A high triglyceride to high-density lipoprotein cholesterol ratio is associated with poor renal outcome in IgA nephropathy patients

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Research Article

Keywords: Triglyceride, High-density lipoprotein cholesterol, IgA nephropathy, Prognosis, TG/HDL-C ratio

Posted Date: February 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1354712/v1

Abstract

Background: Dyslipidemia is common in patients with chronic kidney disease. However, whether markers of atherogenic dyslipidaemia correlate with outcomes in IgA nephropathy (IgAN) patients as in the general population is uncertain. The aim of this study was to explore the prognostic value of the serum triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio to predict ESRD in IgAN patients.

Methods: A total of 1149 patients from West China Hospital of Sichuan University were retrospectively analysed between 2008 and 2018, with a median follow-up of 54.0 months. The demographic, clinical and pathological data of all patients at the time of biopsy were collected. Receiver operating curve (ROC) was used to determine the optimal threshold for the TG/HDL ratio at baseline to predict ESRD during follow-up. Prognostic values were assessed by univariate and multivariate Cox regression analyses and Kaplan–Meier curves.

Results: The optimal cut-off value for the TG/HDL-C ratio was 1.495. The correlation analysis showed that the TG/HDL-C ratio was negatively correlated with the eGFR (r = 0.248, $P < 0.001$) but positively correlated with proteinuria (r = 0.229, $P< 0.001$) and serum uric (r =0.306, $P< 0.001$). Patients with a higher TG/HDL-C ratio tended to have hypertension [odds ratio (OR), 1.702; 95% CI, 1.298-2.233; $P<0.001$] and more severe pathologic lesions with tubular atrophy/interstitial fibrosis (OR, 3.593; 95% CI, 2.528-5.107; $P<0.001$). A high TG/HDL ratio was strongly correlated with worse renal survival in IgAN patients (log-rank: $P <0.001$). Multivariate Cox analysis demonstrated that an elevated TG/HDL-C ratio (HR 2.118, 95% CI 1.333-3.367, $P=0.002$) was an independent risk marker to predict ESRD.

Conclusion: The TG/HDL-C ratio may serve as potential prognostic biomarkers in IgAN patients.

Background

Immunoglobulin A (IgA) nephropathy (IgAN), characterized by diffusely deposited IgA in the kidneys, is the most prevalent primary glomerulonephritis and a leading cause of end-stage renal disease (ESRD), in which 20–40% of IgAN patients reach ESRD 10–20 years after the initial diagnosis[1]. Recognizing risk factors of ESRD would be beneficial for to slowing the progression of IgAN.

Abnormal lipoprotein metabolism, as indicated by a high level of triglycerides (TGs) or a low level of high-density lipoprotein cholesterol (HDL-C), is common in chronic kidney disease (CKD)[2]. However, TG levels fluctuate substantially based on feeding status, thus limiting its utility as a predictive biomarker[3]. The combination of TG and HDL-C, which is the TG/HDL-C ratio, could therefore overcome this problem and has been proposed as a more practical and easy-to-use atherogenic marker than the individual lipid measures alone[4]. Evidence has indicated that it is a good marker for cardiovascular disease (CVD) [4, 5] and is correlated with the prevalence of CKD[6, 7]. Moreover, it was used as a prognostic factor for different classes of diseases, including mortality in peritoneal dialysis[8], coronavirus disease 2019[9], type 2 diabetes[10], and CKD[11]. However, there is still a lack of research on the relationship between the

TG/HDL-C ratio and IgAN. Whether the TG/HDL-C ratio could be another predictor of IgAN progression remains unknown. To clarify these issues, we conducted this study.

Materials And Methods

Patients

A total of 1449 patients from West China Hospital of Sichuan University between 2008 and 2018 were initially enrolled. patients with systemic disease, such as systemic lupus erythematosus, diabetes, Henoch-Schönlein purpura, liver cirrhosis or disorder of liver function, malignancy, etc., and without complete clinical and pathologic data were excluded in this study. Patients were followed up for at least 12 months or until study-defined endpoints were reached. Finally, 1149 adult biopsy-proven IgAN patients (age > 14 years) were enrolled. The research was in compliance with the Declaration of Helsinki and was approved by the ethical committees of West China Hospital of Sichuan University (2019-33). Informed consent was obtained from each patient or their legal guardians prior to treatment.

Clinical Data

Patient information, including age, sex, clinical manifestations, laboratory indexes, renal pathology reports, and treatment strategies, was obtained from electronic medical records. Laboratory values included 24-h proteinuria (UPRO), hematuria level (URBC), hemoglobin (Hb), serum albumin (ALB), serum creatinine (Cr), estimated glomerular filtration rate (eGFR), uric acid (UA), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C). The TG/HDL-C ratio was obtained by dividing the serum triglyceride level by the plasma high-density lipoprotein cholesterol level. Hypertension was defined as blood pressure > 140/90 mmHg or the use of antihypertensive agents[12]. eGFR was calculated using the CKD-EPI equation[13]. Anemia and hyperuricaemia was defined as described previously[14]. Renal biopsy samples were evaluated by an experienced pathologist and a nephrologist according to the Oxford classification[15]

Treatments

All patients received optimal support treatment, including a full dose of angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs). Glucocorticoids and immunosuppressant therapy included cyclophosphamide (2 mg/kg daily for 3 months), mycophenolate mofetil (1–2 g daily for 6–8 months), tacrolimus (0.03–0.05 mg/kg daily for 6–8 months) or cyclosporin was used based on pathological classification and clinical severity according to the guidelines.

Outcome definition

The renal outcome was progression to ESRD, defined by commencement of renal replacement therapy or an eGFR < 15 mL/min/1.73 m^2.

Statistical Analysis

Continuous variables are expressed as the means ± SDs or medians (interquartile ranges). Categorical variables were expressed as numbers and percentages (%). Student's t test or the Mann–Whitney U test was used for continuous variables, and the χ2 test was used for categorical variables. The optimal thresholds of the TG/HDL ratio were obtained according to the highest Youden's index using receiver operating curve (ROC) analyses. Kidney survival in each group was estimated by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard models were used to evaluate the influence of clinical and pathological variables on renal outcomes. Three statistical models were used in analysis: model 1 (demographics + pathological features + TG/HDL-C), model 2 (demographics + clinical features + TG/HDL-C) and model 3 (demographics + clinical + pathological features + TG/HDL-C). All of these data were analysed by the software package SPSS 23.0 software package (SPSS, Chicago, IL, USA) and GraphPad Prism 8.0. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinicopathological Characteristics

A total of 1149 biopsy-proven IgA nephropathy patients from West China Hospital of Sichuan University were finally enrolled in this retrospective study (**Figure 1**). The demographic, clinical, and pathologic characteristics of the included patients are shown in **Table 1**. The median age of the patients was 33 (26-42) years, and 44.5% were men. The median follow-up period was 54.0 months, ranging from 35.6 to 73.2 months. ROC analysis revealed that the optimal cut-off TG/HDL-C ratio with which to predict the progression of ESRD in patients with IgAN was 1.495 (**Supplementary Figure 1**). Thus, according to their TG/HDL-C ratio at the time of renal biopsy, patients were divided into two groups: a high TG/HDL-C group (TG/HDL ≥ 1.495, N=383) and a low TG/HDL group (TG/HDL-C < 1.495, N=766). The median eGFR in the high TG/HDL-C and low TG/HDL-C groups was 99.9 and 81.3 mL/min/1.73 m^2, respectively. Compared with the low TG/HDL-C group, patients in the high TG/HDL-C group had a higher incidence of anemia, hyperuricemia and hypertension (all P <0.001), a higher proportion of males (P <0.001), and worse renal function (P<0.001). Moreover, higher levels of TG (P<0.001), TC (P=0.003), UPRO (P<0.001), and Cr (P<0.001) and lower HDL-C (P<0.001) and URBC (P=0.009) levels were observed in the high TG/HDL-C group. Regarding pathological lesions, patients with a high TG/HDL-C always had mesangial hypercellularity (P=0.031), segmental glomerulosclerosis (P=0.028) and tubular atrophy/interstitial fibrosis (P<0.001).

Table 1

Demographic and clinicopathological characteristics of 1149 IgAN patients

parameters	Total	Group 1 (TG/HDL<12.44)	Group2 (TG/HDL ≥ 12.44)	*P*
	N=1149	N=766	N=383	
Age	33(26-42)	31(25-41)	36(27-44)	<0.001
Gender(male)	511(44.5)	304(39.7)	207(54.0)	<0.001
HTN (%)	338(29.4)	188(24.5)	150(39.2)	<0.001
CKD stages (%)				<0.001
Stage 1	615(53.5)	455(59.4)	160(41.8)	
Stage 2	290(25.2)	178(23.2)	112(29.2)	
Stage 3	202(17.6)	118(15.4)	84(21.9)	
Stage 4	39(3.4)	13(1.7)	26(6.8)	
Stage 5	3(0.3)	2(0.3)	1(0.3)	
Pathologic				
M1	863(75.1)	562(73.4)	301(78.6)	0.031
E1	53(4.6)	36(4.7)	17(4.4)	0.486
S1	707(61.5)	456(59.5)	251(65.5)	0.028
T1-2/T0	245(21.3)	142(18.5)	103(26.9)	0.001
C1-2/C0	246(21.4)	163(21.3)	83(21.7)	0.468
Clinical				
Cr	83.4(65.2-109.0)	79.0(62.0-102.0)	94.0(72.0-127.0)	<0.001
eGFR	93.3(65.8-117.6)	99.9(71.1-120.1)	81.3(54.7-105.5)	<0.001
ALB	40.0(35.9-43.1)	40.0(36.0-43.2)	40.0(35.8-43.0)	0.694
HDL	1.39(1.11-1.73)	1.54(1.31-1.87)	1.06(0.89-1.26)	<0.001
TG	1.5(1.1-2.1)	1.2(0.9-1.5)	2.5(2.0-3.5)	<0.001
TC	4.8(4.1-5.7)	4.7(4.1-5.5)	5.0(4.2-5.8)	0.003
UPRO(g/d)	1.5(0.8-3.0)	1.3(0.7-2.7)	2.0(1.0-3.5)	<0.001
URBC (/HP)	18.0(6.0-60.5)	19.5(6.8-68.0)	15.0(5.0-47.0)	0.009
Anemia	164(14.3)	90(11.8)	74(19.3)	<0.001
Hyperuricemia	467(40.6)	263(34.3)	204(53.3)	<0.001

Treatment				0.034
SC	439(38.2)	308(40.2)	131(34.2)	
GC only	432(37.6)	289(37.7)	143(37.3)	
IT and/or GC	278(24.2)	169(22.1)	109(28.5)	
Follow-up (m)				
duration	54.0(35.6-73.2)	56.4(36.2-75.0)	48.2(34.5-67.6)	<0.001
ESRD	78(6.8)	32(4.2)	46(12.0)	<0.001

Note: Data presented as median (first-third interquartile range) or number (percentage).

Abbreviations: HTN, hypertension; CKD, chronic kidney disease; M, mesangial proliferation; E, endocapillary proliferation; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; C, crescents; Cr, creatinine; eGFR, estimated glomerular filtration rate; ALB, albumin; HDL, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; UPRO, 24 h urine protein; URBC, urinary red blood cell counts; SC, supportive care; GC, corticosteroids; IT, immunosuppressive therapy; ESRD, end stage renal disease

Correlation of the TG/HDL-C ratio with clinical parameters and pathological lesions

The correlations between the TG/HDL-C levels and clinicopathological findings are illustrated in **Table 2 and Table 3.** Our results showed that TG/HDL-C was significantly negatively correlated with the eGFR (r = -0.248, $P < 0.001$) but positively correlated with proteinuria (r = 0.229, $P < 0.001$) and serum uric (r =0.306, $P< 0.001$). Logistic regression analysis was conducted to analyse the relationship between TG/HDL and clinicopathologic features. The high TG/HDL-C group IgAN patients were more likely to have hypertension [odds ratio (OR), 1.702; 95% CI, 1.298-2.233; $P<0.001$] and pathologic lesions with tubular atrophy/interstitial fibrosis (OR, 3.593; 95% CI, 2.528-5.107; $P<0.001$) and segmental sclerosis (OR, 1.293; 95% CI, 1.001-1.669; $P=0.049$)

Table 2

Correlation between related variables and TG/HDL-C

	Variables	Correlation coefficient (r)	*P* value
TG/HDL-C	UPRO	0.229	<0.001**
	Hb	0.034	0.249
	UA	0.306	<0.001**
	ALB	-0.034	0.249
	eGFR	-0.248	<0.001**

Note: * stands for $P< 0.05$, ** stands for $P< 0.01$

Abbreviations: UPRO, 24 h urine protein; Hb, hemoglobin; UA, uric acid; ALB, albumin; eGFR, estimated glomerular filtration rate.

Table 3

Logistics Regression Models for the relationship between TG/HDL-C and kidney pathologic lesion

	OR	95%CI	*P* value
M	1.332	0.995-1.784	0.054
E	0.942	0.522-1.700	0.842
S	1.293	1.001-1.669	0.049*
T_{1-2}/T_0	3.593	2.528-5.107	<0.001**
C_{1-2}/C_0	1.184	0.883-1.588	0.260
HTN	1.702	1.298-2.233	<0.001**

Note: * stands for $P< 0.05$, ** stands for $P< 0.01$

Abbreviations: M, mesangial proliferation; E, endocapillary proliferation; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; C, crescents; HTN, hypertension

Renal Survival

During a median follow-up period of 54.0 (35.6-73.2) months, a total of 78 (6.8%) patients developed ESRD. Kaplan–Meier survival analysis and log-rank tests were used to determine the association of the TG/HDL-C ratio with patient survival. Our results demonstrate that TG/HDL-C ≥1.495 was significantly associated with ESRD (**Figure 2**, $P < 0.001$). Subgroup analysis of mesangial hypercellularity and tubular

atrophy/interstitial fibrosis, eGFR<60 mL/min/1.73 m^2 and proteinuria for ESRD by Kaplan–Meier analysis is shown in **Figure 3**. Our results indicated that a high TG/HDL-C ratio was a risk factor for ESRD in patients with IgAN, especially patients with eGFR<60 mL/min/1.73 m^2 (*P* = 0.028) **(Figure 3. A)**, 24-hour urine protein ≥1 g/day (*P*< 0.001) **(Figure 3. B)**, or mesangial hypercellularity and tubular atrophy/interstitial fibrosis **(Figure 3. C&D)** in pathologic lesions.

TG/HDL-C as an Independent Risk Factor for Progression of IgAN to ESRD

To evaluate risk factors for ESRD in patients with IgAN, we performed univariate and multivariable Cox regression analyses, in which univariate analysis showed that a high TG/HDL-C ratio was significantly associated with a higher risk of ESRD (HR=3.265, 95% CI: 2.077-5.132, *P*<0.001). Then, three models were used for multivariate Cox regression (**Table 4 and Supplementary Table 1&2**),which indicated that high TG/HDL-C was an independent factor of renal endpoints (model 1: HR 2.781, 95% CI 11.755-4.408, *P*<0.001; model 2: HR 2.311, 95% CI 1.457-3.666, *P*<0.001; model 3: HR 2.118, 95% CI 1.333-3.367, *P*=0.002).

Table 4

Analysis of factors associated with renal outcomes in model 3 (demographics+ clinical indicators+ pathological features+ TG/HDL-C).

Parameter	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
high TG/HDL-C	3.265	2.077-5.132	<0.001	2.118	1.333-3.367	0.002
Male	1.894	1.208-2.970	0.005			
Age	0.991	0.971-1.012	0.420	0.951	0.927-0.975	<0.001
HTN	3.142	2.011-4.910	<0.001			
M1	8.73	2.772-27.893	<0.001	4.528	1.414-14.503	0.011
E1	2.224	1.070-4.625	0.032			
S1	1.598	0.991-2.576	0.054			
T_{1-2}/T_0	12.564	7.550-20.907	<0.001	3.580	1.988-6.446	<0.001
C_{1-2}/C_0	1.296	0.790-2.125	0.305			
UPRO>1.0g	3.290	1.813-5.971	<0.001			
URBC>5/HP	0.950	0.561-1.610	0.850			
Anemia	3.876	2.447-6.140	<0.001			
Hyperuricemia	4.889	2.938-8.137	<0.001			
Hypoalbuminemia	2.226	1.285-3.857	0.004			
CKD stages (stages4-5/1-3)	15.956	9.205-27.660	<0.001**	9.128	4.727-17.626	<0.001
Treatment			0.007**			0.032**
GC/SC	0.676	0.378-1.211	0.188	0.461	0.256-0.832	0.010
IT/SC	1.656	0.992-2.764	0.054	0.821	0.490-1.378	0.456

Abbreviations: HTN, hypertension; M, mesangial proliferation; E, endocapillary proliferation; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; C, crescents; UPRO, 24 h urine protein; URBC, urinary red blood cell counts; SC, supportive care; GC, corticosteroids; IT, immunosuppressive therapy;

Discussion

Dyslipidemia is common in China, with a prevalence of 41.9%, and is commonly characterized by the presence of high TG and low HDL-C in CKD [16]. Recently, the combination of TG and HDL-C, the TG/HDL-

C ratio, has attracted increasing attention for its better predictive power for cardiovascular events and insulin resistance than the lonely combination[7, 17]. Noticeably, several studies have shown a positively relationship between the TG/HDL-C ratio and renal function decline in CKD patients[6, 7, 16, 18]. However, whether dyslipidemia has a role in IgAN progression remains unknown.

In this study, in a cohort of 1149 biopsy-proven IgAN patients, 78 (6.8%) patients developed ESRD. A higher TG/HDL-C ratio in patients with IgAN was associated with more severe clinical features and pathologic lesions. Our further analysis revealed a higher serum TG/HDL-C level was a risk factor for the progression to ESRD (HR 2.118, 95% CI 1.333–3.367, $P = 0.002$).

Previous studies have reported that the reduction in renal function in patients is related to high TG/HDL-C levels[11, 16], but no study has focused on IgAN patients. To our knowledge, this is the first study assessing the correlation between the TG/HDL-C ratio and ESRD in IgAN patients. Moreover, the TG/HDL-C ratio has a greater influence in advanced IgAN patients (eGFR < 60 mL/min/1.73 m^2) or these with 24-hour urine protein of ≥ 1 g/day in our study. This might be due to the slow progression of mild renal disease, especially within a limited follow-up period[14]. Additionally, we would like to stress that high TG/HDL-C patients tend to have hypertension and more severe renal pathologic lesions of segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis. Considering that abnormalities in lipid parameter levels could accelerated atherosclerosis is plausible to believe that pathology of IgAN patients with a high TG/HDL-C level.

Abnormalities in lipid parameter levels could lead to impaired renal function and accelerated atherosclerosis[19]. TG usually increases in the early stages of CKD and is associated with delayed catabolism and decreased activity of hepatic TG lipase and peripheral lipoprotein lipase. However, based on feeding status, TG levels could fluctuate substantially, thus limiting its utility as a predictive biomarker[3]. HDL-C, inversely associated with outcomes, decreases in patients with CKD[11]. The combination of these two markers could therefore overcome this problem and lead to a far more consistent, stable, fasting measurement of dyslipidaemia, which has indeed attracted much more attention in disease prognosis, including cardiovascular disease[4], diabetes[10], and peritoneal dialysis[8]. Here, the potential mechanisms by which the TG/HDL-C ratio serves as a prognostic biomarker in IgAN patients may be as follows. TG/HDL-C is a reliable indicator of insulin resistance, which induces oxidative stress. Oxidative stress impairs the activation of nuclear factor erythroid-2-related factor-2, which protects against kidney tissue injury[16]. The filtered proteins, such as fatty acids, phospholipids, and cholesterol contained in the filtered proteins (albumin and lipoproteins), could include direct toxic effects of lipids on glomerular cells and promote matrix production [2, 20]. Moreover, these materials act as damage-associated molecular patterns (DAMPs) and are recognized by Toll-like receptors (TLR2 and TLR4), which can activate inflammatory responses, causing tubulointerstitial fibrosis and injury in the reabsorption process[21, 22]. Additionally, further tissue injury is contributed owing to impaired HDL-mediated reverse cholesterol transport by limiting the unloading of the excess cellular cholesterol and phospholipid burden[21]. Thus, in the future, recognizing the TG/HDL-C ratio as a

potentially modifiable risk factor for patients may allow the utilization of preventative strategies to optimize both treatment and survival outcomes.

Some limitations warrant consideration. First, this was a retrospective study based on a single-center database. Further multicenter validation in different ethnic populations was needed. Second, the mean follow-up time of 54 months was relatively short. In addition, no data are available on the relationship between the TG/HDL-C ratio and CVD mortality.

Conclusion

The TG/HDL-C ratio may serve as a potential prognostic biomarker in IgAN patients. More attention must be paid to patients with advanced IgAN who have a high TG/HDL-C ratio, eGFR < 60 mL/min/1.73 m^2, and 24-hour urine protein of ≥ 1 g/day.

Declarations

Ethics approval and consent to participate

The research was in compliance with the Declaration of Helsinki and was approved by the ethical committees of West China Hospital of Sichuan University (2019-33). Informed consent was obtained from each patient or their legal guardians prior to treatment.

Consent for publication

All participants signed the consent form and agreed to use data for publish.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

This study is partly supported by the National Key R&D Program of China (2020YFC2006503) & (2020YFC2006500).

Authors' contributions

GP, AQ, SW, LD, XL, and DY collected and analysed the data. GP and AQ wrote the main manuscript text. YT, XZ and JT reviewed and edited the manuscript. WQ supervised all the work and revised the manuscript.

Acknowledgements

We are indebted to all the people who kindly participated in this study.

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Figures

Figure 1

Flow diagram.

Figure 2

Kaplan-Meier analysis for the endpoint of ESRD stratified by the cutoff point of the TG/HDL-C

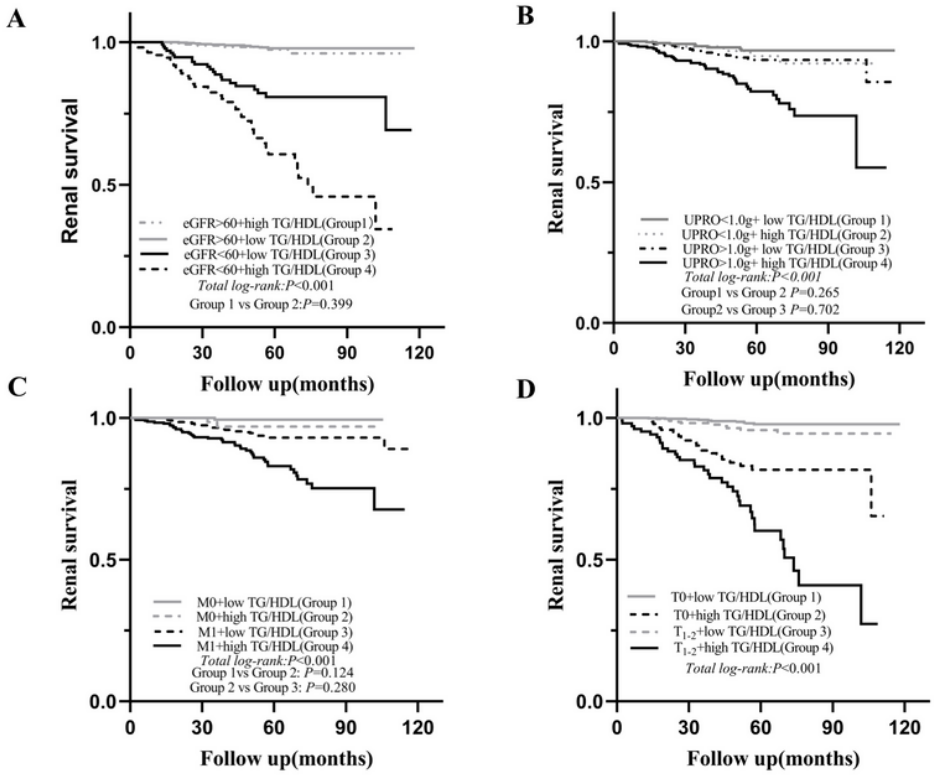

Figure 3

Subgroup Kaplan-Meier analysis for endpoint of ESRD; eGFR (A), UPRO (B), M (C), T (D); eGFR, estimated glomerular filtration rate; UPRO, 24 h urine protein; M, mesangial proliferation; T, tubular atrophy/interstitial fibrosis;

Supplementary Files

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- SupplementaryFigure1.tif
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