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Higher triglyceride-glucose index is associated with severe proteinuria and decreased renal function in patients with primary membranous nephropathy

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Abstract

Background In recent years, the triglyceride-glucose (TyG) index has emerged as a reliable surrogate marker of insulin resistance (IR). This study aimed to investigate the association between the TyG index and severe proteinuria or decreased renal function in patients with primary membranous nephropathy (PMN).

Methods We consecutively enrolled 536 patients with PMN hospitalized at Peking University Third Hospital from January, 2014 to December, 2023. The TyG index was calculated as Ln[fasting triglyceride (mg/dL)×fasting blood glucose (mg/dL)/2]. All participants were categorized into quantiles according to the TyG index. Severe proteinuria was defined as 24 h urine protein > 3.5 g/d, and decreased renal function was defined as the estimated glomerular filtration rate < 90 mL/min/1.73m^2. Multivariable logistic regression, restricted cubic spline (RCS) curves, and receiver operating characteristic (ROC) curves were used for analysis.

Results Among 536 patients with PMN, 355 patients had severe proteinuria and 149 patients had decreased renal function. The levels of TyG index was significantly elevated in PMN patients with severe proteinuria or decreased renal function. The RCS analysis revealed a positive linear relationship of the TyG index with the risk of severe proteinuria (*P* for non-linear = 0.317) or decreased renal function (*P* for non-linear = 0.199) in patients with PMN. Using the lowest quantile as the reference, multivariate-adjusted logistic regression indicated that patients in the highest quantile of the TyG index had a significantly increased risk of severe proteinuria [odds ratio (OR) = 2.08, 95% confidence interval (CI): 1.44–3.01, *P* < 0.001] and decreased renal function (OR = 1.57, 95% CI: 1.04–2.36, *P* = 0.032). The area under the ROC curve (AUC) of the TyG index is 0.613 (95% CI: 0.564–0.662) for severe proteinuria and 0.590 (95% CI: 0.536–0.643) for decreased renal function.

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Conclusion Our findings indicated that the TyG index has a positive linear correlation with severe proteinuria or decreased renal function in patients with PMN.

Keywords Triglyceride-glucose index, Primary membranous nephropathy, Proteinuria, Renal function

Introduction

Primary membranous nephropathy (PMN) is a kidney-specific autoimmune disease caused by the attack of autoantibodies against podocyte antigens leading to the formation of in situ immune complexes [1]. However, the pathogenesis of PMN is still far from being completely elucidated, and 40–60% of patients with nephrotic syndrome will ultimately progress to end-stage renal disease (ESRD) or die from cardiovascular events [2]. Recently, the American Heart Association (AHA) first proposed the definition of cardiovascular-kidney-metabolic (CKM) syndrome and defined it as a health disorder that results from a systemic pathophysiological interaction between obesity, diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD) [3]. Insulin resistance (IR) plays a key role in the pathogenesis of CKM syndrome, which led us to focus on the relationship between IR and CKD.

IR is characterized by reduced sensitivity or responsiveness to the effects of insulin metabolism, including insulin-mediated glucose processing, and has been widely recognized as an independent risk factor for the development of CVD [4]. Insulin also influences the kidney since the insulin receptor is expressed on renal tubular cells and podocytes [5]. In addition, the strong correlation of IR with salt-sensitive arterial hypertension indicates the involvement of the kidney in IR and CVD [6]. The triglyceride-glucose (TyG) index, calculated by fasting triglyceride (TG) and fasting blood glucose (FBG), has been considered as a simple and reliable surrogate marker of IR [7, 8]. Studies have demonstrated that the TyG index plays an important role in assessing IR and predicting the risk of adverse outcomes, such as hypertension, diabetes and atherosclerosis [9–11].

Previous studies showed that in patients with primary glomerular diseases, IR and concomitant DM are associated with an increased risk of cardiovascular comorbidity, and PMN was found to be independently associated with a higher risk of CVD [12]. Lee et al. also demonstrated that patients with PMN were at higher risk of cardiovascular events [13]. Previous studies also found that the TyG index was associated with increased risk of diabetic kidney disease (DKD) [14], renal function worsening [15], and ESRD in patients with DM [16]. In addition, the TyG index was found to be associated with increased likelihood of albuminuria in United States adults [17]. However, the mutual association between the TyG index and PMN remains unclear. Based on the above clues, we hypothesized that the TyG index may be associated with the clinical severity of PMN based on the level of proteinuria and renal function. If confirmed, for the prevention of early ESRD, TyG index might be considered as part of the early goals of therapy of the nephrotic syndrome of PMN.

Therefore, the current study aimed to investigate the association between the TyG index and severe proteinuria or decreased renal function in patients with PMN.

Methods

Study population and design

Clinical data of PMN patients hospitalized in the nephrology department of Peking University Third Hospital from January, 2014 to December, 2023 were retrospectively collected. 612 patients diagnosed with membranous nephropathy (MN) after renal biopsy were included for participants screening. Patients aged < 18 years old were excluded ($n = 4$). Patients combined with other types of kidney diseases ($n = 14$), including IgA nephropathy (IgAN), diabetic nephropathy (DN), lupus nephritis (LN), hepatitis B associated nephritis were excluded. Patients combined with malignant tumor ($n = 9$) and autoimmune diseases ($n = 5$) were excluded. Patients who were pregnant ($n = 10$) were excluded. Patients with missing data of TG or FBG were excluded ($n = 36$). Finally, 536 patients with PMN were enrolled into this study. Flow chart of study participants was shown in Fig. 1.

Study outcomes

Severe proteinuria was defined as the value of 24 h urine protein > 3.5 g/d at baseline. Decreased renal function was defined as the estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [18].

Data collection and definitions

Clinical characteristics, including age, sex, duration of MN, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), history of smoking and drinking, the medical history of hypertension, DM, coronary heart disease (CHD), stroke, and hyperlipidemia were collected retrospectively. Laboratory indicators, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), 24 h urine protein, serum albumin (ALB), serum uric acid (SUA), blood urea nitrogen (BUN), serum creatinine

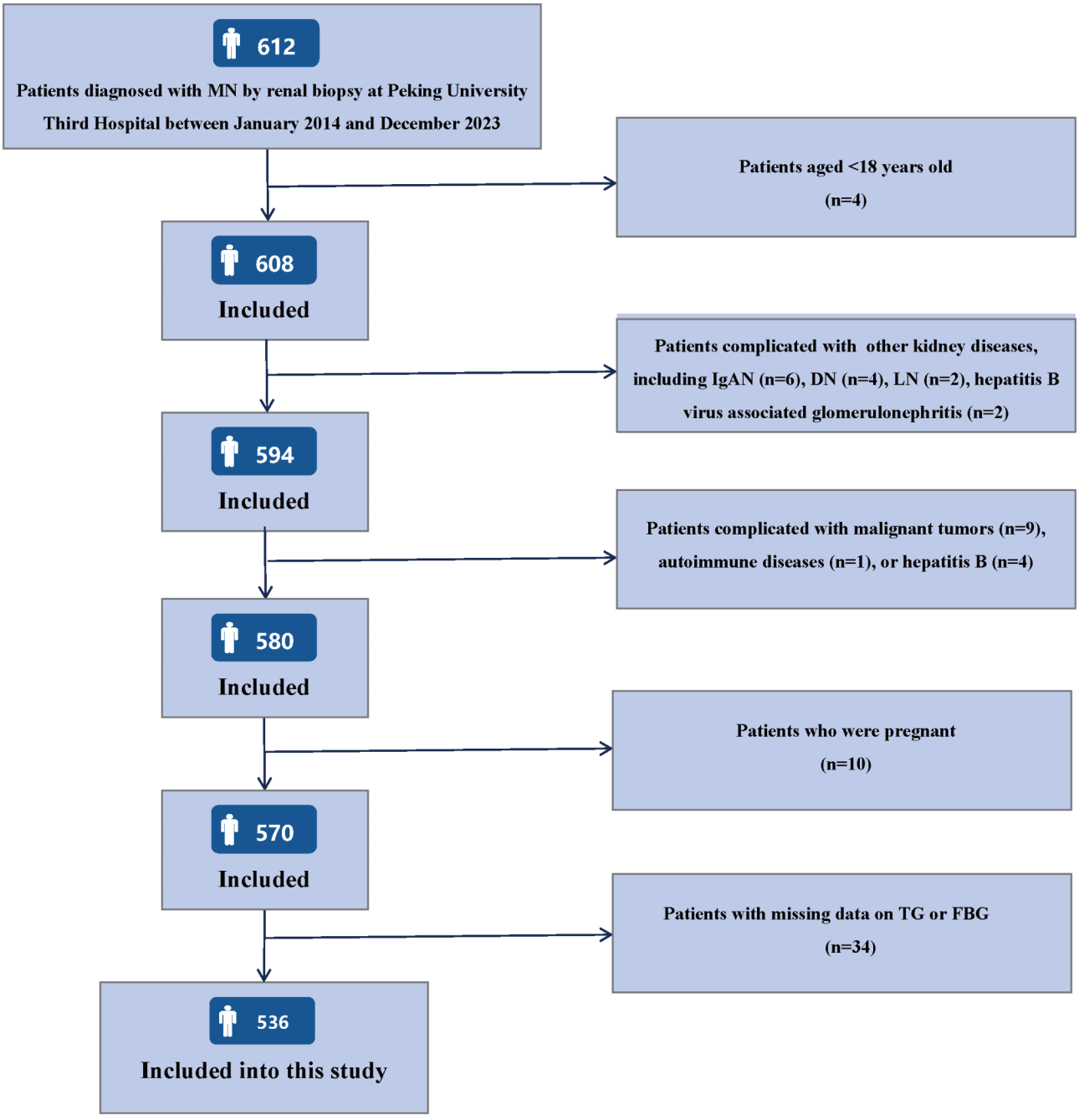

Fig. 1 Flow chart for participant selection

(Scr), eGFR, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, and hemoglobin (HGB) were also collected at baseline.

Hypertension was defined as a self-reported history of hypertension, or SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or currently using antihypertensive drugs [19]. DM was defined as a self-reported history of DM, or FBG ≥ 7.0 mmol/L, or 2-hour plasma glucose ≥ 11.1 mmol/L, or HbA1c ≥ 6.5%, or currently using hypoglycemic drugs [20]. Hyperlipidemia was defined as a self-reported history of hyperlipidemia, or TC ≥ 6.22 mmol/L, or TG ≥ 2.26 mmol/L, or HDL-C < 1.04 mmol/L, or LDL-C ≥ 4.14 mmol/L, or currently using lipid-lowering drugs [21]. The TyG index was defined as Ln[fasting TG (mg/dL)×FBG (mg/dL)/2] [22].

Statistical analysis

Continuous variables were presented as mean with standard deviation or median with interquartile range, whereas categorical variables were presented as

proportions. Independent sample t-test or the Mann-Whitney U test was used to test group differences for continuous variables, and the Chi-square test was used for categorical variables. Kruskal-Wallis test was used to evaluate the differences in groups divided by TyG index (quantiles). When the baseline TyG index was treated as a continuous variable, restricted cubic spline (RCS) curves were used to depict the association between TyG index and the risk of severe proteinuria or decreased renal function in patients with PMN. Spearman correlation analysis was used to investigate the correlation between the baseline TyG index and other clinical parameters. Multivariate logistic regression models were employed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) in different models. The area under the curve (AUC) of receiver operating characteristic (ROC) curves was used to evaluate the predictive ability of the TyG index. Furthermore, we conducted subgroup analyses based on the stratification of sex, age, BMI, smoking, history of hypertension, history of DM, eGFR, and 24 h urine protein. In addition, an interaction term was added to investigate the heterogeneity of associations between these subgroups using log likelihood ratio test model. P-value < 0.05 (two-sided) was considered to be statistically significant. All analyses were preformed using R software (version 4.3.1).

Results

Baseline characteristics according to the level of 24 h urine protein or renal function

PMN patients were divided into severe proteinuria group (24-hour urinary protein > 3.5 g/d, $n = 355$) and non-severe proteinuria group (24-hour urinary protein ≤ 3.5 g/d, $n = 181$). In addition, PMN patients were also divided into decreased renal function group (eGFR < 90 mL/min/1.73 m2, $n = 149$) and non-decreased renal function group (eGFR ≥ 90 mL/min/1.73 m^2, $n = 387$) for further analysis. As shown in Table 1, there were many differences in baseline clinical characteristics in patients with and without severe proteinuria, or in patients with and without decreased renal function. It was worth noting that compared to patients without severe proteinuria, the level of TyG index was significantly increased in patients with severe proteinuria (9.15 ± 0.68 vs. 8.88 ± 0.58, $P < 0.001$). Compared to patients without decreased renal function, the level of the TyG index was also significantly increased in patients with decreased renal function (9.18 ± 0.63 vs. 9.01 ± 0.67, $P = 0.006$).

Clinical characteristics according to quantiles of the TyG index

Further, PMN patients were divided into four groups according to quartiles of the TyG index, which were as follows: Q1 (TyG index < 8.58, $n = 134$), Q2 (8.58 ≤ TyG index < 8.99, $n = 134$), Q3 (8.99 ≤ TyG index < 9.48, $n = 133$), and Q4 (TyG index ≥ 9.48, $n = 135$). As shown in Table 2, compared to patients with the lowest quartile of the TyG index, patients with the highest quartile of the TyG index had higher levels of BMI, DBP, higher proportion of DM, and higher proportion of hyperlipidemia ($P < 0.05$). In terms of laboratory indicators, compared to patients with the lowest quartile of the TyG index, patients with the highest quartile of the TyG index had higher levels of TC, TG, FBG, HbA1c, 24 h urine protein, Scr, ESR, CRP, WBC, and HGB, while had lower levels of HDL-C and eGFR ($P < 0.05$).

Correlation analysis of the TyG index and other clinical parameters

Spearman correlation analysis was used to analyze the correlation between the TyG index and other important clinical parameters. As shown in Table S1, the TyG index was positively correlated with BMI, DBP, FBG, HbA1c, TC, TG, 24-hour urinary protein, ESR, WBC, and HGB, while negatively correlated with HDL-C and eGFR in patients with PMN.

The dose-response relationship between the TyG index and severe proteinuria or decreased renal function

The dose-response relationship between the TyG index and severe proteinuria or decreased renal function in patients with PMN was evaluated by RCS curves. As shown in Fig. 2A, a positive linear correlation was found between the TyG index and severe proteinuria in patients with PMN (P for non-linear = 0.317). As shown in Fig. 2B, the results showed that there was also a positive linear correlation between the TyG index and decreased renal function in patients with PMN (P for non-linear = 0.199).

Logistic regression analysis of the association between the TyG index and severe proteinuria or decreased renal function in patients with PMN

Logistic regression analysis was used to clarify the association between the TyG index and severe proteinuria in patients with PMN, which were as follows: Model 1: adjusted for sex and age; Model 2: adjusted for variables in model 1 plus smoking, drinking, BMI, hypertension, DM, and hyperlipidemia; Model 3: adjusted for variables in model 2 plus eGFR, SUA, HbA1c, HDL-C and LDL-C. The results showed that a higher TyG index was associated with increased risk of severe proteinuria in patients with PMN. As shown in Table 3, this association was significant both in the unadjusted model [OR (95%CI): 1.99 (1.47–2.69), $P < 0.001$] and the fully adjusted model [OR (95%CI): 2.08 (1.44–3.01), $P < 0.001$]. Then we transformed the baseline TyG index from a continuous variable to a categorical variable. Compared to the lowest

Table 1 Clinical baseline characteristics of PMN patients with different levels of proteinuria and renal function

Variables	Overall (*n* = 536)	Severe proteinuria (*n* = 355)	Non-severe proteinuria (*n* = 181)	*P*-value	eGFR < 90 mL/min/1.73 m^2 (*n* = 149)	eGFR ≥ 90 mL/min/1.73 m^2 (*n* = 387)	*P*-value
Age (years)	51 ± 14	51 ± 14	50 ± 15	0.176	59 ± 11	47 ± 13	**< 0.001**
Male (n,%)	331 (61.75%)	240 (67.61%)	91 (50.28%)	**< 0.001**	104 (69.8%)	227 (58.66%)	**0.023**
MN duration (months)	4 (1, 12)	4 (1, 12)	4 (2, 12)	0.442	6 (2, 18)	4 (1, 11)	**< 0.001**
BMI (kg/m^2)	25.87 ± 3.91	26.37 ± 3.80	24.88 ± 3.96	**< 0.001**	26.17 ± 3.61	25.75 ± 4.02	0.238
SBP (mmHg)	136 ± 19	139 ± 19	131 ± 17	**< 0.001**	141 ± 20	134 ± 18	**< 0.001**
DBP (mmHg)	84 ± 12	86 ± 11	80 ± 11	**< 0.001**	86 ± 12	84 ± 11	0.110
Smoking (n, %)	180 (33.58%)	139 (39.15%)	41 (22.65%)	**< 0.001**	64 (42.95%)	116 (29.97%)	**0.006**
Drinking (n, %)	136 (25.37%)	103 (29.01%)	33 (18.23%)	**0.009**	36 (24.16%)	100 (25.84%)	0.772
Hypertension	304 (56.72%)	207 (58.31%)	97 (53.59%)	0.342	105 (70.47%)	199 (51.42%)	**< 0.001**
DM	87 (16.23%)	64 (18.03%)	23 (12.71%)	0.145	39 (26.17%)	48 (12.40%)	**< 0.001**
CHD	16 (2.99%)	13 (3.66%)	3 (1.66%)	0.307	12 (8.05%)	4 (1.03%)	**< 0.001**
Stroke	32 (5.97%)	20 (5.63%)	12 (6.63%)	0.789	21 (14.09%)	11 (2.84%)	**< 0.001**
Hyperlipidemia	430 (80.22%)	298 (83.94%)	132 (72.93%)	**0.004**	125 (83.89%)	305 (78.81%)	0.229
Serum PLA2R-Ab (RU/mL)	34.66 (4.01, 127.14)	65.12 (11.19, 179.31)	7.39 (1.33, 44.94)	**< 0.001**	27.50 (2.42, 115.14)	35.29 (4.66, 134.88)	0.273
HDL-C (mmol/L)	1.28 ± 0.37	1.25 ± 0.36	1.33 ± 0.39	**0.012**	1.19 ± 0.33	1.31 ± 0.39	**< 0.001**
LDL-C (mmol/L)	4.04 (3.00, 5.50)	4.42 (3.29, 5.94)	3.65 (2.74, 4.46)	**< 0.001**	4.01 (2.99, 5.14)	4.05 (3.00, 5.69)	0.355
TC (mmol/L)	7.19 ± 2.41	7.69 ± 2.52	6.20 ± 1.83	**< 0.001**	6.99 ± 2.40	7.27 ± 2.42	0.225
TG (mmol/L)	2.09 (1.43, 3.05)	2.22 (1.52, 3.34)	1.76 (1.35, 2.63)	**< 0.001**	2.26 (1.62, 3.33)	2.01 (1.37, 2.90)	**0.024**
FBG (mmol/L)	5.10 ± 1.17	5.17 ± 1.27	4.98 ± 0.94	0.056	5.40 ± 1.27	4.99 ± 1.11	**0.001**
TyG index	9.06 ± 0.66	9.15 ± 0.68	8.88 ± 0.58	**< 0.001**	9.18 ± 0.63	9.01 ± 0.67	**0.006**
HbA1c (%)	5.75 ± 0.75	5.79 ± 0.81	5.67 ± 0.61	0.055	6.00 ± 0.81	5.66 ± 0.70	**< 0.001**
24 h urine protein (g/d)	4.92 (2.84, 8.16)	6.88 (4.95, 9.93)	2.12 (1.48, 2.89)	**< 0.001**	5.59 (3.14, 9.71)	4.69 (2.75, 7.65)	**0.004**
Serum ALB (g/L)	29.48 ± 6.37	27.35 ± 5.48	33.67 ± 5.90	**< 0.001**	29.63 ± 6.76	29.43 ± 6.22	0.749
SUA (μmo/L)	377.16 ± 91.12	379.21 ± 92.56	373.13 ± 88.34	0.459	397.36 ± 94.47	369.38 ± 88.7	**0.002**
BUN (mmol/L)	4.9 (3.9, 6.2)	5.0 (4.0, 6.4)	4.7 (3.0. 7,6)	**0.032**	6.3 (5.3, 8.5)	4.5 (3.7, 5.5)	**< 0.001**
Scr (μmo/L)	68 (58, 83)	71 (60, 86)	64 (55, 78)	**0.001**	92 (83, 105)	63 (54, 72)	**< 0.001**
eGFR (mL/min/1.73 m^2)	100.66 ± 26.44	99.19 ± 28.67	103.55 ± 21.16	**0.047**	69.16 ± 18.54	112.79 ± 17.5	**< 0.001**
ESR (mm/h)	29 (16, 51)	34 (19, 56)	23 (10, 36)	**< 0.001**	36 (23, 65)	27 (14, 45)	**< 0.001**
CRP (mg/dL)	0.20 (0.15, 0.32)	0.20 (0.15, 0.32)	0.18 (0.14, 0.31)	**0.030**	0.24 (0.19, 0.47)	0.18 (0.14, 0.27)	**< 0.001**
WBC (×10^9/L)	6.82 ± 2.12	6.96 ± 2.24	6.55 ± 1.83	**0.022**	7.16 ± 2.14	6.69 ± 2.10	**0.022**
HGB (g/L)	137 ± 20	137.92 ± 20.64	136.1 ± 18.16	0.295	132 ± 21	139 ± 19	**< 0.001**

TyG index quartile, the highest TyG index quartile had a 158% increased risk of severe proteinuria in the fully adjusted model.

In addition, logistic regression was also used to clarify the association between the TyG index and decreased renal function, which were as follows: Model 4: adjusted for sex and age; Model 5: adjusted for variables in model 4 plus smoking, drinking, BMI, hypertension, DM, and hyperlipidemia; Model 6: adjusted for variables in model 2 plus 24 h urine protein, HGB, SUA, HbA1c, HDL-C, and LDL-C. The results showed that a higher TyG index was associated with increased risk of decreased renal function in patients with PMN. As shown in Table 3, this association was significant both in the unadjusted model [OR (95%CI): 1.46 (1.10–1.94), $P = 0.008$] and the fully adjusted model [OR (95%CI): 1.57 (1.04–2.36), $P = 0.032$]. Furthermore, compared to the lowest TyG index quartile, the highest TyG index quartile had a 248% increased risk of decreased renal function in the fully adjusted model.

Evaluation of the impact of the TyG index on severe proteinuria or decreased renal function by ROC analysis

We used ROC analysis to evaluate the predictive ability of the TyG index for severe proteinuria or decreased renal function in patients with PMN. As shown in Figure 3, the AUC for evaluating severe proteinuria is 0.613 (95% CI: 0.564–0.662), and the AUC for evaluating decreased renal function is 0.590 (95% CI: 0.536–0.643).

Subgroup analysis

Subgroup analyses revealed that the association between the TyG index and severe proteinuria was inconsistent across several populations. As shown in Fig. 4A, the interaction test suggested that the association between the TyG index and severe proteinuria was influenced by

Table 2 Clinical characteristics of patients according to the TyG index quartiles

Variables	Q1 (*n* = 134)	Q2 (*n* = 134)	Q3 (*n* = 133)	Q4 (*n* = 135)	*P*-value
TyG index	8.28 ± 0.24	8.80 ± 0.12	9.21 ± 0.14	9.94 ± 0.45	**< 0.001**
Age (years)	50 ± 15	50 ± 15	52 ± 14	51 ± 12	0.447
Male (n,%)	86 (64.18%)	84 (62.69%)	75 (56.39%)	86 (63.7%)	0.529
MN duration (months)	4 (1, 12)	5.5 (2, 12)	5 (1.3, 12)	4 (1.25, 10)	0.152
BMI (kg/m^2)	24.59 ± 4.06	25.63 ± 3.98	26.40 ± 3.81	26.85 ± 3.44	**< 0.001**
SBP (mmHg)	135 ± 19	137 ± 17	135 ± 17	137 ± 21	0.675
DBP (mmHg)	83 ± 12	83 ± 11	84 ± 12	87 ± 11	**0.016**
Smoking (n, %)	50 (37.31%)	44 (32.84%)	42 (31.58%)	44 (32.59%)	0.761
Drinking (n, %)	32 (23.88%)	33 (24.63%)	33 (24.81%)	38 (28.15%)	0.857
Hypertension (n, %)	65 (48.51%)	80 (59.70%)	76 (57.14%)	83 (61.48%)	0.144
DM (n, %)	7 (5.22%)	16 (11.94%)	21 (15.79%)	43 (31.85%)	**< 0.001**
CHD (n,%)	4 (2.99%)	6 (4.48%)	3 (2.26%)	3 (2.22%)	0.672
Stroke (n, %)	4 (2.99%)	10 (7.46%)	10 (7.52%)	8 (5.93%)	0.359
Hyperlipidemia (n, %)	80 (59.70%)	95 (70.90%)	121 (90.98%)	134 (99.26%)	**< 0.001**
PLA2R-Ab (RU/mL)	30.23 (3.45, 83.72)	23.55 (3.94, 105.16)	35.38 (3.33, 168.45)	57.43 (9.55, 168.56)	0.071
HDL-C (mmol/L)	1.43 ± 0.43	1.32 ± 0.39	1.20 ± 0.29	1.15 ± 0.30	**< 0.001**
LDL-C (mmol/L)	3.80 (3.01, 4.93)	4.27 (3.03, 6.05)	4.29 (3.28, 5.84)	3.95 (2.74, 5.54)	0.051
TC (mmol/L)	6.28 ± 1.72	7.18 ± 2.76	7.17 ± 2.14	8.13 ± 2.56	**< 0.001**
TG (mmol/L)	1.17 (0.98, 1.36)	1.73 (1.52, 1.99)	2.44 (2.12, 2.78)	4.14 (3.54, 5.59)	**< 0.001**
FBG (mmol/L)	4.47 ± 0.65	4.88 ± 1.02	5.25 ± 0.91	5.81 ± 1.49	**< 0.001**
HbA1c (%)	5.57 ± 0.65	5.65 ± 0.64	5.76 ± 0.67	6.02 ± 0.92	**< 0.001**
24 h urine protein (g/d)	3.86 (2.23, 6.60)	4.20 (2.48, 6.64)	5.19 (2.95, 7.98)	6.92 (3.63, 10.46)	**< 0.001**
Serum ALB (g/L)	29.35 ± 6.61	29.42 ± 6.77	30.32 ± 5.84	28.85 ± 6.19	0.235
SUA (μmo/L)	370.99 ± 86.72	375.00 ± 89.47	377.67 ± 100.41	384.91 ± 87.78	0.649
BUN (mmol/L)	5.0 (3.8, 6.3)	4.6 (3.7, 5.6)	5.2 (4.1, 6.3)	5.0 (4.1, 6.5)	0.071
Scr (μmo/L)	65 (56, 78)	69 (57, 82)	69 (57, 84)	72 (61, 86)	**0.031**
eGFR (mL/min/1.73 m^2)	107.40 ± 28.68	101.77 ± 25.11	96.20 ± 26.23	97.27 ± 24.34	**0.002**
ESR (mm/h)	25 (12, 33)	28 (14, 45)	33 (18, 53)	38 (19, 57)	**< 0.001**
CRP (mg/dL)	0.17 (0.13, 0.27)	0.18 (0.14, 0.34)	0.21 (0.16, 0.33)	0.23 (0.16, 0.35)	**0.002**
WBC (×10^9/L)	6.24 ± 1.70	6.92 ± 2.00	6.71 ± 2.08	7.41 ± 2.47	**< 0.001**
HGB (g/L)	132.66 ± 18.17	135.83 ± 19.51	136.25 ± 20.63	144.44 ± 19.25	**< 0.001**

sex and the history of smoking (P for interaction < 0.05). Female sex and history of smoking were suggested to be effector modifiers. As shown in Fig. 4B, the interaction test suggested that the association between the TyG index and decreased renal function was influenced by sex (P for interaction = 0.017). The sex of female was suggested to be an effector modifier.

Discussion

In this single-center cross-sectional study, the TyG index was found to be positively associated with severe proteinuria and decreased renal function in patients with PMN confirmed by renal biopsy. After fully adjusting potential covariates, the positive association between the TyG index and severe proteinuria or decreased renal function remained stable, suggested that the TyG index was an independent risk factor for severe proteinuria or decreased renal function in patients with PMN. The ROC analyses revealed the predictive ability of the TyG index for severe proteinuria or decreased renal function in patients with PMN. Subgroup analyses found that female sex was an effector modifier of the association between the TyG index and severe proteinuria or decreased renal function, and smoking history was found to be an effector modifier of the association between the TyG index and severe proteinuria.

Several previous studies showed that the proportion of albuminuria gradually increased with the increase of the TyG index and an elevated TyG index was independently associated with albuminuria, suggesting that

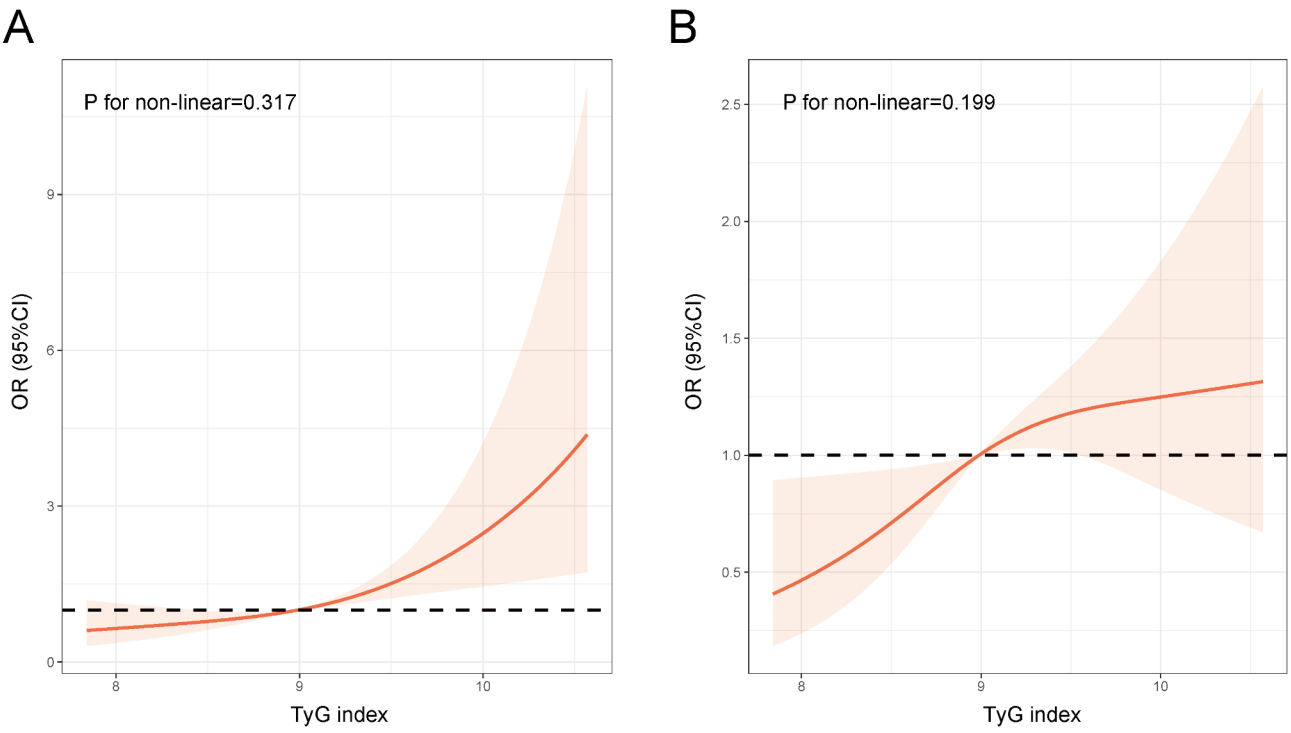

Fig. 2 Association between the TyG index and severe proteinuria or decreased renal function in patients with PMN. (**A**) Association between the baseline TyG index and severe proteinuria in patients with PMN. (**B**) Association between the baseline TyG index and decreased renal function in patients with PMN. The red solid line represented unadjusted ORs of the baseline TyG index across the whole range. The black dot line represents the reference line when OR = 1

Table 3 The association between the TyG index and severe proteinuria or decreased renal function in patients with PMN

	TyG index OR (95%CI), *P*	Q1	Q2 OR (95%CI), *P*	Q3 OR (95%CI), *P*	Q4 OR (95%CI), *P*	*P* for trend
The association between the baseline TyG index and severe proteinuria						
Unadjusted model 1	1.99 (1.47, 2.69) < 0.001	Ref	1.03 (0.63, 1.68) 0.901	1.56 (0.94, 2.57) 0.084	2.74 (1.60, 4.71) < 0.001	< 0.001
Model 1	2.01 (1.48, 2.74) < 0.001	Ref	1.04 (0.63,1.71) 0.872	1.65 (0.99, 2.76) 0.056	2.79 (1.61, 4.84) < 0.001	< 0.001
Model 2	1.76 (1.23, 2.50) 0.002	Ref	0.95 (0.57, 1.58) 0.834	1.32 (0.76, 2.30) 0.329	2.12 (1.14, 3.94) 0.017	0.012
Model 3	2.08 (1.44, 3.01) < 0.001	Ref	0.73 (0.42, 1.26) 0.257	1.26 (0.69, 2.29) 0.446	2.58 (1.32, 5.07) 0.006	0.004
The association between the baseline TyG index and decreased renal function						
Unadjusted model 2	1.46 (1.10, 1.94) 0.008	Ref	1.25 (0.70, 2.25) 0.456	1.98 (1.13, 3.48) 0.017	2.37 (1.36, 4.12) 0.002	0.001
Model 4	1.58 (1.16, 2.16) 0.003	Ref	1.30 (0.68, 2.49) 0.425	2.14 (1.14, 4.00) 0.018	2.84 (1.53, 5.25) < 0.001	< 0.001
Model 5	1.46 (1.02, 2.09) 0.039	Ref	1.28 (0.65, 2.50) 0.471	2.09 (1.05, 4.15) 0.035	2.68 (1.32, 5.46) 0.007	0.003
Model 6	1.57 (1.04, 2.36) 0.032	Ref	1.50 (0.73, 3.08) 0.267	2.38 (1.14, 4.95) 0.021	3.48 (1.58, 7.66) 0.002	0.001

Model 1 adjusted for sex and age; model 2 adjusted for variables in model 1 plus smoking, drinking, BMI, hypertension, DM, and hyperlipidemia; model 3 adjusted for variables in model 2 plus eGFR, SUA, HbA1c, HDL-C, and LDL-C at baseline; model 4 adjusted for sex and age; model 5 adjusted for variables in model 4 plus smoking, drinking, BMI, hypertension, DM, and hyperlipidemia; model 6 adjusted for variables in model 2 plus 24 h urine protein, HGB, SUA, HbA1c, HDL-C, and LDL-C at baseline

the TyG index may be a potential epidemiological tool to quantify the role of metabolic dysfunction in albuminuria [17, 23]. In addition, in the general population, a high TyG index was associated with future renal function decline [24]. A study suggested an increasing trend of homeostatic model assessment of IR was associated with a higher risk of CKD [25], whereas among clinical IR surrogate markers, the TyG index is significantly associated with a higher risk of renal function decline. Another study also indicates that the association between the TyG index and renal function in patients with DKD [16]. For IgAN patients, more urine protein, lower eGFR, > 50% of glomeruli with mesangial hypercellularity and higher BMI were correlated with IR [26]. However, there is currently lack of research exploring the association between the TyG index and renal function indicators in patients with PMN. Accordingly, in our study, we explored the relationship between the TyG index and severe proteinuria or decreased renal function in patients with PMN. Compared to patients without severe proteinuria, the

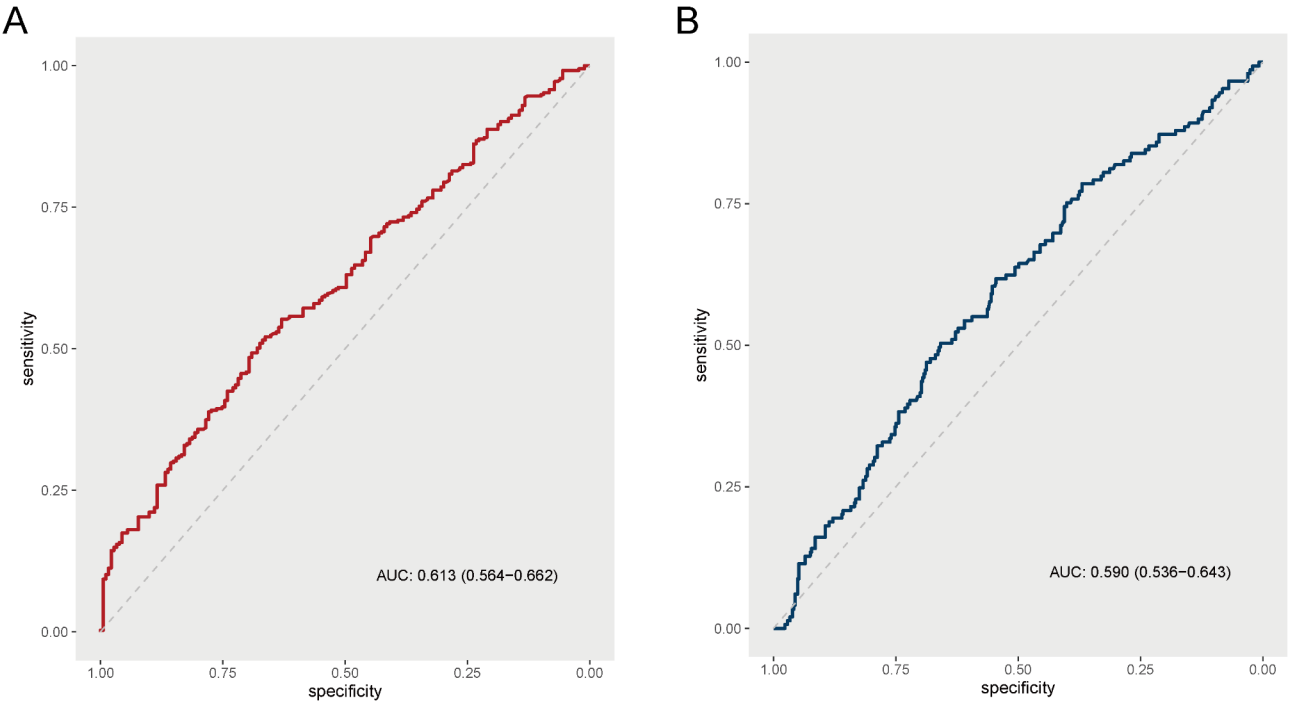

Fig. 3 ROC analysis to evaluate the predictive ability of the baseline TyG index for severe proteinuria or decreased renal function. (**A**) ROC curve for severe proteinuria. (**B**) ROC curve for decreased renal function

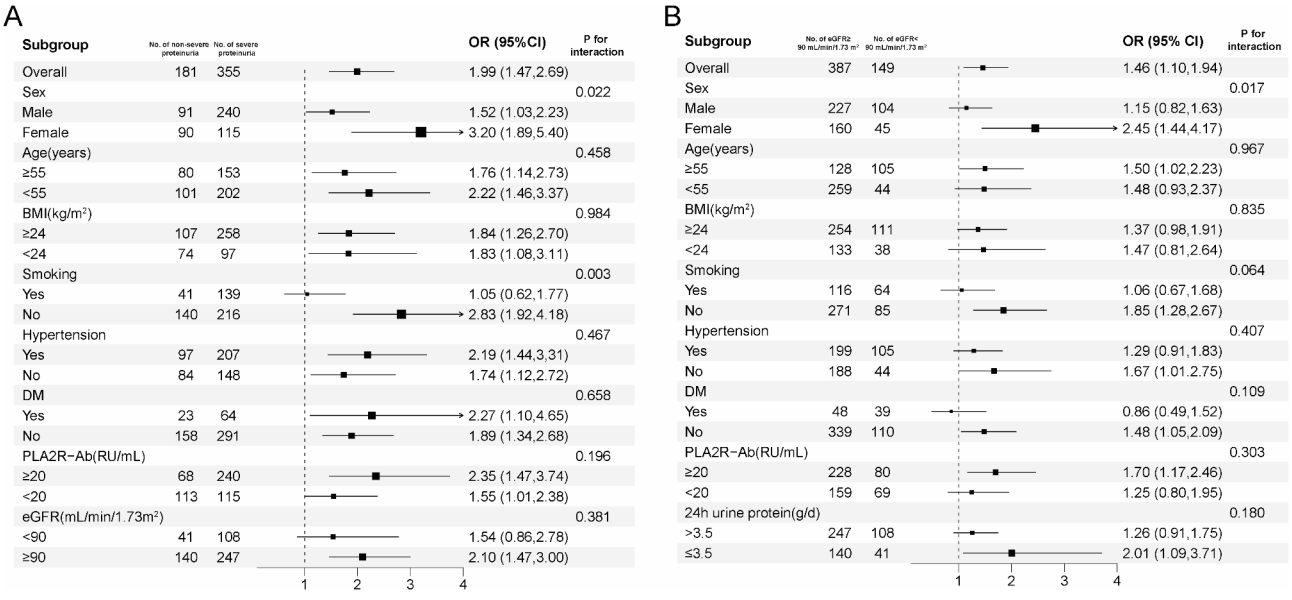

Fig. 4 Subgroup analysis of the association between the TyG index and the risk of severe proteinuria or decreased renal function in patients with PMN. (**A**) Subgroup analysis for the outcome of severe proteinuria. (**B**) Subgroup analysis for the outcome of decreased renal function

TyG index level in patients with severe proteinuria was significantly increased (9.15 ± 0.68 vs. 8.88 ± 0.58, $P < 0.001$). Compared to patients without decreased renal function, the TyG index level in patients with decreased renal function was significantly increased (9.18 ± 0.63 vs. 9.01 ± 0.67, $P = 0.006$). Further, patients were divided into four groups according to the TyG index quartiles. Using the lowest quantile as the reference, multivariate-adjusted logistic regression suggested that patients in the highest quantile of the TyG index had a significantly increased risk of severe proteinuria (OR = 2.08, 95% CI: 1.44–3.01, $P < 0.001$) and decreased renal function (OR = 1.57, 95% CI: 1.04–2.36, $P = 0.032$). Spearman correlation analysis also identified that the TyG index of PMN patients was

positively correlated with 24 h urinary protein, while negatively correlated with eGFR. To our knowledge, our findings are the first to reveal that in patients with PMN, the TyG index was positively associated with severe proteinuria and decreased renal function.

The pathophysiological mechanism between the TyG index and the kidney disease has not been fully elucidated, while, many clues indicated that the impact of IR on kidney function is multifaceted, including a decrease in bioavailable Nitric oxide that lead to attenuated tubuloglomerular feedback, hyperfiltration, and increased tubular sodium retention. In addition, IR also promotes glomerular mesangial expansion, glomerular hypertrophy, and renal interstitial fibrosis that elicit the occurrence of hypertension and albuminuria, all of which accelerate the progression of kidney disease [27]. Moreover, chronic inflammation and oxidative stress caused by IR may be the basis between the TyG index and the kidney disease. Lipid metabolism disorders can cause ectopic lipid accumulation in the kidney, accelerating apoptosis in renal intrinsic cells, affecting the synthesis and secretion of inflammatory mediators and adipokines [28], and also affecting kidney hemodynamics through mechanical effects [29]. IR can also interfere the balance of vasoactive factors, accelerating the progression of kidney fibrosis [30]. In our study, the dose-response relationship between the TyG index and severe proteinuria or decreased renal function in PMN patients was evaluated by RCS curves. Our results showed that with the increase of the TyG index, the risk of severe proteinuria or decreased renal function gradually increased, and the association was found to be linear. In addition, logistic regression showed that the positive association between the TyG index and severe proteinuria or decreased renal function in patients with PMN remained stable even after fully adjusting for potential covariates. We further used the ROC analysis to evaluate the predictive ability of the TyG index for severe proteinuria or decreased renal function in patients with PMN. The AUC was 0.613 (95% CI: 0.564–0.662) for severe proteinuria and 0.590 (95% CI: 0.536–0.643) for decreased renal function, suggesting that the TyG index may be a simple and practical clinical tool to evaluate the renal function status of PMN patients.

Finally, the subgroup analysis revealed that the association between the baseline TyG index and severe proteinuria was inconsistent across several populations. The interaction test suggested that the association between the baseline TyG index and severe proteinuria was influenced by the sex of female and smoking history, while the interaction test suggested that the association between the TyG index and decreased renal function was influenced by the sex of female. Many studies have revealed the sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. A study showed women have a higher prevalence of CKD stages 3–5 than men, whereas men have a higher prevalence of albuminuria and hence CKD stages 1–2. Moreover, men have a faster decline in kidney function, progress more frequently to kidney failure and have higher mortality and risk of cardiovascular disease than women [31]. While, the population-based studies indicate that women present a higher prevalence of CKD and experience less CVD than men in all CKD stages [32]. In addition, a study suggested that sex was significant and independent risk factors in patients with IMN with hypertension [33]. Therefore, more research is still needed on sex differences in PMN patients.

Importantly, our study for the first time explored the correlation between the TyG index and severe proteinuria or decreased renal function in a large Chinese PMN population. However, our study also has several limitations. Firstly, due to the retrospective nature and the lack of long-term follow-up data, we could not explore the relationship between the TyG index and the prognosis of PMN, such as whether TyG index can predict the occurrence of ESRD in PMN, and to provide guidance for clinical management. In addition, the study was conducted at a single center and lack of external validation cohort which may lead to inaccurate data analysis. Future studies with a larger sample size and multi-center design are needed to determine whether the TyG index level has important clinical implications in patients with PMN.

Conclusion

In patients with PMN, the TyG index has a positive linear correlation with severe proteinuria and decreased renal function. This finding supports the clinical application of the TyG index, a reliable surrogate marker of IR, for assessing proteinuria or renal function in patients with PMN.

Abbreviations

TyG	Triglyceride-glucose
IR	Insulin resistance
PMN	Primary membranous nephropathy
RCS	Restricted cubic spline
AUC	Area under the ROC curve
ROC	Receiver operating characteristic
CI	Confidence interval
OR	Odds ratio
ESRD	End-stage renal disease
AHA	American Heart Association
CKM	Cardiovascular-kidney-metabolic
DM	Diabetes mellitus
CVD	Cardiovascular disease
CKD	Chronic kidney disease
TG	Triglyceride
FBG	Fasting blood glucose
DKD	Diabetic kidney disease
MN	Membranous nephropathy
IgAN	IgA nephropathy
DN	Diabetic nephropathy

LN	Lupus nephritis
eGFR	Estimated glomerular fltrationrate
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CHD	Coronary heart disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
HbA1c	Glycosylated hemoglobin
ALB	Albumin
SUA	Serum uric acid
BUN	Blood urea nitrogen
Scr	Serum creatinine
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
WBC	White blood cell count
HGB	Hemoglobin

Supplementary Information

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Supplementary Material 1

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Author contributions
Y.G. and Z.W. contributed equally to this work and share first authorship. Y.G. developed the concept and designed the study. Data were collected and analyzed by Z.D., Z.W., and Y.G..Y.G. and Z.W. wrote the manuscript. Y.G., Z.W., and Y.W. revised the manuscript. All authors reviewed the manuscript and gave their final approval for publication.

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Data availability
The raw datasets analyzed in this study are available from the corresponding author upon reasonable request and with permission from the institutional review board.

Declarations

Ethics approval and consent to participate
The research was conducted in line with the Declaration of Helsinki and received full approval from the Ethics Committee of Peking University Third Hospital (M2018132). Written informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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