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戴亚男, 刘媛, 许宇辰, 蔡青青, 王妍, 周宇红, 程蕾蕾, 葛均波

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· 论 著 ·

多学科参与的 ICI 相关心肌炎风险评估量表的建立及验证

戴亚男^{1,2}, 刘媛^{2*}, 许宇辰², 蔡青青³, 王妍⁴, 周宇红⁴, 程蕾蕾^{1,2}, 葛均波²

1. 复旦大学附属中山医院心脏超声诊断科, 上海市心血管病研究所, 上海市影像医学研究所, 上海 200032
2. 复旦大学附属中山医院心内科, 上海市心血管病研究所, 心脏病全国重点实验室, 国家卫生健康委缺血性心脏病重点实验室, 中国医学科学院病毒性心脏病重点实验室, 国家放射与治疗临床医学研究中心, 上海 200032
3. 复旦大学附属中山医院药剂科, 上海 200032
4. 复旦大学附属中山医院肿瘤内科, 上海 200032

[摘要] 目的 在多学科合作基础上, 建立免疫检查点抑制剂 (immune checkpoint inhibitor, ICI) 相关心肌炎风险评估量表, 并验证其诊断效能。方法 通过多学科合作, 结合肿瘤科和心内科临床经验、文献数据以及患者实际情况, 开发 ICI 相关心肌炎风险评估量表。纳入 2020 年 10 月至 2024 年 10 月在复旦大学附属中山医院进行免疫治疗的 101 例恶性肿瘤患者作为验证队列, 根据量表评分将其分为低风险组 (0~1 分)、中风险组 (2~4 分)、高风险组 (≥ 5 分)。采用 Cox 比例风险模型评估量表预测风险分层与实际评估结果的相关性。通过 ROC 曲线评估该量表预测 ICI 相关心肌炎的价值。通过 Cohen's Kappa 系数评估量表评分与实际结果之间的一致性。结果 根据量表评分预测为 ICI 相关心肌炎低风险 28 例 (27.7%)、中风险 8 例 (7.9%)、高风险 65 例 (64.4%); 实际评估为 ICI 相关心肌炎低危 46 例 (45.5%)、中危 8 例 (7.9%)、高危 47 例 (46.5%)。Kaplan-Meier 生存曲线显示高风险组累积 ICI 相关心肌炎发生率高于中低风险组 ($P < 0.05$)。多变量调整后 Cox 比例风险模型显示, 高风险组 ICI 相关心肌炎风险约为低风险组的 4 倍。ROC 曲线分析显示, 该量表预测 ICI 相关心肌炎的 AUC 平均达 0.81, 准确度 0.74, Cohen's Kappa 系数为 0.55。实际高危组中无患者预测为低风险; 实际低危组 16 例患者预测为高风险。结论 该 ICI 相关心肌炎风险评估量表预测效能较高, 为肿瘤科医生提供了一个简单且较有效的多学科诊疗参考工具, 有助于提高其对 ICI 相关心肌炎的早期识别能力。

[关键词] 免疫检查点抑制剂; 心肌炎; 风险评估量表; 多学科诊断**[中图分类号]** R 730.51; R 542.2⁺1 **[文献标志码]** A

Development and validation of a multidisciplinary risk assessment scale for immune checkpoint inhibitor-associated myocarditis

DAI Yanan^{1,2}, LIU Yuan^{2*}, XU Yuchen², CAI Qingqing³, WANG Yan⁴, ZHOU Yuhong⁴, CHENG Leilei^{1,2}, GE Junbo²

1. Department of Echocardiography, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai Institute of Medical Imaging, Shanghai 200032, China
2. Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, NHC Key Laboratory of Ischemic Heart Diseases, Key Laboratory of Viral Heart Diseases, Chinese Academy of Medical Sciences, National Clinical Research Center for Interventional Medicine, Shanghai 200032, China
3. Department of Pharmacy, Zhongshan Hospital, Fudan University, Shanghai 200032, China
4. Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

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[作者简介] 戴亚男, 博士, 博士后. E-mail: neverbeangrydana@163.com

*通信作者 (Corresponding author). Tel: 021-64041990, E-mail: liu.yuan@zs-hospital.sh.cn

[Abstract] **Objective** To develop a risk assessment scale for immune checkpoint inhibitor (ICI)-associated myocarditis based on multidisciplinary collaboration, and to evaluate its diagnostic performance. **Methods** Based on multidisciplinary cooperation, integrating clinical experience from oncology and cardiology, literature data, and patient conditions, a risk assessment scale for ICI-associated myocarditis was developed. A total of 101 patients with malignancies who received immunotherapy at Zhongshan Hospital, Fudan University, from October 2020 to October 2024 were included as the validation cohort. Patients were stratified into low-risk (0-1 point), medium-risk (2-4 points), and high-risk (≥ 5 points) groups based on their scale scores. The association between predictive risk stratifications and actual assessment results was assessed using the Cox proportional hazards regression model. The predictive value of the scale for ICI-associated myocarditis was evaluated using receiver operating characteristic (ROC) curve. Agreement between the scale scores and actual assessment results was assessed using Cohen's Kappa coefficient. **Results** Based on the scale predictive results, 28(27.7%), 8(7.9%), 65(64.4%) patients were at low risk, medium risk, and high risk for ICI-related myocarditis, respectively; however, 46(45.5%), 8(7.9%), 47(46.5%) were at low risk, medium risk, and high risk actually. Kaplan-Meier survival analysis showed that the cumulative incidence of ICI-related myocarditis in the high-risk group was significantly higher than that in the medium- and low-risk groups ($P < 0.05$). In the multivariable-adjusted Cox proportional hazards model, the ICI-related myocarditis risk in high-risk group was about 4 times that in the low-risk group. ROC curve analysis demonstrated that the average area under the curve (AUC) for predicting ICI-related myocarditis was 0.81, with an accuracy of 0.74. The Cohen's Kappa coefficient was 0.55, indicating moderate agreement. In the actual high-risk group, no patient was predicted to be at low risk; in the actual low-risk group, 16 patients were predicted to be at high risk. **Conclusions** This risk assessment scale for ICI-associated myocarditis shows high predictive performance. It provides oncologists with a simple yet effective multidisciplinary diagnostic reference tool, potentially enhancing early identification of ICI-associated myocarditis.

[Key Words] immune checkpoint inhibitor; myocarditis; risk assessment scale; multidisciplinary diagnosis

免疫检查点抑制剂 (immune checkpoint inhibitor, ICI) 作为肿瘤治疗领域的革命性突破, 通过解除 T 细胞免疫抑制显著改善了多种晚期恶性肿瘤患者的临床预后。然而, 免疫相关不良事件 (immune-related adverse events, irAEs) 已成为制约 ICI 应用的瓶颈。其中, ICI 相关心肌炎因病理进程隐匿及高致死率备受关注。ICI 相关心肌炎发病率为 0.1%~1%, 但进展为重症后的病死率可超过 50%^[1-2], 且约 60% 的死亡发生在确诊后 30 d 内。因此, 随着 ICI 应用的扩展, 亟需早期识别高危人群的方法和工具优化诊断策略, 而多学科合作模式在 ICI 相关心脏毒性管理中尤为重要^[3]。

目前, ICI 相关心肌炎多学科管理面临两大挑战。(1) 跨学科诊疗: ICI 相关心肌炎的早期识别需要突破传统单学科诊疗模式的局限。既往由肿瘤科与心内科在疾病管理中承担核心职能, 肿瘤科负责免疫治疗的风险评估与暂停决策, 心内科主导心脏损伤标志物监测与评估。但是, 该疾病病理进程复杂, 诊断时需整合多维度信息, 如肿瘤科须把握 irAEs 时序特征, 心内科须动态监测心脏特异性生物标志物, 影像科须精准判读心

脏磁共振特征性表现, 检验科则须对心脏微环境进行评估。而多学科团队 (multidisciplinary team, MDT) 制度可使 ICI 相关心肌炎诊断准确率提高 37%^[4-6], 但学科间知识壁垒仍导致 23%~41% 的诊断延迟^[7]。(2) 早期识别: 疾病进展的不可逆性要求突破传统诊断标准的时效性局限。因此, 亟需构建整合多学科数据的早期预警模型, 如肿瘤治疗周期中的动态风险分层、亚临床期生物标志物组合^[3]。本研究拟建立一个高效融合多学科数据的早期评估体系, 并加以验证。

1 资料与方法

1.1 ICI 相关心肌炎风险评估量表的建立 量表所有条目的选择和赋值基于相关文献, 以及心血管病学、肿瘤学、放射学、药剂学和数据科学等多学科领域专家的充分讨论与评估。专家团队共 10 名成员, 包括 3 名心血管病学专家、2 名肿瘤学专家、2 名放射学专家、2 名药剂学专家和 1 名数据科学专家。职称构成: 高级 3 名, 副高级 3 名, 中级 3 名, 博士后 1 名。评分条目包括患者的基本信息 (如年龄和体能评分), 既往病史

（如冠心病、瓣膜病变、风湿结缔组织疾病），典型临床表现（如胸闷、呼吸困难、肌肉酸痛、眼睑下垂），实验室指标（如C反应蛋白、N末端脑钠肽前体、D-二聚体、肌钙蛋白），以及影像学（如心脏超声、心脏磁共振成像）和心电图等检查结果^[8-16]。结合ICI治疗后心肌损伤表现，初步形成ICI相关心肌炎风险评估量表。

通过权重分配对量表中各指标进行量化。初步分配基于高质量文献^[8-21]和本团队临床经验，如参考相关文献^[17-18]及临床经验，将存在肌肉酸痛、眼睑下垂赋值为5分；初步赋值完成后，团队开展内部审查会议，由上述各专家分别对相应领域条目逐一进行讨论。根据讨论结果，对部分条目进行调整，形成ICI相关心肌炎风险评估量表（表1）。

表1 ICI相关心肌炎风险评估量表
Table 1 Risk assessment scale for ICI-associated myocarditis

Item	Notes	Score
Age	≥75 years	1
ECOG PS	≥2 points	1
Coronary artery disease		1
Valvular disease		1
History of rheumatic connective tissue disease		1
Chest tightness and dyspnea		1
Muscle soreness and ptosis		5
C-reactive protein	Elevated	1
BNP/NT-proBNP	Elevated	1
D-dimer	Elevated	1
Elevated troponin	Not exceeding three times the ULN	2
	Elevated more than three times the ULN	5
Electrocardiogram abnormality	New-onset conduction block or premature beats	2
Echocardiographic abnormality	LVEF≥50%	1
	LVEF<50%	5
Optional	Cardiac MRI indicating cardiac dysfunction	5
Total score	Sum of all the above scoring items	
0-1	Low risk: treatment can be continued	
2-4	Medium risk: cardiology consultation recommended	
≥5	High risk: suspend ICI treatment	

ICI: immune checkpoint inhibitor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BNP: brain natriuretic peptide; ULN: upper limit of normal; LVEF: left ventricular ejection fraction.

1.2 ICI相关心肌炎验证队列及风险预测 纳入2020年10月至2024年10月在复旦大学附属中山医院进行ICI治疗的恶性肿瘤患者101例。排除标准：（1）年龄≤18岁；（2）有心力衰竭、心肌炎、严重心脏瓣膜病、心肌梗死、房颤、恶性心律失常及脑梗死病史；（3）接受蒽环类药物抗肿瘤治疗；（4）在免疫治疗前通过冠状动脉造影诊断为严重冠状动脉疾病，并接受经皮冠状动脉介入治疗；（5）病历资料不完整或必要信息缺失；（6）接受ICI治疗期间，参与其他临床队列

研究；（7）患有血液系统恶性肿瘤。终点事件为诊断为ICI相关心肌炎^[22-23]。采用患者免疫治疗开始时的基线指标水平，通过上述风险评估量表预测患者发生ICI相关心肌炎的风险。根据预测结果将患者分为低风险组（0~1分）、中风险组（2~4分）、高风险组（≥5分）。随访时间为从免疫治疗开始当天至发生终点事件或最后随访日期。

1.3 ICI相关心肌炎实际风险评估 ICI相关心肌炎临床实际风险由多学科专家团队根据指南^[10]和

临床实践评估,按照病情严重程度及临床干预措施,将患者评估为高危、中危、低危。(1)高危:确诊为ICI相关心肌炎,死亡风险或不良心血管事件发生风险较高,需立即停止免疫治疗,采取针对性治疗,并密切监测。(2)中危:患者可继续行免疫治疗,但需密切随访,监测心肌标志物和心电图,并在必要时完善心脏磁共振检查,以明确是否存在ICI相关心肌炎;患者可接受心肌保护和营养支持治疗,以降低进展为高危状态的风险。(3)低危:患者能够接受现有免疫治疗方案,无须调整,且无明显心脏毒性相关临床表现或实验室指标异常,定期随访和心脏监测即可满足临床管理需求。

1.4 统计学处理 采用R 4.4.1和Python 3.10软件进行数据处理。构建多因素Cox比例风险模型,评估量表评分与终点事件之间的相关性。模型1调整年龄、性别、高血压、糖尿病;模型2在模型1的基础上调整使用他汀类药物和使用抗高血压药物。采用ROC曲线评估量表预测ICI相关心肌炎的价值;通过Cohen's kappa系数评估量表预测结果和实际评估结果的一致性。检验水准(α)为0.05。

2 结果

2.1 验证队列基线资料 101例患者中,男性67例(66.3%),平均(64.72±10.02)岁,平均随访91(46,288)d,47例(46.5%)发生ICI相关心肌炎。患者其他基线资料见表2。

2.2 验证队列ICI相关心肌炎风险分层 ICI相关心肌炎风险评估量表预测结果显示,免疫治疗开始时,28例(27.7%)患者为低风险,8例(7.9%)患者为中风险,65例(64.4%)患者为高风险。实际评估结果显示,ICI相关心肌炎低危、中危、高危患者分别有46例(45.5%)、8例(7.9%)、47例(46.5%)。

2.3 生存曲线及Cox分析 Kaplan-Meier生存曲线(图1)显示:随访期间,高风险组患者ICI相关心肌炎累积发生率(90.9%)明显大于低风险组(0)、中风险组(27.1%)。Cox分析(表3)显示:以低风险组为参考,模型1中,中风险

组、高风险组发生ICI相关心肌炎的风险分别升高3%、3.65倍;模型2中,中风险组、高风险组发生ICI相关心肌炎的风险分别升高2%、3.33倍。

表2 验证队列基线资料

Table 2 Baseline characteristics of the validation cohort

n=101	
Index	n(%)
Male	67(66.3)
Smoke	2(2.0)
Alcohol consumption	1(1.0)
Total cholesterol abnormality	1(1.0)
Hypertension	16(15.8)
Diabetes	5(5.0)
Age≥75 years	12(11.9)
ECOG PS≥2 points	7(6.9)
Coronary artery disease	9(8.9)
Valvular disease	7(6.9)
History of rheumatic connective tissue disease	0
Chest tightness and dyspnea	14(13.8)
Muscle soreness and ptosis	8(7.9)
Elevated C-reactive protein	14(13.9)
Elevated BNP/NT-proBNP	36(35.6)
Elevated D-dimer	14(13.9)
Elevated troponin	67(66.3)
Electrocardiogram abnormality	22(21.8)
Echocardiographic abnormality	44(43.6)
MRI abnormality	12(11.9)
Use of statin	7(6.9)
Use of antihypertensive medication	15(14.9)
Endpoint event	47(46.5)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; BNP: brain natriuretic peptide.

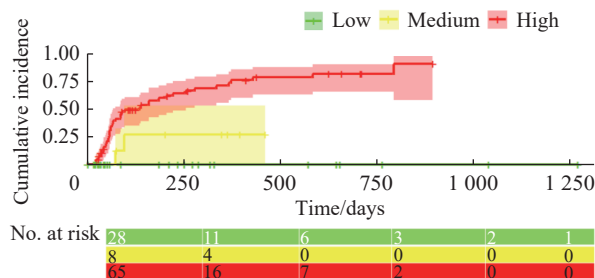


图1 各组患者发生ICI相关心肌炎的Kaplan-Meier生成曲线分析

Figure 1 Kaplan-Meier analysis for ICI-associated myocarditis in three groups of patients

ICI: immune checkpoint inhibitor.

表 3 风险评估量表预测 ICI 相关心肌炎风险的 Cox 分析

Table 3 Cox proportional hazards analysis of risk assessment scale predicting ICI-associated myocarditis				
Model	Prediction	HR	95%CI	P
Model 1	Low		Ref	
	Medium	1.03	1.00-1.53	0.03
	High	4.65	2.48-8.60	0.01
Model 2	Low		Ref	
	Medium	1.02	1.00-1.25	0.02
	High	4.33	2.35-7.81	0.01

ICI: immune checkpoint inhibitor. Model 1: adjusted for age, sex, hypertension, and diabetes; Model 2: adjusted for statin use and antihypertensive medication use based on Model 1.

2.4 风险评估量表预测效能分析 ROC 分析结果 (图 2) 显示: 风险评估量表预测 ICI 相关心肌炎的平均 AUC 为 0.81, 准确度 0.74、灵敏度 0.90、特异度 0.60, 截断值为 6 分。Cohen's Kappa 系数为 0.55。混淆矩阵 (表 4) 显示: 实际为高危, 预测为高风险 45 例 (44.6%); 实际为低危, 预测为低风险 27 例 (26.7%); 无实际为高危的患者被预测为低风险; 实际为低危, 预测为高风险 16 例 (15.8%)。

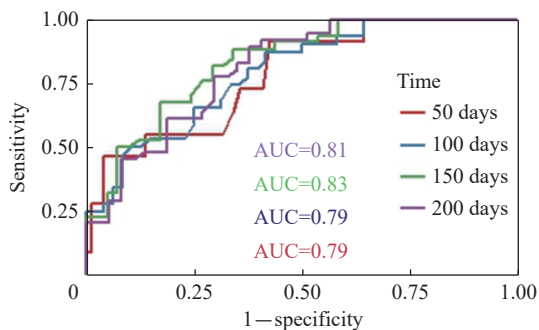


图 2 风险评估量表预测 ICI 相关心肌炎发生风险的时间依赖性 ROC 曲线分析

Figure 2 Time-dependent ROC curves analysis of risk-assessment scale predicting ICI-associated myocarditis

ICI: immune checkpoint inhibitor.

表 4 3×3 混淆矩阵

Actually	Prediction		
	Low	Medium	High
Low	27	3	16
Medium	1	3	4
High	0	2	45

3 讨论

心脏疾病的诊断过程, 如详细的病史采集、体格检查、影像学检查、心电图和生物标志物分析等常超出非心脏科医生的专业范围^[24]。ICI 相关心肌炎是一种由自身免疫反应介导的心肌炎症性疾病。由于 ICI 相关心肌炎发病率不高, 同时缺乏特异性的生物标志物和临床表现, 诊断更困难。ICI 相关心肌炎易与肿瘤治疗相关不良反应混淆, 肿瘤科医师较难单独诊断该疾病^[25]。因此, 建立 MDT 十分必要。多学科合作能有效提高 ICI 相关心肌炎的诊断效率和治疗效果, 尤其在早期发现和及时干预方面具有显著优势^[26]。

然而, 多学科合作也面临诸多难点: (1) 团队构建需要协调不同专业领域的医生, 可能受到各人员工作时间和资源分配的限制, 管理难度较大^[27]; (2) 肿瘤科医生与心脏科医生的专业背景差异使其疾病诊疗思维方式和处理方法不同, 导致一定的沟通障碍, 进而影响临床决策效率和质量^[28]; (3) 由于患者常需要频繁的多学科会诊和检查, 可能导致治疗周期延长、治疗费用增加^[29]。

本研究制定的风险评估量表预测 ICI 相关心肌炎的准确度达 0.74。多变量调整后, Cox 比例风险模型显示, 该量表预测为高风险患者的 ICI 相关心肌炎风险增加。Kaplan-Meier 生存曲线分析进一步验证了这一结果, 显示预测为高风险患者的累积事件发生率高于中、低风险组。ROC 曲线分析结果显示, 该量表预测 ICI 相关心肌炎高风险的价值较高。因此, 该基于多学科合

作的量表有助于打破学科壁垒,辅助肿瘤科医生预测 ICI 相关心肌炎风险。

此外,本研究中无实际高危患者预测为低风险,表明该量表未出现低估风险的误判情况;实际低危患者中,16 例(15.8%)预测为高风险,表明该量表存在过度警告情况,但该过度警告率可接受。该量表已转化为微信小程序(肿心评估),并完成计算机软件著作权登记(登记号:2022SR0245216)。

由于样本来源单一,在量表开发过程中可能存在数据偏倚;量表的临床验证也基于特定医院和地区的患者数据。因此,量表在不同人群中的适用性和普及性有待多中心研究验证。

综上所述,本研究在多学科合作基础上,通过权重建模,纳入心肌酶谱、炎症标志物、异常心电图表现及影像学特征等关键指标,构建了一个科学、可操作性强的 ICI 相关心肌炎风险评估量表。结果表明该量表能有效识别高危患者。本研究填补了国内 ICI 相关心肌炎风险评估量表的空白,使肿瘤科医师无须依赖多学科会诊即可初步评估 ICI 相关心肌炎风险,促进该 irAE 的早期识别、诊断和干预,进而改善患者预后。

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作者贡献 戴亚男:收集文献,数据收集、分析,文章撰写;刘媛:文章撰写,论证论点;许宇辰、蔡青青、周宇红:数据收集、整理;王妍:论证论点;程蕾蕾、葛均波:确定论点,研究指导,项目管理。

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