冠状动脉慢血流与外周血淋巴细胞和单核细胞比值之间的关联性分析

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摘 要:目的 探究淋巴细胞和单核细胞比值(lymphocyte-to-monocyte ratio, LMR)与冠状动脉慢血流(slow coronary flow, SCF)现象之间的关联性。**方法** 回顾性收集98例2016年9月~2017年11月在凤翔县中医医院因可疑有冠状动脉疾病,行冠状动脉造影检查的患者为研究对象。采用血液分析仪进行全血细胞计数。采用数字血管造影系统,基于心肌梗死后的血栓溶栓(thrombolysis in myocardial infarction, TIMI)计帧法检测冠状动脉血流量。根据冠状动脉造影结果将研究对象分为两组,包括45例SCF患者组和53例正常冠状动脉血流健康(normal coronary flow, NCF)对照组。采用Logistic回归分析LMR与SCF发生之间的关联性。**结果** 相比NCF患者,SCF患者组的高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)水平、嗜中性粒细胞、单核细胞计数,嗜中性粒细胞与淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR),C-反应蛋白(C-reactive protein, CRP)和心肌梗死后的血栓溶栓(thrombolysis in myocardial infarction, TIMI)帧数较高,但淋巴细胞计数和LMR较低,差异均有统计学意义($t=1.630$~7.834, 均$P<0.05$)。LMR与左前降支(left anterior descending, LAD)动脉,左回旋支(left circumflex, LCX)侧动脉和右冠状(right coronary artery, RCA)动脉的TIMI帧数呈现负向关联性($r=-1.31$, -1.05和-0.76,均$P<0.001$)。LMR单变量(OR=0.76, 95% CI=0.57~0.93, $P=0.003$)和多变量(OR=0.32, 95% CI=0.14~0.91, $P=0.011$)。logistic回归分析均发现LMR的升高与SCF的发生风险呈现负向关联性。**结论** LMR与SCF的发生风险呈现负向关联性,可以作为SCF发生的一种预测性标志物。

关键词:冠状动脉慢血流;淋巴细胞和单核细胞比值;炎性标志物;冠状动脉造影;关联性分析
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Association of Slow Coronary Flow with Peripheral Blood Lymphocyte-to-Monocyte Ratio

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Abstract: Objective To investigate the association between lymphocyte-to-monocyte ratio (LMR) and slow coronary flow (SCF) phenomenon. **Methods** A total of 98 patients who had performed coronary angiography for suspected coronary artery disease, were retrospectively enrolled in the present study from June 2016 to November 2017 in Fengxiang Hospital. Whole blood counts were performed using a blood analyzer. Coronary blood flow was measured by a digital angiography system based on thrombolysis in myocardial infarction (TIMI) frame counting method after myocardial infarction. According to the results of coronary angiography, all subjects were divided into two groups, including 45 SCF patients and 53 normal coronary flow (NCF) controls. Logistic regression was used to analyze the association between LMR and SCF. **Results** Higher level of HDL, neutrophils and monocyte counts, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP) and thrombolysis in myocardial infarction (TIMI) frame counts, and lower level of lymphocyte counts were found among SCF group than NCF group, the difference was statistically significant ($t=1.630$~7.834, all $P<0.05$). LMR was negatively associated with

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frame counts of left anterior descending (LAD), left circumflex artery (LCX) and right coronary artery (RCA) (r = −1.31, −1.05, −0.76, all P <0.001). In addition, increased LMR was negatively associated with risk of SCF in both univariate (OR =0.76, 95% CI =0.57 ~0.93, P =0.003) and multiple (OR =0.32, 95% CI =0.14 ~0.91, P =0.011) logistic regression models. **Conclusion** LMR was negatively associated with risk of SCF, and LMR may play as a predictive biomarker of incident SCF.

Keywords: slow coronary flow; lymphocyte-to-monocyte ratio; inflammatory markers; coronary angiography; correlation analysis

冠状动脉慢血流(slow coronary flow, SCF)为血管造影显示正常或接近正常的冠状动脉远端血管床延迟显影的现象[1-2]。尽管SCF的病理生理机制尚不明确,但炎症在SCF形成过程中可能扮演重要角色[3-4]。目前研究表明,作为炎性反应的重要标志物,嗜中性粒细胞与淋巴细胞比率(neutrophil-to-lymphocyte ratio, NLR)与SCF的发生存在关联性[5-6]。此外,作为重要的免疫细胞、淋巴细胞和单核细胞也在炎症反应中发挥作用。已有研究发现淋巴细胞与动脉粥样性冠心病患者的不良预后相关[7-8],单核细胞计数的增加与较差的心血管预后相关[9-10]。淋巴细胞与单核细胞比值(lymphocyte to monocyte ratio, LMR)的降低被证实与肿瘤和心脏疾病的不良结局存在关联[11-14]。LMR为炎性反应的一个新的间接标志物,SCF是心血管疾病发生的早期生物学事件,但目前尚缺乏LMR与SCF关联性的研究。本研究旨在探讨LMR在SCF发生中的作用,从而为预测严重心血管疾病的发生提供重要线索。

1 材料与方法

1.1 研究对象 本研究回顾性收集2016年9月~2017年11月在凤翔县中医医院因可疑有冠状动脉疾病,行冠状动脉造影检查的患者为研究对象。收集患者的诊疗信息,包括既往病史、影像学检查等资料。排除既往患有血液和心脏疾病[如贫血、血液恶质病、失代偿性的心脏衰竭、室壁运动异常(left ventricular ejection fraction, LVEF)低于50%、明显心脏瓣膜病、血管重建史、近期3个月内患有急性冠状动脉综合征、近期心肌梗死史],恶性肿瘤,自身免疫性疾病,或伴随有肾脏和/或肝衰竭、使用皮质类固醇和非甾体类抗炎药的患者。最终共纳入98例研究对象。本研究经本院医学伦理委员会批准。

1.2 试剂和仪器 采用血液分析仪(F-800, Sysmex)及其原配套试剂进行全血细胞计数。采用瑞士罗氏Modular PPI全自动生化分析仪及其配套的校准液、质控物和试剂测定CRP的水平。采用德国西门子数字血管造影系统(AXIOM Artis)并以碘普罗胺为造影剂(GE, Healthcare),基于心肌梗死后的血栓溶栓(thrombolysis in myocardial infarction, TIMI)计帧法检测冠状动脉血流量。

1.3 方法 每位患者在行冠状动脉造影前采集空腹12h外周静脉血样,LMR = 总淋巴细胞计数/单核细胞计数。以30帧/s记录显影剂到达冠状动脉远端位置的帧数,冠状动脉的三个远端位置包括左前降支(left anterior descending, LAD)动脉,左回旋支(left circumflex artery, LCX)侧动脉和右冠状动脉(right coronary artery, RCA),标准平均帧数,分别为36.2 ±2.6,22.2 ±4.1和20.4 ±3.0帧/s。若患者帧数超过任何一个标准位置正常范围2个标准差以上则被判断为存在SCF现象[15],其他为正常冠状动脉血流(normal coronary flow, NCF)。根据冠状动脉造影检查结果是否存在SCF现象分为病例组和对照组,包括45例SCF患者和53例正常冠状动脉血流健康对照(NCF)。其中两组患者男性分别为34例和38例,平均年龄55.2 ±9.3岁和53.7 ±8.1岁。两组间高血压(31.0% vs 35.1%)和糖尿病(21.4% vs 25.7%)的患病情况有较好的可比性。

1.4 统计学分析 计量和分类资料分别以均数 ± 标准差($\bar{x} \pm s$)和频数(百分比)表示。两组间计量和分类资料分布的比较分别采用两独立样本资料的t检验或卡方检验。采用简单线性相关分析LMR与TIMI帧数之间的线性相关性。并进一步采用多变量Logistic回归分析SCF发生的风险比(odds ratio, OR)及其95%置信区间(confidence Intervals, CI)。采用SPSS 17.0软件进行统计分析,以P <0.05为差异有统计学意义。

2 结果

2.1 SCF患者和NCF两组间临床检查信息分布的比较 见表1。相比NCF组,SCF组的HDL-C水平、嗜中性粒细胞和单核细胞计数,NLR,CRP和TIMI帧数较高,但淋巴细胞计数和LMR较低,差异有统计学意义(均P <0.05)。

2.2 LMR与LAD,LCX和RCA的TIMI帧数的关联性分析 见图1。LMR与LAD(图1a)、LCX(图1b)和RCA(图1c)的TIMI帧数呈线性相关(r = −1.31, −1.05, −0.76,均P <0.001)。

2.3 多变量分析LMR与SCF之间的关联性 表1中SCF和NCF患者间HDL-C, NLR, LMR和CRP水平分布的差异有统计学意义,故将这些变量纳入Logistic回归分析中,见表2。单变量Logistic回归分析发现HDL和LMR的升高与SCF的发生风险呈现负向关联;NLR的升高可引起SCF发生风险的增加。多变量Logistic回归分析发现,仅有LMR的升高与降低的SCF发生风险相关联。

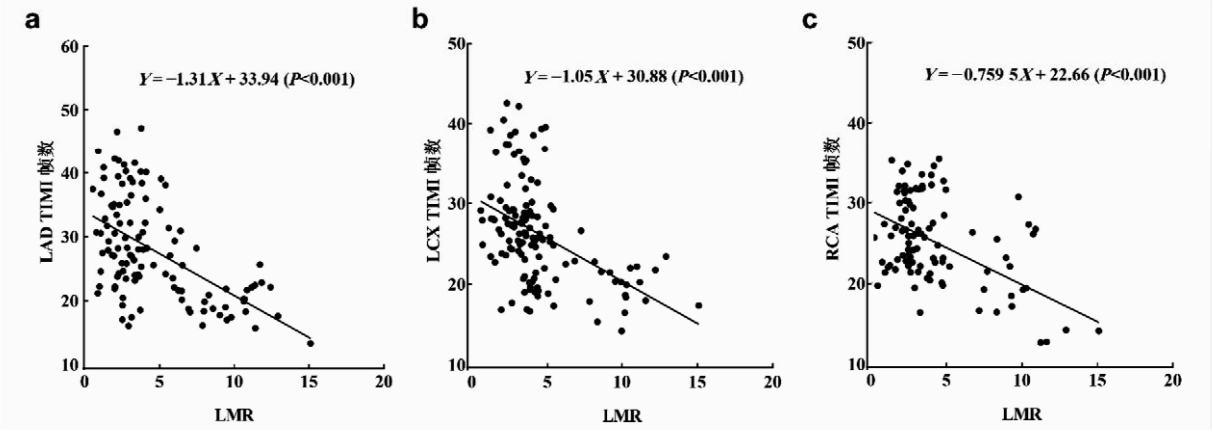

图1 LMR与LAD,LCX和RCA的TIMI帧数的关联性分析

表1 SCF组和NCF组间临床检查信息分布的比较($\bar{x}\pm s$)

项目	SCF组(n=45)	NCF组(n=53)	t	P
血糖(mmol/L)	6.1 ± 2.5	6.4 ± 2.4	0.853	0.107
肌酐(mmol/L)	0.08 ± 0.02	0.07 ± 0.02	0.771	0.415
总胆固醇(mmol/L)	5.1 ± 0.9	5.2 ± 0.8	0.665	0.511
LDL(mmol/L)	3.1 ± 1.0	3.1 ± 0.7	0.032	0.913
HDL(mmol/L)	1.0 ± 0.2	1.2 ± 0.2	3.174	0.002
TG(mmol/L)	1.8 ± 0.9	1.9 ± 0.8	1.283	0.214
血红蛋白(g/dl)	14.9±1.3	14.6±1.1	0.576	0.673
WBC(10^9/L)	7.9±1.4	7.2±1.2	1.980	0.054
嗜中性粒细胞(10^9/L)	4.7±1.2	4.4±1.1	2.103	0.042
淋巴细胞(10^9/L)	2.1±0.7	2.3±0.6	1.630	0.011
单核细胞(10^9/L)	1.1±0.5	0.7±0.3	4.352	<0.001
LMR	2.2±1.3	3.2±1.4	5.177	<0.001
NLR	2.3±0.9	1.9±0.6	4.885	<0.001
PLR	122.2±39.3	117.7±33.8	1.013	0.299
CRP(mg/L)	2.3±1.3	1.7±0.9	3.390	0.001
TIMI帧数 LAD	45.2±9.3	23.7±6.1	7.834	<0.001
LCX	31.2±8.3	19.7±5.8	2.330	0.021
RCA	8.2±8.4	13.7±4.1	2.851	0.007

表2 多变量Logistic回归分析LMR与SCF之间的关联性

变量	单变量模型		多变量模型	
	OR(95% CI)	P	OR(95% CI)	P
HDL(mmol/L)	0.74(0.83~0.92)	0.031	0.76(0.86~1.09)	0.875
NLR	1.78(1.17~2.22)	<0.001	1.13(0.85~1.42)	0.476
LMR	0.76(0.57~0.93)	0.003	0.32(0.14~0.91)	0.011
CRP(mg/L)	1.06(0.84~1.18)	0.321	1.09(0.84~1.20)	0.128

3 讨论

SCF与心肌功能障碍、冠状动脉痉挛、心瓣膜病、结缔组织疾病有关[16]。然而,SCF现象的病理生理学机制仍然不确定,已有研究指出SCF和炎性反应的关联性。现存的假说包括小血管功能障碍、血管收缩和扩张之间的不平衡以及血小板功能障碍,且SCF可能是一种早期的动脉粥样硬化形式[4]。鉴于炎症在动脉粥样硬化的所有阶段中均扮演着重要角色,Turhan指出血浆可溶黏附分子、细胞间黏附分子-1(ICAM-1)和血管细胞黏附分子-1(VCAM-1)可能为SCF患者内皮激活或炎症标志物,而且SCF患者血清ICAM-1和VCAM-1显著高于NCF对照组[6]。也有研究指出SCF患者YKL-40水平与TFC和hs-CRP呈正相关[17]。血液黏稠度是由全血和血浆蛋白浓度计算而来的,可作为SCF一个重要而独立的预测指标[18]。最近的研究也发现,由全血细胞计数(complete blood count, CBC)中NLR和单核细胞-高密度脂蛋白比率可作为SCF的炎症标志物[5,22]。

由CBC得到的LMR被认为是一种新的炎症标志物,可作为全身系统炎症反应的一个独立指示物,并在预测各种恶性肿瘤预后中发挥作用[19-20]。LMR也与血管疾病如外周动脉疾病和冠状动脉疾病相关[22-23]。在本项研究中,我们发现了LMR与SCF之间的独立关联性,SCF患者比NCF患者有更高程度的LMR降低水平。另外,KUTRTUL等[14]发现LMR与ST段抬高性心肌梗死患者的术后无复流呈现独立相关性。潜在的生物学机制可能为减少淋巴细胞计数反映了机体血清儿茶碱和皮质醇水平的升高,该过程是全身系统对压力的一种响应,可进一步的促使淋巴细胞凋亡增多、淋巴细胞增殖的降低、下调淋巴细胞系统细胞分化和再分配[8]。在该过程中,单核细胞作为一种不同类型的白细胞扮演关键角色,它会主动与血小板结合在一起,形成血栓前期的血小板-单核细胞聚合体,该聚合体的调节功能在急性冠脉综合征患者中呈现活跃状态[24]。炎症在SCF现象的病理生理过程中起着重要作用。已有研究证实SCF患者具有较高的C-反应蛋白水平[13]。动脉粥样硬化作为一种特殊的炎症过程,伴随SCF患者

的发生。淋巴细胞与单核细胞比值的降低可反映炎症反应水平的升高,从而与升高的SCF发生风险呈现负相关[24]。淋巴细胞减少可能表明免疫反应被抑制,并可能与心脏疾病不良预后有关[25-26]。因而,所有WBC分类计数,包括单核细胞、嗜酸性粒细胞、中性粒细胞和淋巴细胞(反向关联)与增加的不良冠状动脉预后风险有关[27]。由于本研究样本量较少,且为横断面研究,无法确立LMR与SCF发生的因果关系,故该研究结果需在更大的人群队列研究中验证。

综上所述,我们推测LMR可能与SCF现象存在关联性,在SCF患者中LMR显著降低并与TIMI帧数呈良好负相关,因而LMR可能作为一种标志物来预测可能发生的SCF现象和心血管事件。该研究可为不良心血管事件的临床早期发现和干预提供线索。

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