Association of Triglyceride-Glucose index with risk of microalbuminuria in Chinese children with type 1 diabetes

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Research

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Abstract

Objective

The triglyceride-glucose index (TyG index) has been regarded as a useful alternative marker for the early identification of insulin resistance (IR). Accordingly, the objective of the present study is to explore the association of the TyG index with microalbuminuria (MA) in T1DM children.

Methods

The study retrospectively enrolled 129 patients ((boys/girls = 51/78) with T1DM in the Endocrine inpatient wards of Tianjin Children's Hospital from June 2017 to May 2019. 43 patients with MA were randomly matched 1:2 with 86 patients without MA based on the Propensity Score Matching. TyG index was calculated as follows: ln[fasting triglycerides (mg/dL)×fasting plasma glucose (mg/dL)/2].

Results

TyG index and related lipid parameters were significantly higher in patients with MA compared with those without (all $p < 0.05$). Multivariable logistic regression analysis revealed that the TyG index in patients with MA was 2.166 times compared with those without (OR = 2.166; 95% CI, 1.559–3.009; $p < 0.001$). FPG (OR = 1.068; 95% CI, 1.026–1.112; $p = 0.001$), HBA1c (OR = 1.193; 95%CI, 1.066–1.334; $p = 0.002$), and the occurrence of DKA (OR = 9.863; 95% CI, 2.764–35.192; $p < 0.001$) were still associated with a higher MA risk. ROC curves analysis shown that the area under the curve (AUC) of the TyG index for predicting MA was the largest (0.78) compared with fasting plasma glucose (FPG) and HAB1c. The cumulative incidence of MA in the higher TyG index group was significantly higher than that in the lower TyG index group in 15 years ($p < 0.001$).

Conclusions

The TyG index was significantly correlated with MA levels. An elevated TyG index had a significantly greater risk of MA events independent of DKA, even after adjusting for confounding risk factors. The TyG index was more specific than FPG and HBA1c in predicting MA. Compared to patients with a lower TyG index, those with a higher TyG index had an apparently higher cumulative incidence of MA.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease with genetic predisposition and environmental influences predominantly early in life, which induces pancreatic β-cell autoimmunity eventually resulting in both loss of function and destruction[1]. Diabetic nephropathy (DN), a major microvascular complication of both T1DM and T2DM, is an important reason of end-stage renal disease (ESRD) in the

developed countries. The initial stage of nephropathy is characterized by the onset of persistent microalbuminuria (MA) and hyperfiltration[2]. Chronic hyperglycemia is considered to be the major pathogenic factor involved in MA[3].

Insulin resistance (IR), is a metabolic state in which the responsiveness of target tissues to normal insulin concentrations is reduced and plays an important role in these outcomes, especially in T2DM and metabolic syndrome[4]. The homeostasis model assessment (HOMA), derived from the fasting levels of insulin and glucose, is a robust tool used as a surrogate measure for IR. An insulin-free equation for estimating IR was developed because of the measurement of fasting insulin is cumbersome with no standard assay available[5]. The triglyceride-glucose index (TyG index) has been regarded as a useful alternative marker for the early identification of IR individuals[6]. Research had shown that the value of the TyG index in reflecting metabolic health status and predicting the development of diabetes[7]. A Rural Chinese Cohort Study suggested higher TyG index can increase the risk of incident T2DM[8]. A study firstly estimated the cut-off values of the TyG index for metabolic syndrome in adolescents[5].

The TyG index, a factor easily available from a common lipid profile at no extra cost, is a better risk predictor of cardiovascular events than FPG or HbA1c and provides additional information of clinical significance[9]. Patients with a higher TyG index were more likely to develop hypertension[10], incident arterial stiffness, and nephric microvascular damage than those with a lower TyG index[11]. More importantly, the TyG index could be used as another target other than FPG or HbA1c to further reduce risk and facilitate the development of more drugs to improve IR[9].

IR not only is a feature of obesity and T2DM but also can be present in patients with T1DM[12, 13]. Its role in the development of T1DM has been gaining increasing interest. In a model (the nonobese diabetic mouse) of T1DM, a study concluded that IR driven by lipid- and glucose- independent mechanism was already present in the liver of prediabetic mice[14, 15]. However, population-based studies of the TyG index in T1DM children with MA, especially in the occurrence of DN, are lacking. The purpose of this study was to explore the association of the TyG index with the risk of MA in Chinese children with T1DM.

2 Materials And Methods

2.1 Subjects

The present study is a single-center, retrospective study among patients who were diagnosed with T1DM and treated with insulin being subcutaneous injections such as Novolin and Novorapid in the Endocrine inpatient wards of Tianjin Children's Hospital between June 2017 and May 2019. The inclusion criteria for T1DM include: (1) previously or newly diagnosed T1DM under treatment of antidiabetic medication (insulin); (2) the typical symptoms of diabetes with a random blood glucose ≥ 11.1 mmol/L, and/or fasting plasma glucose (FPG) ≥ 7.0 mmol/L, and/or 2-h blood glucose after oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L; (3) HbA1c level ≥ 6.5% on admission. We defined the concentration of MA < 30mg/L for T1DM patients without MA, and MA ≥ 30mg/L for T1DM patients with MA. Ultimately, a total

of 129 children with T1DM were included in the present study. 43 patients with MA were randomly matched 1:2 with 86 patients without MA based on the Propensity Score Matching. They were aged from 10 months to 15 years. Major medical abnormalities, including central nervous system diseases, angiocardiopathy, or life-threatening medical illnesses (infections or cancer) were excluded. All subjects were Han Chinese.

After the study procedure was explained in detail to the parents of patients included in the study, they signed the informed consent document. Before this study began, the research protocol was approved by the Institutional Review Board of Tianjin Children's Hospital.

2.2 Data collection and measures

Data of demographic and clinical characteristics, including age, sex, weight, height, medical history, and medical treatment were extracted from the medical information recording system of Tianjin Children's Hospital. BMI was calculated as follows: BMI = weight (kg)/ [height (m)]^2.

Blood samples were collected before an initial insulin therapy. The plasma was separated, aliquoted, and stored at -70°C before use. The routine hematology and biochemical parameters, including lipid profiles [triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)], FPG, HbA1c, C-peptide, CRP, and PCT were measured by standard laboratory methods at the diagnostic laboratory of Tianjin Children's hospital.

T1DM patients were screened for the presence of MA in a random spot urine collection at the time of visit. We used the level of MA < 30mg/L for T1DM patients without MA,and MA ≥ 30mg/L for T1DM patients with MA.

The TyG index was calculated using the formula: ln [fasting TGs (mg/dL) ×FPG (mg/dL)/2]

2.3 Statistical analysis

Continuous variables were presented as Mean ± SD or median [IQR] in the case of normal or non-normal distribution, and differences between the two groups were examined by independent-sample t-test or Mann–Whitney U test correspondingly. Categorical variables were described as counts (percentages) and compared by χ2 test or Fisher's exact test appropriately. The correlation was computed using the Pearson correlation coefficient. The correlations between MA levels and clinical variables were visualized using hierarchical clustering and presented as a heatmap. Multivariable logistic regression analysis was performed to predict risky variables of MA including age, sex, and BMI as covariates. ROC curves of TyG index, FPG, and HBA1c were used to predict MA in T1DM Children. Cumulative hazards in T1DM patients with and without MA groups were calculated and compared using the R language. Statistical analyses were carried out using SPSS version 21. All analyses were 2-tailed, with significance set at $P < 0.05$.

3 Results

3.1 Comparison of demographic and clinical variables in patients with and without MA

A total of 129 T1DM patients (51 boys, 78 girls) were enrolled in the present study. The median age was 7.0 years in both groups. The median [IQR]BMI of patients without MA was 15.90 [14.8,17.1] kg/m2, and 15.21 [14.1,16.4] kg/m2 in patients with MA. Baseline characteristics of the total patients and groups stratified by the occurrence of MA were presented in Table 1.

Table 1
Baseline clinical characteristics of T1DM patients with or without MA

Characteristics	**T1DM without MA (n = 86)**	**T1DM with MA (n = 43)**	***P* value**
Age, median [IQR]	7.0[5.0,10.0]	7.0[4.0,11.0]	p = 0.074
Girls (%)	52(60.465)	26(60.465)	
Boys (%)	34(39.535)	17(39.535)	p = 1.000
BMI, median [IQR]	15.90[14.8,17.1]	15.21 [14.1,16.4]	p = 0.086
FPG, median [IQR]	16.7[9.6,25.18]	24.47[18.7,33.76]	P = 0.001
HBA1c, median [IQR]	11.0[8.2,12.9]	13.0[11.7,14.2]	p < 0.001
C-peptide, median [IQR]	0.11[0.01,0.22]	0.13[0.06,0.18]	p = 0.456
TG, median [IQR]	0.78[0.36,2.65]	4.20[1.40,8.11]	p < 0.001
TC, mean (SD)	2.64(0.967)	3.18(1.232)	P = 0.008
HDL-C, median [IQR]	1.39[1.01,1.67]	0.74[0.53,1.06]	p < 0.001
LDL-C, median [IQR]	2.61[1.92,3.32]	3.23[2.28,4.03]	P = 0.016
TyG index, mean (SD)	9.61(1.383)	11.08(1.290)	p < 0.001
CRP, median [IQR]	0.9[0.2,3.0]	0.9[0.2,5.1]	p = 0.650
PCT, median [IQR]	0.06[0.04,0.11]	0.09[0.05,0.23]	p = 0.015
Without DKA (%)	36(41.860)	3(6.977)	
With DKA (%)	50(58.140)	40(93.023)	p < 0.001
Abbreviations:			
T1DM, type 1 diabetes mellitus; MA, microalbuminuria; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;			
The TyG index was calculated using the formula: ln [fasting TGs (mg/dL)×FPG (mg/dL)/2].			

FPG, HbA1c, and TyG index in patients with MA were significantly higher compared with those without($p < 0.001$). There was no significant difference in C-peptide, CRP, and PCT between the two groups (all $p > 0.05$). The MA patients had higher TG, TC, and LDL-C levels (all $p < 0.05$). In contrast, HDL-C was lower in patients with MA ($p < 0.001$). The incidence of DKA increased significantly in T1DM children with MA compared with those without($P < 0.001$). Analysis of covariance (ANCOVA) was further conducted to control for the effects of gender, age, and BMI, significant differences still existed between the two groups.

3.2 Correlation analysis between MA levels and clinical variables

To examine the relationship between MA and clinical indicators, Pearson correlation analysis was used. The results shown that MA levels were positive correlated with FPG ($r = 0.28$, $p = 0.001$), HbA1c ($r = 0.22$, $p = 0.011$), and TyG index ($r = 0.37$, $p < 0.001$). Correlations between the MA levels and risk factors were shown in Table 2. Heatmap shown the pairwise correlation coefficients of clinical variables in T1DM patients with and without MA (shown in Fig. 1).

Table 2
Correlations between the microalbuminuria levels and risk factors

	MA (mg/L)	
Characteristics	r	*P* value
Age(months)	0.11	p = 0.233
BMI (kg/m2)	-0.01	p = 0.274
FPG (mmol/L)	0.28	p = 0.001
HbA1c (%)	0.22	p = 0.011
CRP (mg/L)	0.05	p = 0.753
PCT (ng/ml)	0.03	p = 0.695
TyG index	0.37	P < 0.001

3.3 Multivariable logistic regression analysis of risk factors

As reported in Table 3, in the multivariable logistic regression analysis that was adjusted for age, sex, and BMI, the TyG index remained an independent factor. The results revealed that the TyG index in patients with MA was 2.166 times compared with those without MA (OR = 2.166; 95% CI, 1.559–3.009; $p < 0.001$). FPG (OR = 1.068; 95% CI, 1.026–1.112; $p = 0.001$), HBA1c (OR = 1.193; 95%CI, 1.066–1.334; $p = 0.002$), and the occurrence of DKA (OR = 9.863; 95% CI, 2.764–35.192; $p < 0.001$) were still associated with a higher MA risk.

Table 3
Odds ratios for microalbuminuria estimated using multivariable logistic regression.

	unadjusted			adjusted		
	OR	95% CI	*P* value	OR	95% CI	*P* value
FPG	1.068	[1.027,1.111]	0.001	1.068	[1.026,1.112]	0.001
HBA1c	1.188	[1.072,1.316]	0.001	1.193	[1.066,1.334]	0.002
C-peptide	0.492	[0.032,7.580]	0.611	0.351	[0.021,5.882]	0.467
TyG index	2.159	[1.566,2.976]	< 0.001	2.166	[1.559,3.009]	< 0.001
CRP	1.024	[0.977,1.072]	0.322	1.031	[0.978,1.086]	0.255
PCT	1.013	[0.963,1.065]	0.629	1.020	[0.968,1.075]	0.455
DKA						
0						
1	9.600	[2.753,33.475]	< 0.001	9.863	[2.764,35.192]	< 0.001

3.4 Cumulative incidence of MA in the lower TyG index and higher TyG index groups

ROC curves analysis shown that the area under the curve (AUC) of the TyG index for predicting MA was the largest (0.78), with the highest Youden index (0.453). The TyG index of 10.650 was determined as the optimal cut-off point for predicting MA with a sensitivity of 67.4% and the best specificity of 77.9%. ROC curves of TyG index, FPG, and HBA1c predicting MA in T1DM Children were shown in Fig. 2.

The cumulative incidence of MA was shown in Fig. 3. The cumulative incidence of MA in the higher TyG index group was significantly higher than that in the lower TyG index group in 15 years ($p < 0.001$).

4 Discussion

In our present study, we retrospectively investigated the predictive significance of IR assessed by the TyG index for MA in Chinese children with T1DM. The major findings were listed as follows:(1) The TyG index was significantly correlated with MA levels; (2) An elevated TyG index had a significantly greater risk of MA events independent of DKA, even after adjusting for confounding risk factors; (3) The TyG index was more specific than FPG and HBA1c in predicting MA; (4) Compared to patients with lower TyG index, those with higher TyG index had an apparently higher cumulative incidence of MA in 15 years. To our knowledge, our study is the first to compare the value of FPG, HbA1c, and TyG index to predict the risk of MA events in T1DM children.

Insulin resistance (IR), characterized by a decrease in cell sensitivity to insulin, is one of the leading causes of metabolic abnormalities[5]. Lipidomics studies of young and at-risk patients that progressed to clinical disease revealed that some classes of lipids shown dysregulation in the blood. A few lipid metabolites were found to be associated with T1DM[16]. The prevalence of hypertriglyceridemia and low HDL-C are key metabolic abnormalities in patients with IR and represent diabetic dyslipidemia. Metabolomics techniques have shown that patients who progress to diabetes have different levels of certain lipids when compared with persons who remain non-diabetic[1]. Diabetic patients with dyslipidemia commonly suffer from a higher risk of adverse outcomes[17].

The TyG index is an advantageous surrogate marker of IR among adolescents, as it is a non-invasive method that uses common components to clinical practice, making it accessible and low cost[9]. Besides, the TyG index has the advantage of being based on FPG levels, which is directly related to the development of IR, β-cell dysfunction, pre-DM, and T2DM in young adults. Thus, the FPG of the TyG index may potentiate it for the prediction of diabetes concerning lipid ratio[8]. IR with higher TG and lower HDL-C concentrations is a clustered pathway of different metabolic disorders[4]. A population-based study explored the associations of lipid parameters with prevalent IR and diabetes. The potential value of using the Non-HDL-C/HDL-C ratio and TG/HDL-C ratio as the dyslipidemia management tool among patients with diabetes should be given more consideration in the clinical approach[17]. A study confirmed that the index provided a good alternative to the gold standard test for recognizing IR in children aged 7–17[18].IR is an increasingly important issue for the early identification of children at risk, and the TyG index offers the advantage that it not requires insulin measurements and is based on routine laboratory assessments.

The global burden of DN is rising along with an increasing prevalence of diabetes, which is a leading reason of kidney disease. Regular screening to detect DN can prompt early intervention, which can reduce the incidence of ESRD and healthcare costs, and increase ESRD-free survival[19]. Levels of MA are seen as clinically relevant advanced stages of kidney disease because of their strong association with subsequent ESRD[20].

In our study, the MA patients had higher TG, TC, and LDL-C levels. In contrast, HDL-C was lower in patients with MA. It is clear that dyslipidemia contributes significantly to the excess risk of MA events. In addition, inflammatory protein levels in the serum have been associated with the presence of MA in T1DM patients. High serum concentrations of CRP were correlated with higher urinary albumin-to-creatinine ratio quartiles[3]. However, we have not found the relationship between CRP, PCT, and MA. Several studies supported the clinical significance of the TyG index for the assessment of vascular damage. An elevated TyG index was closely correlated with a higher risk of arterial stiffness and nephric microvascular damage[11]. A study reported that the TyG index demonstrated a positive linear correlation with urinary albumin to creatinine ratio[21]. Zhao et al. found that a higher TyG index was associated with a higher risk of chronic kidney disease and MA. The TyG index could be a predictor of incident DN and play a role in nephric microvascular damage[11]. In the future, more studies are needed to explore the relationship between the TyG index and microvascular damage, such as MA, DN, retinopathy, cardiac microvascular dysfunction, and markers of endothelial injury.

Anyway, recognition of these metabolic alterations may aid in studies of disease progression and may open a time window for MA prevention strategies, it is reasonable to recommend the TyG index as an effective and convenient indicator. The TyG index can identify patients with a higher risk of MA events, which may promote more positive therapies such as exercise, diet management, and even medication treatment to reduce the risk[11]. For T1DM patients, even if they have reached the guideline-guide targets for FPG and HbA1c, the TyG index can identify patients at increased risk and prompt them to consider more aggressive treatments to avoid developing into DN, especially ESRD.

The following limitations of our study should be addressed. Firstly, the findings were restricted to a selected group of Chinese patients from a single center. Hence, results should be interpreted with caution. Secondly, although we did find a significant association between the TyG index and MA, other potential factors were not evaluated in the present study, such as dietary characteristics and other concomitant therapies influencing glucose metabolism and lipid levels. Thirdly, we had a comparatively small sample size of subjects, which had become smaller when dividing into two groups. Therefore, the results and conclusions in our study should be regarded as preliminary. A larger sample size and multicenter trials are necessary to confirm our findings.

5. Conclusions

The TyG index was significantly correlated with MA levels. An elevated TyG index had a significantly greater risk of MA events independent of DKA, even after adjusting for confounding risk factors. The TyG index was more specific than FPG and HBA1c in predicting MA. Compared to patients with a lower TyG index, those with a higher TyG index had an apparently higher cumulative incidence of MA.

Declarations

Acknowledgments

The authors appreciate all the participants in the study.

Statement of Ethics

This study conforms to the medical ethics regulations approved by the Ethics Committee of Tianjin Children’s Hospital (Tianjin University Children’s Hospital), and the study approval reference number is 2016021. All the parents of participants signed the informed consent under institutional review board-approved protocols.

Conflict of Interest Statement

All the authors have no conflict of interest.

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Author contributions

L.G., X.W., and J.S. are responsible for the work described in this paper. M.Z., and J.G. conceived, designed, and/or planned the study, and interpreted the results. X.Z., C.G., and L.P. conducted data analysis. J.S. and X.W. drafted the manuscript. C.C., W.Y., and L.L. critically reviewed and/or revised the manuscript for important intellectual content. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the privacy of research participants but are available from the corresponding author upon reasonable request.

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Figures

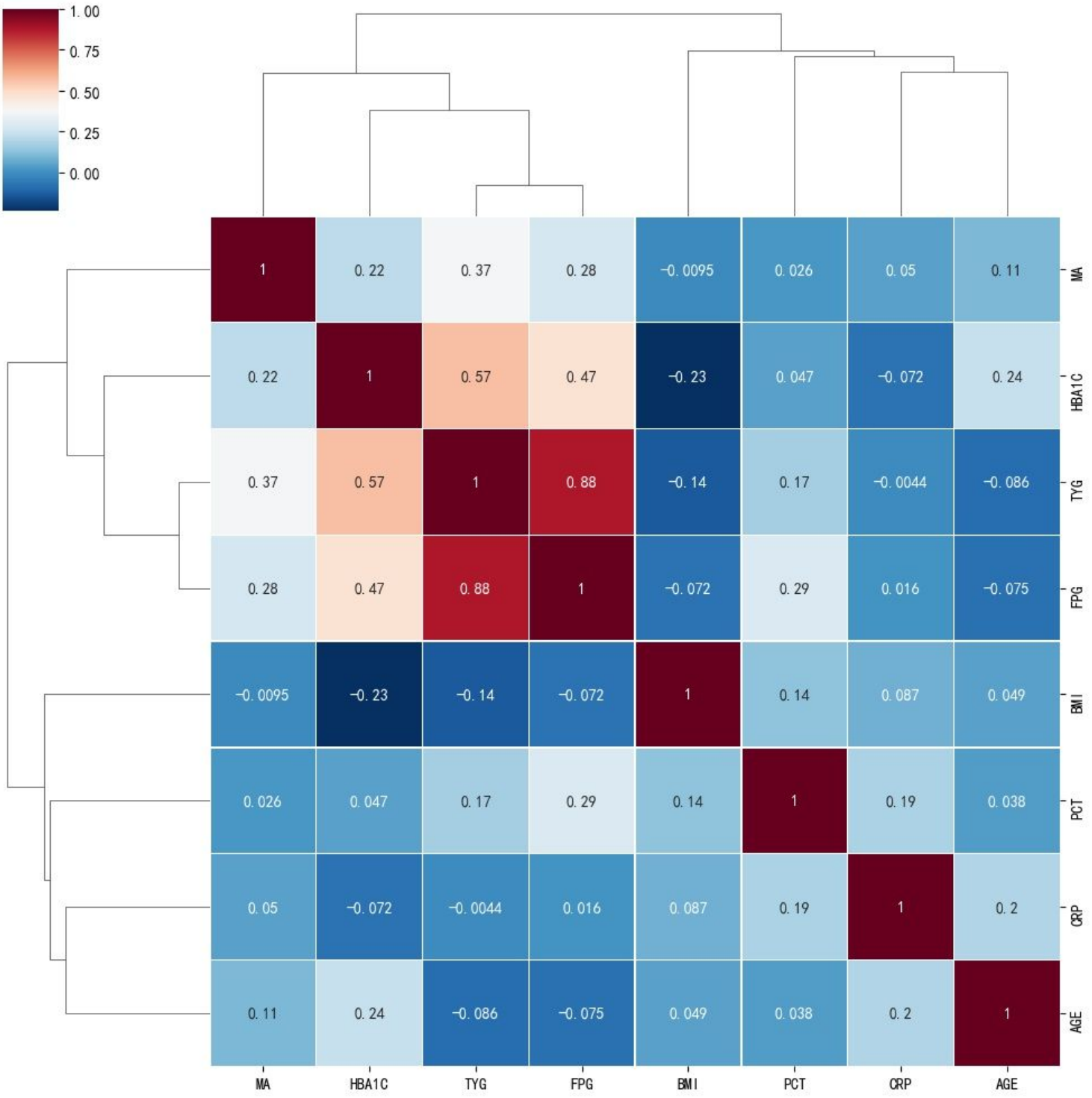

Figure 1

Heatmap showing the pairwise correlation coefficients of clinical variables in type 1 diabetes (T1DM) patients with and without microalbuminuria.

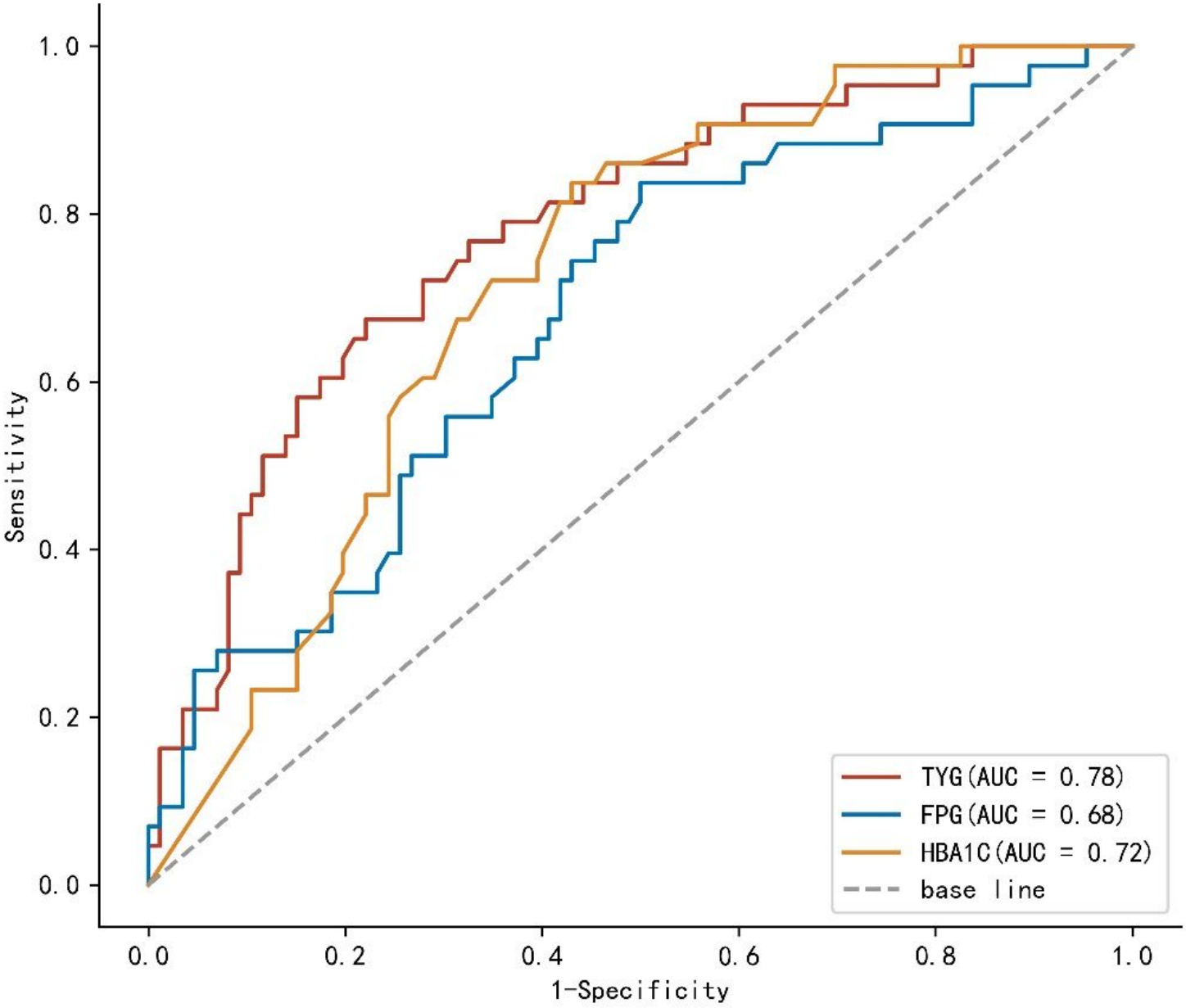

Figure 2

ROC curves of TyG index, FPG and HBA1c predicting MA in T1DM Children.

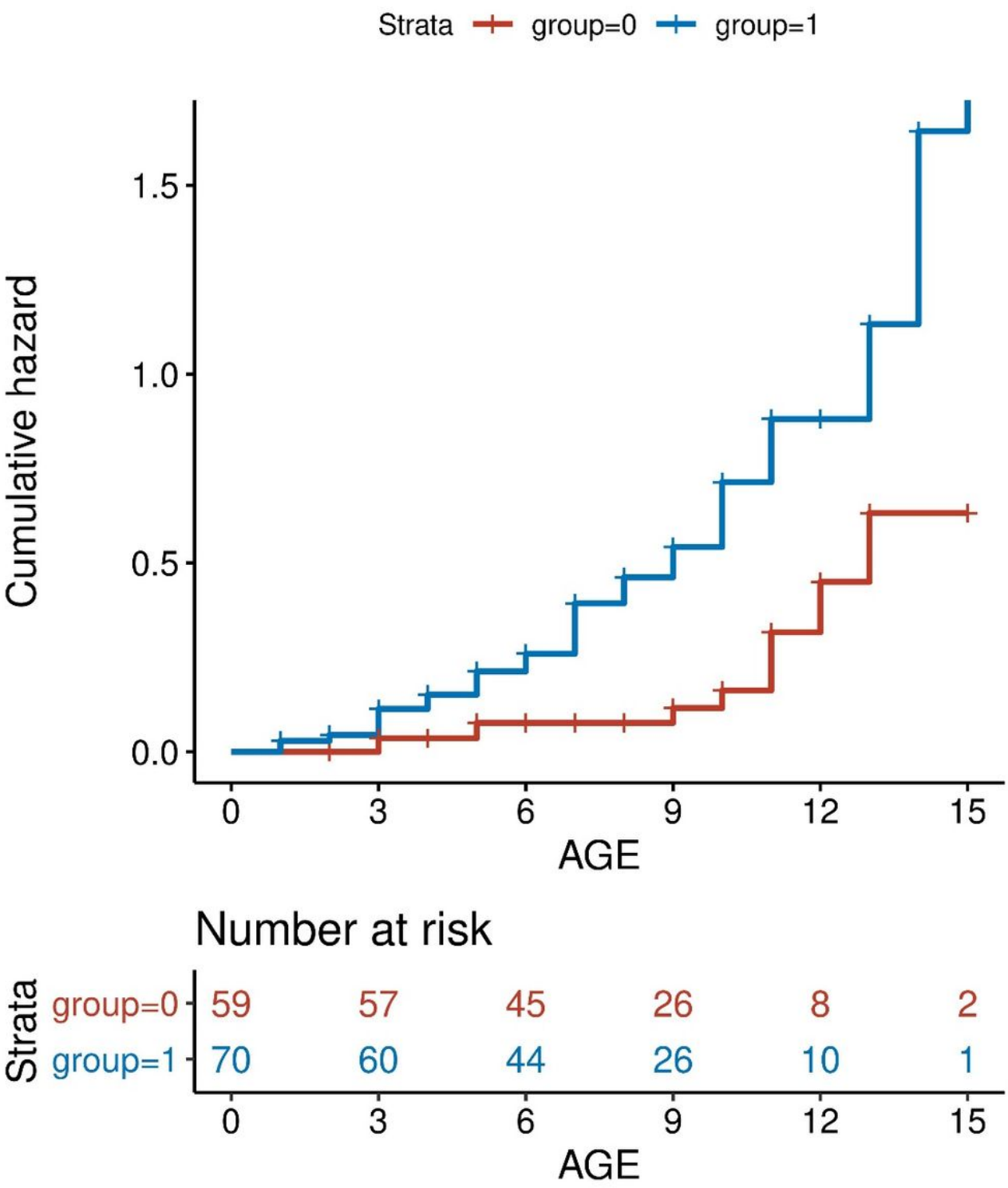

Figure 3

Cumulative incidence of microalbuminuria in the lower TyG index and higher TyG index groups.