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Original Article

Cyclosporine minimization decreases the risk of post-transplantation diabetes mellitus: 10-year single center experience in west China

Jiu-Lin Song, Wei Gao, Ming Li, Lu-Nan Yan, Jia-Yin Yang, Tian-Fu Wen, Bo Li, Wen-Tao Wang, Hong Wu, Ming-Qing Xu, Zhe-Yu Chen, Yong-Gang Wei, Li Jiang, Jian Yang

Department of Liver Surgery, West China Hospital of Sichuan University, Liver Transplantation Center, Chengdu, Sichuan Province, China

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Abstract: Post-transplantation diabetes mellitus (PTDM) is a serious metabolic complication after liver transplantation (LT) with calcineurin inhibitor (CNI) immunosuppression. To investigate the impact of minimum CsA strategy after 6 months on PTDM and identify the risk factors of PTDM, we retrospectively analyzed the data of 168 liver recipients with cyclosporine A (CsA) between March 1999 and September 2013 in West China Hospital Liver Transplantation Center. Of the 168 recipients with median follow-up time of 32 months (6-195 months) in this study, 44 (26.2%) recipients developed PTDM after 6 months post-LT and the cumulative incidence increased with follow-up. The mean cCsA of the PTDM group was significantly higher than that of the non-PTDM group (7.66 ng/mL±3.41 vs. 4.47 ng/mL±2.22, P<0.05). And the PTDM group recipients had lower 1-, 3-, 5-, 10-year overall survival rates (83.8%, 56.2%, 49.2%, 49.2% vs. 92.5%, 78.5%, 73.6%, 70.1%, *P*<0.05) and allografts survival rates (92.7%, 81.5%, 71.3%, 71.3% vs. 98.4%, 92.8%, 91.2%, 88.8%, *P*<0.05) than the others. The best cutoff of mean cCsA to predict PTDM was 129.5 ng/mL after 6 months post-LT. Multivariate analysis showed that elder recipient at LT (age >50), hypertension pre-LT, dyslipidemia pre-LT, and high mean cCsA (≥129.5 ng/mL) 6 months post-LT were independent risk factors of PTDM after liver transplantation. Late minimum CsA strategy after 6 months decreased the risk of PTDM after liver transplantation.

Keywords: Post-transplantation diabetes mellitus, liver transplantation, minimum cyclosporine, calcineurin inhibitor

Introduction

Post-transplantation diabetes mellitus (PTDM) is a serious complication after liver transplantation (LT) due to its negative impact on allograft and recipient survival [1]. PTDM frequently develops in the early post-transplant period and increases over time [2]. Recent studies have shown that prevalence of PTDM varies from 2% to 53% in the first year [2, 3]. PTDM has additionally been linked with all-cause mortality, increased susceptibility to infections, rejection episodes, chronic graft dysfunction, and decreased quality of life [4, 5]. Previous researches have identified that recipient age, high body mass index (BMI), non-white ethnicity, family history of diabetes, hepatitis C virus infection and high dose of immunosuppressants are risk factors for the development of PTDM in liver recipients [2, 6].

Calcineurin inhibitors (CNI), such as cyclosporine A (CsA) and tacrolimus, are still mainstream immunosuppressants indicated for liver recipients in the last decades [7]. Both cyclosporine and tacrolimus attenuate T-cell response via inhibition of calcineurin phosphatase [8], thereby effectively reduce the rejection episodes and increase the allografts survival [9]. However, prolonged exposure to CNI leads to adverse effects, including nephrotoxicity, neurotoxicity, and diabetogenic effect [10]. Some studies suggested that minimization of CNI can reduce the incidence of complications. A meta-analysis [11] including 32 trials with 1383 liver recipients showed that several centers achieved

in minimizing CNI to prevent renal impairment, but the initial minimum trough concentration of CsA (cCsA) levels varied from 32 to 250 ng/mL. A retrospective study in our center recommended that cCsA<150 ng/mL at 3 month was protective for renal function post-LT [12]. However, all the minimum cutoffs and ranges of cCsA are arbitrary and limited within early periods after transplantation, and there is no study concerning the association between long-term level of cCsA and development of PTDM. In this study, we aim to identify the risk factors for PTDM and determine the ideal long-term range of cCsA to prevent PTDM.

Materials and methods

Patient population

We retrospectively analyzed the data of consecutive adult patients who received liver transplantation between March 1999 and September 2013 in West China Hospital Liver transplantation Center. All recipients were last followed till July 2015 or recorded when dead and withdrawn. We included the recipients who were older than 18 years old at transplantation, followed up and survived for more than 6 months, and administrated with CsA-dominant regimens after liver transplantation. Eventually, we collected the demographic and clinical data of 168 recipients in our study. All the allografts were voluntarily donated from cadaveric and living donors. All the donations and transplantations had been approved by the West China Hospital ethics Committee and in accordance with the ethic principle of Declaration of Helsinki. Both the West China hospital liver transplantation center and China Liver Transplant Registry have approved and supported the methods and statistics of this study.

Immunosuppression protocols and adjustment of CsA

The initial immunosuppressive therapy was triple combination regimen after transplantation consisting of glucocorticoids, mycophenolate mofetil (MMF), and CsA. The methylprednisolone was intravenously administrated at the first day after transplantation, then gradually reduced daily and discontinued after one week. And substituted prednisone was also generally tailored and discontinued within 3 months after transplantation. MMF was taken orally between 1.0 g/d and 1.5 g/d individually, and was discontinued when severe side effects occurred and for recipients with long-term stable graft function after 6 months post-LT. Rapamycin was substitute of MMF or auxiliary for liver tumor recipients with the dose of 1 mg per day.

The initial dose of CsA was 5-10 mg/kg per day and adjusted according to allograft function and cCsA, which were monitored daily during the first week, weekly during the first month, monthly within 3 months and every 3-6 months thereafter after transplantation. The ideal range of cCsA was 120-150 ng/mL during the first 3 months post-LT. If rejection episodes diagnosed, prior immunosuppressant dosage was restarted, together with the high dose of glucocorticoids. After 6 months post-LT, we tailored the CsA dosage very carefully and slowly with stable allograft function, to keep the cCsA as low as possible. Crucially, we determined the "mean cCsA", as the average value of cCsA throughout the year when diabetes diagnosed in PTDM group or during the latest year of follow-up in non-PTDM group, to predict the incidence of PTDM.

Surveillance of clinical parameters and definition of PTDM and other terms

After transplantation, the recipients' fasting plasma glucose (FPG) and rapid plasma glucose (RPG) would be monitored at least weekly during the first month, and at 3, 6 and 12 months, then annually thereafter according to the international consensus [13]. Performance of an oral glucose tolerance test (OGTT) would be necessary in recipients with impaired FPG and selected high-risk recipients with normal FPG level. Glycohemoglobin (HbA1c) measurements could be used in stable recipients for the detection of PTDM after the first 3 months post-LT [1]. We also recorded the data of weight, blood pressure, allograft function, lipid profiles, renal function, as well as chronic complications such as moderate to severe infections, cardio-cerebral vascular events, and allografts failures of recipients at each visit after transplantation.

PTDM was defined as newly diagnosed diabetes in the post-transplantation setting according to the American Diabetes Association guidelines [14] as follows: Symptoms of diabetes with RPG ≥ 200 mg/dL (11.1 mmol/L) or

Table 1. Demographic and clinical characteristics between PTDM and non-PTDM recipients (n=168)

Characteristics	Total (n=168)	PTDM (n=44)	Non-PTDM (n=124)	*P* Value
Recipient characteristics				
Age (years)	44.5±10.8	46.7±11.8	43.8±10.3	0.119
Gender (male)	138 (82.1%)	38 (86.4%)	100 (80.6%)	0.534
Blood-type (O/A/B/AB/)	45/66/44/13	13/17/12/2	32/49/32/11	0.804
Child-pugh (A/B/C)	42/81/45	13/15/16	29/66/29	0.082
MELD Scores	14 (6-40)	15.5 (7-37)	14 (6-40)	0.925
BMI ≥ 25 pre-LT	32 (19.0%)	12 (27.3%)	20 (16.1%)	0.106
Hypertension pre-LT	8 (4.8%)	5 (11.4%)	3 (2.4%)	0.030
Dyslipidemia pre-LT	10 (6.0%)	4 (9.1%)	26 (4.8%)	0.291
Indications for LT				
Hepatitis B virus disease	127 (75.6%)	36 (81.8%)	91 (73.4%)	0.311
Hepatitis C virus disease	3 (1.8%)	1 (2.3%)	2 (1.6%)	1.000
Alcoholic cirrhosis	4 (2.4%)	1 (2.3%)	3 (2.4%)	1.000
Tumors	85 (50.6%)	23 (52.3%)	62 (50.0%)	0.796
Mean cCsA (ng/mL)	117.6±61.9	172.5±55.4	98.1±51.6	0.000
Rapamycin administration	17 (10.1%)	5 (11.4%)	12 (9.7%)	0.774
MMF administration	81 (48.2%)	23 (52.3%)	58 (46.8%)	0.531
Complications post-LT				
BMI ≥ 25 post-LT	38 (22.6%)	16 (36.4%)	22 (17.2%)	0.011
Hypertention post-LT	27 (16.1%)	11 (25.0%)	16 (12.9%)	0.061
Dyslipidaemia post-LT	52 (31.0%)	21 (47.7%)	31 (25.0%)	0.008
Cardio-cerebral events post-LT	5 (3.6%)	4 (9.1%)	1 (0.8%)	0.017
CKD post-LT	44 (26.2%)	14 (31.8%)	30 (24.2%)	0.323
AR post-LT	20 (11.9%)	6 (13.6%)	14 (11.3%)	0.680
CR post-LT	5 (3.0%)	4 (9.1%)	1 (0.8%)	0.017
Infection post-LT	32 (19.0%)	13 (29.5%)	19 (15.3%)	0.039
Donor characteristics				
Age (years)	30.8±7.6	32.6±7.9	30.2±7.46	0.080
Gender (male)	147 (87.5%)	39 (88.6%)	108 (87.1%)	0.791
Donor type (LDLT)	17 (10.1%)	6 (13.6%)	11 (8.9%)	0.389

PTDM: Post-transplantation diabetes mellitus; Age: Age at transplantation; MELD: Model for end-stage liver disease; BMI: Body mass index; LT: Liver transplantation; cCsA: Trough concentration of cyclosporine A; MMF: Mycophenolate mofetil; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection; LDLT: Living donor liver transplantation.

FPG ≥ 126 mg/dL (7.0 mmol/L) or 2 h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT or HbA1c ≥ 6.5%. Artery hypertension was defined as systolic blood pressure over 140 mmHg or diastolic pressure over 90 mmHg twice at different time [15]. Dyslipidemia was defined as total plasma cholesterol ≥ 6.22 mmol/L (as Hypercholesterolemia), triglyceride ≥ 2.26 mmol/L (as Hypertriglyceridemia) or high density lipoprotein cholesterol (HDL-C) <1.04 mmol/L [15]. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 for at least 3 consecutive months [16]. Acute rejection (AR) was defined either by liver biopsy or recovery of liver function from high-dose methylprednisolone pulse therapy. If chronic rejection (CR) was suspected, liver biopsy was also carried out for conformation. The model for end stage liver disease (MELD) score was calculated according to the UNOS Formul for each recipient before transplantation [17].

Statistics analysis

Continuous variables were described as mean ± standard deviation. Categorical variables were expressed as percentages. Comparable analysis using Chi-square test was performed

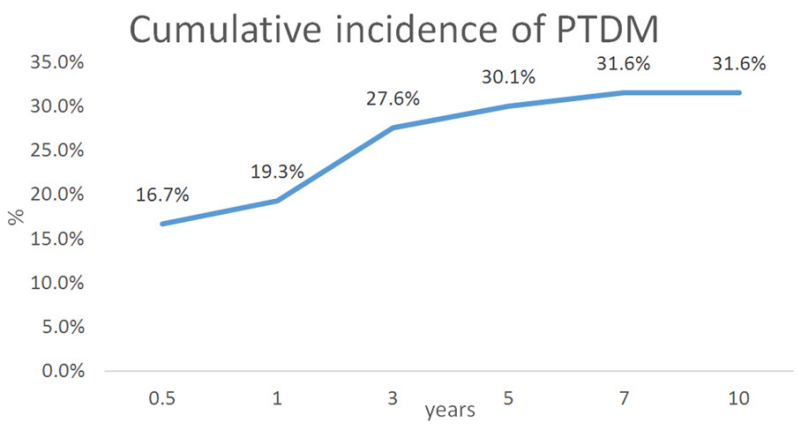

Figure 1. Cumulative incidence of PTDM. PTDM: Post-transplantation diabetes mellitus.

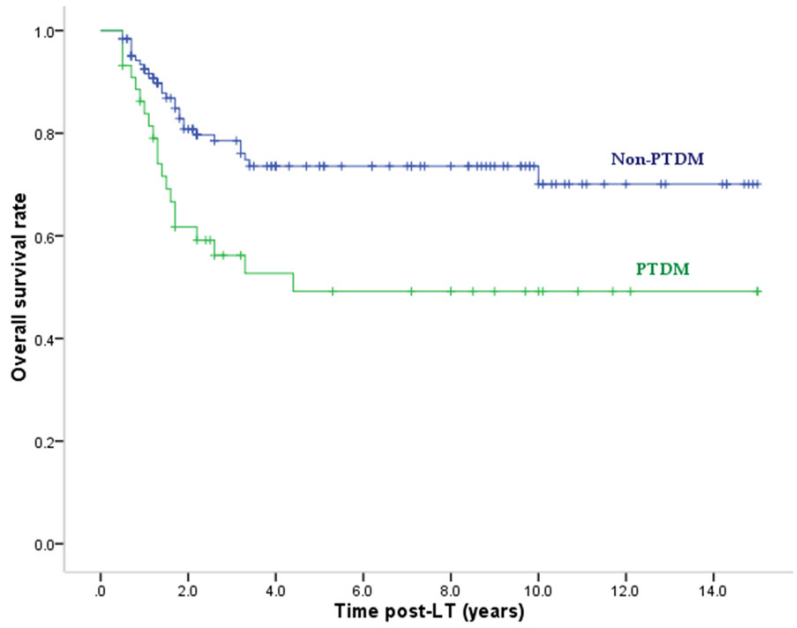

Figure 2. Overall survival rate of recipients between non-PTDM and PTDM groups (P<0.05). PTDM: Post-transplantation diabetes mellitus; LT: Liver Transplantation.

for categorical variables. Quantitative descriptive variables were compared by independent sample Student's *t*-test. Survivor curves were analyzed using the Kaplan-Meier method. The best cutoff of mean cCsA after 6 months post-LT was determined by receiver operating characteristic (ROC) curve. The incidence and risk factors of PTDM over time were analyzed by univariate analysis, multivariate Cox regression, and also the Kaplan-Meier method. Statistical analysis was performed using SPSS version 21.0 statistical software (SSPS Company, Chicago, IL, USA). *P* values of less than 0.05 were considered statistically significant.

Results

Recipient and donor characteristics

A total of 973 liver recipients underwent liver transplantation between March 1999 and September 2013 in West China Hospital Liver transplantation Center. According to the inclusion criteria, 168 recipients were finally enrolled in our study. The demographical and clinical records of enrolled recipients were analyzed retrospectively in **Table 1**. Recipients were followed for a median of 32 months (6-195 months). Recipients were mean 44.5 ±10.8 (18-70) years old, predominantly in male gender (82.1%). HBV associated diseases (75.6%) were the most common etiology indicated for liver transplantation, and only 3 recipients suffered from HCV disease (1.1%), and approximately half of recipients (50.6%) had liver tumors. Pre-LT baseline included overweight/obesity (BMI ≥ 25) in 32 (19.0%) recipients, hypertension in 8 (4.8%) recipients, and dyslipidemia in 10 (6.0%) recipients. The median MELD score of all the recipients was 14 (range, 6-40). MMF was still administrated in 81 (48.2%) recipients, and 17 (10.1%) recipients were adjuvant with Rapamycin. Donors were mean at 30.8±7.6 (18-70) years old, and more likely to be male gender (87.5%). There were 17 recipients (10.1%) receiving living donor liver transplantation.

Prevalence of PTDM and other complications

Eventually, there were 44 recipients (26.2%) developed PTDM during the whole follow-up period. The cumulative incidence of PTDM

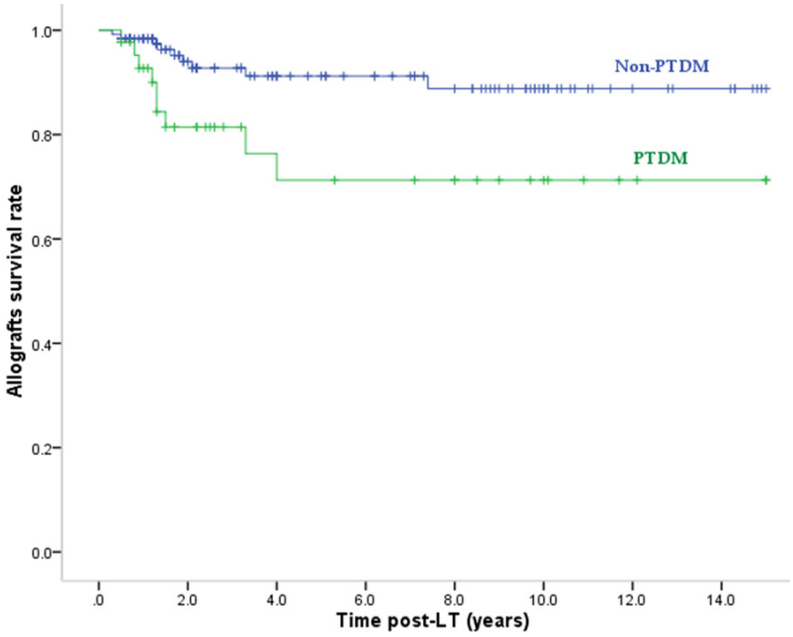

Figure 3. Allografts survival rate of recipients between non-PTDM and PTDM groups (P<0.05). PTDM: Post-transplantation diabetes mellitus; LT: Liver Transplantation.

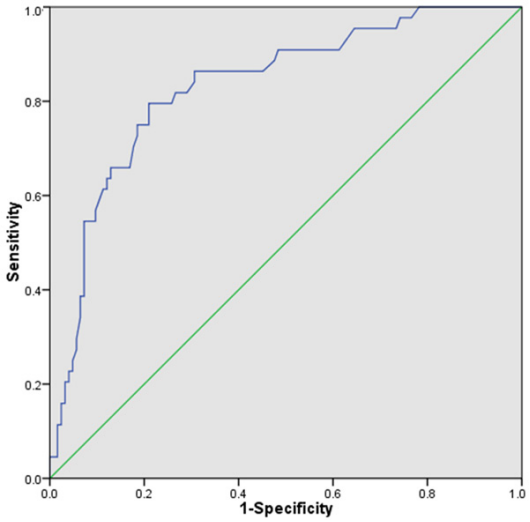

Figure 4. Receiver operating characteristic (ROC) curve for mean cCsA after 6 months post-LT to predict PTDM.

increased over time and the 0.5-, 1-, 3-, 5-, 10-year incidence rates were 16.7%, 19.3%, 27.6%, 30.1% and 31.6%, respectively (**Figure 1**). We analyzed the demographical and clinical parameters between recipients with and without PTDM, shown in **Table 1**. Other common complications post-LT included overweight/obesity (BMI ≥ 25) in 38 (22.6%) recipients, hypertension in 27 (16.1%) recipients, dyslipidemia in 52 (31.0%) recipients, and CKD in 44 (26.2%) recipients. There were 20 (11.9%) and 5 (3.0%) recipients had been diagnosed as AR and CR, respectively. Predictably, we found that PTDM recipients developed more overweight/obesity (36.4% vs. 17.2%, *P*< 0.05), dyslipidemia (47.7% vs. 25.0%, *P*<0.05), Cardiocerebral vascular events (9.1% vs. 0.8%, *P*<0.05), CR (9.1% vs. 0.8%, *P*<0.05), and moderate to severe infections (29.5% vs. 15.3%, *P*<0.05) than non-PTDM recipients after transplantation. Otherwise, PTDM group recipients had lower 1-, 3-, 5-, 10-year overall rates (83.8%, 56.2%, 49.2%, 49.2% vs. 92.5%, 78.5%, 73.6%, 70.1%, *P*< 0.05) and allografts rates (92.7%, 81.5%, 71.3%, 71.3% vs. 98.4%, 92.8%, 91.2%, 88.8%, *P*<0.05) than the non-PTDM group recipients, as shown in **Figures 2** and **3**.

Definition of the cutoff of mean cCsA after 6 months post-LT

In our center, the cCsA were measured and recorded at each visit. The "mean cCsA" was calculated and determined as the average level of cCsA throughout the year when diabetes diagnosed in PTDM group, or throughout the latest year till the end of follow-up in non-PTDM group. Our study suggested that the mean cCsA of PTDM group (7.66 ng/mL ±3.41) was higher than that of the non-PTDM group to predict incidence of PTDM, using ROC curve (**Figure 4**). The diagnostic value of cutoff of 129.5 ng/mL for mean cCsA showed that the area under the curve (AUC) was 0.832 (95% CI 0.762-0.902, *P*<0.05), with sensitivity of 0.795 and specificity of 0.790.

To explore the impact of different exposure of mean cCsA on long-term survival quality and status of recipients post-LT, we divided all the recipients into two groups: low mean cCSA (<129.5 ng/mL) group (n=107) and high mean

Table 2. Clinic complications between different groups of mean cCsA

Complications post-LT	Low-cCsA Group (n=107)	High-cCsA Group (n=61)	*P* value
Overweight/Obesity (BMI ≥ 25)	22 (20.6%)	16 (26.2%)	0.398
Hypertention	18 (16.8%)	9 (14.8%)	0.726
Dyslipidaemia	25 (23.4%)	27 (44.3%)	0.005
Cardio-cerebral events	1 (0.9%)	4 (6.6%)	0.059
CKD	27 (25.2%)	17 (27.9%)	0.709
AR	11 (10.3%)	9 (14.8%)	0.389
CR	1 (0.9%)	4 (6.6%)	0.059
Infection	19 (17.8%)	13 (21.3%)	0.573

cCsA: Trough concentration of cyclosporine A; BMI: Body mass index; LT: Liver transplantation; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection.

Table 3. Univariate analysis of risk factors for PTDN

Clinical factor	HR	95% CI	*P* value
Recipient characteristics			
Elder recipient (age >50)	1.656	0.907-3.022	0.097
Male recipient gender	1.454	0.615-3.441	0.394
Blood-type (O/A/B/AB)	1.060	0.832-1.349	0.638
Child-pugh (A/B/C)	1.040	0.679-1.592	0.858
MELD Score	1.005	0.970-1.043	0.768
BMI ≥ 25 pre-LT	1.709	0.880-3.319	0.114
Hypertension pre-LT	3.902	1.525-9.983	0.005
Dyslipidaemia pre-LT	1.758	0.628-4.918	0.283
Hepatitis B virus disease	1.550	0.720-3.336	0.263
Hepatitis C virus disease	1.289	0.177-9.392	0.802
Alcoholic cirrhosis	1.198	0.165-8.707	0.859
Tumors	1.334	0.732-2.432	0.347
With Rapamycin	1.223	0.482-3.107	0.672
With MMF	1.145	0.634-2.069	0.654
High mean cCsA (≥ 129.5 ng/mL)	15.992	7.184-35.598	0.000
BMI ≥ 25 post-LT	2.173	1.175-4.019	0.013
Hypertention post-LT	1.778	0.897-3.521	0.099
Dyslipidaemia post-LT	2.279	1.259-4.126	0.007
Donor characteristics			
Donor age at LT (per year)	1.028	0.995-1.062	0.101
Male donor gender	0.924	0.364-2.345	0.868
Donor type (LDLT)	0.667	0.282-1.579	0.357

PTDM: Post-transplantation diabetes mellitus; LT: Liver transplantation; MELD: Model for end-stage liver disease; BMI: Body mass index; MMF: Mycophenolate mofetil; cCsA: Trough concentration of cyclosporine A; CKD: Chronic kidney disease; AR: Acute rejection; CR: Chronic rejection; LDLT: Living donor liver transplantation.

cCsA (≥ 129.5 ng/mL) group (n=61). We analyzed the common complications post-LT between two different mean cCsA groups (**Table 2**). Interestingly, we found that the low mean cCsA group recipients developed less (23.4%) dyslipidemia than high mean cCSA group (44.3%, *P*<0.05). However, there was no statistically difference in other complications between two groups.

Risk factors for PTDM post-LT

We examined more than 20 demographic and clinical parameters to identify the risk factors of PTDM with univariate Cox regression analysis (**Table 3**). We identified all the statistically significant factors and some proven strong risk factors in previous studies as candidates for multivariate Cox regression analysis. As a result, elder recipient at LT (age > 50), hypertension pre-LT, dyslipidemia pre-LT and high mean cCsA (≥ 129.5 ng/mL) after 6 months post-LT were independent risk factors of PTDM (**Table 4**).

Discussion

PTDM is a common transplantation associated complication resulting in poor outcomes, varying in prevalence of 14-61% in liver recipients [18]. Our study reported that there were 26.2% of recipients developed PTDM and the incidence increased with follow-up [2, 19]. The variation of prevalence of PTDM may result from different diagnosis criteria and limited follow-up durations. Our study adopted the American Diabetes Association guidelines recommended by international consensus. As shown herein, the risk of PTDM was extremely prevalent within the first 3 years and tended to be constant after 5 years post-LT. Recipients with

Table 4. Multivariate analysis of risk factors for PTDM

Clinical factor	HR	95% CI	*P* value
Elder recipient (age >50)	2.160	1.113-4.192	0.023
Hypertension pre-LT	3.007	1.070-8.450	0.037
Dyslipidaemia pre-LT	3.482	1.207-10.049	0.021
High mean cCsA (≥ 129.5 g/mL)	20.009	8.756-45.722	0.000

cCsA: Trough concentration of cyclosporine A; LT: Liver transplantation.

PTDM developed more obesity, dyslipidemia, cardio-cerebral vascular events, rejection episodes, moderate to severe infections, and allografts loss, which also adversely affect recipients survival [20]. Hereby, recipients with PTDM suffered from poorer overall and allografts survival than the non-PTDM ones in our study, which is in accordance with previous research [4].

Immunosuppression is the major transplant-specific risk factor for development of PTDM. Corticosteroid minimization is a common strategy to attenuate risk of PTDM [21], but the risk/benefit assessment of corticosteroid sparing strategy in long-term outcome is still unclear. Therefore, we discontinued the corticosteroids within the first 3 months post-LT in our center. Additionally, transient hyperglycemia is common in the early post-transplant period, as well as consequence of rejection therapy, infections and other critical conditions [13]. Diagnosis of PTDM is recommended for recipients with stable maintenance immunosuppression and allograft function. So we analyzed the blood glucose data after 6 months post-LT to avoid the residual effects of corticosteroids on metabolic profiling [22] and the initial hyperglycemic peaks in stable recipients.

CNIs, including tacrolimus and CsA, were diabetogenic through inhibiting a signaling pathway crucial for β-cell growth and function [23]. Tacrolimus has been proven effective in reducing rejections, allograft loss and mortality, but it contributed to high risk of PTDM versus CsA [7, 9, 24]. So CsA has become the maintenance immunosuppression for the early recipients or alternative therapy of tacrolimus if PTDM poorly controlled. Previous studies reported that CNI minimization strategy can reduce the risk of renal dysfunction [11], hepatocellular carcinoma recurrence [25], and CsA withdrawn might improve long-term metabolic parameters [26]. A recent meta-analysis of 56 randomized controlled trials demonstrated less PTDM and better overall graft survival with reduced CNI exposure [27]. However, all the cutoffs and the ranges of cCsA were limited within early periods (4 to 26 weeks) after transplantation and assessed within short follow-up duration (6-12 months). Our study firstly explored the impact of the long-term (6 months later) cCsA level on PTDM with 10-year experience, and used the ROC curve to determine the best cutoff of mean cCsA as 129.5 ng/mL. Multivariate cox regression analysis showed that exposure to high mean cCsA (≥ 129.5 ng/mL) was independent risk factor of PTDM post-LT (HR 20.009, 95% CI 8.756-45.722, P<0.05). Exposure to high mean cCsA also increased the risk of dyslipidemia. But there were no difference in the burden of overweight/obesity, hypertension, CKD, and moderate to severe infections after transplantation between different levels of CsA exposure. Interestingly, exposure to low mean cCsA after 6 months post-LT had negative impact on triggering episodes of acute and chronic rejections. We recommended to adjust and maintain the mean cCsA below 129.5 ng/mL after 6 months post-LT, which might be sequel of early minimum CNI strategies, to reduce chronic complications and improve long-term survival rates.

Additionally, multivariate analysis also showed that elder recipients (age >50) at LT, hypertension pre-LT and dyslipidemia pre-LT were independent risk factors in the development of PTDM. Increasing age has been proven significant in pathogenesis of type 2 diabetes in the general population [28]. A previous study concerning 15,309 kidney recipients showed that a 29% increase of relative risk in incidence of PTDM for every 10-year age increment of recipients in UNOS database [29]. Another UNOS study by Kuo et al [30] reported that increased age (>50 years) was an independent predictor for PTDM with a 24.1% increased risk in 15,463 adult liver recipients. Otherwise, comorbidity of hypertension was usually common (more than 50%) in diabetes patients [31], and hypertension contributed to fourfold increment of cardiovascular risks in patients with diabetes [32]. It is supposed that insulin resistance and the

consequent hyperinsulinemia was interacted with increased retention of renal sodium, and hyperactivity of sympathetic tone and renin-angiotensin-aldosterone system [33]. Patients with type 2 diabetes had an increased prevalence of lipid abnormalities, contributing to high risk of cardiovascular diseases [14]. Pérez-Flores et al [34] reported that pre-transplant hypertriglyceridemia was risk factor for developing PTDM in renal transplant recipients taking tacrolimus. So pre-transplant screening and post-transplantation surveillance of high-risk candidate recipient for PTDM was crucial.

In conclusion, PTDM has adverse effects on liver transplantation outcome, and four certain factors have been identified associated with diabetes pathogenesis in adult liver recipients. Interestingly, mean cCsA level is the only moldable factor and low exposure of CsA is feasible and safe in our study. So an appropriate minimization of cCsA is important to prevent PTDM after liver transplantation. In accordance with previous early minimum CNI strategy, we recommended to adjust the mean cCsA below 129.5 ng/mL after 6 months post-LT. Limitation is that this study was retrospective and absence of detailed CsA minimum scheme. Therefore, Well-designed prospective clinical trials are needed to confirm our findings and develop a practical CsA adjustment protocol.

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Disclosure of conflict of interest

None.

Authors' contribution

Yan LN and Song JL provided the conception and designed the study; Song JL, Gao W, and Li M made the data analysis; Song JL and Gao W drafted the manuscript; Yan LN and Yang JY revised the manuscript and obtained funding; Li B, Wen TF, Yang JY, Xu MQ, Wang WT, Chen ZY, Wei YG, Jiang L and Yang J provided data acquisition and technical support. All authors have read and approved the final version to be published.

Address correspondence to: Dr. Lu-Nan Yan, Department of Liver Surgery, West China Hospital of Sichuan University, Liver Transplantation Center, Chengdu 610041, Sichuan Province, China. Tel: +86-28-85422867; Fax: +86-28-85422867; E-mail: yanlunan688@163.com

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