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急性心肌梗死患者冠脉搭桥术前中性粒细胞 - 淋巴细胞比率与围术期心肌损伤相关分析 *

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摘要 目的:探讨急性心肌梗死患者冠脉搭桥(CABG)术前中性粒细胞 - 淋巴细胞比率(NLR)与围术期心肌损伤的关系,为临床CABG围术期心肌保护提供参考依据。**方法:**选取2012年1月至2012年6月于首都医科大学附属北京安贞医院因急性心肌梗死接受冠脉搭桥手术(CABG)患者210例,收集术前血常规及术后肌钙蛋白I(cTnI)及肌酸激酶同工酶(CK-MB),计算NLR;采用四分位法根据NLR水平将患者分为四组,比较各组cTnI及CK-MB峰值,多元逐步回归分析NLR与cTnI及CK-MB峰值的相关性。**结果:**随着NLR水平升高,高血压病史和射血分数<50%患者比例逐渐增多;白细胞计数、术后CK-MB及cTnI峰值、术后血肌酐值均逐渐增加;多元逐步回归分析显示,NLR、WBC分别与cTnI峰值呈正相关($r=0.526, r=0.186, P<0.05$)。**结论:**术前NLR、WBC与cTnI峰值呈正相关,NLR可能是反应急性心肌梗死患者冠脉搭桥围术期心肌损伤的良好标志物。

关键词:冠脉搭桥术;围术期心肌损伤;中性粒细胞 - 淋巴细胞比率;肌钙蛋白 I

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Correlation of Preoperative Neutrophil to Lymphocyte Ratio with Perioperative Myocardial Injury after Coronary Artery Bypass Surgery in Patients with AMI*

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ABSTRACT Objective: To study the correlation of preoperative neutrophil to lymphocyte ratio(NLR) with perioperative myocardial injury after coronary artery bypass surgery (CABG) in patients with AMI at admission. **Methods:** Two hundred and ten CABG patients with AMI, admitted to Beijing Anzhen Hospital from January 2012 to June 2012. Preoperative white blood cells count (WBC), neutrophil count (NC), lymphocyte count (LC), postoperative troponin I (cTnI) and creatine kinase isoenzyme (CK - MB) were measured at admission and NLR were calculated. Patients were divided into four groups according to NLR. Difference in their peak cTnI and CK-MB values were compared and correlation of NLR with peak cTnI and CK-MB values was analyzed. **Results:** With the increment of NLR, the proportions with hypertension history or ejection fraction < 50%, WBC, peak cTnI and CK-MB values were significantly higher [A1]. Multiple stepwise regression analysis showed that the WBC and NLR were positively correlated with the peak cTnI value ($r=0.526, r=0.186, P<0.05$). **Conclusions:** The WBC count and NLR are positively correlated with the peak cTnI values after coronary artery bypass surgery in patients with AMI at admission in a significant linear manner, indicating that NLR is a good indication for perioperative myocardial injury after coronary artery bypass surgery in patients with AMI.

Key words: Coronary artery bypass surgery; Perioperative myocardial injury; Neutrophil to lymphocyte ratio; Cardiac troponin I

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前言

冠脉搭桥术(coronary artery bypass graft, CABG)是手术治疗急性心肌梗死的主要方法, CABG会引起不同程度的心肌损

伤,从而影响手术效果^[1]。急性心肌梗死(AMI)是冠心病的严重类型,是一个复杂的与多种因素相关的疾病,炎症在这一过程中扮演了重要的角色^[2];研究证实,中性粒细胞 - 淋巴细胞比率(neutrophil-lymphocyte ratio, NLR),是一个简便易行的炎症标

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记物,是冠心病预后的独立预测指标^[3-6],也是冠脉搭桥术及PCI病人预后的最强预测指标^[7,8]。肌酸激酶同工酶(CK-MB)及肌钙蛋白I(cTnI)峰值是被广泛认同的心肌损伤标志物,能很好的反应心肌损伤程度。目前国外关于术前NLR与CABG患者围术期CK-MB和cTnI峰值的相关性的研究较少,国内尚未见报道。因此,本研究主要探讨术前NLR是否可作为评价急性心肌梗死患者冠脉搭桥围手术期心肌损伤程度的指标,旨在为临床CABG围术期心肌保护提供参考依据。

1 资料与方法

1.1 病例资料

收集自2012年1月至2012年6月就诊于首都医科大学附属北京安贞医院因急性心肌梗死行CABG患者共计210例。纳入标准:所有入选病例均符合WHO急性心肌梗死的诊断标准:(1)胸痛持续>30 min,舌下含服硝酸甘油症状无改善;心电图出现两个及以上的相邻胸前导联或Ⅱ、Ⅲ、avF导联中任两个导联ST段抬高幅度>0.1mV并出现动态演变;血清心肌酶学有动态变化;(2)选取急性心肌梗死21d内的非急诊冠脉搭桥手术患者。排除标准:合并全身急慢性感染性疾病、恶性肿瘤、血液系统、各种风湿免疫性疾病及使用免疫调节剂、近期剧烈体力活动等各种因素引起肌肉损伤、严重肝肾功能不全患者。

1.2 研究方法

记录一般临床资料:(1)记录手术年龄、性别、体重指数、十八导联心电图及危险因素,包括高血压、糖尿病、高脂血症、吸烟史,并检测血脂、血肌酐水平。(2)所有患者均于冠脉搭桥术前3天内抽取静脉血。采用电阻法与激光计数相结合的原理,进行白细胞分类计数;将所有患者将平均NLR大小由小到大

排列,按四分位法分为四组。(3)连续监测术后第12h、24h、48h时CK-MB及cTnI峰值,并分析WBC、NLR与CK-MB及cTnI峰值的相关性。

1.3 实验室检查

应用美国Abbott公司推出的CELL-DYN3700血细胞分析仪,采用电阻法与激光计数相结合的原理,进行白细胞分类计数及分类。TG、TC、HDL-C、LDL-C生化指标使用HITACHI7020全自动生化分析仪分析检测,试剂均购自南京普朗生物技术有限公司。CK-MB测定使用德国Human生化公司提供的试剂盒,cTnI由美国雅培公司提供的化学发光仪及其配套试剂及对照品。

1.4 统计学处理

采用SPSS18.0统计软件,计量资料用均数±标准差表示,计数资料用百分构成比表示,单因素分析中,计数资料用卡方检验,计量资料服从正态分布时用方差分析,不服从正态分布时用非参数统计(秩和检验)。相关性用多元逐步回归分析,P<0.05为差异有统计学意义。

2 结果

2.1 患者一般情况

210例急性心肌梗死行CABG患者临床资料见表1:男性患者169例(80.5%),女性41例(19.5%),平均年龄(60.20±9.04)岁(范围38-89岁);吸烟患者124例(59.0%);糖尿病患者58例(27.6%);高血压患者121(57.6%);高脂血症患者45例(21.4%);射血分数<50%患者54例(25.7%),WBC(7.09±1.88)×10⁹/L,L(1.87±0.57)×10⁹/L,N(4.63±1.67)×10⁹/L,NLR2.72±1.41。

表1 急性心肌梗死患者CABG术前患者一般情况
Table1 General condition in preoperative CABG patients with AMI

Variable	male(n=169)	famale(n=41)
Age(years)	59.07±8.61	64.90±6.38
Smoking(n)	122	2
Systemic hypertension(n)	93	28
Diabetes mellitus(n)	42	16
Hypercholesterolemia(n)	34	11
LVEF<50%(n)	44	10
Left main stenosis(n)	41	10
WBC(×10 ⁹ /L)	7.22±1.88	6.49±1.78
NC(×10 ⁹ /L)	4.72±1.68	4.25±1.57
LC(×10 ⁹ /L)	1.90±0.58	1.74±0.52
NLR	2.73±1.43	2.66±1.36

注:WBC:白细胞计数;NC:中性粒细胞计数;LC:淋巴细胞计数;NLR:中性粒细胞-淋巴细胞比率;LVEF:左室射血分数。

Note: WBC: White blood cells; NC: neutrophil counts; LC: lymphocyte counts; NLR: neutrophil- lymphocyte Ratio;

LVEF: Left ventricular ejection fraction.

2.2 急性心肌梗死患者CABG术前不同NLR水平患者资料比较

入选的210例患者按照中性粒细胞-淋巴细胞比率(NLR)分为四组,中位数NLR为2.34,第25和75百分位数

1.79和3.19。随着NLR的升高,高血压病史和射血分数<50%患者比例逐渐增多,白细胞计数、术后CK-MB及cTnI峰值、术后血肌酐值均显著增加,差异有统计学意义(P<0.05, P<0.01)。

组手术年龄、性别、体重指数、吸烟、糖尿病、高脂血症、术前血红蛋白、空腹血糖、TG、TC、LDL-C、HDL-C 比较,差异无统计学意义($P>0.05$,表2)。

表2 各组急性心肌梗死患者 CABG 术前临床特征比较
Table 2 Comparison of clinical features of patients before surgery

Variable	Quartile1 (0.96-1.78) (n=53)	Quartile2 (1.79-2.33) (n=53)	Quartile3 (2.34-3.18) (n=52)	Quartile4 (3.19-9.78) (n=52)	X ² /F	P
Age(years)	58.66± 8.75	59.77± 9.75	60.02± 8.80	62.4± 8.66	1.603	0.190
Female, n (%)	9(17.0)	12(22.6)	11(21.2)	9(17.3)	0.796	0.850
BMI(kg/m ²)	25.55± 2.46	24.92± 2.47	24.94± 3.19	24.63± 3.06	1.001	0.394
Smoking, n(%)	29(54.7)	36(67.9)	28(53.8)	31(59.6)	2.727	0.436
Diabetes mellitus,n(%)	16(30.2)	14(26.4)	11(21.2)	17(32.7)	1.970	0.579
Hypertensionn(%)	23(43.4)	39(73.6)	28(53.8)	31(59.6)	10.311	0.016
Hypercholesterolemia, n(%)	9(17.0)	15(28.3)	11(21.2)	10(19.2)	2.261	0.520
Creatinine(μ mol/L)	79.27± 14.65	78.04± 17.59	78.23± 19.98	84.13± 16.39	1.432	0.234
WBC(× 10 ⁹ /L)	6.18± 1.44	6.61± 1.46	7.22± 1.74	8.34± 2.10	15.747	<0.001
FG(mmol/L)	5.69± 1.37	6.10± 1.77	5.70± 1.44	6.00± 1.63	0.930	0.426
TG(mmol/L)	1.70± 1.06	1.93± 1.59	1.98± 1.36	1.62± 0.78	1.000	0.392
TC(mmol/L)	4.09± 1.24	4.12± 1.12	4.25± 0.91	4.24± 1.25	0.275	0.844
HDL-C(mmol/L)	0.90± 0.20	0.93± 0.17	4.25± 0.91	4.24± 1.25	0.661	0.575
LDL-C(mmol/L)	2.52± 1.07	2.39± 0.87	2.63± 0.67	2.66± 1.08	0.910	0.437
LVEF < 50%,n(%)	8(15.1)	14(26.4)	10(19.2)	22(42.3)	11.783	0.008
Postoperative cTnI(ng/ml)	1.86± 1.36	2.92± 2.10	5.03± 4.84	15.32± 12.87	41.056	<0.001
Postoperative CK-MB(U/L)	8.95± 6.24	12.16± 8.94	15.27± 14.69	39.01± 35.97	24.242	<0.001
Postoperative creatinine(μ mol/L)	90.02± 31.09	90.66± 33.207	92.53± 57.31	114.5± 70.90	2.791	0.041

注:计量资料用均数± 标准差表示或计数资料用 n (%)表示;缩写词:PLR:中性粒细胞-淋巴细胞比率;WBC:白细胞计数;cTnI:肌钙蛋白 I;CK-MB:肌酸激酶同工酶;TG:三酰甘油;TC:总胆固醇;HDL-C:高密度脂蛋白胆固醇;LDL-C:低密度脂蛋白胆固醇;FG:空腹血糖;LVEF:左室射血分数。

Note: Values are expressed as the mean ± standard deviation or n (%) for categorical variables; Abbreviations: NLR, neutrophil-lymphocyte ratio; WBC, white blood count; cTnI: Cardiac troponin I; CK - MB: creatine kinase isoenzyme; TG: Triglycerides; TC: Total cholesterol; HDL-C: High density level of apolipoprotein cholesterol; LDL-C: High density level of apolipoprotein cholesterol; LVEF: Left ventricular ejection fraction; FG: fasting plasma glucose.

2.3 急性心肌梗死患者 CABG 术前 NLR 与围术期心肌损伤标志物相关分析

多元逐步回归分析显示,急性心肌梗死患者 CABG 术前 NLR 与 cTnI 峰值呈正相关($r=0.526, P<0.05$);术前 NLR 与 WBC 呈正相关($r=0.661, P<0.05$);与高血压病史、射血分数及术后肌酐峰值及术后 CK-MB 无相关性($P>0.05$);cTnI 峰值与 WBC 呈正相关($r=0.186, P<0.05$)。

3 讨论

冠脉搭桥术作为治疗冠状动脉硬化性心脏病的主要方法之一,能有效地改善患者心肌缺血缺氧状态,提高生活质量。围术期心肌损伤是影响 CABG 术后顺利康复的重要因素。心肌 cTnI 是目前反映心肌细胞损伤中敏感性和特异性最好的标志物,CK-MB 次之。Paparella 等^[9]观测 AMI 病人患病 21 天内行非急诊 CABG 的术前 cTnI 水平与术后并发症相关性,结果高 cTnI 组术后低心排、急性肾衰、主动脉球囊反搏应用及死亡发生率明显高于低 cTnI 组,提示 AMI 患者 cTnI 与 CABG 术后并发症密切相关。

研究报道,CABG 患者术前 NLR 与反应围术期心肌损伤

的标志物肌钙蛋白释放量之间均存在显著正相关^[9]。本研究 210 例 CABG 患者,均测量术前 WBC 计数及其分类,计算 NLR,并选择能够反应围术期心肌损伤的 CK-MB 和 cTnI 峰值进行相关性分析。结果显示,术前 WBC、NLR 与 cTnI 峰值均呈正相关。提示术前 WBC 和 NLR 水平可能对反映 CABG 患者早期评估围术期心肌损伤、识别高危患者,并采取相应治疗措施具有重要指导意义。

国外研究显示 NLR 显著升高是冠心病患者心源性死亡、心肌梗死、PCI 术患者近期及远期死亡率的独立危险因素^[10],也是心脏手术后并发症、住院及中、远期死亡率的独立危险因素^[11]。最近研究发现,白细胞中某些亚组分对评估心血管危险有较高的预测价值,其中 NLR 的价值更高。与白细胞计数相比,NLR 是一个更好的远期死亡预测因子^[12]。Patrick 等^[13]研究显示 NLR 是 CABG 的重要预测因子,其比值大于 3.36 时,围术期并发症、术后 3.6 年内死亡率最高。本研究显示随着 NLR 的增高,CABG 的住院死亡率也呈现逐步递增趋势,各组间两两比较差异均具有统计学意义。单因素分析显示,死亡组 NLR 较存活组显著增高($P<0.001$),通过多元分析显示,NLR 是 CABG 住院及出院死亡率的可预测指标,其预测价值大于白

细胞计数的预测价值,这与文献报道一致。类似的先前研究,术前升高的 NLR 和术后新发房颤也相关^[13]。

中性粒细胞、淋巴细胞不同的活化状态在冠心病的发生发展中可能起到关键的作用,分析其原因:升高的 NLR 作为独立的预测因子,整合了两种白细胞亚型的预测风险为单一危险因素,NLR 比其他任何单一的指标具有更好的预测价值。这可能主要取决于以下两个因素,首先,在通常的生理条件下,比如脱水状态或在体外的血液样本可能会影响到白细胞各亚型的绝对值,而对 NLR 影响相对较小。例如:运动及儿茶酚胺可增加中性粒细胞和淋巴细胞的数量,而 NLR 改变不大;其次,NLR 是两种不同却互补的免疫途径的比值。中性粒细胞主要介导非特异性炎症反应,分泌多种炎性介质,引起进一步的组织损伤,如释放花生四烯酸代谢物和血小板聚集因子、具有细胞毒性的氧自由基、过氧化物酶、弹性蛋白酶、各种水解酶如酸性磷酸酶等,上述物质均可导致动脉粥样硬化斑块破裂^[14-17]。Nick 等^[18]对 3027 例经冠脉搭桥旁路移植术患者进行回顾性研究发现,术前增高的 WBC 与围术期 CK-MB 的释放量呈正相关。淋巴细胞在动脉粥样硬化的过程各阶段炎症反应中也发挥着重要的调节作用。在急性期,淋巴细胞减少是应激反应过程中的常见表现,常继发于皮质类激素水平升高,可作为急性心肌梗死的早期标志。也有报道称减少淋巴细胞减少是由炎症急性期淋巴细胞凋亡增加引起。我们证实减少的外周血淋巴计数在非特异性炎症过程中起着重要作用,淋巴细胞也显示了与动脉粥样硬化进程的关系和心脏不良事件的相关性^[19,20]。淋巴细胞调节平滑肌增殖经 γ 干扰素^[21],它控制了动脉粥样硬化狭窄的进程。Lomivorotov 等^[22]在研究显示,较低的术前外周血淋巴细胞计数对于心脏手术病人术后的并发症可以进行有效预测。

CABG 术后早期评估心肌损伤程度、患者预后、心肌保护措施效果等对临床治疗有重要作用,术前 NLR 的应用,使得术前评估 CABG 围术期心肌损伤更为简单、方便且易广泛普及。借助术前 NLR 可一定程度上早期评估风险,但如何通过标志物检测,结合临床表现综合判断,提高心肌损伤诊断准确率,并给予患者早期干预和得到有效的治疗,减少心肌损伤是今后心外科医生及研究人员努力研究的热点。

综上所述,本文证实血浆 NLR 升高与冠脉搭桥术患者围术期心肌损伤独立相关,NLR 作为简单的生物标志物,可更好地指导临床医师对 CABG 患者围术期的临床治疗决策,以为临床 CABG 围术期心肌保护提供进一步的信息。本研究为回顾性、单中心观察性研究、例数较少,因而分析受到各种固有的不可预知的混淆因素干扰,希望今后加大样本量进一步分析。

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