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Association between preoperative lipid profiles and new-onset diabetes after transplantation in Chinese kidney transplant recipients: A retrospective cohort study

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Abstract

Background: This study investigated the association between the preoperative lipid profiles and new-onset diabetes after transplantation (NODAT) in Chinese kidney transplant recipients (KTRs).

Methods: In this study, of 1140 KTRs registered between January 1993 and March 2018 in Zhongshan Hospital, Fudan University, 449 were enrolled. Clinical data, obtained through a chart review of the patient records in the medical record system, were evaluated, and NODAT was diagnosed based on the American Diabetes Association guidelines. Multivariate Cox regression analysis was conducted to determine whether the preoperative lipid profiles in KTRs were independently associated with NODAT incidence. The preoperative lipid profiles were analyzed as continuous variables and grouped into tertiles. Smooth curve fitting was used to confirm the linear associations.

Results: During a median follow-up of 28.03 (interquartile range 12.00–84.23) months, 104 of the 449 (23.16%) participants developed NODAT. The multivariate model analysis, adjusted for all potential covariates, showed that increased values of the following parameters were associated with NODAT (hazard ratio, 95% confidence interval): preoperative total cholesterol (TC; 1.25, 1.09–1.58, $p = 0.0495$), low-density lipoprotein cholesterol (LDL-C; 1.33, 1.02–1.75, $p = 0.0352$), non-high-density lipoprotein cholesterol (non-HDL-C; 1.41, 1.09–1.82, $p = 0.0084$), TC/HDL-C (1.28, 1.06–1.54, $p = 0.0109$), and non-HDL-C/HDL-C (1.26, 1.05–1.52, $p = 0.0138$). However, the association between the preoperative triglyceride, HDL-C, or TG/HDL-C and NODAT was not significant.

Conclusions: Preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C were independent risk factors for NODAT.

Yangli Ye and Jian GAO are joint first authors.

KEYWORDS
kidney transplantation, low-density lipoprotein cholesterol, new-onset diabetes after transplantation, non-high-density lipoprotein cholesterol, total cholesterol

1 | INTRODUCTION

Long-term management of chronic complications after renal transplantation is crucial for both graft function and patient survival. New-onset diabetes after transplant (NODAT) is an important risk factor for reduced post-transplantation survival rate and occurs in 7%–46% of all kidney transplant recipients (KTRs).[1-3] NODAT significantly increases the risk of cardiovascular disease and infection among KTRs, with a resultant increase in the mortality risk.[4] Therefore, early recognition of KTRs at a higher risk for NODAT and initiation of intensive medical intervention might be crucial to improve outcomes in KTRs. Elevated total cholesterol (TC) and triglyceride (TG) levels are risk factors for type 2 diabetes in the non-transplant population.[5,6] Preoperative dyslipidemia is frequently observed among KTRs and might be attributable to various causes, including impaired renal function and abnormal lipid excretion.[7] Previous studies have mainly discussed the association between preoperative TG levels and NODAT in KTRs, and some research has reported that TG increased the risk for NODAT only in recipients treated with tacrolimus (FK506).[8-11] Moreover, Boloori et al. reported that decreased high-density lipoprotein cholesterol (HDL-C) levels were a significant risk factor for not only the first incidence but also recurrent hyperglycemia episodes.[12] However, Szili-Torok et al. reported that the HDL-C efflux capacity, rather than the HDL-C level, was a protective factor against NODAT.[13] The proprotein convertase subtilisin/kexin type 9, a low-density lipoprotein cholesterol (LDL-C) receptor-regulating pathway, is associated with an increased risk for NODAT.[14] However, the controversial results regarding the lipid-diabetes association in KTRs and the dose-response relationship between the preoperative lipid profiles and NODAT have not been comprehensively analyzed and remain uncertainty.

Therefore, this study aimed to investigate the association between the preoperative lipid profiles and NODAT incidence and to predict the risks and prevent the development of NODAT in the Chinese KTRs population.

2 | METHODS

2.1 | Inclusion and exclusion criteria for participants

The study patient screening and enrollment process is shown in Figure 1. For inclusion in this retrospective cohort study, patients (n = 1140) who underwent renal transplantation between January 1993 and March 2018 in Zhongshan Hospital, Fudan University, Shanghai, PR China were considered. After excluding participants who were younger than 18 years (n = 10), those who did not have baseline lipid information (n = 246), patients who had undergone multi-organ transplantation or renal re-transplantation (n = 47), those who died or experienced allograft failure in the first 3 months

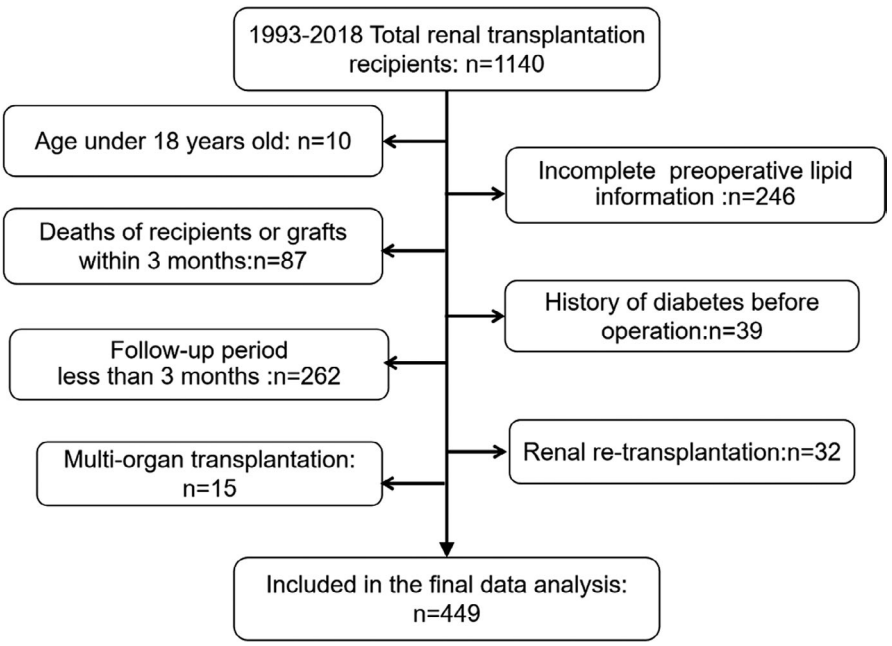

FIGURE 1 Flow diagram showing patient selection

post-transplantation (n = 87), those with follow-up for <3 months (n = 262), or patients who had diabetes at baseline (n = 39), we included a total of 449 patients in this study.

The study protocol was approved by the institutional review board of Zhongshan Hospital, Fudan University, while no written informed consent was required, because all the data employed in the retrospective observational study were anonymous. Since it was established, the Kidney Transplant Center at Zhongshan Hospital has operated in compliance with the Declaration of Helsinki (as revised in Brazil 2013) and its later amendments, and the use of kidney from executed prisoners has been firmly rejected. All donor kidneys for transplantation were obtained either from voluntary donors or from the patient's family members.

2.2 | Data collection

We conducted a chart review and extracted patient demographics and clinical information from electronic and paper medical records of the Zhongshan Hospital. Preoperative data points included the date of operation, sex, age, body mass index (BMI), history of hypertension and diabetes, use of lipid-lowering drugs, hepatitis C virus (HCV) and cytomegalovirus (CMV) infection, type of donor, and biochemical indicators, including the serum creatinine, fasting plasma glucose (FPG), TC, TG, HDL-C, and LDL-C levels. The value of non-HDL cholesterol was calculated by subtracting HDL-C from TC. TC/HDL-C, TG/HDL-C, and non-HDL/HDL-C were calculated from the TC, TG, non-HDL, and HDL-C ratio, respectively. BMI was calculated

TABLE 1 Baseline demographic and clinical parameters

	Non-NODAT 345 cases	NODAT 104 cases	p-value
Male (n, %)	239 (69.28%)	77 (74.04%)	0.351
Age (years)	37.88 ± 11.59	42.26 ± 12.49	<0.001***
BMI (kg/m^2)	21.61 ± 3.07	22.27 ± 4.21	0.023*
Preoperative TC (mmol/L)	4.08 ± 1.08	4.33 ± 1.09	0.037*
Preoperative TG (mmol/L)	1.52 ± 1.08	1.76 ± 1.25	0.054
Preoperative HDL-C (mmol/L)	1.22 ± 0.46	1.15 ± 0.42	0.145
Preoperative LDL-C (mmol/L)	2.28 ± 0.88	2.49 ± 0.82	0.036*
Preoperative Non-HDL-C (mmol/L)	2.86 ± 1.01	3.18 ± 1.01	0.004**
Preoperative TG/HDL-C	1.45 ± 1.28	1.84 ± 1.68	0.055
Preoperative TC/HDL-C	3.56 ± 1.12	4.03 ± 1.32	<0.001***
Preoperative non-HDL-C/HDL-C	2.55 ± 1.12	3.01 ± 1.32	<0.001***
Preoperative FPG (mmol/L)	4.81 ± 0.78	5.18 ± 1.06	<0.001***
Preoperative serum creatinine (μmol/L)	981.02 ± 340.95	929.24 ± 305.07	0.165
Time of follow-up (months)	59.00 ± 44.78	64.14 ± 53.76	0.329
Family history of diabetes	12 (3.48%)	15 (14.42%)	<0.001***
Polycystic kidney	11 (3.81%)	9 (10.00%)	0.022*
Preoperative use of lipid-lowering drugs [n (%)]	110 (31.88%)	34 (32.69%)	0.877
HCV infection [n (%)]	34 (9.86%)	11 (10.58%)	0.258
CMV infection [n (%)]	16 (4.64%)	15 (14.42%)	<0.001***
Donor [n (%)]			
Deceased donors	162 (54.73%)	55 (59.78%)	0.394
Living donors	134 (45.27%)	37 (40.22%)	
Acute rejection [n (%)]	42 (14.74%)	12 (17.39%)	0.582
Use of IL-2Ra [n (%)]	231 (66.96%)	56 (53.85%)	0.015*
Maintenance drug [n (%)]			
CsA	192 (55.65%)	58 (55.77%)	
FK506	153 (44.35%)	46 (44.23%)	

Data are given as the mean ± SD or n (%) according to the type and distribution.

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; CsA, cyclosporin A; FK506, tacrolimus; FPG, fasting plasma glucose; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; IL-2Ra, interleukin-2 receptor antagonists; LDL-C, low-density lipoprotein cholesterol; NODAT, new-onset diabetes after transplantation; TC, total cholesterol; TG, triglyceride.

*p<0.05.; **p<0.01.; ***p<0.001.

as the ratio of weight (kg) to the height (m) squared. Perioperative information included the occurrence of acute rejection, the use of interleukin-2 receptor antagonists (IL-2Ra), medications in the immunosuppressant regimen, and survival status. Routine blood tests (eg, FPG, lipid, renal, and liver function, HCV/CMV markers, monitoring of plasma drug concentration of the immunosuppressive regimen) were conducted during the outpatient visits to the follow-up clinic, which were scheduled every month for the first postoperative year and every 2–3 months after that. The venous blood samples were collected in the morning after overnight fasting for 8–12 h.

2.3 | Immunosuppressive regimen

In this patient population, IL-2Ra was selectively administered to KTRs with a high rejection risk. On the day of the surgery, most patients received 500 mg intravenous methylprednisolone, and the dose was tapered every day to reach a daily dose of 40 and 30 mg by the third and seventh postoperative days, respectively. After 1 week following the surgery, the methylprednisolone dose was tapered by 5 mg every week to reach a daily dose of 15 mg. Subsequent dose reduction depended on the patient's condition. The standard triple immunosuppressive treatment administered in our center comprised cyclosporine A or FK506, mycophenolate mofetil or acetazolamide, and corticosteroids. Cyclosporine A was replaced with FK506 following the occurrence of side effects, such as kidney or liver dysfunction, gingival hyperplasia, malignancy, or chronic rejection.

2.4 | Definition of NODAT

NODAT was defined in accordance with the American Diabetes Association guidelines (2014).[15,16] However, as data on postprandial blood glucose and glycated hemoglobin levels were unavailable at the study center, NODAT was mainly diagnosed on the basis of the FPG level ≥126 mg/dl (7.0 mmol/L), with more than two consecutive confirmatory records on different days. Fasting referred to no caloric intake for at least 8 h. Furthermore, the use of oral antidiabetic drugs or insulin therapy was considered to be diagnosis for NODAT. Given the operative stress and the heavy dose of immunosuppressants, the blood glucose levels in the first three postoperative months were not considered for a NODAT diagnosis. The exposure of this study was the preoperative lipid profiles. The primary endpoint was the NODAT incidence during follow-up. The cohort was assigned to two groups, namely, NODAT group and non-NODAT group.

2.5 | Statistical analyses

The normally distributed continuous variables are presented as means±standard deviations (SDs) and were analyzed using the Student *t* test. The non-normally distributed variables are presented as medians and interquartile ranges (IQRs) and were analyzed using the unpaired two-tailed Student's *t* test or the Mann-Whitney *U* test. The categorical variables are presented as numbers and percentages and were analyzed using the unadjusted chi-square or Fisher's exact test (Table 1).

We performed univariate (Table 2) and multivariate (Table 3) analyses. The Cox regression analysis was performed to identify the independent associations between the preoperative lipid profiles and the risk of NODAT development, and variables that were previously proved to be risk factors for NODAT or were considered to be closely associated with the development of NODAT clinically were tested as potential confounders. Furthermore, the covariates were adjusted whether they changed the matched hazard ratio (HR) by at least 10% when added to the crude model. The results of the univariate analysis have shown that age, BMI, family history of diabetes, CMV infection, polycystic kidney disease, and elevated preoperative FPG were all statistically significantly associated with NODAT. Thus, these variables were selected as confounders. The use of IL-2Ra and maintenance therapy were considered to be closely associated with the development of NODAT clinically and changed the matched hazard ratio when added to the crude model obviously, these variables were also adjusted in the final model. Since sex has an impact on lipid metabolism, even the results of the univariate analysis shown that sex was not statistically significantly associated with NODAT, we also took sex as a confounding factor into the analysis.

Considering that the association may not be linear or monotonic, the preoperative lipid variables were analyzed as continuous variables and grouped into tertiles (T1, T2, and T3, respectively) as follows: TC (≤3.60, 3.61–4.45, and ≥4.46 mmol/L), TG (≤1.08, 1.09–1.69, and ≥1.70 mmol/L), HDL-C (≤0.98, 0.99–1.30, and 1.31 mmol/L), LDL-C (≤1.90, 1.91–2.56, and ≥2.57 mmol/L), non-HDL-C (≤2.46, 2.47–3.31, and ≥3.32 mmol/L), TG/HDL-C (≤0.88, 0.89–1.54, and ≥1.55), TC/HDL-C (≤2.99, 3.00–4.00, and ≥4.01), and non-HDL-C/HDL-C (≤2.02, 2.03–3.02, and ≥3.03). We converted the tertiles of preoperative lipid variables into a categorical variable and calculated the *p* for trend to verify the preoperative lipid parameters as continuous variables and to observe the possibility of non-linearity. The results are presented as HRs with a 95% confidence interval (CI). The findings from both unadjusted and multivariate-adjusted models are listed in Table 3.

We used smooth curve fitting to further observe the association between the preoperative lipid profiles and the risk of NODAT. Analyses using restricted cubic spline confirmed that the associations between the preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C with NODAT were linear (Figure 2). The area between the two dotted lines is expressed as a 95% CI. Each point shows the preoperative lipid level and is connected to form a continuous line. Subgroup analysis after adjustments to assess whether there was a consistent association between preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C with NODAT were modeled (Tables S1–S5).

All statistical analyses were conducted using Empowerstats (http://www. EmpowerStats.com.cn) and R (version 3.2; http://

TABLE 2 The results of univariate analysis for NODAT

	Univariate analysis	
Variables	**HR 95% CI**	***p*-value**
Sex (male versus female)	0.78 (0.51, 1.22)	0.2796
Age (per 1 year)	1.03 (1.01, 1.04)	0.0013**
BMI (per 1 kg/m^2)	1.07 (1.01, 1.14)	0.0161*
Preoperative FPG (per 1 mmol/L)	1.56 (1.31, 1.85)	<0.0001***
Preoperative usage of lipid-lowering drugs	0.82 (0.54, 1.23)	0.3334
Preoperative hypertension	1.10 (0.64, 1.87)	0.7361
Family history of diabetes	3.09 (1.78, 5.35)	<0.0001***
CMV	2.68 (1.55, 4.64)	0.0004***
HCV	1.41 (0.57, 3.47)	0.4527
Polycystic kidney	2.35 (1.18, 4.69)	0.0152**
Donor (deceased and living donors)	0.99 (0.65, 1.51)	0.9733
Preoperative TC (per 1 mmol/L)	1.16 (1.00, 1.35)	0.0477**
Preoperative TG (per 1 mmol/L)	1.12 (1.00, 1.25)	0.0543
Preoperative HDL-C (per 1 mmol/L)	0.67 (0.41, 1.09)	0.1053
Preoperative LDL-C (per 1 mmol/L)	1.26 (1.04, 1.54)	0.0205*
Preoperative non-HDL-C (per 1 mmol/L)	1.39 (1.15, 1.69)	0.0008***
Preoperative TG/HDL-C	1.23 (1.05, 1.44)	0.0088**
Preoperative TC/HDL-C	1.31 (1.14, 1.51)	0.0002***
Preoperative non-HDL-C/HDL-C	1.30 (1.13, 1.50)	0.0002***
Time of follow-up (per 1 month)	0.99 (0.99, 1.00)	0.0290*
Use of IL-2Ra	0.71 (0.48, 1.04)	0.0815
Acute rejection	1.09 (0.58, 2.04)	0.7845
Maintenance drug		
CsA	0.69 (0.46, 1.03)	0.0708
FK 506	1.45 (0.97, 2.17)	

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; CsA, cyclosporin A; FK506, tacrolimus; FPG, fasting plasma glucose; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; IL-2Ra, interleukin-2 receptor antagonists; LDL-C, low-density lipoprotein cholesterol; NODAT, new-onset diabetes after transplantation; TC, total cholesterol; TG, triglyceride.

*p<0.05.; **p<0.01.; ***p<0.001.

www.R-project.org/). A double-tailed $p < 0.05$ was considered statistically significant in all analyses.

3 | RESULTS

3.1 | Comparisons of baseline demographics and clinical parameters

Of 449 participants recruited to this study, 104 (23.16%) developed NODAT during a median follow-up period of 28.03 (IQR 12.00–84.23) months. The mean age (±SD) of the participants in this study population was 38.90 ± 11.94 years, and 316 (70.38%) were male. The demographics and clinical characteristics of the study participants are summarized in Table 1. Compared with the non-NODAT group, the NODAT group comprised significantly older patients who had higher BMI; higher preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, non-HDL-C/HDL-C and FPG levels; and higher prevalence of polycystic kidney disease, CMV infection, family history of diabetes, and IL-2Ra usage (all $p < 0.05$). There was no statistically significant difference in the remaining variables among the two groups ($p > 0.05$). Moreover, based on the lipid index distribution of KTRs (Figure S1), the preoperative TC level was higher than 5.18 mmol/L, the TG level was higher than 1.7 mmol/L, the HDL-C level was lower than 1.04 mmol/L, the LDL-C level was higher than 1.4 mmol/L, and the non-HDL-C level was higher than 2.2 mmol/L in 14.48%, 32.52%, 40.31%, 87.08%, and 75.50% of patients in the KTRs group, respectively.

3.2 | Univariate analysis

The results of the univariate analysis are shown in Table 2. These results revealed that age, BMI, family history of diabetes, CMV infection, polycystic kidney disease, duration of follow-up, and elevated preoperative FPG, TC, LDL-C, non-HDL-C, TG/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C levels were all associated with NODAT.

TABLE 3 Hazard ratios of lipid levels for NODAT by Cox regression

		Crude model			Model I[a]			Model II[b]		
Variables	**Number**	**HR (95%CI)**	***p*-value**	***p* for trend**	**HR (95%CI)**	***p*-value**	***p* for trend**	**HR (95%CI)**	***p*-value**	***p* for trend**
Preoperative TC (mmol/L)		1.21 (1.02, 1.44)	0.0262*		1.29 (1.06, 1.59)	0.0132*		1.25(1.09, 1.58)	0.0495*	
T1: ≤3.60	153	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 3.61–4.45	148	0.97 (0.58, 1.64)	0.9163	0.0102*	1.04 (0.69, 1.76)	0.7325	0.0003**	1.06 (0.59, 1.93)	0.8404	0.0163*
T3: ≥4.46	148	1.79 (1.12, 2.85)	0.0147*		1.78 (1.06, 1.98)	0.0148*		2.00 (1.11, 3.62)	0.0209*	
Preoperative TG (mmol/L)[c]		1.27 (1.04, 1.54)	0.0162*		1.22 (1.01, 1.48)	0.0378*		1.08 (0.87, 1.35)	0.4850	
T1: ≤1.08	154	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 1.09–1.69	149	0.87 (0.53, 1.44)	0.5966	0.1578	0.82 (0.70, 1.22)	0.7246	0.2673	0.84 (0.48, 1.47)	0.5404	0.7730
T3: ≥1.70	146	1.37 (0.87, 2.17)	0.1756		1.25 (0.84, 1.91)	0.1343		1.06 (0.62, 1.83)	0.8261	
Preoperative HDL-C (mmol/L)		0.67 (0.40, 1.10)	0.1113		0.67 (0.41, 1.10)	0.1157		0.74 (0.43, 1.27)	0.2744	
T1: ≤0.98	152	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 0.99–1.30	153	0.55 (0.34, 0.89)	0.0147*	0.1312	0.56 (0.34, 0.79)	0.0164*	0.7422	0.58 (0.34, 1.00)	0.0482*	0.5588
T3: ≥1.31	144	0.71 (0.45, 1.11)	0.1314		0.84 (0.65, 1.07)	0.1539		0.86 (0.51, 1.47)	0.5833	
Preoperative LDL-C (mmol/L)		1.29 (1.05, 1.59)	0.0158*		1.40 (1.08, 1.80)	0.0097**		1.33 (1.02, 1.75)	0.0352*	
T1: ≤1.90	152	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 1.91–2.56	149	1.03 (0.61, 1.74)	0.9070	0.0041**	1.08 (0.63,1.53)	0.8075	0.0007**	1.01 (0.55, 1.82)	0.9868	0.0114*
T3: ≥2.57	148	1.93 (1.21, 3.08)	0.0058**		2.03 (1.34, 3.27)	0.0037**		1.97 (1.11, 3.51)	0.0203*	
Preoperative non-HDL-C (mmol/L)		1.39 (1.15, 1.69)	0.0008***		1.34 (1.11, 1.63)	0.0028**		1.41 (1.09, 1.82)	0.0084**	
T1: ≤2.46	157	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 2.47–3.31	152	0.76 (0.44, 1.33)	0.3362	0.0008***	0.81 (0.47, 1.42)	0.4567	0.0010**	1.05 (0.57, 1.93)	0.8854	0.0015**
T3: ≥3.32	140	2.06 (1.31, 3.24)	0.0018**		1.68 (1.27, 2.24)	0.0003***		2.49 (1.37, 4.51)	0.0026**	
Preoperative TG/HDL-C		1.23 (1.05, 1.44)	0.0088**		1.20 (1.02, 1.40)	0.0245*		1.34 (0.97, 1.85)	0.0726	
T1: ≤0.88	149	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 0.89–1.54	151	1.17 (0.72, 1.91)	0.5263	0.1922	1.01 (0.78, 1.31)	0.9401	0.5714	1.04 (0.61, 1.78)	0.8911	0.8058
T3: ≥1.55	149	1.37 (0.85, 2.21)	0.1935		1.12 (0.88, 1.42)	0.3503		0.92 (0.49, 1.74)	0.7956	
Preoperative TC/HDL-C		1.31 (1.14, 1.51)	0.0002***		1.27 (1.10, 1.47)	0.0009***		1.28 (1.06, 1.54)	0.0109*	
T1: ≤2.99	147	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 3.00–4.00	153	1.09 (0.63, 1.86)	0.7599	0.0008***	1.08 (0.64, 1.93)	0.5470	0.0005***	1.16 (0.65, 2.08)	0.6120	0.0090**
T3: ≥4.01	149	2.15 (1.34, 3.46)	0.0015**		2.11 (1.27, 3.40)	0.0010**		2.17 (1.21, 3.90)	0.0094**	
Preoperative non-HDL/HDL-C		1.30 (1.13, 1.50)	0.0002***		1.27 (1.10, 1.46)	0.0011**		1.26 (1.05, 1.52)	0.0138*	

Variables	Number	Crude model			Model I[a]			Model II[b]		
		HR (95%CI)	*p*-value	*p* for trend	HR (95%CI)	*p*-value	*p* for trend	HR (95%CI)	*p*-value	*p* for trend
T1: ≤2.02	151	1.00 (Reference)			1.00 (Reference)			1.00 (Reference)		
T2: 2.03–3.02	151	1.14 (0.67, 1.94)	0.6198	0.0010***	1.15 (0.81, 1.91)	0.3727	0.0010**	1.24 (0.70, 2.20)	0.4641	0.0116*
T3: ≥3.03	147	2.16 (1.34, 3.47)	0.0016		2.48 (1.16, 3.89)	0.0018**		2.08 (1.17, 3.71)	0.0124*	

Note: Results are given as hazard ratio (95% confidence interval) *p*-value.

[a]Model I adjust for: Sex; Age; BMI.

[b]Model II adjust for: Sex; Age; BMI; Family history of diabetes; Polycystic kidney; CMV infection; Preoperative FPG; Triglyceride; Use of IL-2Ra; Maintenance drug.

[c]Model II adjust for: Sex; Age; BMI; Family history of diabetes; Polycystic kidney; CMV infection; Preoperative FPG; Use of IL-2Ra; Maintenance drug.

*$p<0.05$.; **$p<0.01$.; ***$p<0.001$.

Furthermore, we found that sex, preoperative use of lipid-lowering drugs, hypertension, preoperative TG and HDL-C levels, use of IL-2Ra, and maintenance therapy were unassociated with NODAT.

3.3 | Association between the preoperative lipid profiles and the risk of NODAT

The crude and multivariate-adjusted models are shown in Table 3. Overall, both continuous and categorical analyses showed that the preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C levels were significantly associated positively with incident NODAT (all $p < 0.05$). They were independent predictors of diabetes after adjusting for other covariates. In the crude model, the following variables were positively associated (HR, 95% CI) with NODAT: preoperative TC (1.21, 1.02–1.44, $p = 0.0262$), TG (1.27, 1.04–1.54, $p = 0.0162$), LDL-C (1.29, 1.05–1.59, $p = 0.0158$), non-HDL-C (1.39, 1.15–1.69, $p = 0.0008$), TG/HDL-C (1.23, 1.05–1.44, $p = 0.0088$), TC/HDL-C (1.31, 1.14–1.51, $p = 0.0002$), and non-HDL-C/HDL-C (1.30, 1.13–1.50, $p = 0.0002$) levels. However, HDL-C levels were non-significantly negatively associated with NODAT (HR 0.67, 95% CI 0.41–1.10, $p = 0.1113$). When TG and TG/HDL-C were assessed as tertiles, the *p* for trend through the tertiles were statistically insignificant. As shown in Table 3, further adjustments of Model I for sex, age, and BMI did not substantially alter the results. In the multivariate analysis (Model II), the preoperative TC (HR 1.25, 95% CI 1.09–1.58, $p = 0.0495$), LDL-C (HR 1.33, 95% CI 1.02–1.75, $p = 0.0352$), non-HDL-C (HR 1.41, 95% CI 1.09–1.82, $p = 0.0084$), TC/HDL-C (HR 1.28, 95% CI 1.06–1.54, $p = 0.0109$), and non-HDL-C/HDL-C (HR 1.26, 95% CI 1.05–1.52, $p = 0.0138$) were still significantly associated with NODAT, and further adjustments for additional covariates did not weaken the association. As shown in Table 3, when TC was assessed as tertiles, the adjusted HR of NODAT for participants in T3 (≥4.46 mmol/L) was 2.00 (95% CI 1.11–3.62) compared with those in T1 (≤3.60 mmol/L, *p* for trend = 0.0163). Similarly, the risk of NODAT increased approximately twofold in participants in T3 (≥2.57 mmol/L) than in those in T1 (≤1.90 mmol/L) with LDL-C levels (HR 1.97, 95% CI 1.11–3.51, *p* for trend = 0.0114). Subjects in T3 (≥3.32 mmol/L) had a higher risk of NODAT (HR 2.49, 95% CI 1.37–4.51) than those in T1 (≤2.46 mmol/L) with non-HDL-C levels (*p* for trend = 0.0015) (Table 3). Similarly, a higher TC/HDL (≥4.01) was associated with a higher risk of NODAT (HR 2.17, 95% CI 1.21–3.90, *p* for trend = 0.0090), and a similar association between a higher non-HDL-C/HDL-C (≥3.03) and NODAT risk was also found (HR 2.08, 95% CI 1.17–3.71, *p* for trend = 0.0116). The results of these analyses were consistent with those for the continuous variables, confirming the positive associations. The preoperative TG was positively associated with NODAT (HR 1.22, 95% CI 1.01–1.48, $p = 0.0378$) when only adjusted for sex, age and BMI. However, after further adjustment, the association between the risk of NODAT and preoperative TG (HR 1.08, 95% CI 0.87–1.35, $p = 0.4850$) was not significant. The preoperative TG/HDL-C was positively associated with NODAT (HR 1.20, 95% CI 1.02–1.40, $p = 0.0245$) when only

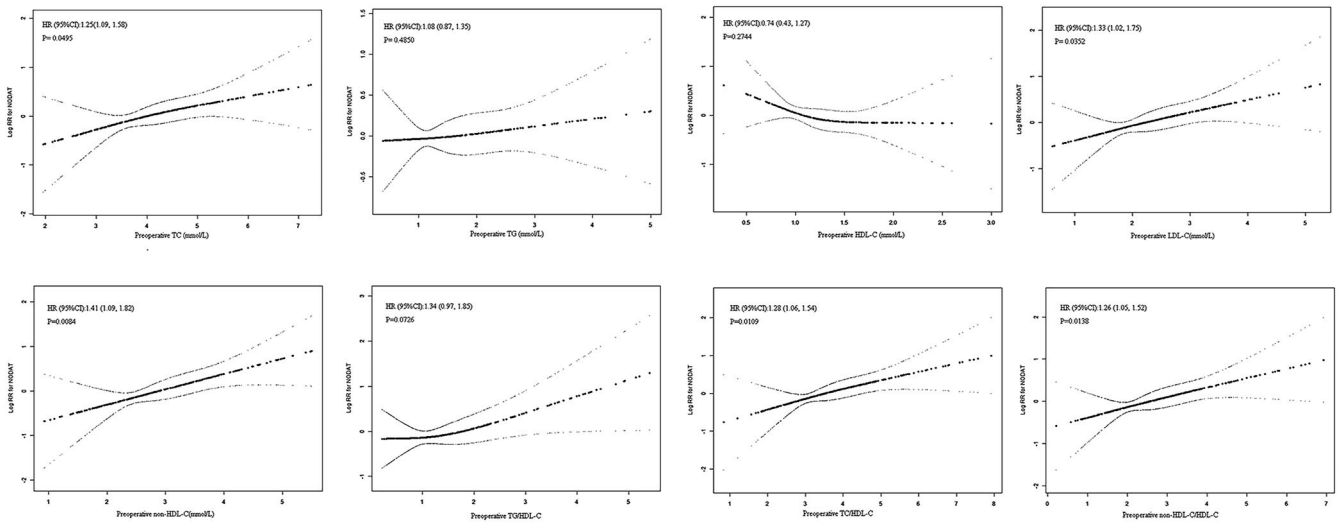

FIGURE 2 The relationship between preoperative lipid profiles and NODAT. The area between two dotted lines is expressed as a 95% confidence interval. Each point shows the preoperative lipid level and is connected to form a continuous line. Preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C are independent risk factors for NODAT. However, the association between preoperative TG, HDL-C, or TG/HDL-C and NODAT was not significant

adjusted for sex, age, and BMI; however, after adjusting for other covariables, the association with NODAT was not significant (HR 1.34, 95% CI 0.97–1.85, p = 0.0726). The association between preoperative HDL-C (HR 0.74, 95% CI 0.43–1.27, p = 0.2744) and NODAT was negative although non-significant. This suggests that preoperative HDL-C is a protective factor of NODAT, but its effect is easily influenced by other factors.

Based on the results of the above analyses, the preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C levels proved to be significant predictors of NODAT. Thus, we further analyzed the dose-response association between preoperative lipid profiles and the risk of NODAT. Consistently, a linear association was confirmed between the higher risk of NODAT development and preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C, using spline smoothing fitting, while adjusting for age, BMI, sex, family history of diabetes, polycystic kidney disease, CMV infection, preoperative FPG and TG levels, use of IL-2Ra, and maintenance pharmacotherapy (Figure 2). These positive associations between preoperative lipid TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C and the risk of NODAT were evident in all of the subgroups considered and persisted after careful adjustments (Tables S1–S5).

4 | DISCUSSION

In the present retrospective cohort study, we investigated the association of preoperative lipid profiles with NODAT in Chinese KTRs, showing that higher preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C values had a positive and independent correlation with the increased risk of NODAT. The results of this study demonstrate that the association between preoperative HDL-C and NODAT was negative although non-significant (HR 0.74, 95% CI 0.43–1.27, p = 0.2744). Moreover, the association between preoperative TG/HDL-C and NODAT was positive although not significant (HR 1.34, 95% CI 0.97–1.85, p = 0.0726). The results indicated a strong predictive value of the preoperative lipid profiles for NODAT.

Kidney transplantation is an effective treatment for end-stage renal failure, and the 5-year graft survival has reached 80%.[17] Besides the advancement in surgical techniques and medical care, long-term management of chronic complications has been crucial for this success. NODAT is an important risk factor for the decreased survival rate. Thus, the identification of individuals with a higher risk for developing NODAT is challenging, although it has potentially significant benefits if preventive measures are implemented. The lipid profiles are reproducible and inexpensive indicators that can be readily collected during blood testing and routine clinical management. Based on the results of this study, the preoperative lipid profiles were characterized by widespread dyslipidemia in the KTR group. The preoperative KTR population is at a high risk of cardiovascular disease; therefore, the LDL-C and non-HDL-C levels should be controlled to <1.4 and <2.2 mmol/L, respectively.[18] The preoperative lipid profiles exceeded the recommended ranges in most of our KTRs, which was consistent with the reports from previous studies.[19] Impaired renal function and abnormal lipid excretion contribute to the frequent occurrence of preoperative dyslipidemia in KTRs.[7]

In this study, we observed a linear association between a higher risk of NODAT and the preoperative TC, LDL-C, non-HDL-C TC/HDL-C, and non-HDL-C/HDL-C levels that were evident in all subgroup analyses that were considered and after careful adjustments. Consistently, previous studies have reported that TC is a predictor of T2DM incidence in the Chinese population and have identified TC/HDL-C as a predictor of T2DM incidence in the Iranian population.[20,21] The non-HDL-C level has been reported to be a predictor of diabetes risk in the non-transplant population when the TG level is

sometimes too high to obtain an accurate value of the LDL-C level.[22] Furthermore, non-HDL-C/HDL-C is a predictor of insulin resistance.[23] Research has indicated that β-cell function is impaired in individuals with elevated TC and LDL-C levels at a relatively early stage even with normal glucose tolerance; however, TG/HDL-C and TG could be predictors of insulin resistance although not of β-cell function.[24,25] The TG levels fluctuate widely because of dietary intake or weight changes, which cannot effectively represent the state of insulin resistance. This might be the reason for the positive, although non-significant, association of preoperative TG/HDL-C with NODAT. Moreover, the results of our study suggest that the association between preoperative HDL-C and NODAT was negative although non-significant. It is reasonable to speculate that the preoperative lipid levels should be more strictly controlled in KTRs to prevent the development of NODAT, and strategies focusing on lowering preoperative lipid may be beneficial for prolonging graft survival.

The underlying mechanisms of the potential effects of preoperative lipid on the development of NODAT are incompletely understood. These may involve impaired insulin secretion and insulin resistance. The excess cholesterol accumulation may contribute to β-cell dysfunction in NODAT,[21] and the β-cell impaired ATP-binding cassette transporter A1 (ABCA1) can lead to impaired glucose tolerance and β-cell dysfunction, thereby influencing insulin secretion.[26-28] Islet cholesterol deposition may lead to increased islet amyloid polypeptide aggregation and islet amyloid formation, further worsening β-cell function and challenges to glucose homeostasis.[29] Xia et al, indicated that insulin secretion from pancreatic β-cells is mediated by the opening of voltage-gated Ca^{2+} channels and exocytosis of insulin-dense core vesicles. Endogenous cholesterol plays a critical role in the regulation of insulin secretion through the modulation of the functional activity of Ca^{2+} channels and insulin secretory granule mobilization and membrane fusion. The dysregulation of cellular cholesterol may result in impaired β-cell function, which has been implicated as a possible pathogenic mechanism for type 2 diabetes.[30] A study showed that there were inverse trends between β-cell function and TC, LDL-C, and TC/HDL-C, although not in TG/HDL-C, in the Chinese population with normal glucose tolerance.[31] Another possible reason might be that insulin resistance accounts for the development of NODAT in patients with preoperative dyslipidemia.[32,33] Dyslipidemia is often accompanied by abdominal obesity, which increases insulin resistance in peripheral tissues.[34,35] Further research is needed to elucidate the mechanism underlying the role of lipid profiles in the development of NODAT.

This study offers notable strengths. First, to the best of our knowledge, this is the first study to comprehensively analyze the association between the preoperative lipid profiles and the NODAT incidence in Chinese KTRs. Several possible risk factors that affect the NODAT incidence were adjusted in our analysis to arrive at clearer conclusions. Second, we provide reference cutoff values for the early recognition of KTRs with an increased risk for NODAT: we found the independent effects of preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C on the development of NODAT.

Furthermore, we recognize some limitations of this study. First, NODAT was mainly diagnosed from the FPG levels. Some patients with normal postoperative FPG levels, although high 2-h postprandial blood glucose levels that met the diagnostic standard for diabetes, could have been missed; therefore, the NODAT incidence could possibly have been underestimated.[36,37] However, the measurement of FPG is more practical and is universally accepted for its utility in defining NODAT. Second, our study was retrospective, and essential residual confounding effects from other unmeasured factors cannot be excluded, because we relied on the extant medical records. For example, incomplete data on the dose of glucocorticoids made it difficult for us to adjust for its possible effects on the development of NODAT. Nonetheless, the dose of prednisone was mostly stable at a minimal maintenance dose of 5–10 mg beyond 3 months after the transplantation, which may have attenuated the confounding effect. Finally, our study was designed as a single-center research. Therefore, the findings of this research need to be validated in multicenter research studies with larger sample sizes and longer follow-up duration.

In summary, the preoperative TC, LDL-C, non-HDL-C, TC/HDL-C, and non-HDL-C/HDL-C were independent predictors for risk of NODAT in the Chinese KTRs population. However, the association between preoperative TG, HDL-C, or TG/HDL-C and NODAT was not significant. More stringent lipid control standards are recommended in KTRs. These findings provide important guidance for the preoperative lipid control of prospective KTRs. The proactive detection and treatment of preoperative dyslipidemia may significantly reduce the NODAT incidence and associated mortality rates after kidney transplantation.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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