.001           |
| Tertile 3                     | 66/694 (9.5)        | 2.55 (1.63–4.00)  | 1.22 (1.16–1.29) | 2.01 (1.27–3.21) | <0.001           |
| Per 1-SD                      |                     |                   |               |                      |                  |

Adjusted variables were age, duration of diabetes, hypertension, previous MI, previous PCI, previous stroke, LVEF, left main disease, multi-vessel disease, FPG, TC, LDL-C, uric acid, hs-CRP, eGFR, HR, hazard ratio; CI, confidential interval; SD, standard deviation.
were 6.6, 10.1, and 13.4%, respectively. Kaplan-Meier analysis indicated that an increased TG/HDL-C ratio was associated with an increased risk of all-cause mortality (P < 0.001; Figure 1). The Cox proportional hazard regression indicated that an increased TG/HDL-C ratio tertile was associated with an increased risk of all-cause mortality, irrespective of whether the unadjusted (P < 0.001) or adjusted (P = 0.046) was used. Moreover, per SD increment in the TG/HDL-C ratio was associated with an increased risk of all-cause mortality in both the unadjusted model (HR: 1.17; 95% CI: 1.10–1.24; P < 0.001) and the adjusted model (HR: 1.20; 95% CI: 1.12–1.27; P < 0.001) (Table 2). The role of the TG/HDL-C ratio in predicting the risk of all-cause mortality was robust after sequential adjustment for potential confounders (Table 3).

ROC analysis indicated that the optimal cutoff value of the TG/HDL-C ratio for predicting all-cause mortality was 1.77 (sensitivity: 53.1% and specificity: 62.8%), and the area under the curve (AUC) was 0.601 (95% CI: 0.561–0.640; P < 0.001). Adding the TG/HDL-C ratio to the model of established risk factors including age, duration of diabetes, previous PCI, LVEF, left main disease, multi-vessel disease, FBG, and eGFR improved the prediction of all-cause mortality in terms of the C-statistic (from 0.799 to 0.812; P = 0.018), and the NRI and IDI were 0.252 (95% CI: 0.112–0.392; P < 0.001) and 0.012 (95% CI: 0.003–0.022; P = 0.012), respectively (Table 4).

The results of subgroup analyses for all-cause mortality are illustrated in Table 5. An elevated TG/HDL-C ratio was associated with an increased risk of all-cause mortality in all subgroups, and the differences between subgroups were not significant based on sex (P = 0.985), smoker (P = 0.173), BMI (P = 0.741), duration of DM (P = 0.090), ACS (P = 0.438), HbA1c (P = 0.524), LDL-C (P = 0.788), insulin treatment (P = 0.265), and revascularization (P = 0.780).

### Table 3: Sensitivity analysis of the association of the triglyceride to high density lipoprotein-C ratio per 1 standard deviation with mortality after separate adjustment for each of the other significant variables.

| Adjustment | 1-SD | 95%CI | P-value |
|------------|------|-------|---------|
| Age        | 1.20 | 1.13–1.28 | <.001   |
| Smoker     | 1.17 | 1.10–1.24 | <.001   |
| Duration of diabetes | 1.17 | 1.10–1.24 | <.001   |
| Hypertension | 1.19 | 1.11–1.26 | <.001   |
| Previous MI | 1.17 | 1.10–1.24 | <.001   |
| Previous PCI | 1.18 | 1.11–1.25 | <.001   |
| Previous stroke | 1.17 | 1.10–1.24 | <.001   |
| LVEF     | 1.20 | 1.12–1.27 | <.001   |
| Left main disease | 1.17 | 1.10–1.24 | <.001   |
| Multi-vessel disease | 1.17 | 1.10–1.24 | <.001   |
| FPG      | 1.17 | 1.10–1.24 | <.001   |
| TC       | 1.16 | 1.09–1.24 | <.001   |
| LDL-C    | 1.16 | 1.10–1.24 | <.001   |
| Uric acid | 1.15 | 1.08–1.23 | <.001   |
| hs-CRP  | 1.17 | 1.10–1.25 | <.001   |
| eGFR   | 1.15 | 1.08–1.23 | <.001   |

### Table 4: Evaluation of predictive models for all-cause mortality and cardiovascular death.

| Endpoint                  | C-Statistic | P-value | NRI (95%CI) | P-value | IDI (95%CI) | P-value |
|---------------------------|-------------|---------|-------------|---------|-------------|---------|
| All-cause mortality       | Original model | 0.799 (0.766–0.833) | Ref. | Ref. | Ref. |
| Cardiovascular death      | Original model | 0.812 (0.780–0.844) | 0.018 | 0.252 (0.112–0.392) | <0.001 | 0.012 (0.003–0.022) | 0.012 |

Original model included age, duration of diabetes, previous PCI, LVEF, left main disease, multi-vessel disease, FBG, and eGFR. TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidential interval; SD, standard deviation.
TABLE 5 | All-cause mortality and cardiovascular death in the various patient subgroups.

| Variable                  | Subgroups | All-cause mortality | Cardiovascular death |
|---------------------------|-----------|---------------------|----------------------|
|                           | ≤1.77     | >1.77 HR (95%CI)    | P for interaction    | ≤1.57    | >1.57 HR (95%CI)    | P for interaction |
| All patient               | Total     | 99/1,274 110/806    | 1.821 (1.388–2.389)  | 36/1,083 | 100/997 3.124 (2.135–4.573) | 0.095 |
| Sex                       | Women     | 45/555 47/358      | 1.661 (1.104–2.500)  | 15/462   | 49/451 3.453 (1.936–6.158) | 0.098 |
|                           | Men       | 54/719 63/448      | 1.956 (1.360–2.813)  | 21/621   | 51/546 2.867 (1.725–4.766) | 0.079 |
| Smoker                    | No        | 61/770 57/489      | 1.498 (1.044–2.150)  | 21/846   | 59/613 3.041 (1.848–5.003) | 0.173 |
|                           | Yes       | 38/504 59/317      | 2.360 (1.566–3.580)  | 15/437   | 41/384 3.262 (1.805–5.893) | 0.285 |
| BMI (kg/m²)               | ≤28       | 79/1,058 91/655    | 1.930 (1.428–2.609)  | 33/905   | 83/608 2.918 (1.949–4.367) | 0.741 |
|                           | >28       | 20/216 19/151      | 1.409 (0.752–2.640)  | 3/178    | 18/159 5.504 (2.613–8.783) | 0.030 |
| Duration of DM (years)    | ≤10       | 53/773 63/491      | 1.933 (1.341–2.785)  | 17/654   | 62/610 4.052 (2.369–6.929) | 0.030 |
|                           | >10       | 46/501 47/315      | 1.697 (1.130–2.548)  | 19/429   | 38/387 2.291 (1.321–3.973) | 0.036 |
| ACS                       | No        | 16/241 15/119      | 1.973 (0.975–3.990)  | 4/241    | 12/119 6.312 (2.036–9.587) | 0.438 |
|                           | Yes       | 83/1,033 95/687    | 1.783 (1.328–2.394)  | 32/842   | 88/878 2.726 (1.819–4.085) | 0.346 |
| HbA1c (%)                 | ≤7.0      | 41/584 46/336      | 2.016 (1.323–3.071)  | 14/499   | 43/421 3.803 (2.081–6.952) | 0.524 |
|                           | >7.0      | 58/690 64/470      | 1.682 (1.179–2.400)  | 22/584   | 57/576 2.700 (1.661–4.415) | 0.524 |
| LDL-C (mmol/L)            | ≤1.8      | 13/149 16/118      | 1.608 (0.773–3.343)  | 8/136    | 11/131 3.853 (1.075–13.810) | 0.788 |
|                           | >1.8      | 86/1,125 94/688    | 1.854 (1.384–2.483)  | 51/947   | 89/866 3.064 (2.055–4.568) | 0.819 |
| Insulin treatment         | No        | 51/751 66/492      | 2.065 (1.433–2.976)  | 18/632   | 61/611 3.616 (2.136–6.112) | 0.265 |
|                           | Yes       | 48/523 44/314      | 1.566 (1.040–2.357)  | 18/451   | 39/386 2.641 (1.511–4.617) | 0.052 |
| Revascularization         | No        | 31/393 35/247      | 1.876 (1.157–3.042)  | 9/327    | 37/313 4.432 (2.139–9.183) | 0.780 |
|                           | Yes       | 68/881 75/559      | 1.796 (1.293–2.494)  | 27/726   | 63/684 2.673 (1.703–4.195) | 0.780 |

BMI, body mass index; DM, diabetes mellitus; ACS, acute coronary syndrome; HbA1c, Hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidential interval.

FIGURE 2 | Kaplan-Meier survival curve for cardiovascular death across triglyceride to high density lipoprotein-C ratio tertiles.

TG/HDL-C Ratio and Cardiovascular Death

A total of 136 patients died from cardiovascular death during the 4-year follow-up, and the proportion of cardiovascular death in tertiles 1, 2, and 3 were 3.9, 6.2, and 9.5%, respectively. Kaplan-Meier analysis suggested that the risk of cardiovascular death was significantly increased with an elevated TG/HDL-C ratio (P < 0.001) and the adjusted model (P = 0.009).

Furthermore, the risk of cardiovascular death was significantly increased per SD increment in the TG/HDL-C ratio in both the unadjusted model (HR: 1.22; 95% CI: 1.16–1.29; P < 0.001) and the adjusted model (HR: 1.27; 95% CI: 1.19–1.36; P < 0.001) (Table 2). Sensitivity analysis revealed that the association between the TG/HDL-C ratio and the risk of cardiovascular death was robust and not altered by sequential adjustment for potential confounders (Table 3).

ROC analysis indicated that the optimal cutoff value of the TG/HDL-C ratio for predicting cardiovascular death was 1.57 (sensitivity: 74.3% and specificity: 53.8%), with an AUC of 0.672 (95% CI: 0.625–0.718; P < 0.001). Adding the TG/HDL-C ratio to the established model improved the prediction of cardiovascular death in terms of the C-statistic (from 0.771 to 0.804; P < 0.001), and the NRI and IDI were 0.508 (95% CI: 0.335–0.680; P < 0.001) and 0.033 (95% CI: 0.015–0.050; P < 0.001), respectively (Table 4).

The results of the subgroup analyses for cardiovascular death based on pre-defined variables are shown in Table 5. An elevated TG/HDL-C ratio tertile was associated with an increased risk of cardiovascular death in all subgroups, and sex (P = 0.552), smoker (P = 0.537), BMI (P = 0.285), duration of DM (P = 0.442), ACS (P = 0.346), HbA1c (P = 0.697), LDL-C (P = 0.345), insulin treatment (P = 0.502), and revascularization (P = 0.476) did not affect the role of TG/HDL-C ratio in predicting the risk of cardiovascular death.
DISCUSSION

This study systematically analyzed the predictive value of the TG/HDL-C ratio for subsequent all-cause mortality and cardiovascular death in diabetic patients with CAD who were treated with statins. An elevated TG/HDL-C ratio was associated with an increased risk of all-cause mortality and cardiovascular death. Sensitivity analyses indicated that the role of TG/HDL-C ratio in predicting subsequent all-cause mortality and cardiovascular death was robust and not altered by sequential adjusted potential confounders. Furthermore, adding the TG/HDL-C ratio to the established model resulted in a significant enhancement of the predictive value. The risk of all-cause mortality and cardiovascular death was significantly increased when the TG/HDL-C ratio was increased in all subgroups, and these associations were not affected by sex, smoker, BMI, duration of DM, ACS, HbA1c, LDL-C, insulin treatment, or revascularization. The above results indicate that the TG/HDL-C ratio is a marker of poor prognosis even in the era of statin treatment and may contribute to the early identification of high-risk diabetic patients and CAD. Furthermore, routine TG/HDL-C ratio calculation may further improve risk stratification for all-cause mortality and cardiovascular death.

LDL-C plays a key role in the development and progression of atherosclerotic CVD (ASCVD) and statins are the first-line therapy for lowering LDL-C levels to reduce ASCVD risk. However, diabetic patients with CAD remain at high cardiovascular risk even after LDL-C reduction, which indicates that there are residual cardiovascular risk factors other than LDL-C. One study found that diabetic patients treated with statins had a high prevalence of persistent atherogenic dyslipidemia (13). Elevated TG levels and lower HDL-C levels, as typical lipid features of diabetes, are considered to indicate atherogenic dyslipidemia in diabetic patients (44, 45). However, the levels of TG and HDL-C are mutually independent, and the single lipid parameter could not reflect the actual status of plasma atherogenicity and CVD risk in the absence of insulin resistance (13). Therefore, the TG/HDL-C ratio could reflect TG and HDL-C simultaneously, and is regarded as a better marker in primary and secondary prevention of CVD (34, 36, 46). A study conducted by Edwards et al. suggested that the TG/HDL-C ratio has better predictive value for mortality than that of individual lipid parameters (47). Furthermore, a high TG/HDL-C ratio may strongly predict the extent of coronary lesions (48, 49). Moreover, the TG/HDL-C ratio is significantly related to vulnerable plaque features in diabetic patients treated with statins (50). Routine lipid examinations do not reflect the actual compositional changes of lipid parameters in diabetic patients with CAD. Therefore, evaluation of the TG/HDL-C ratio may have great clinical significance with regards to risk stratification for diabetic patients with CAD who are treated with statins.

Although previous studies have demonstrated the role of the TG/HDL-C ratio in predicting adverse cardiovascular events in patients with CAD (51–55), the potential role of TG/HDL-C ratio as a prognostic marker for patients with diabetes is still debated. The Swedish National Diabetes Register found that elevated TG/HDL-C ratio could increase the risk of CVD independent of the LDL-C level in obese T2DM patients (56). Yang et al. reported that the TG/HDL-C ratio was an important predictor of MACES in patients with diabetes and CAD (42). Contrary to these studies, several other studies did not find significant associations between the TG/HDL-C ratio and the prognosis of T2DM. Tohidi et al. demonstrated that the TG/HDL-C ratio was not an independent predictor of cardiovascular events in diabetic patients without CVD (57). The sub analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study was not able to establish an independent association between TG/HDL ratio and CVD risk in patients with DM and without history of CVD (43). The potential reasons for this discrepancy could be the variation in definition of endpoints, patient characteristics among studies.

This study is the first to focus on the role of the TG/HDL-C ratio in the prediction of prognosis in diabetic patients with CAD who were treated with statins. Compared with previous studies focusing on patients with diabetes or CAD, this large cohort study included higher risk patients with a higher prevalence of a history of CVD. This study demonstrated that an elevated TG/HDL-C ratio was associated with poor prognosis in diabetic patients with CAD treated with statins. Although higher TG/LDL-C ratio were relevant for chronic kidney disease (CKD) in patients with diabetes (58), TG/LDL-C ratio remained a significant and independent predictor of all-cause mortality and cardiovascular death after adjustment for potential confounders including renal function measures (eGFR). This finding suggested that the association between TG/HDL-C ratio and the risk of mortality might not be mediated by the presence of kidney dysfunction. These associations were persistent in sensitivity and subgroup analyses. An elevated TG/HDL-C ratio was still associated with an increased risk of mortality in patients with LDL-C levels of ≤1.80 mmol/L, suggesting that the ratio may explain part of the residual cardiovascular risk. The use of statins has less impact on the prognostic value of the TG/HDL-C ratio in diabetic patients with CAD. Several potential mechanisms may account for the association of the TG/HDL-C ratio with all-cause mortality and cardiovascular death in diabetic patients with CAD: (1) an elevated TG level and lower HDL-C plays an important role in endothelial dysfunction and atherosclerosis. Combined TG and HDL-C are significantly related to other atherogenic lipid phenotypes, characterized by higher levels of small dense LDL particles along with higher levels of remnant particle cholesterol and non-HDL-C, which contribute to the progression of atherosclerosis (14, 58, 59); (2) the TG/HDL-C ratio is significantly related to insulin resistance and glycemic control in diabetic patients (15, 16, 60, 61). Insulin resistance is related to the progression of atherosclerosis, vulnerability of coronary plaques, and MACES in patients with CAD (62–64). Moreover, a hyperglycemic environment could induce the progression of macrovascular and microvascular disease in diabetic patients, including diabetic nephropathy, CAD and peripheral artery disease, which could cause excess risk of all-cause mortality and cardiovascular death (65, 66).
Additionally, the addition of the TG/HDL-C ratio in the risk prediction model for subsequent all-cause mortality and cardiovascular death was associated with a high predictive value. These results suggest that the use of TG/HDL-C ratio could refine risk stratification for all-cause mortality and cardiovascular death in diabetic patients with CAD who are treated with statins. Moreover, this study identified the optimal cutoff value of the TG/HDL-C ratio in this context, suggesting that the ratio should be maintained at <1.57 to reduce the risk of all-cause mortality and cardiovascular death. The results of this study provide new evidence to reduce all-cause mortality and cardiovascular death in diabetic patients with CAD treated with statins. Further large-scale prospective cohort studies should be performed to verify whether implementation of screening TG/HDL-C ratio will change the prognosis of diabetic patients with CAD.

However, several limitations of this study should be acknowledged. First, the current study was retrospective. The lack of information of waist circumference made it difficult to calculate the fatty liver index. Therefore, fatty liver index was not included in the analysis. Second, the follow-up information was collected by telephone or electronic medical record review. The follow-up information mainly included survival data. Baseline data after 4-year follow-up was not collected. Third, the information about glycemic control optimization and changes in medications was not collected during follow-up. The effect of changes in medications should be taken into consideration in the future, prospective study. Fourth, the complications and severity of T2DM and CAD differ, which could have affected the risk of all-cause mortality and cardiovascular death. Finally, as lipid levels vary among different ethnicities, it is not known whether these findings can be applicable to other ethnicities.

CONCLUSION
An elevated TG/HDL-C ratio was associated with an increased risk of all-cause mortality and cardiovascular death in diabetic patients with CAD who were treated with statins. Moreover, the addition of the TG/HDL-C ratio into the traditional risk model increased the predictive value for subsequent all-cause mortality and cardiovascular death. Therefore, the TG/HDL-C ratio may be a useful marker for evaluating the prognosis in diabetic patients with CAD who are treated with statins.

DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the Ethical Committee of Tianjin Chest Hospital. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS
LW, HC, and JZ participated in the study design. LW, YH, AW, YZ, HY, LR, WQ, and WL participated in data collection. LW, HY, and LR performed the statistical analysis. LW drafted the article. All authors contributed to the article and approved the submitted version.

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