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在线全文

新型凝血标记物在肝移植术后早期并发症中的应用价值*

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【摘要】 目的 探讨凝血酶-抗凝血酶复合物（thrombin-antithrombin complex, TAT）、纤溶酶-α_2抗纤溶酶复合物（plasmin-α_2-plasmin inhibitor complex, PIC）、可溶性血栓调节蛋白（soluble thrombomodulin, sTM）和组织型纤溶酶原激活剂-抑制剂复合物（tissue plasminogen activator-inhibitor complex, tPAIC）与肝移植术后早期并发症的关系。**方法** 分析2021年12月–2022年11月四川大学华西医院重症医学科（intensive care unit, ICU）收治的130例肝移植术后患者围手术期的临床资料（包括血浆TAT、PIC、sTM和tPAIC）。根据患者术后30 d内是否发生Clavien-Dindo (CD) Ⅲb级及以上并发症，将患者分为并发症组和无并发症组。单因素分析及二元多因素logistic回归模型确定肝移植术后30 d内并发症的危险因素。**结果** 肝移植术后30 d内CDⅢb级及以上并发症的发生率为33.1%（43/130）。并发症组患者MELD评分、手术时间、术中红细胞用量、术中血浆用量以及术后ICU入院时血浆TAT、PIC、sTM和tPAIC均高于无并发症组（P<0.05）。logistic回归显示移植期间每输注1 U红细胞，肝移植术后30 d内并发症概率增加15.1%〔95%置信区间（confidence interval, *CI*）：1.070 ~ 1.239, P<0.001〕，术后ICU入院时血浆sTM每增加1 TU/mL，肝移植术后30 d内并发症概率增加13.7%（95%*CI*：1.060 ~ 1.220, P<0.001）。**结论** 肝移植术后ICU入院时血浆sTM是肝移植术后30 d内并发症的重要危险因素，对sTM的额外评估可能有助于预测肝移植术后早期的并发症。

【关键词】 肝移植 新型凝血标志物 手术后并发症

Application Value of Novel Coagulation Markers in Predicting Postoperarative Complications in the Early Stage After Liver Transplantation

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【Abstract】 Objective To investigate the relationship between thrombin-antithrombin complex (TAT), plasmin-α_2-plasmininhibitor complex (PIC), soluble thrombomodulin (sTM), and tissue plasminogen activator-inhibitor complex (tPAIC) and postoperative complications in the early stage after liver transplantation (LT). **Methods** We analyzed the perioperative clinical data, including plasma TAT, PIC, sTM, and tPAIC, of 130 post-LT patients admitted to the intensive care unit (ICU), West China Hospital, Sichuan University between December 2021 and November 2022. Patients were divided into two groups, a complication group and a non-complication group, according to whether they experienced complications of Clavien-Dindo (CD) grade Ⅲb and above within 30 days after the surgery. Univariate analysis and binary multivariate logistic regression models were used to determine the risk factors for complications within 30 days post-LT. **Results** The incidence of complications of CD grade Ⅲb and above within 30 days post-LT was 33.1% (43/130). Patients in the complication group had significantly higher scores for the Model for End-Stage Liver Disease (MELD), operative time, intraoperative red blood cell transfusion volume, intraoperative plasma transfusion volume, and plasma TAT, PIC, sTM and tPAIC measured at the time of admission to ICU after the operation than those in the non-complication group did (all P<0.05). Logistic regression showed that for every single U of red blood cells transfused during the transplant surgery, the probabilities of complications within 30 days post-LT increased by 15.1% (95% confidence interval [*CI*]: 1.070-1.239, P<0.001) and for the increase of every single TU/mL of plasma sTM measured upon post-LT admission to ICU, the probabilities of complications increased by 13.7% (95% *CI*: 1.060-1.220, P<0.001). **Conclusion** Plasma sTM measured upon admission to ICU after LT is an independent risk factor for complications within 30 days post-LT, and additional assessment of sTM may help predict complications in the early stage post-LT.

【Key words】 Liver transplantation Novel coagulation markers Postoperative complications

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肝移植(liver transplantation, LT)是终末期肝病患者最有效的治疗方法,由于免疫抑制剂和外科技术的革新,手术短期结局已显著改善。然而,术后并发症发病率高仍是其亟须解决的问题,术后并发症显著增加器官功能障碍的发病率、死亡率以及经济成本,某些并发症(如肾损伤、出血)可能反过来影响凝血功能,致使凝血功能复杂多变,管理极具挑战[1-4]。此外,凝血功能紊乱是LT术后常见的临床表现,并与血栓事件、出血、器官功能障碍等术后并发症的风险增加有关[5-8],通过凝血功能监测,可以更早地发现这些并发症,进而予以相应治疗,改善预后。因此,凝血功能监测不仅有助于评估LT术预后,还为临床实践提供指导,具有广阔的发展前景。然而,目前的凝血监测手段并不能满足此类患者的需求[9-10],尚需进一步研究凝血功能监测的技术和方法。

目前,一组包括凝血酶-抗凝血酶复合物(thrombin-antithrombin complex, TAT)、纤溶酶-α_2抗纤溶酶复合物(plasmin-α_2-plasmin inhibitor complex, PIC)、可溶性血栓调节蛋白(soluble thrombomodulin, sTM)和组织型纤溶酶原激活剂-抑制剂复合物(tissue plasminogen activator-inhibitor complex, tPAIC)等凝血标志物的实验室检测已应用于临床,既往研究数据表明这些标志物与血栓前状态以及多种血管相关性疾病有关[11-13]。然而,目前尚未见这些标志物与LT术后并发症的相关报道。因此,本研究选择TAT、PIC、sTM和tPAIC进行研究,重点关注这些凝血标志物与LT术后早期并发症之间的关系,现报告如下。

1　材料与方法

1.1　对象与设计

本研究为单中心、前瞻性、观察性研究,以我院重症医学科(intensive care unit, ICU)2021年12月–2022年11月期间收治的LT术后转入的终末期肝病患者为研究对象。纳入标准:①年龄≥18岁;②手术方式为经典式或背驼式植入。排除标准:①因急性肝衰竭行LT的患者;②二次LT的患者;③暴露因素或结局指标等重要数据缺失的病例。本研究获四川大学华西医院伦理委员会批准(2022年审2号),并获得受试者的书面知情同意。

1.2　患者管理

手术采用静吸复合全身麻醉,手术结束立即转入ICU进行血流动力学监测和规范化术后护理。免疫抑制采用他克莫司、吗替麦考酚酯和糖皮质激素的三联方案,他克莫司为首选药,自术后第1或2天开始口服或管喂给药。方案启动后及时监测血药浓度及肾功能,根据结果及临床症状调整药物剂量或更改治疗方案。如无禁忌症,自术后第1或2天每日皮下给予低分子肝素4 000 IU预防性抗凝。

1.3　数据收集及方法

1.3.1　临床资料的收集

记录患者围手术期临床资料,并随访患者术后30 d内如出血、血栓、感染等并发症的发生情况以及生存状况。根据Clavien-Dindo(CD)分级系统对术后并发症进行分级,同一患者发生多次或者多级并发症按最高分级计算。根据患者是否发生CD-Ⅲb级及以上并发症〔a:出现需要全身麻醉干预的手术、内镜或放射介入的并发症;b:出现危及生命的单个或者多个器官功能障碍(包括脑出血、缺血性卒中等中枢神经系统并发症以及透析);c:患者死亡〕,将患者分为并发症组和无并发症组。

1.3.2　计算终末期肝病模型(model for end-stage liver disease, MELD)评分

MELD按照公式MELD= 3.78×ln(总胆红素)+11.2×ln(INR)+9.57×ln(血清肌酐)+6.43×病因计算。其中,总胆红素、INR和血清肌酐为术前最后一次的测值。总胆红素、血清肌酐单位为mg/dL,病因设胆汁或酒精性肝病为0,其他为1。

1.3.3　TAT、PIC、sTM和tPAIC的检测

ICU入院时采集静脉血2.7 mL(枸橼酸钠抗凝血管),1 500 *g*离心15 min提取血浆用于TAT、PIC、sTM和tPAIC的测定(日本,Sysmex公司,HISCL5000全自动分析仪及配套试剂)。

1.4　统计学方法

正态分布连续资料以$\bar{x}\pm s$描述,偏态分布连续资料以中位数(四分位间距)描述,分类资料以例数或构成比表示。组间比较采用χ^2检验、Mann-Whitney *U*检验、*F*检验等。单因素分析及二元多因素logistic回归模型以确定并发症的危险因素。$P<0.05$为差异有统计学意义。

2　结果

2.1　基本情况

研究期间共收治150例LT术后患者,根据纳入、排除标准剔除20例患者(二次LT患者3例,急性肝衰竭接受LT患者3例,重要数据缺失14例),最终纳入130例患者(图1)。

研究人群平均年龄为(50.4±9.7)岁,体质量指数(body mass index, BMI)为(23.55±3.36) kg/m^2。LT适应征为病毒性肝炎(伴或不伴肝癌)97例、酒精性肝炎10例、胆汁性淤积性肝炎7例、自身免疫性肝炎4例、特发性肝硬化6例、肝癌4例和罕见肝病2例。

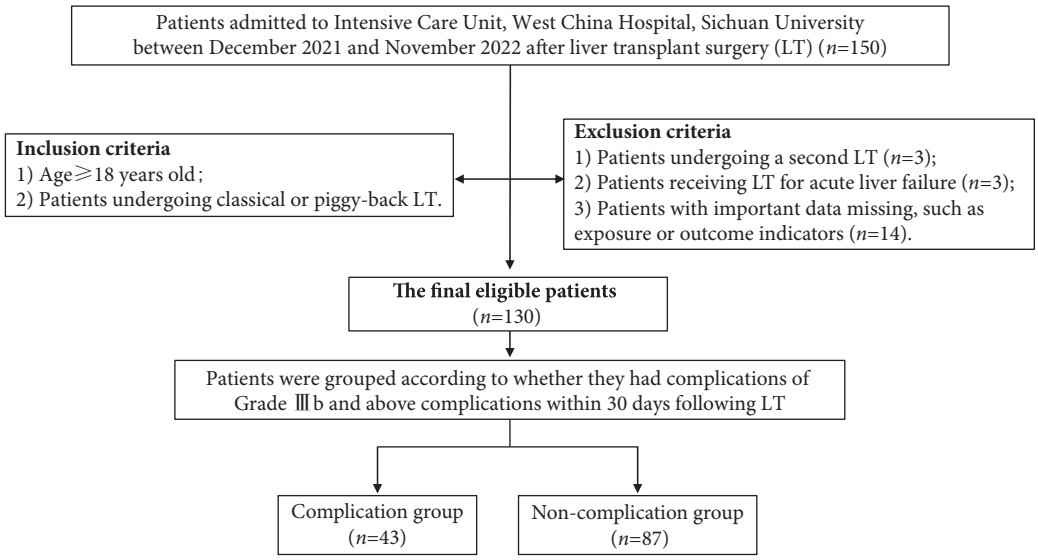

图 1 研究流程图

Fig 1 Flow diagram of the study

2.2 并发症发生情况

43例(33.1%)患者LT术后30 d内发生CD-Ⅲb级及以上并发症，其中CD-Ⅲb级2例(1.5%)，CD-Ⅳ级28例(21.5%)和CD-Ⅴ级13例(10.0%)。这些并发症包括急性呼吸衰竭12例、急性肾衰竭透析治疗11例、脓毒性休克9例、腹腔或消化道出血3例、肝血管血栓形成4例、胆道问题2例和其他并发症2例。

2.3 临床资料对比

并发症组患者MELD评分、手术时间、术中红细胞以及血浆用量均高于无并发症组($P<0.05$)。两组患者其余的临床资料如年龄、性别、BMI、病因、供体特征等的比较，差异均无统计学意义。并发症组患者LT术后ICU入院时外周血TAT、PIC、sTM和tPAIC浓度均高于无并发症组，且差异有统计学意义($P<0.05$)。见表1。

2.4 LT术后并发症的危险因素

将表1的所有变量纳入二元多因素logistic回归模型(似然比法)确定LT术后并发症的危险因素。结果显示术中红细胞用量和术后ICU入院时血浆sTM是LT术后30 d内并发症的独立危险因素，移植期间每输注1 U红细胞，LT术后30 d内并发症概率增加15.1%〔95%置信区间(confidence interval, *CI*)：1.070 ~ 1.239, $P<0.001$〕，术后ICU入院时血浆sTM每增加1 TU/mL，LT术后30 d内并发症概率增加13.7%(95%*CI*：1.060 ~ 1.220, $P<0.001$)。见表2。

3 讨论

鉴于LT手术风险相对较高、器官可用性有限以及术

表 1 两组患者围术期临床资料对比

Table 1 Comparison of the perioperative clinical data of the two groups

Variable	Complication group (*n*=43)	Non-complication group (*n*=87)	*P*
Recipient characteristics			
Age/yr.*	52 (46-57)	51 (45-56)	0.523
Male/case (%)	34 (79.1)	69 (79.3)	1.000
BMI/(kg/m^2)*	24.72 (21.26-26.20)	23.72 (20.96-25.35)	0.183
MELD score*	22.5 (13.3-26.9)	15.3 (9.4-23.1)	0.008
HBV or HCV/case (%)	29 (67.4)	68 (78.2)	0.204
Graft and surgical characteristics			
Donor age/yr.*	48 (43-56)	50 (39-57)	0.558
(DBD/DCD)/case	16/27	24/63	0.314
Operation time/h*	6.92 (6.28-8.58)	6.00 (5.27-7.13)	0.001
Anhepatic stage/min*	68 (56-79)	62 (53-73)	0.141
CIT/h*	5.967 (4.400-8.500)	5.217 (4.167-7.617)	0.347
WIT/min*	27 (23-35)	28 (22-38)	0.692
RBC/U*	11 (7-14)	4.5 (3-8.5)	<0.001
Plasma/mL*	850 (600-1 550)	600 (0-1 050)	0.001
Postoperative coagulation markers			
TAT/(ng/mL)*	29.3 (23.0-54.6)	26.8 (13.4-37.4)	0.033
PIC/(μg/mL)*	2.98 (1.23-8.29)	1.83 (0.84-5.28)	0.039
sTM/(TU/mL)*	20.9 (19.0-24.8)	16.4 (13.5-18.9)	<0.001
tPAIC/(ng/mL)*	21.6 (17.7-29.2)	19.6 (13.9-23.8)	0.008

BMI: body mass index; MELD: model for end-stage liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; DBD: donation after brain death; DCD: donation after circulatory death; WIT: warm ischemia time; CIT: cold ischemia time; RBC: red blood cell; TAT: thrombin-antithrombin complex; PIC: plasmin-α_2-plasmin inhibitor complex; sTM: soluble thrombomodulin; tPAIC: tissue plasminogen activator-inhibitor complex. * Median (P_{25}-P_{75}).

表 2 LT术后30 d内并发症的危险因素

Table 2 Risk factors for complications within 30 days after LT

Variable	Beta	*P*	*OR*	95% *CI*
RBC/U	0.141	<0.001	1.151	1.070-1.239
sTM/(TU/mL)	0.129	<0.001	1.137	1.060-1.220

LT: liver transplantation; *OR*: odds ratio; *CI*: confidence interval; RBC: red blood cell; sTM: soluble thrombomodulin.

后并发症对短期和长期临床成功的负面影响，早期标志物识别术后并发症对实施患者分层策略、采取科学合理的治疗以及改善患者总生存期至关重要。

肝病既存的止血障碍，加上术中特定的止血变化，LT术后早期凝血功能障碍常见，显著增加出血、血栓性事件、器官功能障碍甚至死亡的风险[6]。凝血功能障碍涉及内皮功能障碍、组织因子大量释放、促/抗凝血因子受损以及免疫反应等多重因素的相互作用[14-15]。总体而言，这些过程促使LT术后早期止血平衡向促凝转化，导致微循环障碍和灌注减少，进一步加重组织损伤，进而影响术后病程及临床结局[16-17]。此外，LT术后可能出现如肾损伤、出血等并发症，可能反过来影响凝血功能[18-19]，监测凝血功能有助于更早地发现这些并发症，予以针对性治疗，从而改善患者的生存率。因此，凝血功能监测参数与患者预后密切相关，凝血功能监测不仅有助于评估LT术后预后，还为临床实践提供指导。根据细胞基础的凝血理论，凝血功能涉及内皮细胞、促凝血和抗凝血系统之间的相互作用[20]。因此，本研究选择反映凝血系统早期激活的TAT，反映纤溶系统活化的PIC，反映内皮功能状况的sTM和tPAIC进行研究。这些指标基于化学免疫发光法进行检测，对内皮损伤程度、凝血和纤溶系统激活程度进行综合评估，较常规凝血检测项目（如INR）准确度和灵敏度更高，检测耗时更短，适合临床开展应用。本研究通过分析130例LT术后患者围术期临床资料与术后早期并发症间的关系，重点关注凝血标志物TAT、PIC、sTM和tPAIC对LT术后早期并发症的潜在预测意义。研究发现并发症组患者LT术后ICU入院时血浆TAT、PIC、sTM和tPAIC水平明显高于无并发症组患者，多因素分析显示sTM是LT术后30 d内并发症的独立危险因素，术后ICU入院时血浆sTM每增加1 TU/mL，LT术后30 d内并发症概率增加13.7%。

血栓调节蛋白（thrombomodulin，TM）是一种内皮细胞跨膜糖蛋白，作为凝血酶的受体，可加速蛋白C的活化，从而加速降解因子Ⅴa和因子Ⅷa以及抑制凝血反应并限制纤维蛋白形成，在维持血管内皮抗凝特性和稳定性方面起着关键作用[21-22]。当内皮细胞受到损伤时，TM以sTM的形式释放到血液中，因此内皮的完整性可以通过确定sTM的血浆水平来评估。在与脓毒症、急性呼吸衰竭、急性肾损伤等内皮损伤相关疾病的研究中，观察到血浆sTM水平的升高，并且sTM与这些疾病的发病率和死亡率相关[23-28]。因此，血浆sTM水平升高可能提示内皮病变的实验室证据，间接提示天然抗凝系统通过蛋白C和蛋白S的有效性降低而受损。除了作为内皮损伤的生物标志物外，一些研究者甚至还考虑了sTM与血管内微血栓形成的适当因果关系，最终提出内皮功能障碍可能是某些疾病（如脓毒症）的理想替代靶点，因为它先于器官功能障碍的发展，并参与器官灌注、血管通透性和凝血级联反应激活的发病机制[29-31]。本研究发现LT术后并发症患者的血浆sTM水平升高，sTM与LT术后早期并发症间存在关联。这一事实表明LT术后凝血功能障碍的机制更多地与微循环中内皮损伤和抗凝系统的有效性降低有关，并且这些改变可能参与LT术后早期并发症的发生发展。因此，对LT术后患者进行sTM的额外评估，有助于早期预警不良事件，有望为临床提供更准确的凝血监测信息，并且可能为后续临床中对于LT术后患者的管理提供潜在的策略。

此外，本研究发现移植期间红细胞用量是LT术后30 d内并发症的重要危险因素，移植期间每输注1 U红细胞，术后30 d内CD-Ⅲb级及以上并发症概率增加15.1%。同样地，一项多中心研究发现移植期间每输1 U红细胞，严重并发症的概率增加11%，30 d内死亡的概率增加13%[32]。本研究结果和既往数据表明移植期间红细胞输注的有害影响，提示限制术中红细胞用量可降低大手术后主要并发症风险[33-34]。

本研究尚存不足之处：患者数量较少、随访时间过短、选择性偏倚、缺乏全面动态的实验室检查等，有必要进一步更大规模、更长时间的研究，以确定TAT、PIC、sTM和tPAIC与LT术后短期和长期结局的关系。

综上所述，LT术后ICU入院时的血浆sTM是LT术后30 d内并发症的重要危险因素，对sTM的额外评估可能有助于预测LT术后早期的并发症，但其临界值应在适当的临床环境和适当的临床人群中重新评估。

*　　*　　*

作者贡献声明　张雪负责论文构思、研究方法和初稿写作，郭军、张中伟和杨家印负责数据审编，张雪和胡海负责正式分析，郭军和康焰负责经费获取，张雪、陈思敏、郭军和杨家印负责调查研究，张中伟和康焰负责研究项目管理和监督指导，张中伟和杨家印负责提供资源，陈思敏负责验证和可视化，郭军、胡海和康焰负责审读与编辑写作。所有作者已经同意将文章提交给本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

利益冲突　所有作者均声明不存在利益冲突

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