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ORIGINAL ARTICLE

Retrospective Study

# Minimizing tacrolimus decreases the risk of new-onset diabetes mellitus after liver transplantation

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## Abstract

**AIM:** To investigate the impact of minimum tacrolimus (TAC) on new-onset diabetes mellitus (NODM) after liver transplantation (LT).

**METHODS:** We retrospectively analyzed the data of 973 liver transplant recipients between March 1999 and September 2014 in West China Hospital Liver Transplantation Center. Following the exclusion of ineligible recipients, 528 recipients with a TAC-dominant regimen were included in our study. We calculated and determined the mean trough concentration of TAC (cTAC) in the year of diabetes diagnosis in NODM recipients or in the last year of the follow-up in non-NODM recipients. A cutoff of mean cTAC value for predicting NODM 6 mo after LT was identified using a receptor operating characteristic curve. TAC-related complications after LT was evaluated by $\chi^2$ test, and the overall and allograft survival was evaluated using the Kaplan-Meier method. Risk factors for NODM after LT were examined by univariate and multivariate Cox

regression.

**RESULTS:** Of the 528 transplant recipients, 131 (24.8%) developed NODM after 6 mo after LT, and the cumulative incidence of NODM progressively increased. The mean cTAC of NODM group recipients was significantly higher than that of recipients in the non-NODM group (7.66 ± 3.41 ng/mL *vs* 4.47 ± 2.22 ng/mL, $P < 0.05$). Furthermore, NODM group recipients had lower 1-, 5-, 10-year overall survival rates (86.7%, 71.3%, and 61.1% *vs* 94.7%, 86.1%, and 83.7%, $P < 0.05$) and allograft survival rates (92.8%, 84.6%, and 75.7% *vs* 96.1%, 91%, and 86.1%, $P < 0.05$) than the others. The best cutoff of mean cTAC for predicting NODM was 5.89 ng/mL after 6 mo after LT. Multivariate analysis showed that old age at the time of LT (> 50 years), hypertension pre-LT, and high mean cTAC (⩾ 5.89 ng/mL) after 6 mo after LT were independent risk factors for developing NODM. Concurrently, recipients with a low cTAC (< 5.89 ng/mL) were less likely to become obese (21.3% *vs* 30.2%, $P < 0.05$) or to develop dyslipidemia (27.5% *vs* 44.8%, $P < 0.05$), chronic kidney dysfunction (14.6% *vs* 22.7%, $P < 0.05$), and moderate to severe infection (24.7% *vs* 33.1%, $P < 0.05$) after LT than recipients in the high mean cTAC group. However, the two groups showed no significant difference in the incidence of acute and chronic rejection, hypertension, cardiovascular events and new-onset malignancy.

**CONCLUSION:** A minimal TAC regimen can decrease the risk of long-term NODM after LT. Maintaining a cTAC value below 5.89 ng/mL after LT is safe and beneficial.

**Key words:** Liver transplantation; Minimum tacrolimus; New-onset diabetes mellitus; Immunosuppressants; Allografts failure



**Core tip:** New-onset diabetes mellitus (NODM) is a common and severe metabolic complication that develops after liver transplantation. It is more prominent in recipients with tacrolimus (TAC)-dominant regimens. In this study, we found that the incidence of NODM is TAC concentration (cTAC)-dependent. Using a receiver operating characteristic curve, we identified that a cutoff cTAC of 5.89 ng/mL was predictive of NODM development after 6 mo after LT. And recipients exposed to low mean cTAC developed less other TAC related complications. The strategy of maintaining cTAC below 5.89 ng/mL after 6 mo after LT is therefore safe and beneficial.

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## INTRODUCTION

Liver transplantation (LT) has become a standard curative treatment for end-stage liver disease, and the 5-year survival rate of recipients has reached over 70%[1]. However, improved long-term survival is accompanied by increasingly prevalent post-operative metabolic complications[2]. Recent studies have shown that the prevalence of new-onset diabetes mellitus (NODM) after transplantation is approximately 16%-61%, depending on the medical center[3,4]. The development of post-LT NODM is associated with an increased risk of cardiovascular disease, rejection, infection, neuropsychiatric problem, allograft failure and even death[5,6]. Previous studies have found that old age, obesity, non-Caucasian ethnicity, family history of diabetes, hepatitis C virus infection and certain immunosuppressive agents are risk factors for the development of post-LT NODM in Western populations[7].

Tacrolimus (TAC), a calcineurin inhibitor, has become the most commonly used immunosuppressive agent worldwide over the past two decades[8]. Compared to cyclosporine, TAC effectively reduces acute rejection (AR) and increases allograft survival in liver recipients[8,9]. However, prolonged exposure to TAC leads to significant adverse events, including nephrotoxicity, neurotoxicity, and diabetogenic effects[10]. Some studies have suggested that higher trough concentrations of TAC (cTAC) after transplantation are associated with increased risk of complications[11-13], and many LT centers have recommended different minimal TAC regimens[14-16]. According to the current practice, target TAC level falls within the range of 10-15 ng/mL in the first month after transplantation, then is maintained at 5-10 ng/mL[17]. A prospective study has reported that reducing cTAC within the range of 5-8 ng/mL combined with mycophenolate mofetil (MMF) administration early did not increase the risk of rejection within 26 wk[18]. Jia *et al*[14] proposed that an early cTAC of 5-7 ng/mL would be safe and effective. A previous study performed in our center suggested that cTAC < 8 ng/mL after 1 mo and cTAC < 6 ng/mL after 3 mo are protective against chronic kidney disease (CKD) after LT[19]. However, all target cutoffs or ranges for cTAC are arbitrary, and there are no studies concerning the long-term maintenance of cTAC level after LT and its impact on NODM development. In this study, we aim to identify the risk factors for NODM and to determine the ideal long-term range of cTAC for preventing chronic complications.

## MATERIALS AND METHODS

### *Patient population*

We performed a retrospective study of 973 Chinese patients who received liver transplantation between March 1999 and September 2014 in the West China Hospital Liver Transplantation Center. All recipients were followed until June 2015 or until death or withdrawal. We excluded patients who had been diagnosed as diabetics before transplantation; those aged younger than 18 years old at transplantation; and those followed up for less than 6 mo, who died within 6 mo, and who received a cyclosporine-dominant regimen after liver transplantation. Finally, we collected demographic and clinical data of 528 recipients for this study. All liver grafts were voluntarily donated after cardiac death or by living donors. All donations were approved by the West China Hospital Ethics Committee and were in accordance with the ethical principles of the Declaration of Helsinki. Both the West China Hospital Liver Transplantation Center and the China Liver Transplant Registry approved and supported this study and its methods.

### *Definition of NODM and other clinical terms*

NODM was defined as a composite endpoint consisting of the first occurrence of at least one of four parameters: two occurrences of a fasting plasma glucose level $\geqslant$ 7.0 mmol/L more than 30 d apart; oral hypoglycemic agent use for more than 30 consecutive days; insulin therapy for more than 30 consecutive days; or hemoglobin A1c $\geqslant$ 6.5%[20]. Arterial hypertension was defined as systolic blood pressure over 140 mmHg or diastolic pressure over 90 mmHg occurring twice at different time points[21]. Dyslipidemia was defined as total plasma cholesterol $\geqslant$ 6.22 mmol/L (*i.e.,* hypercholesterolemia), triglyceride $\geqslant$ 2.26 mmol/L (*i.e.,* hypertriglyceridemia) or high density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L[21]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 $m^2$ for at least 3 consecutive months[22]. AR was defined either by liver biopsy or recovery of liver function *via* high-dose methylprednisolone pulse therapy. If chronic rejection (CR) was suspected, liver biopsy was performed for confirmation. The Model for End-stage Liver Disease (MELD) score was calculated according to the United Network for Organ Sharing (UNOS) formula for each recipient before LT[23].

### *Immunosuppression protocol*

The mode of initial immunosuppressive therapy was a triple-drug regimen after transplantation consisting of corticosteroids, TAC and MMF. Methylprednisolone was given intravenously at a 200 mg dose on the first day after transplantation, then gradually decreased daily and discontinued after one week. Alternative oral prednisone was also generally discontinued within 3 mo after transplantation. The initial dose of TAC was 0.05-0.10 mg/kg per day and was adjusted according to liver function and TAC trough concentration. MMF was individualized between 1.0 g/d and 1.5 g/d initially and was discontinued when severe side effects occurred and in long-term survivors with stable graft function after 6 mo after LT. Rapamycin was given as an alternative to MMF or an auxiliary for liver tumor at a dose of 1 mg/d.

### *Monitoring TAC trough concentrations and other clinical parameters*

TAC trough concentrations were monitored daily during the first week following transplantation, weekly during the first month after LT, monthly within 3 mo and every 3-6 mo thereafter. The ideal serum trough level of TAC was 5-10 ng/mL during the first 3 mo after LT. Allograft function and cTAC were monitored closely while adjusting the TAC dose. If AR occurred, the prior dosage was reinstated, together with an increase in prednisone or the administration of high-dose methylprednisolone. After 6 mo post-LT, we reduced the TAC dosage very slowly and carefully while closely monitoring allograft function to maintain cTAC as low as possible. After transplantation, the recipients' fasting plasma glucose level was monitored at 3, 6 and 12 mo, then annually thereafter according to international consensus guidelines[24]. A 2-h 75 g glucose tolerance test was performed in recipients with impaired fasting glucose. We also recorded the weight, blood pressure, serum lipid level, renal function, and chronic complications such as moderate to severe infections, cardio-cerebral vascular events, new-onset malignancy and allograft failures of each recipient at each visit after transplantation.

### *Statistical analysis*

Quantitative descriptive data were expressed as the mean ± SD or median (minimum to maximum). Qualitative descriptive data were expressed as percentages. Univariate analysis using the $\chi^2$ and, when appropriate, Fisher's exact test was performed for qualitative descriptive variables. Quantitative descriptive variables were analyzed by independent sample Student's *t* test if the data were normally distributed or by the rank-sum test if the data were non-normally distributed. Survivor curves were analyzed using the Kaplan-Meier method and were compared using the log-rank test. The best cutoff mean cTAC after 6 mo was determined using a receiver operating characteristic (ROC) curve. Independent risk factors for NODM were identified by a stepwise forward Cox regression model. Candidate risk factors with a *P* value < 0.05 in univariate analysis were included in the multivariate analysis. Statistical analysis was performed using SPSS version 21.0 statistical software (SPSS Company, Chicago, IL, United States). *P* values of less than 0.05 were considered statistically significant. The statistical

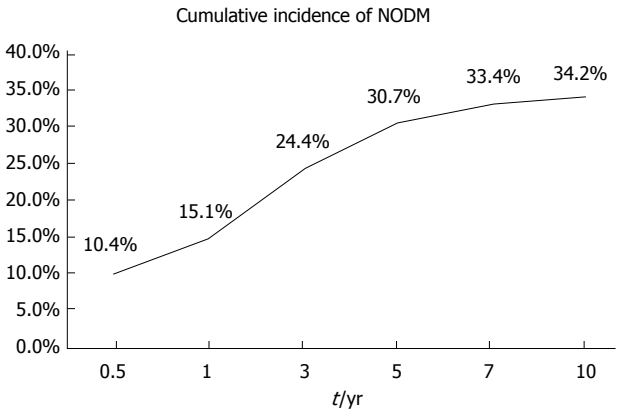


**Figure 1 Cumulative incidence of new-onset diabetes mellitus over a 10-year period after liver transplantation.** NODM: New-onset diabetes mellitus.

methods used in this study were reviewed by Ji-Zheng Qin from West China School of Public Health, Sichuan University.

## RESULTS

### *Recipient and donor characteristics*

A total of 973 recipients underwent LT between March 1999 and September 2014 in West China Hospital Liver Transplantation Center. Following the exclusion of ineligible recipients, 528 recipients were included in this study. The demographical and clinical records of recipients meeting the inclusion criteria were reviewed retrospectively. Recipients were followed up for a median of 46 mo (range, 6-173 mo). Recipients were 44.93 ± 9.41 years (range, 18-70 years) old and were predominantly male (87%). HBV (79.5%) was the most common etiology of liver disease; only six recipients had HCV (1.1%), and approximately half of the recipients (50.9%) had liver tumors. The pre-LT baseline included overweight/obesity (BMI ⩾ 25) in 110 (20.8%) recipients, hypertension in 12 (2.3%) recipients, and dyslipidemia in 41 (8.2%) recipients. The median MELD score of all recipients was 13 (range, 6-40). MMF was administered in 322 (61%) recipients, and 129 (24.4%) recipients were also treated with Rapamycin. Donors were aged 34.01 ± 8.75 years (range, 5-65 years) old and were more likely to be male (84.5%). The living donor liver transplantation rate was 29.9%.

### *Prevalence of NODM and other post-LT complications*

Eventually, 24.8% of the study population (131 cases) developed NODM during the follow-up period. The cumulative incidence of NODM increased progressively, and the 1-, 3-, 5- and 10-year incidence rates were 15.1%, 24.4%, 30.7% and 34.2%, respectively (Figure 1). We compared the 26 demographical and clinical parameters between recipients with and without NODM, as shown in Table 1. Common post-LT TAC-related complications included overweight/obesity (BMI ⩾ 25) in 128 (24.2%) recipients, hypertension in 67 (12.7%) recipients, dyslipidemia in 175 (33.1%) recipients, and CKD in 91 (17.2%) recipients. There were 58 (11%) and 20 (3.8%) recipients with AR and CR, respectively. Predictably, we found that NODM recipients experienced more cardio-cerebral vascular events (7.6% *vs* 2.0%, $P < 0.05$), moderate to severe infections (36.7% *vs* 25.2%, $P < 0.05$), and allograft failures (15.3% *vs* 8.1%, $P < 0.05$) than non-NODM recipients. The 1-, 5-, and 10-year overall survival rates ( 86.7%, 71.3%, and 61.1% *vs* 94.7%, 86.1%, and 83.7%, $P < 0.05$) and allograft survival rates (92.8%, 84.6%, and 75.7% *vs* 96.1%, 91%, and 86.1%, $P < 0.05$) in the NODM group were significantly lower than in the non-NODM group, as shown in Figure 2.

### *Definition of the cutoff mean cTAC after 6 mo*

In our center, cTAC was measured and recorded at each visit. The mean cTAC was calculated and determined in the year when diabetes was diagnosed in the NODM group and in the last year of follow-up in the non-NODM group. Our study suggested that the mean cTAC was higher in the NODM group (7.66 ± 3.41 ng/mL) than in the non-NODM group (4.47 ± 2.22 ng/mL, $P < 0.05$; Table 1). A cutoff cTAC of 5.89 ng/mL was identified as predictive of post-LT NODM using an ROC curve (Figure 3). The diagnostic value showed that the area under the curve (AUC) was 0.815 (95%CI: 0.770-0.859, $P < 0.05$) with a sensitivity of 0.733 and a specificity of 0.809. All liver recipients were divided into two groups: a low mean cTAC (< 5.89 ng/mL) group ($n = 356$) and a high mean cTAC (⩾ 5.89 ng/mL) group ($n = 172$).

To evaluate the impact of different mean cTAC levels on the long-term survival of the recipients after LT, we compared the common post-LT complications between the two cTAC groups (Table 2). We found that recipients in the high mean cTAC group were more frequently overweight/obese (30.2% *vs* 21.3%), and were more likely to develop dyslipidemia (44.8% *vs* 27.5%), CKD (22.7% *vs* 14.6%), and moderate to severe infection (33.1% *vs* 24.7%) than recipients in the low mean cTAC group ($P < 0.05$). However, there was no significant difference in other complications between the two groups. Kaplan-Meier survive curves suggested that recipients in the low mean cTAC group had higher 1-, 5-, and 10-year allograft survival rates (96.8%, 92.3%, and 87.4%) than recipients in the high mean cTAC group (92.0%, 82.9%, and 72.0%, $P < 0.05$; Figure 4A). The low mean cTAC group also exhibited higher 1-, 5-, and 10-year overall survival rates (93.7%, 83.8%, and 78.3% *vs* 90.5%, 78.6%, and 71.8%), but the difference was not statistically significant ($P = 0.129$; Figure 4B).

### *Risk factors for post-LT NODM*

We examined more than 20 parameters to identify risk

**Table 1 Demographic and clinical characteristics of recipients with and without new-onset diabetes millitus after liver transplantation (*n* = 528) *n* (%)**

| Characteristics | Total (*n* = 528) | NODM group (*n* = 131) | Non-NODM group (*n* = 397) | *P* value |
|---|---|---|---|---|
| Recipient characteristics | | | | |
| Age (yr) | 44.93 ± 9.41 | 46.24 ± 9.54 | 44.50 ± 9.34 | 0.068 |
| Gender (male) | 446 (84.5) | 144 (87.0) | 332 (83.6) | 0.352 |
| Child-Pugh (A/B/C) | 136/223/169 | 39/44/48 | 97/179/121 | 0.069 |
| MELD Score | 13 (6-40) | 15 (6-40) | 13 (6-40) | 0.010 |
| BMI ⩾ 25 pre-LT | 110 (20.8) | 36 (27.5) | 74 (18.6) | 0.006 |
| Hypertension pre-LT | 12 (2.3) | 7 (5.3) | 5 (1.3) | 0.017 |
| Dyslipidemia pre-LT | 41 (8.2) | 15 (11.5) | 26 (6.5) | 0.069 |
| Indications for LT | | | | |
| Hepatitis B virus disease | 420 (79.5) | 102 (77.9) | 318 (80.1) | 0.582 |
| Hepatitis C virus disease | 6 (1.1) | 1 (0.8) | 5 (1.3) | > 0.990 |
| Alcoholic cirrhosis | 16 (3.0) | 7 (5.3) | 9 (2.3) | 0.137 |
| Tumors | 269 (50.9) | 56 (42.7) | 213 (53.7) | 0.030 |
| Mean cTAC (ng/mL) | 5.26 ± 2.91 | 7.66 ± 3.41 | 4.47 ± 2.22 | < 0.001 |
| Rapamycin administration | 129 (24.4) | 30 (22.9) | 99 (24.9) | 0.638 |
| MMF administration | 322 (61.0) | 78 (59.5) | 244 (61.5) | 0.696 |
| Complications post-LT | | | | |
| BMI ⩾ 25 post-LT | 128 (24.2) | 40 (30.5) | 88 (22.2) | 0.053 |
| Hypertension post-LT | 67 (12.7) | 22 (16.8) | 45 (11.3) | 0.104 |
| Dyslipidaemia post-LT | 175 (33.1) | 63 (48.1) | 112 (28.2) | < 0.001 |
| Cardio-cerebral events post-LT | 18 (3.4) | 10 (7.6) | 8 (2.0) | 0.005 |
| CKD post-LT | 91 (17.2) | 28 (21.4) | 63 (15.9) | 0.148 |
| AR post-LT | 58 (11.0) | 20 (15.3) | 38 (9.6) | 0.071 |
| CR post-LT | 20 (3.8) | 9 (6.9) | 11 (2.8) | 0.062 |
| Infection post-LT | 165 (28.7) | 65 (36.7) | 100 (25.2) | 0.042 |
| Graft failure | 52 (9.8) | 20 (15.3) | 32 ( 8.1) | 0.016 |
| Donor characteristics | | | | |
| Age (yr) | 34.01 ± 8.75 | 33.62 ± 8.33 | 34.13 ± 8.89 | 0.559 |
| Gender (male) | 443 (84.5) | 108 (82.4) | 335 (84.4) | 0.600 |
| Donor type (LDLT) | 158 (29.9) | 34 (26.0) | 124 (31.2) | 0.252 |

NODM: New-onset diabetes mellitus; Age: Age at transplantation; MELD: Model for end-stage liver disease; BMI: Body mass index; LT: Liver transplantation; cTAC: Tacrolimus trough concentration; MMF: Mycophenolate mofetil; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection; LDLT: Living donor liver transplantation.

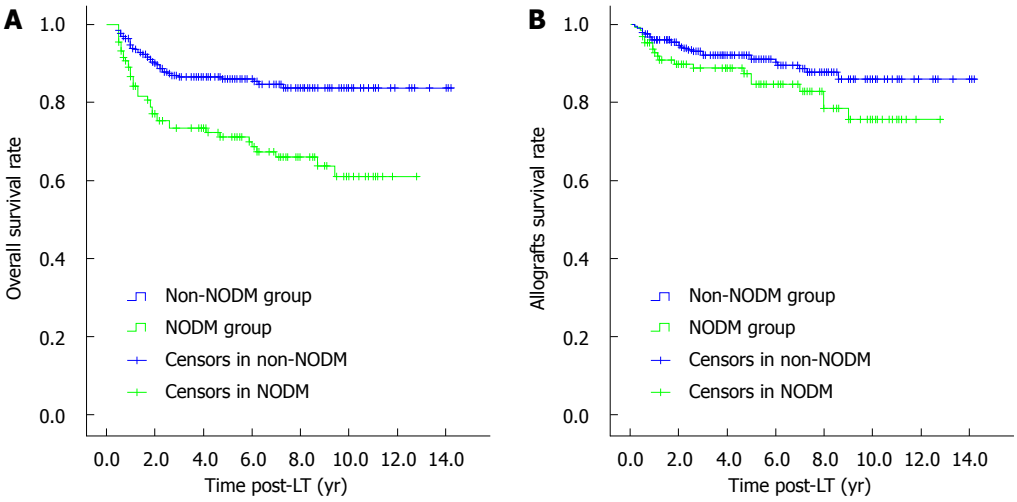


**Figure 2 Survival rates of liver recipients in non-new-onset diabetes mellitus and new-onset diabetes mellitus groups.** A: Overall survival rates ($P < 0.05$); B: Allograft survival rates ($P < 0.05$). NODM: New-onset diabetes mellitus; LT: Liver transplantation.

factors for NODM by univariate Cox regression analysis (Table 3). We chose all statistically significant factors as candidates for multivariate Cox regression analysis. As a result, recipient' age at the time of LT (age > 50 years), pre-LT hypertension, and high mean cTAC (⩾ 5.89 ng/mL) after 6 mo were deemed independent

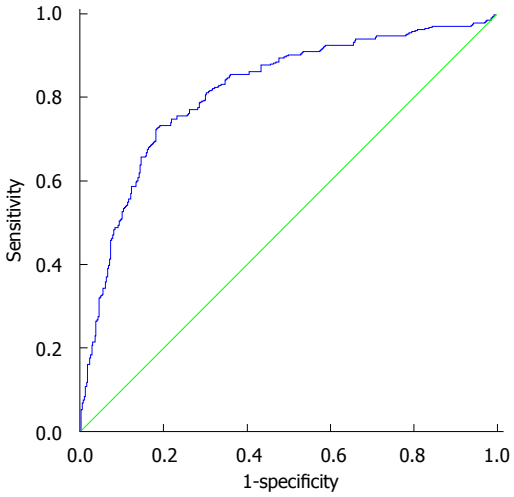


**Figure 3 Receiver operating characteristic curve for mean cTAC after 6 mo to predict new-onset diabetes mellitus after transplantation.**

**Table 2 Clinical complications associated with mean tacrolimus trough concentration *n* (%)**

| Complications post-LT | Low-cTAC group (*n* = 356) | High-cTAC group (*n* = 172) | *P* value |
|---|---|---|---|
| Overweight/obesity (BMI ⩾ 25) | 76 (21.3) | 52 (30.2) | 0.026 |
| Hypertension | 48 (13.5) | 19 (11.0) | 0.431 |
| Dyslipidaemia | 98 (27.5) | 77 (44.8) | < 0.001 |
| Cardio-cerebral events | 12 (3.4) | 6 (3.5) | 0.944 |
| CKD | 52 (14.6) | 39 (22.7) | 0.021 |
| AR | 34 (9.6) | 24 (14.0) | 0.129 |
| CR | 10 (2.8) | 10 (5.8) | 0.090 |
| Infection | 88 (24.7) | 57 (33.1) | 0.042 |
| New-onset malignance | 8 (2.2) | 1 (0.6) | 0.304 |

cTAC: Tacrolimus trough concentration; BMI: Body mass index; LT: Liver transplantation; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection.

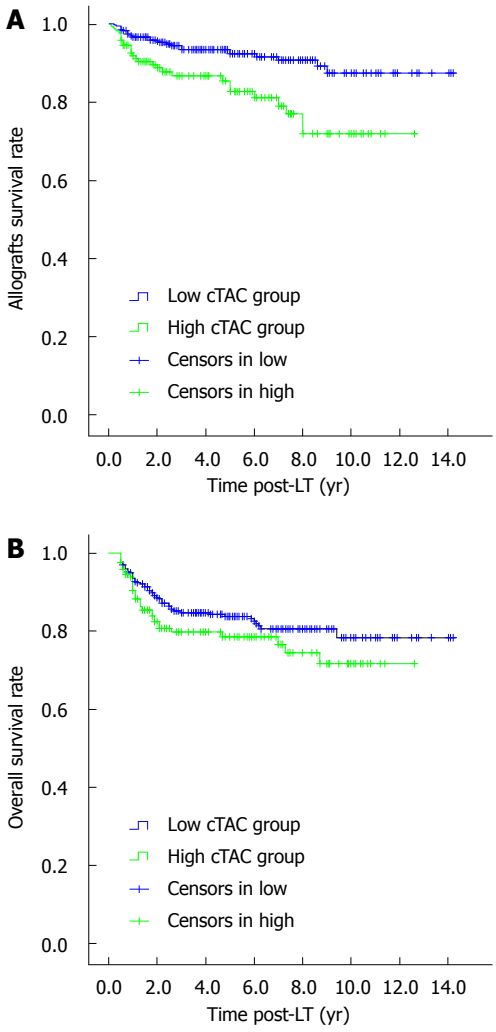


**Figure 4 Survival rates of recipients in low and high mean tacrolimus trough concentration groups (*P* < 0.05).** A: Allograft survival rates; B: Overall survival rate (*P* = 0.129). Low mean cTAC group: mean cTAC < 5.89 ng/mL; High cTAC group: mean cTAC ⩾ 5.89 ng/mL. cTAC: Tacrolimus trough concentration; LT: Liver transplantation.

risk factors for post-LT NODM (Table 4).

## DISCUSSION

With improved long-term survival after transplantation, post-operative NODM in recipients has become more prevalent[25]. Our analysis of 528 liver transplant recipients showed that the cumulative incidence of new-onset DM increased after LT. The recipeints with NODM were more likely to develop dyslipidemia, cardio-cerebral vascular events, moderate to severe infections, and allograft loss, which often reduced recipient survival time[26,27]. Inevitably, recipients with NODM had poorer long-term overall and allograft survival than non-NODM recipients[5].

The immunosuppressive regimen employed after LT is important in decreasing the incidence of NODM. Corticosteroids could cause increased gluconeogenesis by inducing insulin resistance[28]. Previous studies have shown that the diabetogenic risks of corticosteroids are cumulative and dose-dependent and that early tapering of corticosteroids decreased the incidence of diabetes at 1 year after LT[29]. In our center, we therefore attempted to discontinue the use of corticosteroids within the first 3 mo of LT. Therefore, we analyzed blood glucose data after 6 mo to avoid the residual effects of corticosteroids on recipient metabolic profiling[30].

TAC dominant therapies remain the first-line immunosuppressive regimen indicated for liver recipients. By inhibiting *IL-2* gene transcription, TAC decreases post-LT acute and chronic rejection. However, this mechanism may also contribute to insulin resistance and direct toxicity in pancreatic β-cells[31]. Previous studies have reported that TAC-associated chronic complications, such as metabolic disorders[2], renal dysfunction[11], and hepatocellular carcinoma recurrence[13], are related to TAC concentration. To reduce the TAC related complications, it is recommended that cTAC is reduced to 5-10 ng/mL during the first month[14]. However, the

**Table 3 Univariate analysis of risk factors for new-onset diabetes mellitus after liver transplantation**

| Clinical factor | HR | 95%CI | *P* value |
|---|---|---|---|
| Recipient characteristics | | | |
| Elder recipient (age > 50 yr) | 1.568 | 1.096-2.245 | 0.014 |
| Male recipient gender | 0.690 | 0.414-1.150 | 0.155 |
| Child-Pugh (A/B/C) | 0.985 | 0.788-1.232 | 0.895 |
| MELD Score | 1.107 | 0.997-1.037 | 0.088 |
| BMI ⩾ 25 pre-LT | 1.616 | 1.100-2.373 | 0.014 |
| Hypertension pre-LT | 4.458 | 2.058-9.659 | < 0.001 |
| Dyslipidaemia pre-LT | 2.064 | 1.201-3.549 | 0.009 |
| Hepatitis B virus disease | 0.955 | 0.632-1.443 | 0.828 |
| Hepatitis C virus disease | 0.699 | 0.098-5.007 | 0.722 |
| Alcoholic cirrhosis | 2.307 | 1.076-4.948 | 0.032 |
| Tumors | 0.961 | 0.676-1.304 | 0.822 |
| With Rapamycin | 1.168 | 0.744-1.761 | 0.459 |
| With MMF | 0.979 | 0.690-1.387 | 0.903 |
| High mean cTAC (cTAC ⩾ 5.89 ng/mL) | 8.709 | 5.873-12.915 | < 0.001 |
| BMI ⩾ 25 post-LT | 1.345 | 0.927-1.951 | 0.119 |
| Hypertension post-LT | 1.278 | 0.808-2.021 | 0.294 |
| Dyslipidaemia post-LT | 2.014 | 1.429-2.838 | < 0.001 |
| CKD post-LT | 1.140 | 0.925-1.405 | 0.218 |
| AR post-LT | 1.701 | 1.056-2.742 | 0.029 |
| CR post-LT | 2.068 | 1.050-4.074 | 0.036 |
| Donor characteristics | | | |
| Donor age at LT (per year) | 0.994 | 0.975-1.015 | 0.590 |
| Male donor gender | 1.202 | 0.766-1.886 | 0.423 |
| Donor type (LDLT) | 0.859 | 0.581-1.270 | 0.446 |

LT: Liver transplantation; MELD: Model for end-stage liver disease; MMF: Mycophenolate mofetil; cTAC: Tacrolimus trough concentration; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection; BMI: Body mass index; LDLT: Living donor liver transplantation.

cutoffs or the ranges of cTAC were limited within early stages (4-26 wk) after transplantation and arbitrarily identified with no statistical evidence. Our study focused on the impact of long-term (after 6 mo) cTAC level on post-LT NODM and used an ROC curve to determine the best cutoff mean cTAC to be 5.89 ng/mL. Multivariate analysis showed that exposure to cTAC ⩾ 5.89 ng/mL significantly increased the risk of post-LT NODM (HR = 9.474, 95%CI: 6.357-14.119). Similarly, exposure to a high mean cTAC also increased the risk of being overweight or obese, dyslipidemia, CKD, and moderate to severe infection after LT. Fortunately, recipients with a low mean cTAC after 6 mo did not suffer from more acute and chronic rejections. Surprisingly, recipients exposed to a low mean cTAC benefited from longer allograft survival. Thus, we suggest adjusting and maintaining the cTAC below 5.89 ng/mL after 6 mo to reduce chronic complications and improve the overall and allograft survival rates.

Additionally, Cox regression analysis indicated that recipient age (> 50 years) and pre-LT hypertension were independent risk factors in the incidence of post-LT NODM. As we know, increasing age is a significant risk factor for type 2 diabetes in the general population[32]. Correspondingly, diabetes has been a major cause of chronic complications, reduced quality of life and increased incidence of cardiovascular

**Table 4 Multivariate analysis of risk factors for new-onset diabetes mellitus after liver transplantation**

| Clinical factor | HR | 95%CI | *P* value |
|---|---|---|---|
| Elder recipient (age > 50 yr) | 1.925 | 1.335-2.776 | < 0.001 |
| Hypertension pre-LT | 4.220 | 1.931-9.226 | < 0.001 |
| High mean cTAC (cTAC ⩾ 5.89 ng/mL) | 9.474 | 6.357-14.119 | < 0.001 |

cTAC: Tacrolimus trough concentration; LT: Liver transplantation.

adverse events in the elderly. A UNOS study by Kuo *et al*[33] reported older age (> 50 years) to be an independent predictor of post-LT NODM, with a 24.1% risk increase in 15463 adult recipients. Otherwise, the prevalence of hypertension is usually high (> 50%) in diabetes patients[34], and hypertension causes a quadruply increase in cardiovascular risk in people with diabetes[35]. It is assumed that insulin resistance and the consequent hyperinsulinemia interacted with increased renal sodium retention, sympathetic tone and renin-angiotensin-aldosterone system activity[36].

Many studies have reported that BMI ⩾ 25[33,37,38], dyslipidemia[38], and alcoholic cirrhosis[33,39] were independent risk factors for NODM after transplantation, but they were significant only in univariate analysis. HCV-associated liver disease was a high risk factor in previous studies[33,37], but was negative in our study. We assumed that this was due to the low percentage of HCV patients in our center (1.1%), unlike in western countries, where a large number of HCV patients received liver transplants.

In conclusion, some factors are positively related to diabetes progression after LT. Interestingly, mean cTAC is the only controllable factor, so adjusting the dose and trough concentration of TAC is important for preventing post-LT NODM. In accordance with the minimum required tacrolimus dosage early after transplantation, we recommend a decrease in the mean cTAC to < 5.89 ng/mL after 6 mo, as has been practical in Chinese liver transplantation recipients. Limitations of this study are that the data were collected retrospectively and that there was no detailed minimum scheme for timing after transplantation. Therefore, a well-designed prospective clinical trial is needed to confirm our findings and to develop an accepted tacrolimus adjustment protocol.

## COMMENTS

### *Background*

New-onset diabetes mellitus (NODM) is a serious metabolic complication after liver transplantation (LT) and is associated with increased rates of cardiovascular disease, rejection, infection and decreased survival. Tacrolimus has strong diabetic effects *vs* other immunosuppressants and early minimum tacrolimus strategy has been reported to be protective against other complications. The author performed this study to analyze the relationship between tacrolimus concentration (cTAC) and NODM development after 6 mo and to explore the impact of low cTAC on common complications after LT.

### Research frontiers

Due to the negative impact of NODM on the long-term outcome of LT, the study about NODM has been important. cTAC is a controlled risk factor for NODM and early (4-26 wk) minimum tacrolimus strategy is safe and beneficial for LT recipients. This retrospective study indicated that reducing cTAC to below 5.89 ng/mL lately (after 6 mo) could prevent recipients from developing NODM and other complications.

### Innovations and breakthroughs

Early minimum tacrolimus strategy can decrease the risk of renal dysfunction, dyslipidemia and tumor recurrence. But the cutoffs or the ranges of cTAC were limited within early stages (4-26 wk) after transplantation and arbitrarily identified with no statistical evidence. This study focused on the impact of long-term (6 mo) cTAC level on post-LT NODM and used an ROC curve to determine the best cutoff mean cTAC to be 5.89 ng/mL. And further analysis showed that reducing cTAC to 5.89 ng/mL decreased the incidence of other TAC related complications without increasing rejection.

### Applications

Minimizing TAC lately (after 6 mo) to below 5.89 ng/mL is safe and protective against NODM after LT, but multicenter prospective clinical trials are needed to confirm the findings obtained in this study and to develop an accepted tacrolimus adjustment protocol.

### Terminology

NODM is defined as diabetes newly diagnosed after LT, occurring in 16%-61% of recipients. Mean cTAC is determined as the average value of cTAC in the year of diabetes diagnosis in NODM recipients or in the last year of the follow-up period in non-NODM recipients.

### Peer-review

This manuscript revealed that the risk of the new onset diabetes mellitus after liver transplantation is dependent on high mean tacrolimus. The number of patients is remarkable from a single institute.

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