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在线全文

心脏外科术后发生肝素诱导血小板减少症患者的临床特征分析及诊断指标评估*

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【摘要】 **目的** 探讨心脏外科术后疑似肝素诱导血小板减少症（heparin-induced thrombocytopenia, HIT）患者中HIT的确诊率、新发血栓发生率、血小板动态演变模式及临床特征；评估HIT抗体（hit-antibodies, HIT-Ab）、4T's评分和Lillo-Le Louet（LLL）评分对HIT的诊断价值。**方法** 采用回顾性队列研究，纳入2023年4月–2024年12月中国医学科学院阜外医院心脏外科术后疑似HIT患者307例，收集其临床与实验室数据。所有患者均接受4T's评分、LLL评分及HIT-Ab检测。根据最终临床诊断分为非HIT组（n=269）和HIT组（n=38），比较两组血小板演变模式及其他临床特征。根据HIT-Ab浓度分为四组：阴性组（<1.0 U/mL，n=257）、弱阳性组（1.0～4.9 U/mL，n=34）、中阳性组（5.0～9.9 U/mL，n=11）、强阳性组（≥10 U/mL，n=5），分析各组间新发血栓发生率及HIT确诊率等差异，并用受试者工作特征曲线（ROC曲线）评估HIT-Ab浓度、4T's评分和LLL评分对HIT的诊断效能。**结果** HIT确诊率为12.38%（38/307），HIT组新发血栓率为63.16%，高于非HIT组34.57%（P<0.001）。76.32%HIT患者血小板呈双相下降模式（模式A），其发生HIT的风险显著高于模式B患者〔比值比（odds ratio, OR）=10.32，95%置信区间（confidence interval, CI）：4.64～22.95〕。新发血栓发生率随HIT-Ab升高阶梯式递增（阴性组32.7%→强阳性组100%，P<0.001），HIT确诊率从阴性组的0升至弱阳性组的64.71%，中/强阳性组确诊率达100%。HIT-Ab浓度、4T's评分和LLL评分诊断HIT的ROC曲线下面积分别为0.996（95%CI：0.991～1.000）、0.799（95%CI：0.727～0.870）和0.860（95%CI：0.811～0.908）。当HIT-Ab浓度为1 U/mL时，其诊断敏感度为100%，阴性预测值（negative predictive value, NPV）为100%。与传统的HIT高危人群的诊断标准（4T's评分截断值为4分，LLL评分截断值为2分）相比，以最大约登指数选定的4T's评分最佳截断值为5分，LLL评分最佳截断值为3分。**结论** 心脏术后疑似HIT患者新发血栓发生率随HIT-Ab水平升高呈阶梯上升趋势。LLL评分对HIT的诊断价值优于4T's评分。HIT-Ab检测具有较高的敏感度和阴性预测值，是指导早期停用肝素和排除HIT的可靠工具。结合HIT-Ab浓度、血小板演变模式及临床评分，有助于更精准地识别HIT风险、启动替代抗凝治疗及优化抗凝管理策略。

【关键词】 肝素诱导血小板减少症 心脏外科手术 血栓形成 HIT抗体 血小板减少

Analysis of Clinical Characteristics and Diagnostic Indicators in Patients With Heparin-induced Thrombocytopenia After Cardiac Surgery

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[**Abstract**] **Objective** To investigate the diagnosis rate of heparin-induced thrombocytopenia (HIT), the incidence of new thrombosis, the dynamic evolution pattern of platelets, and the clinical characteristics in patients with suspected HIT after cardiac surgery; and to evaluate the diagnostic value of HIT antibodies (HIT-Ab), 4T's score, and Lillo-Le Louet (LLL) score for HIT. **Methods** A retrospective cohort study was conducted. A total of 307 patients with suspected HIT after cardiac surgery at Fuwai Hospital of the Chinese Academy of Medical Sciences from April 2023 to December 2024 were included. Clinical and laboratory data were collected. All patients underwent 4T's score, LLL score, and HIT-Ab

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testing. Patients were divided into the non-HIT group (n = 269) and the HIT group (n = 38) based on the final clinical diagnosis. The platelet evolution patterns and other clinical characteristics of the two groups were compared. HIT-Ab concentration was divided into four groups: negative (< 1.0 U/mL, n = 257), weakly positive (1.0-4.9 U/mL, n = 34), moderately positive (5.0-9.9 U/mL, n = 11), and strongly positive (≥ 10 U/mL, n = 5). Differences in the incidence of new thrombosis and the diagnosis rate of HIT among the groups were analyzed, and the diagnostic efficacy of HIT-Ab concentration, 4T's score, and LLL score for HIT was evaluated using receiver operating characteristic (ROC) curves. **Results** The diagnosis rate of HIT was 12.38% (38/307), and the incidence of new thrombosis in the HIT group was 63.16%, higher than the 34.57% in the non-HIT group (P < 0.001). Among HIT patients, 76.32% showed a biphasic decline pattern of platelets (pattern A), and their risk of HIT was significantly higher than that of patients with pattern B (odds ratio [OR] = 10.32, 95% confidence interval [CI]: 4.64-22.95). The incidence of new thrombosis increased stepwise with higher HIT-Ab concentration (32.7% in the negative group to 100% in the strongly positive group, P < 0.001), and the diagnosis rate of HIT increased from 0 in the negative group to 64.71% in the weakly positive group, reaching 100% in the moderate/strong positive group. The areas under the ROC curves for HIT-Ab concentration, 4T's score, and LLL score for diagnosing HIT were 0.996 (95% CI: 0.991-1.000), 0.799 (95% CI: 0.727-0.870), and 0.860 (95% CI: 0.811-0.908), respectively. When the HIT-Ab concentration was 1 U/mL, the diagnostic sensitivity and negative predictive value (NPV) were both 100%. Compared with the traditional diagnostic criteria for high-risk HIT populations (4T's score cutoff of 4, LLL score cutoff of 2), the optimal cutoff value of 4T's score selected by the maximum Youden index was 5, and the optimal cutoff value of LLL score was 3. **Conclusion** The incidence of new thrombosis in patients with suspected HIT after cardiac surgery increases stepwise with higher HIT-Ab levels. The diagnostic value of the LLL score for HIT is superior to that of the 4T's score. HIT-Ab testing has high sensitivity and negative predictive value, making it a reliable tool for guiding early discontinuation of heparin and excluding HIT. Combining HIT-Ab concentration, platelet evolution pattern, and clinical scores helps more accurately identify HIT risk, initiate alternative anticoagulation therapy, and optimize anticoagulation management strategies.

[Key words] Heparin-induced thrombocytopenia Cardiac surgery Thrombosis HIT antibodies Thrombocytopenia

肝素诱导血小板减少症(heparin-induced thrombocytopenia, HIT)是一种由肝素类药物触发的免疫性并发症,以血小板减少和反常性高凝状态为特征[1]。这一病理过程始于肝素与血小板因子4(platelet factor 4, PF4)结合形成复合物,进而触发HIT抗体(hit-antibodies, HIT-Ab)产生;此类抗体通过激活血小板FcγRⅡa受体,引起血小板消耗与凝血级联反应,最终导致血栓形成[2-3]。在心脏外科手术中,HIT的发生风险尤为突出,这主要与三个关键因素相关:首先,体外循环(cardiopulmonary bypass, CPB)过程中需要一次性使用300 ~ 400 IU/kg的高剂量普通肝素(unfractionated heparin, UFH)[4];其次,围手术期往往需要多环节肝素暴露[5];第三,手术创伤本身会促进血小板活化[6-7]。心脏外科患者因手术复杂、肝素用量大、血管内皮损伤等因素,其HIT发生率远高于普通手术患者,且血栓事件和死亡率显著增高[6, 8-9]。

目前国际上诊断HIT主要依据"临床评估+实验室检测"的策略[10-12]。2018年美国血液学会(ASH)指南推荐将4T's评分作为临床初筛工具,确诊则需要血清素释放试验(serotonin release assay, SRA)或肝素诱导血小板聚集试验(heparin-induced platelet aggregation, HIPA)等功能学检测[13]。然而,这些确证试验因存在方法学限制,在国内开展极为有限。中国《肝素诱导血小板减少症诊疗专家共识》提出[14],在缺乏功能学检测时,可结合4T's评分、HIT-Ab检测(免疫比浊法, automated latex-enhanced immunoturbidimetric assay, LIA)和血小板动态变化进行综合判断。其中,4T's评分≥4分提示中高风险,但心脏外科患者因手术本身易出现血小板减少,导致特异性降低;HIT-Ab检测(如本研究所用免疫比浊法)具有较高敏感性,但存在假阳性问题;此外,近年来提出的Lillo-Le Louet(LLL)评分及血小板动态轨迹分析(如双相下降模式)可能提供额外诊断价值,但尚未形成统一标准[15-16]。这种诊断困境使得临床决策面临巨大挑战。

本研究旨在解决三个关键问题:第一,系统评估HIT-Ab定量检测对心脏外科患者HIT的诊断价值,明确最佳诊断阈值;第二,分析心脏外科HIT患者的独特临床特征,特别是血小板动态演变规律;第三,比较HIT-Ab、4T's评分和LLL评分的诊断效能,优化诊断策略。通过建立整合抗体浓度、血小板变化模式和临床评分的诊断路径,本研究将为临床提供更精准的HIT识别工具,指导及时干预,最终改善患者预后。研究结果将优化心脏外科

HIT诊断的循证依据，并为国际指南的更新提供来自中国人群的重要数据。

1　资料与方法

1.1　研究对象

本研究采用回顾性队列研究。选取2023年4月–2024年12月在中国医学科学院阜外医院行心脏外科手术的疑似HIT患者，根据纳入和排除标准，入组307例为研究对象，其中HIT组38例、非HIT组269例（筛选流程图见图1）。根据HIT-Ab抗体浓度分组，阴性组（< 1 U/mL）257例、弱阳性组（1.0 ~ 4.9 U/mL）34例、中阳性组（5.0 ~ 9.9 U/mL）11例、强阳性组（≥10 U/mL）5例。所有疑似HIT患者均接受HIT风险评估（4T's评分及LLL评分），并检测HIT-Ab，如有连续HIT-Ab检测时，取连续检测中的最高抗体浓度作为最终结果。本研究已通过中国医学科学院阜外医院伦理委员会审查（批准号2023-2134）。

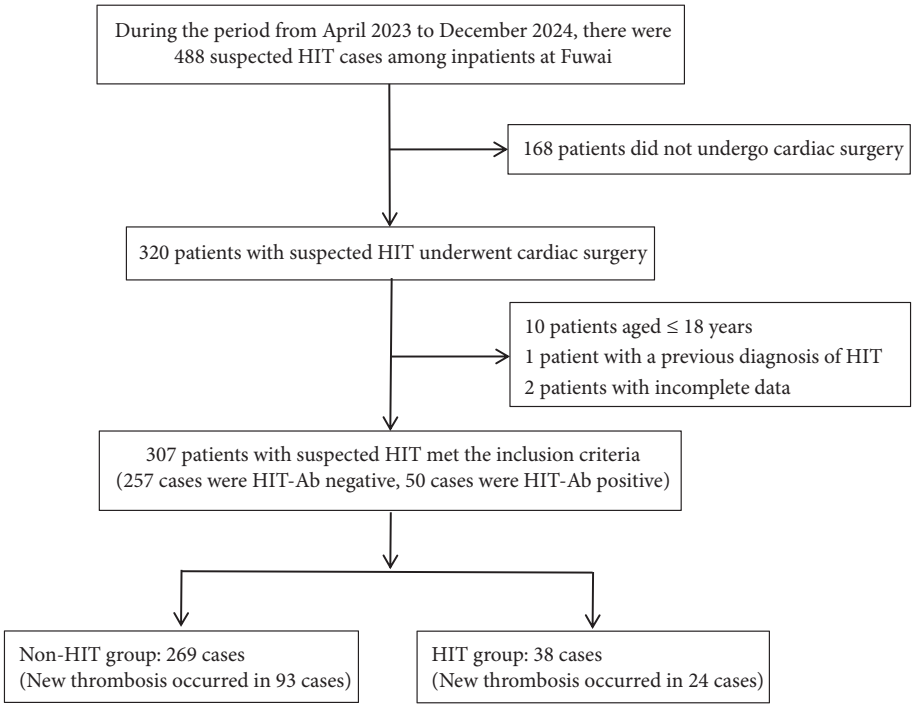

图 1　研究流程图

Fig 1　Research flowchart

纳入标准：①年龄≥18岁；②接受心脏外科手术（包括心脏瓣膜手术、冠状动脉旁路移植术、主动脉手术、心脏移植术等）的患者；③肝素接触史；④肝素治疗后血小板计数较基线下降幅度≥30%；⑤无论是否接受输血、新发血栓事件或肝素替代抗凝治疗。

排除标准：①临床数据不完整；②HIT病史；③有血液系统疾病；④恶性肿瘤患者。

1.2　方法

1.2.1　仪器和试剂

HIT-Ab检测设备为ACL TOP750全自动血凝仪；HIT-Ab检测试剂为肝素诱导血小板减少症抗体检测试剂盒（沃芬，0020302700），试剂为含聚苯乙烯乳胶颗粒的悬液，颗粒表面包被抗PF4-肝素复合物的单克隆抗体（可模拟HIT患者血清中的抗体结合特性）。检测原理是采用乳胶粒子增强免疫比浊法来检测HIT患者血清中抗PF4-肝素复合物的抗体（IgG/IgM/IgA）。HIT-Ab定量结果精确至0.1。

1.2.2　评分判定和相关定义

基于HIT检测申请当天患者记录中可用的信息，为所有病例进行回顾性计算LLL评分；4T's评分依据患者实验室检测时临床医生的评分。4T's评分风险等级划分标准：低风险（0 ~ 3分）、中度风险（4 ~ 5分）、高风险（6 ~ 8分）[12]。LLL评分的HIT概率划分标准：低概率（< 2分）、高概率（≥2分）[15-16]。

4T's评分和LLL评分阳性判断标准：4T's评分≥4分为阳性评分[12]，LLL评分≥2分为阳性评分[15-16]。

血小板计数变化模式：模式A：手术后快速下降，5 d内上升30%，并在5 ~ 10 d之间再次下降；模式B：手术后快速下降并持续，恶化超过4 d[15-16]。

血小板计数最大值（platelet maximum，PLTmax）：根据血小板减少模式不同而有差异。模式A：血小板计数首次下降后恢复至峰值，再出现第二次下降前的最高值；模

式B: 入院后术前血小板计数最大值。

血小板计数最小值(platelet minimum, PLTmin): 血小板计数从峰值下降至最低点的数值。

肝素替代抗凝治疗: 术后使用非肝素类抗凝药物(如阿加曲班、比伐卢定)。

新发血栓标准: 经超声或CT扫描, 确认使用肝素前后是否存在新发血栓, 并记录血栓位置。

确认HIT: 由于SRA方法学限制, 本研究HIT的确诊综合了临床评估、实验室检测及患者停药后的临床症状演变, 进行最终的确诊或排除。

1.2.3 统计学方法

采用Empower Stats及SPSS 25.0统计软件对数据进行处理和分析, 用GraphPad Prism 9.0作图软件进行绘制图谱和表格。非正态分布数据以中位数(P_{25} ~ P_{75})表示, 正态分布数据以$\bar{x} \pm s$表示。组间正态分布连续变量的比较采用独立样本t检验, 非正态分布的定量数据采用Mann-Whitney$U$检验比较差异。对于分类变量使用卡方检验比较差异。以临床综合诊断的HIT结果为金标准, 绘制HIT-Ab诊断效能的受试者工作特征(receiver operating characteristic, ROC)曲线, 以曲线下面积(area under the curve, AUC)判断HIT-Ab对HIT的诊断效能。P< 0.05为差异有统计学意义。

2 结果

2.1 一般资料

所有研究对象的基本信息见表1。在307例疑似HIT

表 1 HIT患者和非HIT患者临床资料和检验结果

Table 1 Clinical data and test results of HIT patients and non-HIT patients

Characteristic	Total	Non-HIT group	HIT group	*P*
Case (%)	307 (100)	269 (87.62)	38 (12.38)	
Sex (male/female)/case	215/92	191/78	24/14	0.323
Age/yr., median (P_{25}-P_{75})	62 (52-69)	61 (53-69)	64 (42-68)	0.890
HIT-Ab/(U/mL), $\bar{x} \pm s$	1.00 ± 3.50	0.24 ± 0.38	6.33 ± 8.20	< 0.001
New thrombosis/case (%)	117 (38.11)	93 (34.57)	24 (63.16)	< 0.001
Death/case (%)	23 (7.49)	20 (7.43)	3 (7.89)	0.920
Alternative anticoagulation/case (%)	61 (19.87)	30 (11.15)	31 (81.58)	< 0.001
4T's scores				
4T's scores (median [P_{25}-P_{75}])	4 (3-5)	4 (3-5)	6 (5-6)	< 0.001
Positive 4T's scores/case (%)	226 (73.62)	189 (70.26)	37 (97.37)	< 0.001
PLTmax/(× 10^9 L^{-1}), $\bar{x} \pm s$	203.50 ± 80.76	198.81 ± 80.51	230.78 ± 77.46	0.014
PLTmin/(× 10^9 L^{-1}), $\bar{x} \pm s$	45.46 ± 25.55	45.93 ± 25.38	42.16 ± 26.89	0.136
Timing of platelet count decrease/d, $\bar{x} \pm s$	6.60 ± 9.25	6.77 ± 9.27	5.45 ± 9.16	0.783
Lillo-Le Louet scores				
Lillo-Le Louet scores (median [P_{25}-P_{75}])	2 (1-3)	2 (1-3)	4 (3-4)	< 0.001
Positive Lillo-Le Louet scores/case (%)	189 (61.56)	151 (56.13)	38 (100)	< 0.001
Duration of CPB/min, median (P_{25}-P_{75})	180 (125-252)	170 (124-246)	238 (153-267)	0.046
Time from heparin exposure to HIT testing/d, median (P_{25}-P_{75})	4 (2-7)	4 (2-6)	7 (5-10)	< 0.001
Platelet kinetics/case (%)				
Pattern A	93 (30.29)	64 (23.79)	29 (76.32)	< 0.001
Pattern B	214 (69.71)	205 (76.21)	9 (23.68)	< 0.001
Type of cardiac surgery/case (%)				
Aortic surgery	50 (16.29)	41 (15.24)	9 (23.68)	0.187
Valve surgery	49 (15.96)	44 (16.36)	5 (13.16)	0.614
CABG	58 (18.89)	54 (20.07)	4 (10.53)	0.159
HT	33 (10.75)	28 (10.41)	5 (13.16)	0.609
Aortic surgery + CABG	31 (10.1)	27 (10.04)	4 (10.53)	0.925
Valve surgery + CABG	30 (9.77)	24 (8.92)	6 (15.79)	0.182
Valve surgery + Aortic surgery	16 (5.21)	16 (5.95)	0 (0)	0.123
Valve surgery + Aortic surgery + CABG	8 (2.61)	5 (1.86)	3 (7.89)	0.063
Other surgeries	32 (10.42)	30 (11.15)	2 (5.26)	0.266

Positive 4T's scores: 4T's scores ≥ 4; Positive Lillo-Le Louet scores: Lillo-Le Louet scores ≥ 2; Pattern A: the platelet count decreased rapidly after surgery, increased by 30% within 5 days, and then decreased again between days 5 and 10; Pattern B: the platelet count decreased rapidly after surgery and this trend persisted, with the condition worsening for more than 4 days; CABG: coronary artery surgery; HT: heart transplant surgery; PLT: platelet; Timing of platelet count decrease: the time from admission and exposure to heparin to the PLT count falling below the normal range.

患者中, HIT的确认率为12.38%(38/307)。相较于非HIT患者, HIT患者的新发血栓发生率增高(34.57% vs. 63.16%, $P<0.001$), 血小板减少模式A的患者比例也更高(23.79% vs. 76.32%, $P<0.001$)。卡方检验结果显示, 相较于模式B, 模式A与发生HIT间存在关联($P<0.001$)。比值比(odds ratio, OR)为10.32〔95%置信区间(confidence interval, CI): 4.64 ~ 22.95〕, 说明模式A是发生HIT的危险因素。HIT患者中, LLL评分均≥2分, 97.37%(37/38)患者的4T's评分≥4分。非HIT患者中, 56.13%(151/269)的患者LLL评分≥2分, 70.26%(189/269)的患者4T's评分≥4分(图2)。

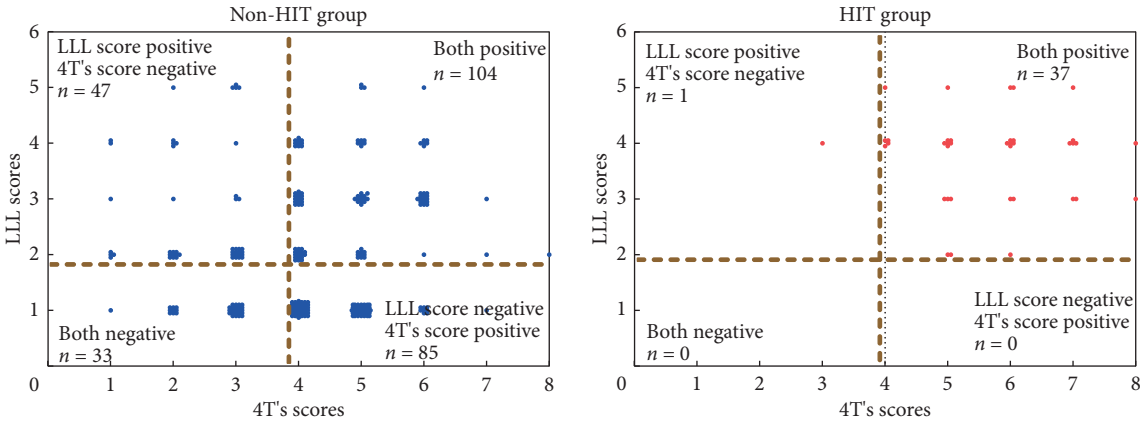

图 2　HIT组和非HIT组患者的HIT评分分布

Fig 2　The distribution of HIT scores among patients in the HIT group and the non-HIT group

LLL scores: Lillo-le louet scores; 4T's scores positive: 4T's scores ≥4; LLL scores positive: LLL scores ≥2.

2.2　不同HIT-Ab滴度组间患者的临床特征

不同HIT-Ab滴度组间新发血栓发生率、HIT确认率比较结果见表2、图3和图4。HIT-Ab阴性组、弱阳性组、中阳性组及强阳性组新发血栓发生率分别为32.4%、64.7%、54.6%和100%, 整体比较差异有统计学意义($P<0.001$), HIT确认率分别为0、64.71%、100%和100%。新发血栓发生率随HIT-Ab浓度的升高而增加, 当浓度达到7.0 IU/mL后维持在100%; HIT确认率一开始随HIT-Ab浓度的升高而增加, 然后小幅度波动, 当浓度3.0 IU/mL后维持在100%。此外, 心脏外科术后疑似HIT患者新发血栓类型以静脉血栓为主(77, 25.08%, 表3)。

2.3　HIT-Ab、4T's和LLL评分系统对HIT诊断效能

HIT-Ab浓度、4T's评分和LLL评分诊断HIT的ROC曲线下面积分别为0.996(95%CI: 0.991 ~ 1.000)、

表 2　不同HIT-Ab滴度组患者的临床特征

Table 2　Clinical characteristics of patients in different HIT-Ab titer groups

Characteristic	Negative group (< 1 U/mL, n = 257)	Weak positive group (1.0-4.9 U/mL, n = 34)	Moderate positive group (5.0-9.9 U/mL, n = 11)	Strong positive group (≥ 10 U/mL, n = 5)	P
Sex (male/female)/case	184/73	22/12	5/6	4/1	0.245
Age/yr., median (P_{25}-P_{75})	62.0 (52.8-69.0)	59.5 (45.5-66.0)	65.0 (53.0-72.0)	68.0 (66.0-71.0)	0.282
HIT-Ab/(U/mL), $\bar{x} \pm s$	0.2 ± 0.3	2.2 ± 1.0	6.1 ± 1.3	23.1 ± 13.5	< 0.001
HIT-positive/case (%)	0 (0)	22 (64.71)	11 (100)	5 (100)	< 0.001
New thrombosis/case (%)	84 (32.7)	22 (64.7)	6 (54.6)	5 (100)	< 0.001
Death/case (%)	16 (6.2)	5 (14.7)	1 (9.1)	1 (20)	0.229
4T's scores (median [P_{25}-P_{75}])	4 (3-5)	5 (5-6)	6 (5.5-6)	7 (7-8)	< 0.001
Moderate risk/case (%)	148 (57.6)	19 (55.9)	3 (27.3)	0 (0)	< 0.001
High risk/case (%)	30 (11.7)	13 (38.2)	8 (72.7)	5 (100)	< 0.001
LLL scores (median [P_{25}-P_{75}])	2 (1-3)	4 (3-4)	4 (3-4.5)	4 (3-4)	< 0.001
Low probability/case (%)	117 (45.53)	1 (2.94)	0 (0)	0 (0)	< 0.001
High probability/case (%)	140 (54.47)	33 (97.06)	11 (100)	5 (100)	< 0.001

Moderate risk of the 4T's scores: patients with a 4T's score of 4 to 5; high risk of the 4T's scores: patients with a 4T's score ≥ 6; low probability of LLL scores: patients with LLL score < 2; high probability of LLL scores: patients with LLL score ≥ 2; the other abbreviations are explained in the note to Table 1.

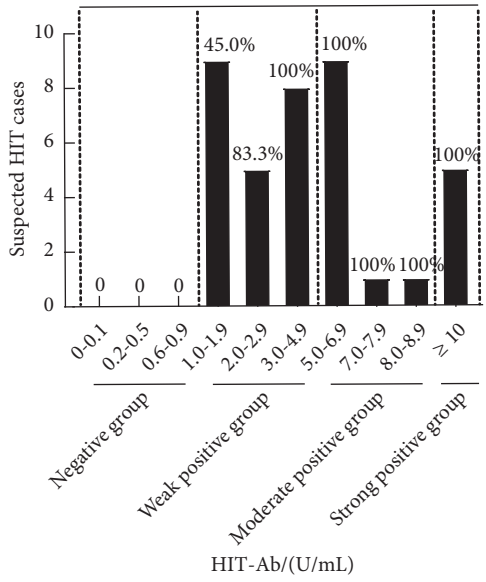

图 3 不同HIT-Ab浓度区间的HIT确认率

Fig 3 Confirmation rates of HIT across different HIT-Ab concentration intervals

Negative group: HIT-Ab < 1 U/mL; weak positive group: HIT-Ab at 1.0-4.9 U/mL; moderate positive group: HIT-Ab at 5.0-9.9 U/mL; strong positive group: HIT-Ab ⩾ 10 U/mL.

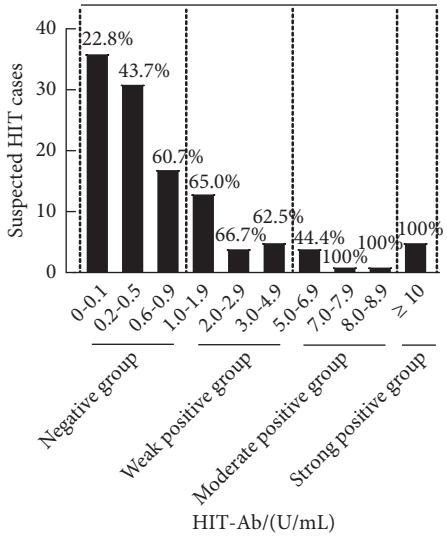

图 4 不同HIT-Ab浓度区间的新发血栓概率

Fig 4 Probability of new thrombosis by different HIT-Ab concentration ranges

All abbreviations are explained in the footnotes to Fig 3.

0.799(95%CI: 0.727 ~ 0.870)和0.860(95%CI: 0.811 ~ 0.908)。当HIT-Ab浓度为1 U/mL时, 其诊断敏感度为100%, 阴性预测值(negative predictive value, NPV)为100%。与传统的HIT高危人群的诊断标准(4T's评分截断值为4分, LLL评分截断值为2分)相比, 以最大约登指数选定的4T's评分最佳截断值为5分, LLL评分最佳截断值为3分。HIT-Ab浓度诊断HIT的最佳截断值为1 U/mL, 详见表4、图5。

表 3 新发血栓类型

Table 3 Types of new-onset thrombosis

Group	New thrombosis/case (%)				Total/case (%)
	Venous thrombosis	Arterial thrombosis	Arterial and venous thrombosis	Microvascular thrombosis	
Negative group (n = 257)	60 (23.35)	8 (3.11)	8 (3.11)	8 (3.11)	84 (32.68)
Weak positive group (n = 34)	15 (44.12)	3 (8.82)	3 (8.82)	1 (2.94)	22 (64.71)
Moderate positive group (n = 11)	2 (18.18)	3 (27.27)	1 (9.09)	0 (0)	6 (54.55)
Strong positive group (n = 5)	0 (0)	0 (0)	4 (80)	1 (20)	5 (100)
Total (n = 307)	77 (25.08)	14 (4.56)	16 (5.21)	10 (3.26)	117 (38.11)
P	0.03	0.001	< 0.001	0.183	< 0.001

表 4 ROC曲线评估HIT-Ab对HIT的诊断效能

Table 4 ROC curve evaluation of the diagnostic efficacy of HIT-Ab for HIT

Indicators	AUC (95% CI)	Cut off point	Specificity/%	Sensitivity/%	PPV/%	NPV/%
4T's scores	0.799 (0.727-0.870)	4 points	29.7	97.4	16.4	98.8
		5 points[a]	59.9	84.2	22.9	96.4
LLL scores	0.860 (0.811-0.908)	2 points	43.9	100	20.1	100
		3 points[a]	66.2	92.1	27.8	98.3
HIT-Ab	0.996 (0.991-1.000)	1 U/mL[a]	95.5	100	76	100

NPV: negative-predictive value; PPV: positive-predictive value. ROC: receiver operating characteristic; AUC: area under the curve. [a] Optimal diagnostic threshold (maximum Youden's index).

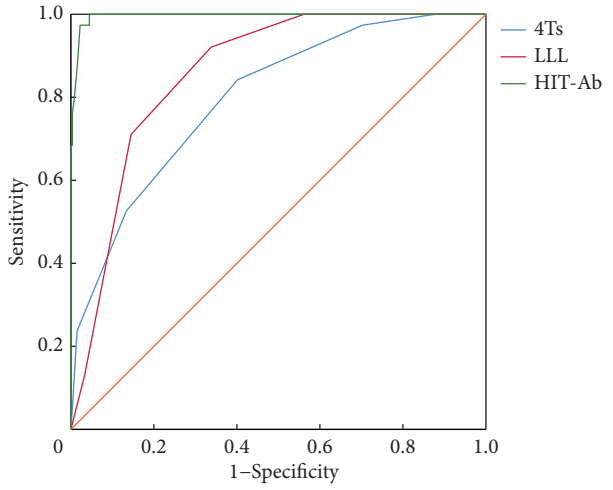

图 5 HIT-Ab、4T's评分和LLL评分诊断HIT的ROC曲线

Fig 5 Receiver operating characteristic curves for HIT-Ab, 4T's score, and LLL score in diagnosing HIT

3 讨论

心脏外科手术因CPB中需一次性接受高剂量的普通肝素治疗，叠加围术期多环节肝素暴露，形成持续抗原刺激环境[4-5, 17]。这种持续、多环节的肝素暴露构成多重风险因素协同作用下HIT的发生。本研究中心脏外科术后HIT的发生率达12.38%(38/307)，显著高于国内外报道的3% ~ 9.1%[8, 18-19]。深入分析发现两大关键因素：其一，本中心复杂手术占比89.6%(包括主动脉夹层、瓣膜置换等)，相较一般心脏手术体外循环时间延长[20]；其二，术后每日血小板动态监测实现100%覆盖，显著提升早期识别敏感度。值得注意的是，尽管本研究中HIT患者血栓的发生率为63.16%(24/38)与国际报道的38% ~ 81%相符[21]，但死亡率为7.89%(3/38)，明显低于文献报道的21.8%[22]。这一积极转归归功于本中心的三级防控体系：首先，基于血小板动态监测实现早期预警；其次，确诊后24 h内规范启用阿加曲班(96.7%患者)替代抗凝治疗；最后，对人工瓣膜及接受维生素K拮抗剂(如华法林)治疗的患者采用阿加曲班群或比伐卢定桥接治疗，避免华法林相关肢体坏疽风险[12, 23]。

本研究通过分析心脏外科术后HIT患者血小板计数的变化规律，揭示了其独特的演变模式。76.32%的HIT患者呈现双相下降模式(模式A)，即术后初期短暂恢复后出现二次下降，这与手术创伤相关的生理性血小板减少形成时间差，可作为HIT高风险提示[22, 24-25]。而23.68%的患者表现为快速单相下降(模式B)，可能与术前肝素暴露产生的HIT-Ab相关，提示对术前肝素使用史的追溯至关重要[25-26]。此外，分析显示，模式A的患者发生HIT的风险显著高于模式B患者(OR= 10.32, 95%CI: 4.64 ~ 22.95, P< 0.001)。上述发现强调，在心脏外科术后患者中，血小板计数的动态演变轨迹(而非单一时间点的绝对值)是鉴别HIT的关键依据。

在临床评分方面，本研究发现相较于4T's评分，LLL评分对HIT的风险评估更有诊断价值，评分阴性可排除HIT(NPV 100%)。另外，本研究通过ROC曲线优化评分截断值显著提升了诊断效能：将4T's评分截断值从4分提高到5分，将LLL评分截断值从2分提高到3分，均可优化其诊断效能。值得注意的是，LLL评分的诊断效能显著优于4T's评分(AUC: 0.860 vs. 0.799, P< 0.001)，可能归因其纳入体外循环时间(HIT组238.5 min vs. 非HIT组170 min)及血小板动态变化模式等心脏外科手术相关指标，提示临床应增加对LLL评分的关注。

本研究证实，1 U/mL的HIT-Ab作为诊断截断值具有卓越效能(AUC= 0.996)，其100%的敏感度与100%的阴性预测值(NPV)使其成为排除诊断的“金标准”。此外，弱阳性组(1.0 ~ 4.9 U/mL)64.71%的HIT确诊率和64.7%的血栓发生率，打破“低滴度无意义”的认知局限，这提示免疫比浊法检测的敏感性可有效识别免疫应答。另外，新发血栓从阴性组的32.4%阶梯式上升至强阳性组的100% (P< 0.001)，且强阳性组80%的患者为动-静脉混合血栓；而HIT确诊率从阴性组的0升至弱阳性组的64.71%，中/强阳性组(≥5.0 U/mL)确诊率达100%，应立即停用所有肝素制剂并启动非肝素抗凝治疗[13, 27]。但仍需警惕PPV为76%的阳性预测值：在此队列中，约24%(12/50)的抗体阳性患者经确诊为非HIT，可能源于自身免疫交叉反应或肝素导管冲洗等短暂性抗体升高[24]，需结合临床症状灵活抗凝。

本研究仍存在局限性。首先，本研究成果是基于单中心实验数据建立的，尚须多中心大样本验证。其次，作为回顾性队列研究，强阳性组样本量较小(n= 5)，可能影响统计效能。再次，本研究中HIT的临床诊断缺乏SRA(金标准)功能学验证，可能影响诊断的准确性。除此之外，本文涉及有序分类变量的分析主要采用普通卡方检验，未对变量等级与结局之间的线性趋势进行检验。因此，文中关于“趋势”的描述仅为基于数据分布的趋势性观察。最后，本研究中涉及多个指标的比较分析，多重比较可能增加假阳性结果的概率。综上所述，本文中观察到的关联为探索性发现，后续有待基于更大规模的前瞻性队列研究进一步验证。

本研究系统阐释了心脏外科术后HIT患者的“抗体浓度-血栓风险”梯度关系，确立HIT-Ab< 1.0 U/mL的核

心排除价值,创新性优化4T's和LLL评分截断值,并揭示血小板双相下降模式的预警意义。未来将着力于三方面的深化研究:建立整合4T's、LLL评分与血小板动态模式的预警模型;开展多中心前瞻性研究验证阶梯路径(尤其关注抗体1.0 ~ 4.9 U/mL群体的干预阈值);探索新型抗凝药在心脏外科术后HIT患者中的安全性及适用条件。通过深化抗体功能学分型(IgG)与血栓机制研究,进一步完善HIT精准诊疗体系。

* * *

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