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·论　著·

急性心肌梗死患者介入治疗后血小板高反应性临床危险因素评分构建

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[摘要] **目的**　建立预测急性心肌梗死患者介入治疗后血小板高反应性的临床危险因素评分,指导临床个体化抗血小板治疗。**方法**　纳入2013年1月至12月于北京协和医学院阜外医院行冠脉介入术治疗的547例急性心肌梗死患者,收集患者的一般临床资料及术后血栓弹力图。将血栓弹力图最大凝块强度(TEG-MA_{ADP})>47 mm定义为存在血小板高反应性。利用患者临床常用指标筛选与血小板高反应性相关的危险因素,将多因素logistic回归分析中$P<0.05$的临床指标纳入血小板高反应性危险评分模型,依据比值比(*OR*)赋予相应分值。**结果**　547例患者中230例(42.05%)存在血小板高反应性,TEG-MA_{ADP}值高于非血小板高反应性患者[(56.16±6.57) mm vs (26.43±13.88) mm, $P<0.001$]。单因素和多因素logistic回归分析发现,高龄(>75岁)、女性、合并糖尿病是血小板高反应性的独立危险因素。依据*OR*值权重赋予高龄(>75岁)3分,女性和合并糖尿病各赋2分,分值范围0~7分。依据得分将患者分为3组:0~2分组、3~5分组和6~7分组,结果显示3组间血小板反应性差异有统计学意义,0~2分组患者的血小板反应性低于3~5分和6~7分组[(37.79±18.45) mm vs (50.04±15.91) mm vs (56.50±15.78) mm; $P<0.001$]。受试者工作特征曲线分析显示得分>2分能有效预测是否存在血小板高反应性(曲线下面积为0.627,95%*CI* 0.579~0.675, $P<0.001$)。**结论**　临床风险评分能帮助快速识别可能存在血小板高反应性的患者,从而指导抗血小板个体化治疗。

[关键词] 血小板反应性;危险因素;危险评分;心肌梗死;经皮冠状动脉介入
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Establishment of a clinical risk score for predicting high on-treatment platelet reactivity in patients with acute myocardial infarction after percutaneous coronary intervention

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[**Abstract**] **Objective**　To construct a risk score for predicting high on-treatment platelet reactivity (HTPR) in patients with acute myocardial infarction after percutaneous coronary intervention, so as to guide individualized antiplatelet therapy. **Methods**　A total of 547 patients with acute myocardial infarction undergoing percutaneous coronary intervention in Fuwai Hospital from Jan. 2013 to Dec. 2013 were enrolled in this study, and their general clinical data and post-operative thrombelastograms (TEG) were collected. The HTPR was defined as ADP-induced platelet-fibrin clot strength (MA_{ADP}) by TEG (TEG-MA_{ADP})>47 mm. Clinical factors available in daily routine were analyzed to screen the related risk factors of HTPR. Clinical factors with a significance level of $P<0.05$ related to HTPR by multivariate logistic analysis were included in risk score model. The scores of variables were determined based on the odds ratio (*OR*) values. **Results**　Among 547 patients, 230(42.05%) had HTPR, the TEG-MA_{ADP} was significantly higher than that of non-HTPR patients ([56.16±6.57] mm vs [26.43±13.88] mm, $P<0.001$). Univariate and multivariate logistic regression analysis showed that the three following factors were independent risk factors of HTPR: older age (>75 years) was weighted by score 3, female and diabetes mellitus both by score 2 according to *OR* values, thus a score ranging from 0 to 7 was developed to predict HTPR. The platelet reactivity (TEG-MA_{ADP}) was (37.79±18.45) mm, (50.04±15.91) mm and (56.50±15.78) mm for score 0-2, 3-5 and 6-7 patients, respectively, and it showed a significant

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difference among three score ranges ($P<0.001$). Receiver operating characteristic curve analysis showed that the score>2 was the best cut-off value to predict HTPR (area under the curve was 0.627, 95% CI 0.579-0.675, $P<0.001$). **Conclusion** Clinical risk score can help to identify patient with high risk of HTPR, so as to guide intensified antiplatelet therapy.

[**Key words**] platelet reactivity; risk factors; risk score; myocardial infarction; percutaneous coronary intervention

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临床实践发现部分患者对抗血小板药物存在抵抗性，导致抗血小板药物疗效不佳和易发生血小板高反应性（high on-treatment platelet reactivity，HTPR）[1]。本研究旨在利用临床基线和常规指标，筛选与 HTPR 相关的危险因素并构建危险因素评分，以帮助医师快速识别急性心肌梗死（acute myocardial infarction，AMI）经皮冠脉介入（percutaneous coronary intervention，PCI）治疗后可能发生血小板高反应性的患者。

1　资料和方法

1.1　*研究对象*　本研究为单中心观察性研究。纳入标准：(1)2013 年 1 月至 12 月于北京协和医学院阜外医院行 PCI 治疗的 AMI 患者；(2)患者术后服用阿司匹林 100 mg/d 加氯吡格雷 75 mg/d 双联抗血小板治疗；(3)有 PCI 治疗后血栓弹力图检测结果。排除标准：缺失血常规、心功能、肾功能等临床指标者。依据文献[2]报道，定义血栓弹力图最大凝块强度（TEG-MA_{ADP}）>47 mm 为存在 HTPR。将所有纳入患者中 TEG-MA_{ADP}>47 mm 的患者归为血小板高反应组（HTPR 组），TEG-MA_{ADP}≤47 mm 的患者归为非血小板高反应组（非 HTPR 组），采用病例对照研究模式进行临床因素-血小板功能关联分析，筛选出与 HTPR 发生相关的临床因素，构建危险因素评分。本研究经阜外医院伦理委员会审批通过，所有患者均已签署知情同意书。研究设计流程如图 1 所示。

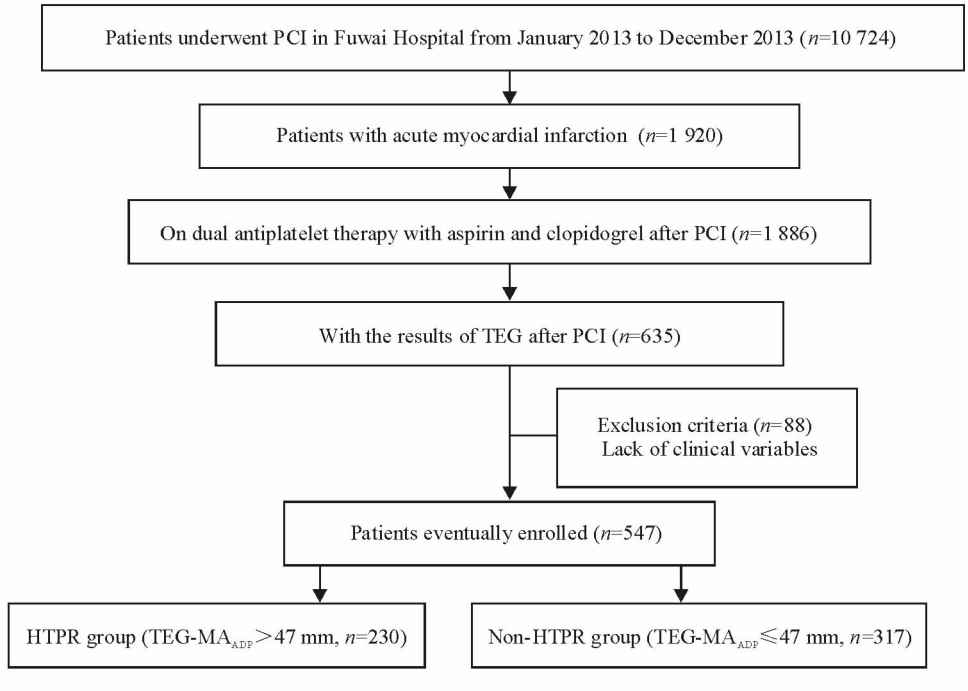

图 1　研究设计流程图

Fig 1　Flow diagram describing the study design

PCI: Percutaneous coronary intervention; HTPR: High on-treatment platelet reactivity; TEG: Thrombelastogram; MA_{ADP}: ADP-induced platelet-fibrin clot strength; ADP: Adenosine diphosphate

1.2　*评分构建*　纳入患者的年龄、性别、体质量指数（BMI）、高血压、高脂血症、糖尿病、吸烟、左室射

血分数(LVEF)、血肌酐(Scr)、血小板(PLT)计数和血红蛋白(Hb)等临床常用变量,用于筛选与HTPR独立相关的临床危险因素并构建评分。对于连续性变量,在分析前依据临床公认界值转换为二分类变量,具体如下:高龄(>75 岁)、肥胖(BMI>30 kg/m^2)、心脏功能减低(LVEF<50%)、肾功能减低(Scr>133 μmol/L)、血小板增多(PLT>300×10^9/L)以及高血红蛋白血症(Hb>160 g/L)。

1.3　统计学处理　采用 SPSS 20.0 软件进行数据处理与分析。计量资料以 $\bar{x}\pm s$ 表示,组间比较采用独立样本 t 检验;计数资料以率表示,组间比较采用 χ^2 检验。采用单因素 logistic 回归分析筛选出与HTPR相关的临床指标($P<0.05$),将这些指标放入多因素 logistic 回归模型中,经校正后进一步筛选出与 HTPR 独立相关的临床危险因素。多因素 logistic 回归模型中 $P<0.05$ 的临床变量被最终纳入评分模型,风险以比值比(odds ratio,OR)和 95% 可信区间(confidence interval,CI)表示,并依据 *OR* 值权重给予赋分,构建 HTPR 临床风险评分。采用受试者工作特征(receiver operating characteristic,ROC)曲线划定能最佳预测 HTPR 的评分界值。检验水准(α)为0.05。

2　结　果

2.1　患者的临床特征　2013 年 1 月至 12 月共 1 920例 AMI 患者在阜外医院行 PCI,其中 1 886 例患者术后服用阿司匹林加氯吡格雷双联抗血小板治疗。635 例患者有 PCI 治疗后 TEG-MA$_{ADP}$ 检测结果,排除 88 例存在临床缺失项的患者,最终 547 例患者纳入本研究。其中 230 例(42.05%)患者存在 HTPR,TEG-MA$_{ADP}$ 值高于非 HTPR 组患者[(56.16±6.57) mm vs (26.43±13.88) mm,$P<0.001$],两组患者的临床基线资料见表 1。

表 1　两组患者的临床特征

Tab 1　Clinical characteristics of patients in two groups

Variable	HTPR group N=230	Non-HTPR group N=317	P value
Age (year), $\bar{x}\pm s$	57.03±11.52	54.59±10.54	0.010
Male n(%)	182(79.13)	288(90.85)	<0.001
BMI (kg·m^{-2}), $\bar{x}\pm s$	25.96±3.27	25.79±3.15	0.550
Hypertension n(%)	139(60.43)	164(51.74)	0.043
Hyperlipemia n(%)	151(65.65)	185(58.36)	0.084
Diabetes mellitus n(%)	80(34.78)	62(19.56)	<0.001
Current smoking n(%)	138(60.00)	221(69.72)	0.018
TEG-MA$_{ADP}$(mm), $\bar{x}\pm s$	56.16±6.57	26.43±13.88	<0.001
Left ventricular ejection fractio n(%), $\bar{x}\pm s$	59.23±8.13	59.66±7.73	0.526
Serum creatinine c_B/(μmol·L^{-1}), $\bar{x}\pm s$	83.10±17.46	83.35±15.89	0.863
Platelet count (×10^9, L^{-1}), $\bar{x}\pm s$	224.93±64.02	213.79±56.68	0.032
Hemoglobin ρ_B/(g·L^{-1}), $\bar{x}\pm s$	131.85±13.85	138.97±12.97	<0.001

HTPR: High on-treatment platelet reactivity; BMI: Body mass index; TEG: Thrombelastogram; MA$_{ADP}$: ADP-induced platelet-fibrin clot strength; ADP: Adenosine diphosphate

2.2　危险评分构建　单因素 logistic 回归分析筛选发现,高龄(>75 岁)、女性、合并高血压、合并糖尿病和血小板增多(PLT>300×10^9/L) 5 个临床因素与 HTPR 的发生相关,详见表 2。进一步行多因素 logistic 回归分析显示,高龄(>75 岁)、女性、合并糖尿病是 HTPR 的独立危险因素。依据 *OR* 值权重赋予相应分值,具体如下:高龄(>75 岁)3 分(*OR*=2.87,95%*CI* 1.19～6.89),女性 2 分(*OR*=2.14,95%*CI* 1.27～3.60),合并糖尿病 2 分(*OR*=2.09,95%*CI* 1.40～3.12),分值范围 0～7 分。多因素 logistic 回归分析及 HTPR 评分构建见表 3。

表 2　临床因素对 HTPR 影响的单因素分析

Tab 2　Univariate analysis of clinical factors related to HTPR

n(%)

Clinical factor	HTPR group N=230	Non-HTPR group N=317	OR(95%CI)	P value
Older (>75 years)	20(8.70)	8(2.52)	3.68(1.59,8.51)	0.001
Female	48(20.87)	29(9.15)	2.62(1.59,4.30)	<0.001
Obesity (BMI>30 kg·m^{-2})	26(11.30)	28(8.83)	1.32(0.75,2.31)	0.339
Hypertension	139(60.43)	164(51.74)	1.43(1.01,2.01)	0.043
Hyperlipidemia	151(65.65)	185(58.36)	1.36(0.96,1.94)	0.084
Diabetes mellitus	80(34.78)	62(19.56)	2.19(1.49,3.23)	<0.001
Current smoking	138(60.00)	221(69.72)	0.65(0.46,0.93)	0.018
Reduced cardiac function (LVEF<50%)	23(10.00)	29(9.15)	1.10(0.62,1.96)	0.737
Reduced renal function (Scr>133 μmol·L^{-1})	6(2.61)	5(1.58)	1.67(0.50,5.54)	0.396
Elevated platelet count (>300×10^9·L^{-1})	30(13.04)	25(7.89)	1.75(1.00,3.56)	0.048
High hemoglobin (>160 g·L^{-1})	3(1.30)	12(3.79)	0.34(0.09,1.20)	0.137

HTPR: High on-treatment platelet reactivity; BMI: Body mass index; LVEF: Left ventricular ejection fraction; Scr: Serum creatinine; OR: Odds ratio; CI: Confidence interval

表 3　临床因素对 HTPR 影响的多因素回归分析及评分构建

Tab 3　Establishment of the risk score for predicting HTPR by multivariate analysis

Clinical factor	OR(95%CI)	P value	Score
Older (>75 years)	2.87(1.19,6.89)	0.018	3
Female	2.14(1.27,3.60)	0.004	2
Hypertension	1.19(0.83,1.71)	0.335	
Diabetes mellitus	2.09(1.40,3.12)	<0.001	2
Elevated platelet count (>300×10^9·L^{-1})	1.69(0.94,3.02)	0.079	

HTPR: High on-treatment platelet reactivity; OR: Odds ratio; CI: Confidence interval

2.3　血小板反应性比较　统计所有患者得分，依据总分将患者分为 3 组：0～2 分为低危组，3～5 分为中危组，6～7 分为高危组，结果显示 3 组间各血小板反应性指标比较差异均有统计学意义（P<0.001），即得分越高血小板反应性越高。各组人数、血小板反应性及 HTPR 比例见表 4。ROC 曲线分析显示得分>2 分能有效预测是否存在 HTPR[曲线下面积（AUC）=0.627，95%CI 0.579～0.675，P<0.001]，灵敏度为 50.9%，特异度为 72.6%。得分>2 分患者的血小板反应性和 HTPR 比例均高于≤2 分的患者（P<0.001）。

表 4　依据评分分组比较血小板反应性

Tab 4　Comparison of platelet reactivity among different score levels

Index	Score 0-2 N=498	Score 3-5 N=45	Score 6-7 N=4	P value
TEG-MA$_{ADP}$(mm), $\bar{x}\pm s$	37.79±18.45	50.04±15.91	56.50±15.78	<0.001
HTPR n(%)	195(39.16)	33(73.33)	2(50.00)	<0.001

HTPR: High on-treatment platelet reactivity; TEG: Thrombelastogram; MA$_{ADP}$: ADP-induced platelet-fibrin clot strength; ADP: Adenosine diphosphate

3　讨　论

诸多研究表明 HTPR 与心肌梗死、脑卒中、支架血栓等缺血性事件显著相关,血小板功能检测和基因检测已被推荐用于临床,旨在帮助识别可能存在 HTPR 的患者[1,3],从而指导个体化治疗,如加大药物剂量、更换药效更强的新型抗血小板药物等[4-5],然而无论是血小板功能检测还是基因检测都存在一定的局限性:(1)都要抽取患者血液,增加了患者和医护人员的负担;(2)普及度均欠缺,部分医院并不具备相关检测设备;(3)都需要耗费一定时间,不利于医师即时优化治疗策略;(4)都增加了患者的医疗费用。因此,本研究提出是否可以利用临床基线和常规指标筛选出与 HTPR 发生相关的临床危险因素,并构建危险评分,旨在通过该评分系统帮助临床医师对患者血小板反应性做出全面评估,快速识别可能发生 HTPR 的患者,省去额外的检测时间和费用,进而给予患者针对性的个体化抗血小板治疗。

本研究通过单因素分析发现高龄(>75 岁)、女性、合并高血压、合并糖尿病和血小板增多(PLT>300×10^9/L)与 HTPR 发生相关。既往也有诸多研究表明这些临床因素与 HTPR 发生密切相关。Cuisset 等[6]和 Silvain 等[7]发现无论是在负荷剂量下还是在维持剂量下检测血小板反应性,年龄>75 岁的患者的 HTRP 比例均高于≤75 岁的患者。既往研究表明女性更易发生 HTPR,考虑主要与性激素水平相关[8-10]。Kim 等[11]分析推测血压增高患者易发生 HTPR,可能与血管剪切应力增加促进血小板黏附、聚集有关。糖尿病是公认的导致 HTPR 发生的重要因素之一,其机制可能与促进血小板激活和增加血管炎症反应密切相关[12-13]。Jakl 等[14]指出血小板计数>400×10^9/L 可导致 HTPR 发生风险增高,可能与增多的血小板是潜在的强有力促聚集因素相关。本研究通过多因素 logistic 回归分析发现,高龄(>75 岁)、女性、合并糖尿病是 HTPR 发生的独立危险因素,被纳入评分构建模型。

本研究是首次在 AMI-PCI 患者中利用临床指标构建 HTPR 危险评分,结果显示得分越高,越容易发生 HTPR,这与既往研究结论相同:Geisler 等[15]在非选择性冠心病(包括各型心绞痛和心肌梗死)患者中建立 PREDICT 评分评估 HTPR 的发生风险,将筛选出的危险因素包括心功能减低(LVEF<55%)赋 3 分、合并糖尿病和肾功能减低(Scr>15 mg/L)各赋 2 分、高龄(>65 岁)和表型为急性冠脉综合征各赋 1 分,结果显示 PREDICT 评分(分值范围 0～9 分)不仅能有效识别 HTPR,还能预测出院后 30 d 的临床事件,得分>5 分的患者临床不良事件显著增加。Droppa 等[16]在稳定冠心病患者中建立 PREDICT-STABLE 评分来预测 HTPR 的风险,将筛选出的危险因素包括高龄(>63 岁)赋3 分、合并糖尿病和超重(BMI>30 kg/m^2)各赋 2 分、心功能减低(LVEF<55%)和肾功能减低(Scr>11 mg/L)各赋 1 分,分值范围 0～9 分,结果显示0～3、4～6、7～9 分 3 组患者间的血小板反应性存在差异,其中 7～9 分组的 1 年不良事件发生率高于0～3 分组。以上研究均表明,临床因素危险评分可以快速有效地帮助医师识别 HTPR 高危患者和评估患者临床预后,为抗血小板治疗策略的选择提供循证依据。

本研究的局限性为研究是单中心观察性研究,故得出的结果仍有待大规模多中心的前瞻性研究证实。此外,研究样本量偏小,统计效能不足以评估临床事件,因此需要通过进一步扩大样本量验证分析评分是否能有效评估患者临床预后。

综上所述,临床因素与 HTPR 发生密切相关,构建临床危险评分能协助医务人员快速识别可能发生 HTPR 的患者,从而指导抗血小板个体化治疗。

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