



## RESEARCH ARTICLE

# A retrospective cohort study of preoperative lipid indices and their impact on new-onset diabetes after liver transplantation

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## Abstract

**Background:** The correlation between preoperative lipid profiles and new-onset diabetes after transplantation (NODAT) remains relatively unexplored in liver transplant recipients (LTRs). Thus, we aimed to investigate the preoperative lipid profiles in Chinese LTRs and evaluate the different influences of preoperative total cholesterol, total triglycerides (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol on the development of NODAT in both sexes.

**Methods:** A total of 767 Chinese LTRs from Zhongshan Hospital were retrospectively evaluated. NODAT was defined according to the American Diabetes Association guidelines; the relationship between each preoperative lipid index and NODAT development was analyzed separately in men and women.

**Results:** Pretransplant hypotriglyceridemia was observed in 35.72% of the total LTRs. In men, only the preoperative TG level was significantly associated with incident NODAT after adjusting for potential confounders (hazard ratio 1.37, 95% confidence interval 1.13-1.66,  $P = .001$ ). There was a nonlinear relationship between the preoperative TG level and NODAT risk. The risk of NODAT significantly increased with preoperative a TG level above 0.54 mmol/L (log-likelihood ratio test,  $P = .043$ ). In women, no significant association was observed.

**Conclusion:** Among male LTRs, a higher preoperative TG level, even at a low level within the normal range, was significantly and nonlinearly associated with an increased risk of NODAT.

## KEYWORDS

hypoglycemia, liver transplantation, new-onset diabetes after transplantation, preoperative lipid index, triglycerides

Liang and Yi are joint first authors.

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## 1 | INTRODUCTION

In an era with significant improvement in short-term survival after liver transplantation, new-onset diabetes after transplantation (NODAT) remains an unresolved problem, limiting the long-term survival of liver transplant recipients (LTRs). Reports indicate that the incidence of NODAT increases to 30% at 1-2 years after transplantation.<sup>1-3</sup> NODAT is one of the most frequently observed and serious post-transplant metabolic complications, placing LTRs at increased risk of acute rejection, infection, cardiovascular disease, and graft failure, thereby compromising the lifesaving potential of liver transplantation in the long term. Therefore, identification of LTRs at increased risk of developing NODAT is of great importance.

Hitherto, multiple risk factors of NODAT have been recognized, including advanced age, high body mass index (BMI), non-white ethnicity, impaired glucose regulation, and chronic exposure to immunosuppressive medication.<sup>3</sup> Recently, the pretransplant lipid profiles, namely the preoperative levels of total triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), and their influences on the development of NODAT have received much attention. In the nontransplant population, it is well established that elevated serum TG levels are closely associated with an increased risk of type 2 diabetes mellitus (T2DM).<sup>4,5</sup> However, there is currently no consensus on this issue in the transplant setting. Previous studies conducted in kidney transplant recipients (KTRs) reported a significant association between preoperative TG and NODAT but failed to confirm an independent influence of TC on the development of NODAT.<sup>6-9</sup> Moreover,

other KTR-based studies suggest that neither TG nor TC is a significant risk factor for NODAT.<sup>10,11</sup> Preoperative HDL-C and LDL-C levels have been less frequently analyzed, and their associations with NODAT remain unclear. Bolori et al<sup>12</sup> identified a protective effect of preoperative HDL-C on incident NODAT, whereas Cosio et al<sup>13</sup> suggested that neither HDL-C nor LDL-C was significantly associated with NODAT.

To date, besides the conflicting results concerning the lipid-diabetes association in KTRs, evidence based on LTRs has been quite limited. Furthermore, sex, as an influential factor for serum lipids,<sup>14</sup> has been rarely examined in previous studies. Against this background, the primary aims of this study are to investigate the preoperative lipid profiles among a large population of Chinese LTRs and evaluate the different influences of TC, TG, HDL-C, and LDL-C on the development of NODAT in both sexes. Through our study, we hope to further clarify the complicated relationship between the pretransplant lipid profile and the onset of NODAT and effectively lower the NODAT incidence by strictly managing pretransplant serum lipid levels.

## 2 | PATIENTS AND METHODS

### 2.1 | Study participants

In this retrospective cohort study, data from all cadaveric liver transplantations performed at Zhongshan Hospital, Fudan University, between April 1, 2001, and December 31, 2016, were collected. Adult LTRs (aged >18 years old) surviving with a functioning allograft beyond the first 3 months after transplantation were eligible. The

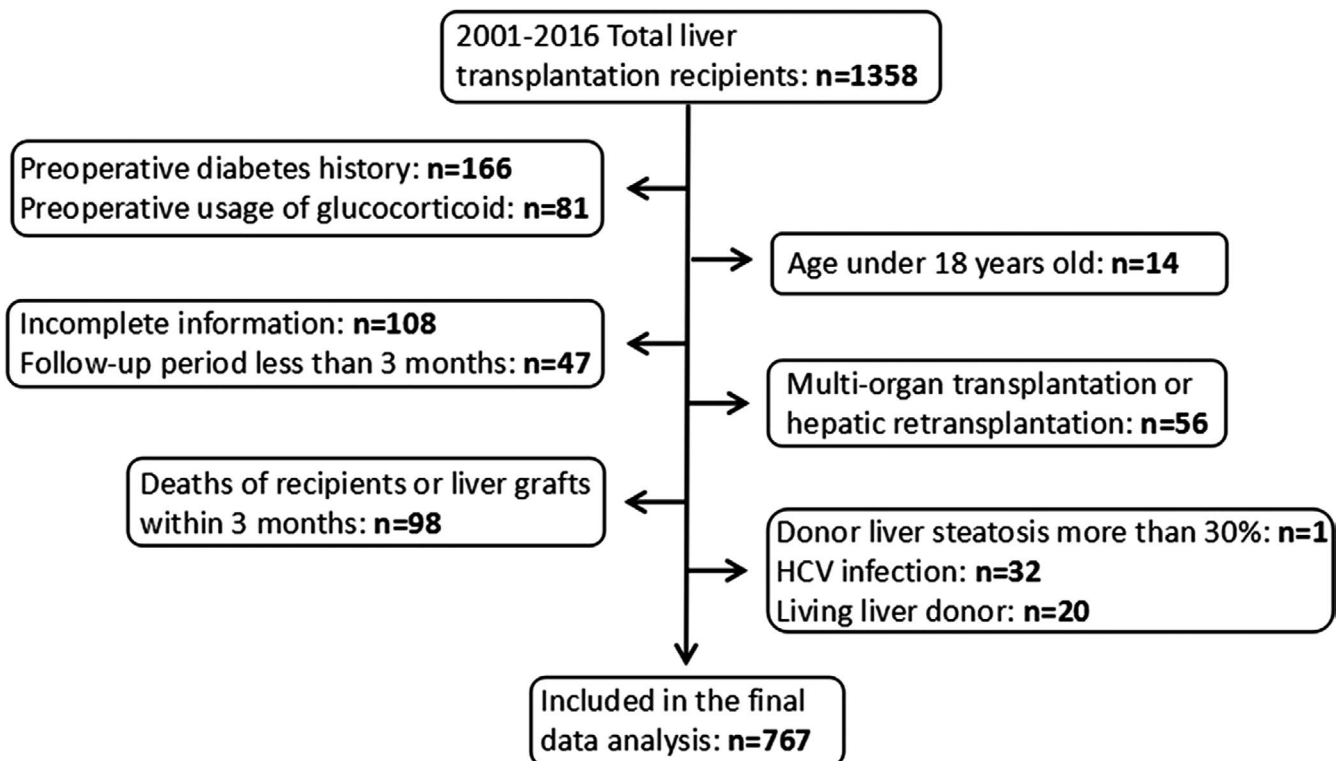


FIGURE 1 Flow diagram showing patient selection. HCV, hepatitis C virus

process of patient selection is shown in Figure 1, and 767 LTRs were ultimately included.

The study protocol was approved by the institutional review board of Zhongshan Hospital, Fudan University. The requirement for written informed consent was waived because the data used in this retrospective observational study were anonymous. Of note, the Liver Transplant Center at Zhongshan Hospital has always complied with the recommendations of the Declaration of Helsinki, and the use of livers from executed prisoners is firmly prohibited. All donor livers for transplantation were obtained either from voluntary donors or the patients' families.

## 2.2 | Data collection

Demographic and clinical information was extracted from inpatient and outpatient medical records from a unified database at Zhongshan Hospital. Preoperative data included the date of operation, sex, age, height, weight, history of hypertension or liver cirrhosis, primary liver diseases, primary liver function (graded by Child-Pugh class), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, and biochemical indicators. Peri- and postoperative information included postoperative fasting plasma glucose (FPG) levels, the presence of donor liver steatosis, the occurrence of acute rejection, medication for immunity induction and immunosuppression, and the survival status of the LTRs. The BMI was calculated as the ratio of weight, in kilograms, to height, in meters, squared. Data on biochemical indicators, including preoperative FPG, TC, TG, HDL-C, and LDL-C levels, were obtained from routine biochemical tests performed at Zhongshan Hospital within 3 months before transplantation. Where multiple results were available, the highest recorded values during this period were selected. Data on postoperative FPG levels were collected from regular follow-up visits, which were at least monthly for the first postoperative year and every 2-3 months thereafter. Details of the blood testing process have been described previously.<sup>14</sup>

## 2.3 | Immunosuppression

The interleukin-2 receptor antagonist (IL-2Ra) was administered selectively to LTRs with a high immunologic risk; postoperative immunosuppression for maintenance comprised prednisone, mycophenolate mofetil (MMF), tacrolimus (FK506), cyclosporine A (CsA), and sirolimus (RAP). A triple immunosuppression regimen with FK506, MMF, and prednisone was most frequently used in our center. FK506 was replaced by CsA if LTRs developed severe headaches or epilepsy. RAP was administered instead of FK506 if LTRs exhibited renal insufficiency or inadequate blood concentrations of FK506. Several LTRs received quadruple immunosuppression with RAP, FK506, MMF, and prednisone following the advice of the attending doctors. The doses of FK506 and RAP were adjusted according to similar target trough levels, and CsA doses were adjusted on the basis of target peak levels.

All LTRs received an intraoperative bolus of 1 g of intravenous methylprednisolone and 360 mg on the following day. The dose was then reduced daily by 40 mg. On the sixth post-transplant day, LTRs switched to oral prednisone (20 mg per day). Thereafter, dose reductions were based on the assessment of the individual patient. Prednisone was usually removed from the regimen within 3 months after transplant but was administered for up to 2 years if needed in some cases.

## 2.4 | Definitions of terms

### 2.4.1 | NODAT

NODAT was defined according to the American Diabetes Association (ADA) guidelines (2014).<sup>15</sup> Since data of postprandial blood glucose and glycated hemoglobin tests were unavailable in our center, the diagnosis of NODAT was mainly based on an FPG level  $\geq 126$  mg/dL (7.0 mmol/L), with two or more consecutive confirmatory records on different days. Fasting referred to no caloric intake for at least 8 hours. Furthermore, LTRs using oral antidiabetic drugs or insulin were also considered to have developed NODAT. Due to the high dose of immunosuppressants and surgical stress, LTRs may present during the first 3 months post-transplant with transient hyperglycemia. Therefore, NODAT was only diagnosed after that period.

### 2.4.2 | Donor liver steatosis

A diagnosis of donor liver steatosis was made if ultrasound-guided liver biopsies showed the presence of 5%-30% steatotic hepatocytes, whereas LTRs with 30% or more steatotic hepatocytes were excluded.

### 2.4.3 | Acute rejection

Acute rejection was defined as the occurrence of cellular rejection, which was confirmed by liver biopsy within the first postoperative year.

### 2.4.4 | HBV and HCV infections

HBV and HCV infections were defined as serological results for hepatitis B surface antigen and anti-HCV antibody, respectively.

## 2.5 | Statistical analyses

Continuous variables are presented as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR) according to the data distribution, whereas categorical data are described as counts and

**TABLE 1** Baseline demographic and clinical parameters

	Female			Male		
	NODAT (41 cases)	Non-NODAT (74 cases)	P-value	NODAT (235 cases)	Non-NODAT (417 cases)	P-value
Age (years)	53.61 ± 10.25	50.22 ± 11.68	.211	50.80 ± 8.84	48.65 ± 9.81	<b>.009</b>
BMI (kg/m <sup>2</sup> )	21.06 ± 3.10	21.27 ± 3.14	.757	23.82 ± 2.87	23.34 ± 2.95	<b>.020</b>
Preoperative TC (mmol/L)	3.67 ± 0.80	3.96 ± 1.58	.807	3.71 ± 1.27	3.86 ± 1.21	.217
Preoperative TG (mmol/L)	0.89 ± 0.47	0.95 ± 0.56	.792	1.10 ± 0.54	1.00 ± 0.48	.106
Preoperative HDL-C (mmol/L)	1.32 ± 0.57	1.16 ± 0.63	.260	1.07 ± 0.53	1.10 ± 0.49	.453
Preoperative LDL-C (mmol/L)	1.96 ± 0.65	2.23 ± 1.13	.449	2.11 ± 1.03	2.27 ± 1.01	.109
Preoperative FPG (mmol/L)	4.92 ± 0.79	4.90 ± 0.97	.400	5.33 ± 1.38	5.04 ± 1.11	<b>&lt;.001</b>
Primary disease [n (%)]						
Primary liver cancer	18 (43.90%)	37 (50.00%)	.201	170 (72.34%)	305 (73.14%)	.948
Decompensated liver cirrhosis	1 (2.44%)	9 (12.16%)		19 (8.09%)	37 (8.87%)	
Severe hepatitis or acute hepatic failure	12 (29.27%)	16 (21.62%)		32 (13.62%)	51 (12.23%)	
Others	10 (24.39%)	12 (16.22%)		14 (5.96%)	24 (5.76%)	
Acute rejection [n (%)]						
No	36 (87.80%)	66 (89.19%)	1.000	199 (84.68%)	368 (88.25%)	.194
Yes	5 (12.20%)	8 (10.81%)		36 (15.32%)	49 (11.75%)	
Preoperative liver function (Child-Pugh class) [n (%)]						
A	20 (48.78%)	38 (51.35%)	.963	136 (57.87%)	266 (63.79%)	.318
B	16 (39.02%)	26 (35.14%)		66 (28.09%)	103 (24.70%)	
C	5 (12.20%)	10 (13.51%)		33 (14.04%)	48 (11.51%)	
Preoperative liver cirrhosis [n (%)]						
No	8 (10.81%)	4 (9.76%)	1.000	18 (7.66%)	42 (10.07%)	.306
Yes	66 (89.19%)	37 (90.24%)		217 (92.34%)	375 (89.93%)	
HBV infection						
No	5 (12.19%)	5 (6.79%)	.518	32 (13.60%)	42 (10.07%)	.171
Yes	36 (87.81%)	69 (93.21%)		203 (86.40%)	375 (89.93%)	
Donor liver steatosis [n (%)]						
No	19 (46.34%)	44 (59.46%)	.176	122 (51.91%)	231 (55.40%)	.392
Yes	22 (53.66%)	30 (40.54%)		113 (48.09%)	186 (44.60%)	
Preoperative hypertension [n (%)]						
No	38 (92.68%)	67 (90.54%)	1.000	217 (92.34%)	379 (90.89%)	.525
Yes	3 (7.32%)	7 (9.46%)		18 (7.66%)	38 (9.11%)	
Use of IL-2Ra [n (%)]						
No	18 (43.90%)	26 (35.14%)	.354	92 (39.15%)	140 (33.57%)	.153
Yes	23 (56.10%)	48 (64.86%)		143 (60.85%)	277 (66.43%)	
Maintenance drug [n (%)]						
FK506	40 (97.56%)	67 (90.54%)	.239	200 (85.11%)	347 (83.21%)	.594
CSA	0 (0.00%)	5 (6.76%)		15 (6.38%)	36 (8.63%)	
RAP	1 (2.44%)	2 (2.70%)		13 (5.53%)	26 (6.24%)	
FK506 + RAP	0 (0.00%)	0 (0.00%)		7 (2.98%)	8 (1.92%)	

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

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

Bold indicates statistical significant value ( $P < .05$ ).

percentages. Sex was considered to be a strong confounder in the lipid-diabetes association<sup>14</sup>; therefore, all analyses in this study were performed separately in women and men. The baseline characteristics in Table 1 were compared using the unpaired two-tailed Student's *t* test or the Mann-Whitney *U* test for continuous variables, the unadjusted chi-squared test or Fisher's exact test for categorical variables, and the rank-sum test for ranked data.

In both sexes, LTRs were divided into two groups by the median of each preoperative lipid index; Cox regression analyses were used to generate adjusted curves of the cumulative incidences of NODAT between LTRs with lower and higher levels of preoperative serum lipids (Figure 2). Multivariate Cox regression analyses were then applied to estimate the independent relationships between each preoperative lipid index, including TC, TG, HDL-C, and LDL-C, and the risk of NODAT development. Different pre-, peri-, and postoperative variables that were previously proven to be risk factors for NODAT or clinically considered as being closely related to the development of NODAT were tested as potential confounders. Eventually, we adjusted for covariates that changed the matched hazard ratio by at least 10 percent when added to the crude models or eliminated from the complete multivariate models for each lipid index (Table 2).<sup>16,17</sup>

On the basis of the results of the multivariate Cox regression analyses, the lipid indices that were significantly associated with incident NODAT were selected and further analyzed using the smoothing function (Figure 3); the threshold effects of the selected lipid indices on incident NODAT according to the smoothing plots (Figure 3) were then investigated using a two-piecewise linear regression model (Figure 3).<sup>18</sup> The inflection point at which the effect of preoperative lipid indices on incident NODAT became significant was determined using trial and error, which included selection of

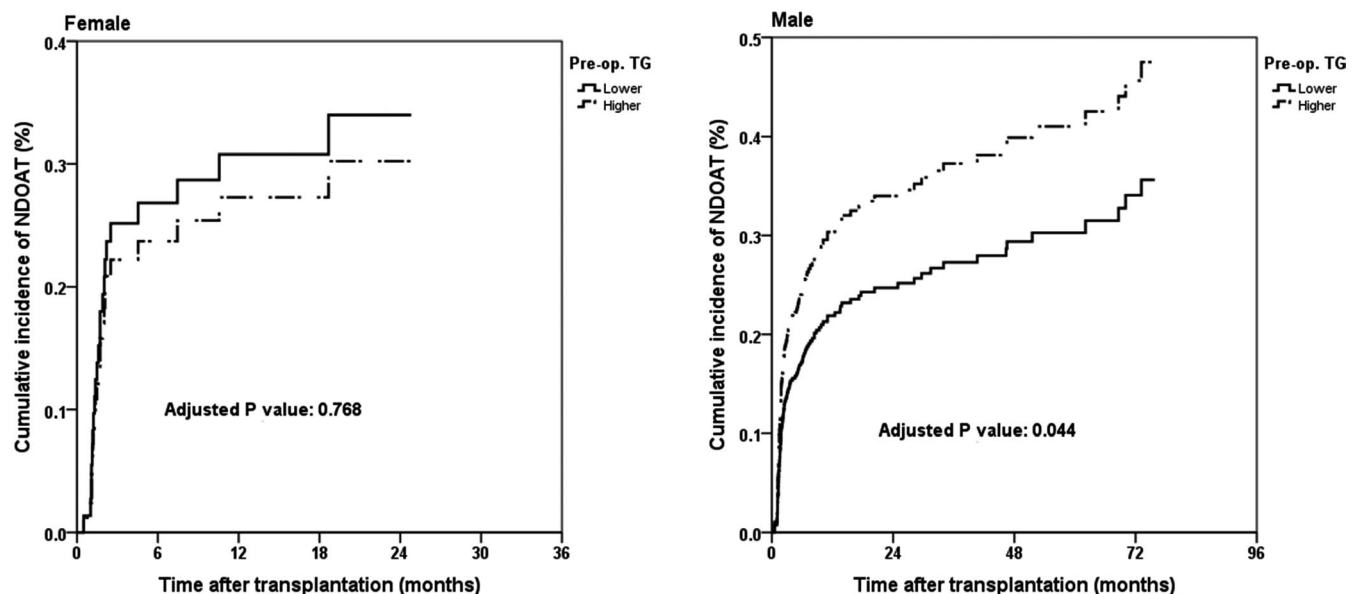
turning points along a predefined interval and choosing the that gave the maximum model likelihood. We also compared the one-line linear regression model with a two-piecewise linear model by conducting a log-likelihood ratio test.

All analyses were performed using Empower(R) (www.empowerstats.com, X&Y solutions, Inc) and R (http://www.R-project.org). A two-sided *P*-value <.05 was considered statistically significant.

### 3 | RESULTS

#### 3.1 | Comparisons of the baseline demographic and clinical parameters

Baseline parameters of men and women on the basis of incident NODAT are shown in Table 1. Overall, 35.7% (41/115) women and 36% (235/652) men developed NODAT (*P* = .936) over a median follow-up period of 12.45 (IQR 3.22-47.31) months and 12.11 (IQR 3.77-42.31) months, respectively (*P* = .929). As Table 1 demonstrates, in women, all baseline parameters were comparable between LTRs with and without NODAT (all *P*-values >.05). However, in men, LTRs with NODAT were significantly older (*P* = .009) and had higher levels of preoperative BMI (*P* = .020) and FPG (*P* < .001) than did those without NODAT; comparisons of the remaining variables revealed no significant differences (*P* > .05). In addition, according to the distribution of LTRs with different levels of each lipid index (Figure S1), 97.13%, 97.65%, and 97.13% of our study population presented normal preoperative levels of TC, TG, and LDL-C, respectively; among them, hypolipidemia for TC, TG, and LDL-C was prevalent in 13.82%, 35.72%, and 41.07% of the total LTRs, respectively (Figure S1).



**FIGURE 2** Comparisons of the cumulative incidence of NODAT between LTRs with higher and lower levels of preoperative TG in both sexes. Adjusted for age, BMI, preoperative liver function (Child-Pugh class), preoperative liver cirrhosis, preoperative hypertension, preoperative FPG. BMI, body mass index; FPG, fasting plasma glucose; LTRs, liver transplant recipients; NODAT, new-onset diabetes after transplantation; TG, total triglyceride

**TABLE 2** Hazard ratios of preoperative lipid indices for incident NODAT

	Female		Male		P for interaction
	Crude model	Adjusted model	Crude model	Adjusted model	
Pre-op. TC <sup>a</sup>	0.89 (0.65, 1.22) 0.462	0.95 (0.63, 1.43) 0.810	1.03 (0.94, 1.13) 0.513	1.08 (1.00, 1.17) 0.056	.362
Pre-op. TG <sup>b</sup>	0.81 (0.35, 1.92) 0.639	0.89 (0.32, 2.45) 0.820	1.30 (1.07, 1.58) <b>0.008</b>	1.37 (1.13, 1.66) <b>0.001</b>	<b>.027</b>
Pre-op. HDL-C <sup>c</sup>	1.41 (0.71, 2.79) 0.327	1.41 (0.60, 3.30) 0.430	0.83 (0.58, 1.18) 0.295	0.86 (0.59, 1.26) 0.447	.263
Pre-op. LDL-C <sup>c</sup>	0.78 (0.51, 1.20) 0.263	0.81 (0.49, 1.32) 0.400	1.03 (0.92, 1.16) 0.599	1.08 (0.97, 1.21) 0.148	.338

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

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HBV, hepatitis B 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, total triglyceride.

Bold indicates statistical significant value ( $P < .05$ ).

<sup>a</sup>Adjusted model: adjusted for age, BMI, preoperative liver function (Child-Pugh class), preoperative liver cirrhosis, preoperative hypertension, acute rejection, donor liver steatosis, preoperative FPG, primary disease.

<sup>b</sup>Adjusted model: adjusted for age, BMI, preoperative liver function (Child-Pugh class), preoperative liver cirrhosis, preoperative hypertension, preoperative FPG.

<sup>c</sup>Adjusted model: adjusted for age, BMI, preoperative liver function (Child-Pugh class), preoperative liver cirrhosis, HBV, preoperative hypertension, acute rejection, donor liver steatosis, use of IL-2Ra, maintenance drug, preoperative FPG, primary disease.

### 3.2 | Cumulative incidence of NODAT according to the preoperative lipid level in men and women

Among the total 767 LTRs, 276 (35.98%) developed NODAT over a median follow-up period of 12.12 (IQR 3.68-43.14) months. The cumulative incidence of NODAT at 1, 3, 5, and 8 years after liver transplantation was 30.3%, 37.7%, 42.4%, and 46.5%, respectively. Further, we evaluated how the cumulative incidence of NODAT varied between LTRs with lower and higher levels of each lipid index in men and women (Figure 2, Figures S2-S4).

Regarding the overall trend of NODAT incidence, women tended to have an earlier onset of NODAT than men, with more than half of the new cases of NODAT occurring within 6 months in women and 12 months in men. For TC, HDL-C, and LDL-C, no significant correlations between preoperative levels and NODAT incidence were observed in both men and women (Figures S2-S4). After adjusting for age, BMI, preoperative liver function, preoperative liver cirrhosis, preoperative hypertension, and preoperative FPG, a higher preoperative level of TG was significantly associated with a higher incidence of NODAT, but only in men ( $P = .044$  for men,  $P = .768$  for women, Figure 2). This suggests that there is a strong link between preoperative TG and NODAT, and sex might play an important role in the association between TG and NODAT.

### 3.3 | Preoperative lipid indices and NODAT risk

#### 3.3.1 | Multivariate Cox regression models analyzing the association between different preoperative lipid indices and NODAT risk

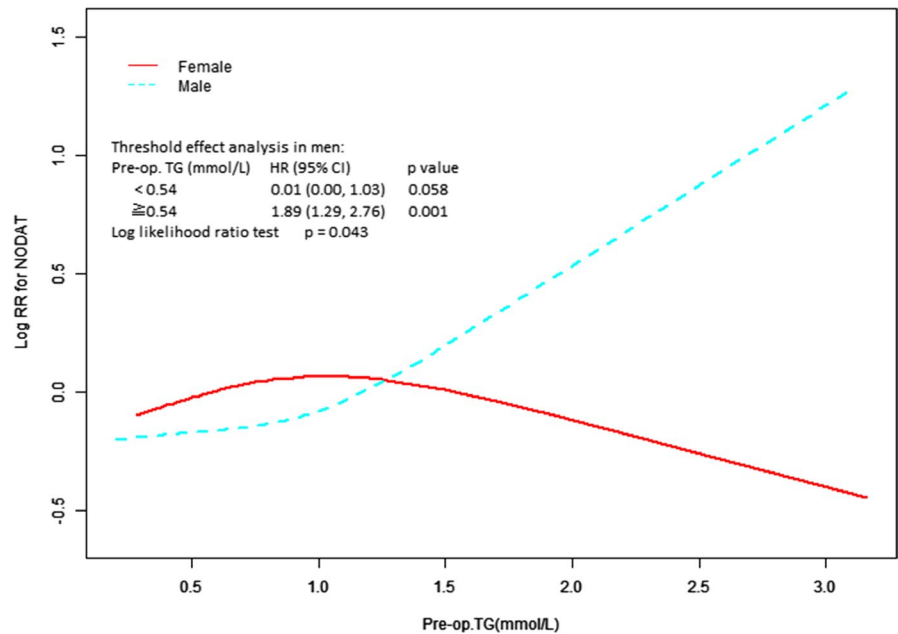
The unadjusted, as well as adjusted, hazard ratios (HRs) of 1 mmol/L change in each lipid index in both men and women are listed in Table 2.

In the crude model for men, only the preoperative TG value was significantly associated with incident NODAT (HR 1.30, 95% confidence interval [CI] 1.07-1.58,  $P = .008$ ); in the fully adjusted model, preoperative TG remained an independent predictor of NODAT, and an increase in TG levels by 1 mmol/L increased the risk of NODAT by 37% (95% CI 1.13-1.66,  $P = .001$ ). Furthermore, in this group, 1 mmol/L increases in preoperative TC levels slightly increased the NODAT risk by 8% after adjustments, without reaching significance (95% CI 1.00-1.17,  $P = .056$ ). However, in both models for women, none of the preoperative lipid indices were significantly associated with NODAT (Table 2). Additionally, we analyzed in the adjusted model the interaction between sex and each lipid index on NODAT outcomes; the results indicated a significant interaction between sex and preoperative TG in inducing NODAT ( $P$  for interaction = .027) suggesting that the influence of preoperative TG on the development of NODAT differed significantly between men (HR 1.37, 95% CI 1.13-1.66,  $P = .001$ ) and women (HR 0.89, 95% CI 0.32-2.45,  $P = .820$ ).

#### 3.3.2 | Analysis of the preoperative TG threshold for predicting NODAT in LTRs

On the basis of the results of the above analyses, preoperative TG levels proved to be a significant predictor of NODAT only in men. Thus, we further analyzed the dose-response relationship between TG and NODAT risk. As shown in the adjusted smoothing plots, there was a nonlinear relationship between preoperative TG and the risk of NODAT development only in men, and the threshold effect analysis suggested a turning point for the preoperative TG level at 0.54 mmol/L (Figure 3). At a preoperative TG level  $< 0.54$  mmol/L, the adjusted dose-response curve was almost a horizontal line, and the relationship between the preoperative TG level and NODAT risk was not statistically significant (HR 0.0123, 95% CI 0.00-1.03,  $P = .058$ ).

**FIGURE 3** Preoperative TG level and NODAT risk dose-response relationship and threshold effect analysis. Adjusted for age, BMI, preoperative liver function (Child-Pugh class), preoperative liver cirrhosis, preoperative hypertension, and preoperative FPG. BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio; NODAT, new-onset diabetes after transplantation; Pre-op., preoperative; RR, relative risk; TG, total triglyceride



However, when the preoperative TG level was  $\geq 0.54$  mmol/L, the NODAT risk increased significantly with increasing preoperative TG levels (HR 1.89, 95% CI 1.29-2.76,  $P = .001$ ).

#### 4 | DISCUSSION

In this large sample of Chinese LTRs, the incidence of NODAT in the first postoperative year increased to 30.3%, which is consistent with the findings of previous reports.<sup>1-3</sup> The preoperative lipid profile of our study population was characterized by prevalent hypocholesterolemia and hypotriglyceridemia, and similar findings were reported by studies of patients with HBV-associated cirrhosis or carcinoma, which are the two leading causes of liver transplantation.<sup>19,20</sup> In the present study, discordant associations between preoperative lipid indices and incident NODAT were observed. On the basis of our results, preoperative lipid indices and NODAT development were not significantly correlated in women. However, in men, higher preoperative TG levels appeared to be associated with a higher risk of NODAT development; we further revealed that a preoperative TG level above 0.54 mmol/L was notably correlated with a significantly increased NODAT risk.

In our study, a 37% increase in the risk of NODAT development was observed with a 1 mmol/L elevation of the preoperative TG level in men, indicating a strong predictive value of the preoperative TG level for NODAT. Dyslipidemia, especially an elevated serum TG level, has long been implicated in the pathogenesis of diabetes in the non-transplant population<sup>21-23</sup>; the ADA recommendation that testing for diabetes should be considered in overweight or obese adults with a TG level above 2.82 mmol/L further highlights the positive association between TG and incident diabetes.<sup>15</sup> However, in the transplant setting, the few studies that investigated the association between preoperative TG and NODAT had been conducted mainly

in KTRs,<sup>6-9</sup> and their results are conflicting. Among those, the studies suggesting a nonsignificant association between preoperative TG and NODAT may be less reliable because of their small sample sizes.<sup>10,11</sup> Moreover, analyses according to the patients' sex have not been previously performed.

In the non-transplant population, hypertriglyceridemia has been widely known to be a significant risk factor for increased insulin resistance and incident diabetes,<sup>24-27</sup> but sustained elevation of the serum TG level within the normal range has also been suggested to be closely correlated with insulin resistance and the development of diabetes.<sup>22</sup> Song et al<sup>28</sup> evaluated the association between TG and T2DM and reported a cutoff value of 1.23 mmol/L in their cross-sectional study of a Chinese community population. Zhang et al<sup>29</sup> found that the cutoff point for TG in predicting insulin resistance was 1.78 mmol/L in men and 1.49 mmol/L in women. However, in LTRs, because of major injuries to hepatocytes caused by advanced liver disease before transplantation, significantly lower levels of preoperative serum lipids were commonly observed than those in the non-transplant population.<sup>20</sup> Thus, it is reasonable to speculate that the corresponding cutoff value of preoperative TG can be even lower in LTRs. However, the dose-response relationship between the baseline TG level and NODAT development among LTRs has not been fully elucidated, and thus, little is known about the optimal cutoff point for preoperative TG levels. Our study is the first to suggest that a preoperative serum TG level of 0.54 mmol/L might be an appropriate cutoff point in male LTRs, as a preoperative TG value above that level was associated with a significantly higher risk of NODAT.

The specific mechanisms by which preoperative TG is involved in the development of NODAT in LTRs remain unclear. Currently, it is recognized that the onset of T2DM and that of NODAT may share common features.<sup>30,31</sup> In both disorders, peripheral insulin resistance is believed to play a central role during the early phase of the

disease, whereas impaired insulin secretion adds to the decompensation of insulin action and finally leads to the manifestation of hyperglycemia. In previous studies, an elevated TG level was reported to reflect an insulin-resistant state.<sup>24</sup> High TG levels can cause ectopic lipid deposition in both pancreatic islets and skeletal muscle through lipotoxicity, leading to subsequent  $\beta$  cell dysfunction and aggravation of insulin resistance.<sup>32,33</sup> Moreover, immunosuppressants, especially FK506, may induce a pronounced decrease in the release of insulin, which would more rapidly accelerate the development of overt NODAT.<sup>31</sup> Furthermore, men were proved to be more prone than women to both dyslipidemia and NODAT,<sup>1,14</sup> which may explain the different results between men and women in our study. However, further studies are required to determine the underlying mechanisms in detail.

In the present study, preoperative TC, HDL-C, and LDL-C levels had no obvious effects on NODAT after multivariate adjustment in both men and women. These findings are consistent with the fact that very few studies have shown a positive association between preoperative TC levels and NODAT.<sup>10,11,13</sup> Whereas elevated LDL-C and reduced HDL-C levels were implicated in the development of T2DM,<sup>21,34</sup> their impact on NODAT requires further clarification.

Thus far, few studies have explored the effects of preoperative serum lipids on the development of NODAT in LTRs. This study, to the best of our knowledge, is the first to preliminarily reveal a significant, nonlinear association between preoperative TG level and NODAT development in Chinese male LTRs; additionally, an optimal cutoff point of 0.54 mmol/L for TG has been suggested. Our study presents a new perspective on the association between preoperative TG and NODAT, stressing the significant impact of the incremental increase in preoperative TG on NODAT risk even when TG is within the normal range. Our findings strongly imply that the evaluation of NODAT risk among LTRs with slightly increased or normal levels of preoperative TG is necessary. Furthermore, our results showed a significant impact of sex on the TG-NODAT relationship.

However, several limitations are worth noting. First, NODAT was defined only by the recorded FPG values. Although the oral glucose tolerance test (OGTT) is regarded as the gold standard for the diagnosis of NODAT, its use is impractical for long-term follow-up and clinical research involving large populations. This study assessed FPG levels, which have been widely used in research on NODAT because of the simplicity and convenience of testing.<sup>1,2</sup> However, it is possible that certain LTRs with postprandial elevation of glucose levels may not be recognized, resulting in an underestimation of the NODAT incidence. Second, our study was retrospective in nature and relied on existing medical records. Incomplete data regarding the dose of glucocorticoids, for example, made it difficult for us to adjust for their possible effects on the development of NODAT. Nonetheless, prednisone was mostly withdrawn or was stable at a minimal maintenance dose of 5–10 mg beyond 3 months after transplantation, which may have attenuated its confounding effect. Third, there was a male predominance among the 767 LTRs (men vs women: 652 vs 115). However, this sex ratio (men: 85%) of our study population was consistent with a male-to-female ratio of

83% according to a national report from the China Liver Transplant Registry.<sup>1</sup> With primary liver cancer being the leading indication for liver transplantation in China, the highly imbalanced sex ratio among LTRs might be explained by the fact that men in China have a much higher incidence of primary liver cancer than do women.<sup>35</sup>

In summary, this study in Chinese LTRs found that a higher level of preoperative TG, even within the normal range, was a significant predictor of NODAT in men. Specifically, a preoperative TG level above 0.54 mmol/L was notably correlated with a significantly increased risk of NODAT development in male LTRs. Thus, in this patient category, maintaining the TG level below 0.54 mmol/L before liver transplantation may be considered important to minimize the risk of NODAT. In the future, multicenter and prospective studies based on Chinese LTRs are needed to further confirm the effects of preoperative serum lipids on NODAT.

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#### SUPPORTING INFORMATION

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

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