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·临床研究·

中性粒细胞-淋巴细胞比值在冠心病经皮冠状动脉介入治疗中的临床意义

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[摘 要] **目的** 探讨中性粒细胞-淋巴细胞比值(NLR)对冠心病患者经皮冠状动脉介入治疗(PCI)后临床结局的影响及对预后的预测价值。**方法** 回顾性分析6 046例于新疆医科大学第一附属医院心脏中心经冠状动脉造影确诊为冠心病并行PCI治疗的患者临床资料,根据受试者工作特征曲线确定患者NLR的最佳截断值,并据此将患者分为低NLR组(1 997例)、中NLR组(2 025例)和高NLR组(2 024例)。分析各组的一般资料、实验室检查指标及预后结局相关指标,多因素分析影响预后的危险因素。采用*Kaplan-Meier*法分析随访期间患者预后生存情况。**结果** 各组患者年龄、心率、男性比例、高血压比例、服用氯吡格雷比例比较差异均有统计学意义($P<0.05$),中NLR组和高NLR组上述指标明显高于低NLR组($P<0.05$)。各组患者NLR、载脂蛋白A1、血糖、尿素氮、肌酐水平比较差异均有统计学意义($P<0.05$),且中NLR组和高NLR组上述指标明显高于低NLR组($P<0.05$),高NLR组高于中NLR组($P<0.05$)。各组患者全因性死亡发生率比较差异具有统计学意义($P<0.05$),高NLR组全因性死亡发生率明显高于中NLR组及低NLR组($P<0.05$)。年龄越大、心率越快、尿素氮越高及服用氯吡格雷是主要不良心脑血管事件(MACCE)发生的独立危险因素($P<0.05$)。*Kaplan-Meier*生存曲线显示,低NLR组患者的生存率高于中NLR组和高NLR组($P<0.001$),中NLR组和高NLR组生存率比较差异无统计学意义($P>0.05$);*Log-rank*检验显示,低NLR组MACCE发生率明显低于中NLR组及高NLR组($P<0.05$)。**结论** NLR高、年龄大、心率快、尿素氮高及服用氯吡格雷的冠心病患者PCI后预后较差,其中NLR能够预测冠心病PCI后患者的临床结局。

[关键词] 经皮冠状动脉介入治疗;冠心病;中性粒细胞-淋巴细胞比值;临床结局;冠状动脉造影

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Clinical significance of neutrophil lymphocyte ratio in percutaneous coronary intervention for coronary heart disease

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Abstract: Objective To investigate the effect of neutrophil to lymphocyte ratio (NLR) on clinical outcomes after percutaneous coronary intervention (PCI) in patients with coronary heart disease and its predictive value on prognosis. **Methods** The clinical data of 6,046

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patients with coronary heart disease diagnosed by coronary angiography and treated by PCI in the Heart Center of First Affiliated Hospital of Xinjiang Medical University were analyzed retrospectively. The optimal cutoff value of NLR was determined by the receiver operating characteristic curve, and the patients were divided into the low NLR group (1,997 cases), middle NLR group (2,025 cases) and high NLR group (2,024 cases). The general data, laboratory examination indexes and prognosis related indexes of each group were analyzed, and the risk factors affecting prognosis were analyzed by multivariate analysis. The survival of patients during follow-up period was analyzed by *Kaplan-Meier* analysis. **Results** There were statistically significant differences in the age, heart rate, and the proportions of men, hypertension, and clopidogrel among groups ($P<0.05$), and the above indexes in the middle NLR group and high NLR group were significantly higher than those in the low NLR group ($P<0.05$). There were statistically significant differences in the levels of NLR, apolipoprotein A1, blood glucose, urea nitrogen and creatinine among groups ($P<0.05$), and the above indexes in the middle NLR group and high NLR group were significantly higher than those in the low NLR group ($P<0.05$), and the high NLR group was higher than the middle NLR group ($P<0.05$). There was statistically significant difference in the incidence of all-cause death among groups ($P<0.05$), and the incidence of all-cause mortality in the high NLR group was significantly higher than those in the middle NLR group and the low NLR group ($P<0.05$). Older age, faster heart rate, higher urea nitrogen, and taking clopidogrel were the independent risk factors for the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE), with statistically significant differences ($P<0.05$). The *Kaplan-Meier* survival curve showed that the survival rate of patients in the low NLR group was higher than those in the middle NLR group and high NLR group ($P<0.001$), and there was no significant difference in the survival rate between middle NLR group and high NLR group ($P>0.05$). *Log-rank* test showed that the incidence of MACCE in the low NLR group was significantly lower than those in the middle NLR group and the high NLR group ($P<0.05$). **Conclusion** Patients with high NLR, old age, fast heart rate, high urea nitrogen and taking clopidogrel have poor prognosis after PCI, among which NLR can predict the clinical outcome after PCI of patients with coronary heart disease.

Keywords: percutaneous coronary intervention; coronary heart disease; neutrophil to lymphocyte ratio; clinical outcome; coronary angiography

冠心病主要是由冠状动脉粥样硬化并阻塞,从而诱发心肌细胞缺血缺氧或坏死导致,严重威胁人们的健康,虽然欧洲冠心病的发病率及病死率呈下降趋势[1],但在亚洲,冠心病是导致患者死亡的主要原因之一[2]。冠心病是一种多因素复杂性疾病[3],其发生发展与冠状动脉粥样硬化所造成的冠状动脉狭窄程度和支数密切相关。经皮冠状动脉介入治疗(percutaneous coronary intervention,PCI)是目前治疗冠心病的有效手段,其可有效恢复冠状动脉血流,改善患者预后[4]。但PCI属于有创治疗,会造成内皮损伤,从而产生炎症因子,这是否会加重冠心病有待进一步研究。研究发现,炎症反应贯穿了动脉粥样硬化发生发展的全过程[5],而中性粒细胞-淋巴细胞比值(neutrophil to lymphocyte ratio,NLR)可反映中性粒细胞和淋巴细胞的变化趋势,且与炎症严重程度呈正相关[6]。研究显示,NLR简单易得,可以作为预测冠心病严重程度的独立指标[7-8]。但是,目前NLR是否能作为预测冠心病患者PCI后预后的独立指标尚未明确,且冠心病患者PCI后的炎症反应是否会影响冠心病的治疗效果也未见报道。因此,探讨NLR对冠心病患者PCI后临床结局的影响及对预后的预测价值具有重要意义。

1 资料与方法

1.1 临床资料

选择2008年1月至2017年12月在新疆医科大学第一附属医院心脏中心就诊的冠心病患者6 050例,患者经冠状动脉造影确诊并行PCI。因失访等原因,最终纳入6 046例,其中男4 495例、女1 551例;平均年龄(58.50±10.84)岁。采用受试者工作特征曲线确定NLR的最佳截断值,据此将患者分为低NLR组(NLR<2.20,n=1 997)、中NLR组(2.20≤NLR<3.33,n=2 025)和高NLR组(NLR≥3.33,n=2 024)。纳入标准:①临床证实为心肌缺血引发的各类心绞痛;②三支关键心外膜动脉内狭窄程度在75%以上(重度狭窄)或完全闭塞部位≥1处;③冠状动脉内存在尚未治疗的狭窄斑块;④存在右冠状动脉发育障碍,后降支、回旋支、前降支处狭窄程度在75%以上(重度狭窄)或完全闭塞;⑤定期随访,临床资料完整。排除标准:①合并恶性肿瘤;②严重肝、肾功能不全;③预计生存期短于6个月;④不能配合随访及遵医嘱治疗。本研究经新疆医科大学第一附属医院医学伦理委员会批准(20140212-50)。

1.2 方法

统计各组患者年龄、性别、心率、糖尿病、高血压、氯吡格雷使用情况等一般资料。

采集患者晨起时空腹肘静脉血,采用全自动生化分析仪及配套试剂按照透光率比浊法分别于术前测定NLR、尿素氮、肌酐、尿酸、血糖、血清总胆固醇(total cholesterol,TC)、三酰甘油(triglyceride,TG)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol,LDL-C)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol,HDL-C)、载脂蛋白A1、载脂蛋白B、脂蛋白(a)。

出院后第1、6、12和24个月通过电话及门诊等进行随访,此后每3年随访1次,随访终点事件为出现主要不良心脑血管事件(major adverse cardiovascular and cerebrovascular events,MACCE)及主要心血管事件(major adverse cardiovascular events,MACE),包括全因性死亡、心源性死亡、卒中、再梗、心衰、再入院。

1.3 统计学分析

采用EpiData 3.1软件录入数据,使用SPSS 21.0软件开展统计学分析。计量数据行正态性检验、方差齐性分析,符合正态分布且方差齐的数据以均数±标准差($\bar{x}\pm s$)表示,多组间比较采用单因素方差分析,进一步两两比较采用*LSD-t*检验;计数数据以率(%)表示,采用χ^2检验。将单因素分析中有统计学意义的指标纳入*COX*比例风险模型开展多因素分析,应用生存函数(*Kaplan-Meier*)分析生存率。以α=0.05为检验水准,选择双侧检验,以*P*<0.05为差异有统计学意义。

2 结果

2.1 各组患者一般资料比较

各组患者年龄、心率、男性比例、服用氯吡格雷比例比较差异均有统计学意义(*P*<0.05),高NLR组上述指标明显高于中NLR组及低NLR组(*P*<0.05);各组糖尿病、高血压比例比较,差异无统计学意义(*P*>0.05),见表1。

表1 各组患者的一般资料比较

变量	低NLR组(*n*=1 997)	中NLR组(*n*=2 025)	高NLR组(*n*=2 024)	*P*
年龄(岁)	58.28±10.49	59.33±10.87	60.85±10.00	0.000
心率(次/分)	74.57±10.57	75.11±10.79	77.02±12.23	0.000
男性[例(%)]	1 356(67.90)	1 537(75.90)	1 602(79.15)	0.000
糖尿病[例(%)]	450(22.53)	503(24.84)	498(24.60)	0.170
高血压[例(%)]	801(40.11)	894(44.15)	860(42.49)	0.129
服用氯吡格雷[例(%)]	583(29.41)	597(29.67)	656(32.73)	0.040

2.2 各组患者实验室检查指标比较

各组患者NLR、载脂蛋白A1、血糖、尿素氮、肌酐水平比较差异均有统计学意义(*P*<0.05),且中NLR组和高NLR组上述指标明显高于低NLR组(*P*<0.05),高NLR组高于中NLR组(*P*<0.05),见表2。

表2 各组患者的实验室指标比较($\bar{x}\pm s$)

变量	低NLR组(*n*=1 997)	中NLR组(*n*=2 025)	高NLR组(*n*=2 024)	*P*
NLR	1.35±0.25	2.09±0.23*	5.07±4.02*#	0.000
尿素氮(mmol/L)	5.43±1.55	5.52±1.621*	5.61±1.87*#	0.004
肌酐(μmol/L)	72.98±17.46	76.01±20.24*	78.75±22.85*#	0.000
尿酸(mmol/L)	322.13±88.90	326.34±86.12	321.35±95.23	0.176
血糖(mmol/L)	6.14±2.75	6.47±3.17*	7.13±3.17*#	0.000
TG(mmol/L)	1.90±1.31	1.89±1.21	1.92±1.29	0.771
TC(mmol/L)	3.96±1.11	3.995±1.12	3.93±1.10	0.156
HDL-C(mmol/L)	1.02±0.47	1.03±0.54	1.01±0.43	0.457
LDL-C(mmol/L)	2.48±0.92	2.48±0.92	2.42±0.88	0.068
载脂蛋白A1(mmol/L)	1.16±0.30	1.18±0.35*	1.20±0.30*#	0.049
载脂蛋白B(mmol/L)	0.85±0.42	0.87±0.40	0.84±0.37	0.184
脂蛋白(a)(mmol/L)	219.36±169.82	221.48±181.45	219.98±178.94	0.931

*:与低NLR组比较,*P*<0.05,#:与中NLR组比较,*P*<0.05

2.3 各组患者随访期间预后结局指标比较

各组患者全因性死亡发生率比较差异具有统计学意义(*P*<0.05),高NLR组全因性死亡发生率明显高于中NLR组及低NLR组(*P*<0.05);各组患者心源性死亡、MACCE、MACE、心衰、卒中、再梗、再入院情况比较差异均无统计学意义(*P*>0.05),见表3。

2.4 *COX*多因素模型分析结果

*COX*分析结果显示:年龄越大、心率越快、尿素氮越高及服用氯吡格雷是MACCE发生的独立危险因素(*P*<0.05),见表4、5。

2.5 *Kaplan-Meier*生存曲线分析

*Kaplan-Meier*生存曲线显示,随着随访时间延长,低NLR组患者的生存率高于中NLR组和高NLR组

表3 各组患者预后结局指标比较[例(%)]

变量	低NLR组(*n*=1 997)	中NLR组(*n*=2 025)	高NLR组(*n*=2 024)	*P*
全因性死亡	81(4.06)*	104(5.14)*	124(6.13)	0.012
心源性死亡	70(3.51)	87(4.30)	94(4.64)	0.179
MACCE	265(13.30)	300(14.81)	297(14.67)	0.302
MACE	245(12.27)	273(13.48)	267(13.19)	0.490
心衰	53(2.65)	72(3.56)	56(2.77)	0.187
卒中	20(1.00)	31(1.53)	31(1.53)	0.246
再梗	69(3.46)	69(2.41)	56(2.77)	0.383
再入院	277(13.87)	282(13.93)	260(12.85)	0.528

*:与高NLR组比较,*P*<0.05

表4 相关变量赋值表

变量	序号	赋值
性别	Y1	男=0,女=1
服用氯吡格雷	Y2	无=0,有=1
年龄	X1	连续变量
心率	X2	连续变量
尿素氮	X3	连续变量

表5 *COX*回归分析MACCE发生的影响因素

变量	*β*	*SE*	*OR/HR*	95%*CI*	*P*
年龄	0.026	0.006	1.027	1.015~1.039	0.000
性别	−0.022	0.141	0.978	0.742~1.289	0.874
心率	0.025	0.005	1.026	1.016~1.035	0.000
高血压	0.236	0.121	1.266	0.999~1.605	0.051
尿素氮	0.074	0.036	1.077	1.004~1.156	0.038
肌酐	0.001	0.003	1.001	0.995~1.006	0.788
载脂蛋白A1	−0.052	0.175	0.949	0.674~1.337	0.766
服用氯吡格雷	0.213	0.079	1.237	1.059~1.445	0.007

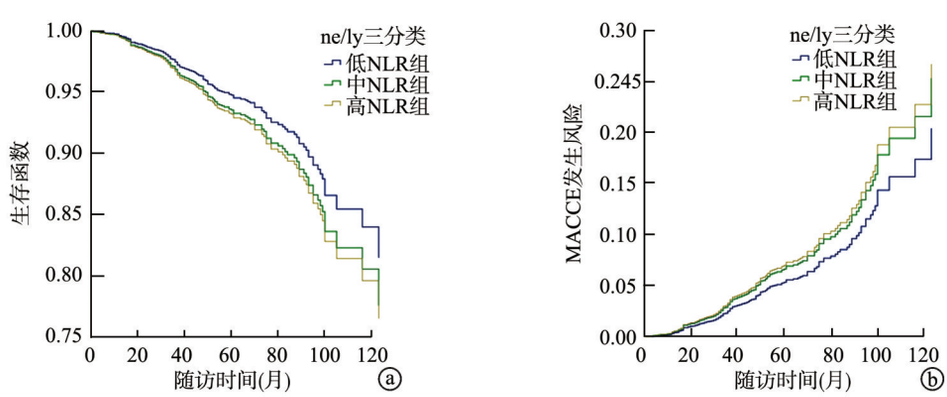
(*P*<0.001),中NLR组和高NLR组生存率比较差异无统计学意义(*P*>0.05);*Log-rank*检验显示,低NLR组MACCE发生率明显低于中NLR组及高NLR组(*P*<0.001),见图1。

3 讨论

冠心病是一种慢性炎症性疾病,其进展可导致患者心脏功能的变化[9]。中性粒细胞数目增加常与炎症反应的发生、发展及严重程度相关;淋巴细胞作为免疫调控因子,其减少与机体应激反应相关[10]。NLR作为炎症标志物,整合了两种白细胞亚型的信息,可反映中性粒细胞及淋巴细胞的平衡情况,避免了单独白细胞亚型在感染、脱水等情况下绝对值受影响的弊端,较其他独立的炎症指标具有更高的临床意义;此外,NLR涉及了细胞免疫与体液免疫两种途径,能更好地反映机体应激程度[11]。中性粒细胞为急性炎症指标,淋巴细胞属于慢性炎症指标,而冠心病是一种慢性炎症性疾病[12-14],用NLR来预测冠心病患者PCI后的预后情况是否可行尚不清楚。因此,探讨NLR对冠心病患者PCI后临床结局的影响及对预后的预测价值很有必要。

已有研究证实,NLR可反映冠状动脉的病变程度,并且可以作为预测冠心病患者PCI后临床结局的独立指标[15-16]。近年来,NLR作为预测心血管疾病患者PCI后的独立预测指标的研究越来越多[17-19],但是均未排除急性心肌梗死与急性冠状动脉综合征,而急性冠状动脉综合征和冠心病不同。冠状动脉粥样硬化斑块破裂会诱发急性冠脉综合征,其属于不完全闭塞及继发性的血栓形成,属于冠心病病理基础的一种,当然并不是所有的冠心病都存在急性冠状动脉综合征表现[20-21]。还有研究纳入了ST段抬高型心肌梗死患者[22]。本研究排除了急性冠状动脉综合征的患者,探讨了术前NLR对冠心病患者PCI后不良结局的影响,结果显示,术前NLR与冠心病患者PCI后全因性死亡的发生密切相关,高NLR组全因性死亡发生率较中NLR组及低NLR组高,与以往研究相似[23-24],说明高NLR是患者预后的影响因素。

本研究排除了非冠心病导致的NLR异常升高的



a:术后生存曲线;b:术后MACCE危险度曲线

图1 患者术后*Kaplan-Meier*曲线

患者,在一定程度上避免了高估NLR对于冠心病患者PCI后临床结局的影响;其次,本研究的样本量较大,时间跨度合理,减少了统计学误差;此外,本研究选取新疆地区特定人群,对患者进行了长达10年的随访,并且患者随访资料完整,提高了研究的可靠性与真实性。但是,本研究为单中心回顾性病例研究,缺少多中心研究对其证实;且没有进行NLR的动态变化分析,未纳入冠心病的所有亚型,因此研究对照异质性较大,存在一定选择偏倚。

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