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·临床研究·

肝移植术后新发糖尿病危险因素及对预后影响的研究*

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摘要 目的：研究肝移植术后新发糖尿病的危险因素以及新发糖尿病对肝移植受者生存率的影响。**方法：**收集 2007 年 7 月至 2014 年 9 月间 143 例接受原位肝移植且术前无糖尿病的患者资料，根据术后是否新发糖尿病分为术后新发糖尿病（NODM）组（33 例）和无糖尿病（non-NODM）组（110 例），采用二元 logistic 回归分析 NODM 的危险因素，Kaplan-Meier 法进行生存分析，Log-rank 法比较两组间生存率的差异。**结果：**单因素比较两组间有显著差异的因素（*P<0.05*）包括，术前 MELD 评分，NODM 组 14.30± 6.70 VS non-NODM 组 11.15± 4.67；Child-Pugh 评分 / 分级，NODM 组 A 级 9 例（26.3%）、B 级 13 例（38.4%）、C 级 11 例（33.3%）VS non-NODM 组 A 级 65 例（59.1%）、B 级 35 例（31.8%）、C 级 10 例（9.1%）；常规应用糖皮质激素，NODM 组 16 例（48.5%）VS non-NODM 组 31 例（28.2%）；肝移植术后第 1 个月血浆他克莫司谷浓度，NODM 组 8.68± 2.61 VS non-NODM 组 7.44± 2.34；术后第 1 个月血清 AST，NODM 组 55.72± 33.34 VS 44.16± 24.17。多因素回归分析结果示，肝移植术前 Child-Pugh 分级（*P*=0.001）：B 级无统计学意义（*P>0.05*），C 级（*P<0.001*，OR=11.996，95%CI：3.340-43.089）和移植术后第 1 个月血浆他克莫司谷浓度（*P*=0.013，OR=1.306，95%CI：1.058-1.612）；NODM 组患者生存率显著低于 non-NODM 组（*P*=0.001）。**结论：**肝移植术前 Child-Pugh 分级 C 级和移植术后第 1 个月血浆他克莫司谷浓度是 NODM 的独立危险因素，NODM 显著降低患者生存率。

关键词：肝移植；新发糖尿病；危险因素；预后

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New-onset Diabetes after Liver Transplantation: an Analysis of Risk Factors and Impacts on Outcomes*

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ABSTRACT Objective: To study the risk factors of new-onset diabetes after liver transplantation and the impacts of new-onset diabetes on the survival of liver transplant recipients. **Methods:** A total of 143 patients who underwent orthotopic liver transplantation during July 2007 to September 2014 and had no preoperative diabetes were enrolled. The patients were divided into the new-onset diabetes mellitus (NODM) group (33 cases) and the non-new onset diabetes mellitus (non-NODM) group (110 cases), according to whether developed diabetes postoperative. The risk factors of NODM were analyzed with binary logistic regression model, patient survival was calculated by Kaplan-Meier curve and compared using log-rank test. **Results:** Differences between the NODM group and non-NODM group in univariate analysis were significant (*P<0.05*) on preoperative MELD score (14.30± 6.70 VS 11.15 ± 4.67), Child-Pugh class A (26.3% VS 59.1%), class B (38.4% VS 31.8%), and class C (33.3% VS 9.1%), corticoid therapy (48.5% VS 28.2%), trough blood concentration of tacrolimus (8.68± 2.61 μg/L VS 7.44± 2.34 μg/L), and serum concentration of AST (55.72± 33.34 U/L VS 44.16± 24.17 U/L) in first month after transplantation. In multivariate analysis, only Child-Pugh class C (*P<0.001*, OR=11.996, 95% CI: 3.340- 43.089), trough blood concentration of tacrolimus (*P*=0.013, OR=1.306, 95% CI: 1.058-1.612) were statistical significant. Patient survival in NODM group was significantly lower than that in non-NODM group (*P*=0.001). **Conclusions:** Child-Pugh class C before liver transplantation and trough blood concentration of tacrolimus in first month posttransplantation were independent risk factors of NODM after liver transplantation. Meanwhile, NODM reduced patient survival significantly.

Key words: Liver transplantation; New-onset Diabetes Mellitus; Risk factors; Outcomes

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前言

新发糖尿病是肝移植等实体器官移植后常见的代谢并发症。与普通人群相比，在肝移植受者中，性别、肥胖和遗传因素等常规危险因素，以及免疫抑制剂和激素的应用、丙肝病毒感染等移植相关危险因素均可影响糖尿病的发生。根据不同文献报道，肝移植术后新发糖尿病的发病率在 8.4%-30%之间[1-5]。中国肝移植注册（China Liver Transplant Registry, CLTR）2011 年发布的报告显示 1980-2010 的 30 年间肝移植术后发生糖尿病者比例为 30.98%，高居术后并发症第二位。肝移植后新发糖尿病会增加心因性死亡、感染和慢性排斥的风险，影响移植物和受者的生存率、降低受者的生活质量[6-9]。本研究旨在通过回顾性分析研究肝移植术后新发糖尿病的危险因素及对新发糖尿病对受者预后的影响。

1 资料与方法

1.1 一般资料

收集自 2007 年 7 月至 2014 年 9 月间在上海市第一人民医院接受公民逝世后器官捐献原位肝移植手术的病例。排除：1）移植时年龄小于 18 岁；2）多器官联合移植；3）术后 1 个月内死亡；4）术前患有糖尿病；5）资料不全。共纳入 143 例病例，其中男性 116 例（81.1%），女性 27 例（19.9%）。移植后免疫抑制治疗以他克莫司标准三联方案（他克莫司 + 霉酚酸酯 + 激素）或无激素方案为主。根据在随访期内是否新发糖尿病，将纳入的 143 例病例分为新发糖尿病（New Onset Diabetes Mellitus, NODM）组和未新发糖尿病（non-New Onset Diabetes Mellitus, non-NODM）组。回顾患者病历资料，收集包括：移植受者的年龄，性别，术前体重指数（Body Mass Index, BMI），终末期肝病模型（Model of End-stage Liver Disease, MELD）评分，Child-Pugh 评分及分级，血型是否匹配，术后是否发生急性排斥，术后是否常规使用激素，术后 1 月的血清转氨酶、肌酐（Creatine, Cr）、尿素（Urea）、胆红素（Bilirubin）、甘油三酯（Triglyceride, TG）、总胆固醇（Total Cholesterol, TC）及免疫抑制治疗的情况等临床数据。对术后 1 月的实验室检查结果取中位数来代表术后第 1 月内的水平。

本研究中糖尿病的诊断标准依据中华医学会《中国 2 型糖尿病防治指南（2017 版）》对糖尿病的诊断标准：空腹血糖≥ 7.0 mmol/L 或葡萄糖负荷后 2h 血糖≥ 11.1 mmol/L[10]或需要接受降糖药物治疗。

1.2 统计分析方法

应用 SPSS 23.0 和 Graphpad Prism 6.0 统计学软件进行统计分析。计量资料用平均数± 标准差表示，采用 t 检验进行比较分析。等级资料采用频数及百分比表示，采用秩和检验进行比较分析。计数资料采用频数及百分比表示，并采用卡方检验或费舍尔精确检验进行比较分析。对肝移植后新发糖尿病可能的危险因素采用二元 logistic 回归逐步回归法进行分析。应用 Kaplan-Meier 曲线和 log-rank 检验进行生存分析和比较。*P< 0.05* 认为有统计学意义。

2 结果

2.1 一般临床资料比较

在收集到的 143 例受者资料中，平均随访时间 35.22± 26.03 个月（随访时间 1-97 个月），NODM 组共 33 人（23.1%），原发疾病中肝硬化占大多数（87.4%）。NODM 组的 MELD 评分、Child-Pugh 评分 / 分级、移植术后采用常规激素方案治疗、移植后第 1 个月他克莫司谷浓度（Tacrolimus trough concentration, C0 TAC），以及术后第 1 个月的血清天冬氨酸氨基转移酶（aspartate aminotransferase, AST）水平、甘油三酯（Triglyceride, TG）水平、直接胆红素（Direct Bilirubin,DB）水平，显著高于 non-NODM 组（*P<0.05*）。详见表 1。

2.2 肝移植术后新发糖尿病的危险因素

将 NODM 组和 non-NODM 组比较分析中差异具有统计学意义的因素纳入二元 logistic 回归模型分析，结果示 Child-Pugh 分级（*P*=0.001）：C 级（*P<0.001*，OR=11.996，95%CI：3.340-43.089）。C0 TAC（*P*=0.013，OR=1.306，95% CI：1.058-1.612）。表明 Child-Pugh 分级 C 级和术后第 1 个月他克莫司谷浓度水平是肝移植后新发糖尿病的独立危险因素。详见表 2。

2.3 肝移植术后新发糖尿病对预后等影响

在随访期间，NODM 组和 non-NODM 组 1、3 及 5 年生存率分别为 57%和 85%、78%和 53%，及 74%和 53%，Kaplan-Meier 生存曲线分析结果示，在随访期内 NODM 组生存率显著低于 non-NODM 组，log-rank 法比较 *P*=0.001，差异具有统计学意义。生存曲线见图 1。

3 讨论

目前大多数研究认为免疫抑制剂是新发糖尿病的重要危险因素，本研究也发现移植术后第 1 个月他克莫司谷浓度水平是新发糖尿病的独立危险因素。他克莫司作为免疫抑制治疗的柱石，其致糖尿病作用及机制已被广泛研究。他克莫司为代表的钙调磷酸酶抑制剂（Calcineurin Inhibitor，CNIs），通过抑制钙调磷酸酶通路，抑制 T 细胞的激活，从而达到免疫抑制的目的。但在 β 细胞中，钙调磷酸酶通路下游靶点与 β 细胞的增殖和生存有关，钙调磷酸酶抑制剂表现为 β 细胞毒性作用。Penfornis 等人的研究也认为移植后新发糖尿病与移植受者术后第 1 个月他克莫司血药浓度相关[11]。Webster 等发现，他克莫司稳态血药浓度低于 10 ng /mL 时，既利于移植器官存活，也可有效降低 NODM 发生率[12]。CsA 的致糖尿病作用弱与他克莫司 [13]，可能的原因是他克莫司结合蛋白 12（FK506 binding protein 12，FKBP12）在 β 细胞中高表达，使得他克莫司在 β 细胞中富集[14]，而 CsA 无此分布规律。而在本研究中，应用 CsA 方案也仅在单因素分析中具有统计学意义。

肝脏作为糖代谢调控的主要脏器，对血糖水平的维持具有重要作用，但很少有研究分析移植受者肝功能对移植术后新发糖尿病的影响。本研究分析了移植受者术前和术后肝功能状态对新发糖尿病的影响，我们发现移植前受者 Child-Pugh 分级 C 级是移植后新发糖尿病的独立危险因素。Child-Pugh 评分 / 分级是常用的评价肝硬化患者肝功能储备的指标。肝硬化与肝源性糖尿病之间的联系早已被认知[15]，Grancini V.等人发现肝硬化患者中糖尿病的发病率随着患者 Child-Pugh 分级依次升

表 1 NODM 组与 non-NODM 组一般临床资料比较

Table 1 Clinical characteristics comparison between NODM group and non-NODM group

	NODM (n=33)	Non-NODM (n=110)	*P*
Age(yrs.)	47.88± 9.10	47.32± 9.66	0.768
Age > 60 yrs.	2 (6.1)	9 (8.2)	0.688
BMI (kg/m^2)	22.94± 3.39	22.92± 3.64	0.981
BMI > 25 kg/m^2	4(22.2%)	16(25.0%)	0.808
Female	8 (24.2)	19 (17.3)	0.370
Etiology			
HBV	25(75.8)	86 (78.2)	0.769
HCV	1(3.0)	2 (1.8)	0.548
HCC	23 (69.7)	66 (60.0)	0.314
Cirrhosis	31 (93.9)	94 (85.5)	0.243
Others	7 (21.2)	9 (8.2)	0.056
MELD	14.30± 6.70	11.15± 4.67	0.003
Child-Pugh			<0.001
A	9(26.3%)	65(59.1%)	
B	13(39.4%)	35(31.8%)	
C	11(33.3%)	10(9.1%)	
Acute Rejection	7 (21.2)	21 (19.1)	0.788
Corticosteroid Therapy	16 (48.5)	31 (28.2)	0.029
CsA Therapy	2 (6.1)	10 (9.1)	0.733
C_0 TAC(μg/L)	8.68± 2.61	7.44± 2.34	0.010
TAC Doses* (μg/kg)	3.99± 1.55	3.84± 1.52	0.634
ALT(U/L)	71.33± 61.90	56.74± 25.99	0.091
AST(U/L)	55.72± 33.34	44.16± 24.17	0.030

NODM: New-onset diabetes mellitus. Non-NODM: non-New Onset Diabetes Mellitus. BMI: Body Mass Index. HBV: Hepatitis B Virus. HCV: Hepatitis C Virus. HCC: Hepatocellular Carcinoma. MELD: Model for End-stage Liver Disease. CsA: Cyclosporin A. TAC: Tacrolimus. C0 TAC: trough blood concentration of tacrolimus. ALT: alanine aminotransferase. AST: aspartate aminotransferase.

*Doses of Tacrolimus were standardized by weights of patients.

表 2 肝移植术后新发糖尿病的危险因素的多因素 logistic 回归分析

Table 2 Multivariate logistic regression on risk factors of new-onset diabetes mellitus after liver transplantation

	OR(95%CI)	*P*
	Child-Pugh	0.001
B	2.808(0.928-8.499)	0.068
C	11.996(3.340-43.089)	<0.001
C_0TAC	1.306(1.058-1.612)	0.013

C_0 TAC: trough blood concentration of tacrolimus.

高[16]。肝源性糖尿病发病机制尚未完全明了,目前认为胰岛素抵抗和β细胞功能紊乱是其重要环节[17]。尽管糖尿病在肝硬化患者中发病率依据不同文献报道约为 35%-55%，但是在余下未达到糖尿病诊断标准的患者中约 10%-40%处于糖尿病前期(即空腹血糖受损或糖耐量受损)。我们推测,糖代谢异常发生率可能与肝硬化严重程度相关,这部分糖代谢调节异常的患者接受肝移植后,在免疫抑制剂等因素对胰岛素合成与分泌的影响和对β细胞的直接损害作用下，糖代谢调节进一步受损,新发糖尿病。因此,我们认为移植前对患者糖代谢状况进行全面评估对移植后新发糖尿病的预防具有重要意义。

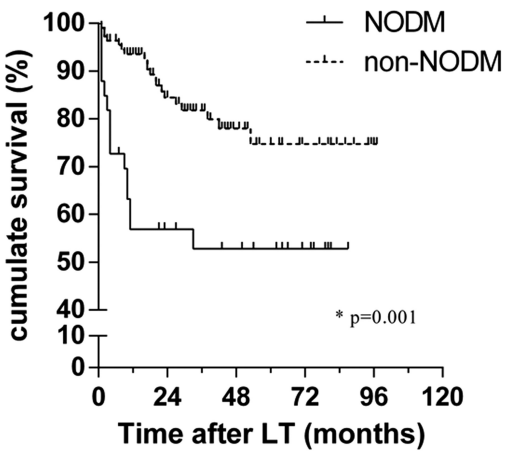

图 1 NODM 组和 non-NODM 组生存分析

Fig.1 Survival analysis for NODM and non-NODM group

Note: Log-rank test on survival between NODM and non-NODM group, *P*=0.001.

NODM: New-onset diabetes mellitus. non-NODM: non-New onset diabetes mellitus. LT: Liver transplantation.

我们还发现肝移植术后第 1 个月血清转氨酶水平在单因素分析中与新发糖尿病具有相关性,但在多因素分析中未发现显著性。血清转氨酶水平能够反映肝脏损伤和肝细胞功能恢复情况,移植肝脏在移植过程中序惯经历了温缺血、冷缺血和缺血再灌注损伤,移植后功能恢复情况还受到免疫抑制治疗的影响，这些因素的影响在移植后早期转氨酶水平上均会有所反映[18, 19]。冷缺血时间、缺血再灌注损伤及免疫抑制剂等均有报道与肝移植术后新发糖尿病具有相关性[20, 21],本研究也发现免疫抑制剂他克莫司的谷浓度水平是新发糖尿病的独立危险因素,因此,我们认为转氨酶水平一定程度上可以作为新发糖尿病风险的一个参考指标。

糖皮质激素能够升高血糖和诱导胰岛素抵抗[22],在其他研究中被认为与 NODM 相关[4],但在本研究中仅在单因素分析中具有统计学意义。丙肝在许多研究中被认为与 NODM 相关[8, 23],但在本研究中未能得到相同结论,我们推测可能是由于单中心所收集的病例资料中 HCV 患者所占比例很小(2.1%)所致。此外,肥胖和超重是普通人群中发生糖尿病的危险因素,但在本研究中与肝移植后新发糖尿病未发现相关性。通常用 BMI 和腹围评估肥胖程度和类别,但在肝移植受者中,大多数终末期肝病患者有腹水，而大量腹水引起的 BMI 增加和腹围增大与患者原本即肥胖很难区分,因此限制了 BMI 的应用。

NODM 与肝移植术后感染、慢性排斥和心血管事件相关,显著增加患者死亡率[24]。Qi Ling 等对中国肝移植注册(CLTR)2000-2013 年间 10 204 例术前无糖尿病的患者资料的研究表明,发生 NODM 的患者生存率显著低于整体生存率[2]。本研究结果与其一致。Jang I. Moon 等对肝移植受者的长期随访(中位随访时间 57.2 个月)研究中发现,NODM 患者因感染、慢性排斥反应引起的移植物功能衰竭和迟发型肝动脉血栓所致死亡率更高[2]。因此,随着随访时间的延长,NODM 与术后感染、心血管事件及慢性排斥反应等并发症之间的关联性需要进一步的研究。

综上所述，移植术前 Child-Pugh 分级 C 级和术后第 1 个月他克莫司谷浓度是 NODM 的独立危险因素,且 NODM 显著降低患者的生存率。由于本研究为单中心回顾性研究且样本量有限,难以避免存在偏倚,在进一步的研究中,需要扩大样本、进行临床前瞻性研究来进一步增加结论的可靠性。

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