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· 论著 ·

外周血炎症标志物与急性缺血性脑卒中的关系

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[摘要] 目的 探讨外周血炎症标志物与急性缺血性脑卒中(AIS)的关系。方法 选择2022年8月至12月海军军医大学(第二军医大学)第一附属医院脑血管病中心收治的80例AIS患者为研究对象,根据美国国立卫生研究院卒中量表(NIHSS)评分,将所有患者分为轻度脑卒中组(NIHSS评分<4分,n=50)和中重度脑卒中组(NIHSS评分≥4分,n=30);根据90 d改良Rankin量表(mRS)评分,将所有患者分为预后良好组(mRS评分为0~2分,n=74)和预后不良组(mRS评分为3~6分,n=6)。收集并比较各组患者的基本临床资料、外周血炎症指标[单核细胞与淋巴细胞比值(MLR)、中性粒细胞与淋巴细胞比值(NLR)、血小板与淋巴细胞比值(PLR)、系统免疫炎症指数(SII)和全身炎症反应指数(SIRI)]等实验室检查结果。结果 与轻度脑卒中组相比,中重度脑卒中组有高脂血症病史的患者比例较高[43.3%(13/30) vs 18.0%(9/50),P=0.014],NLR较高[2.81(1.93,5.97) vs 2.01(1.64,3.37),P=0.028]。与预后良好组相比,预后不良组有高脂血症病史的患者比例较高[83.3%(5/6) vs 23.0%(17/74),P=0.007],但两组间MLR、NLR、PLR、SII、SIRI差异均无统计学意义(均P>0.05)。

结论 中重度脑卒中AIS患者外周血炎症标志物NLR较高。

[关键词] 急性缺血性脑卒中; 炎症标志物; 中性粒细胞与淋巴细胞比值; 病情严重程度; 预后

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Relationships between peripheral blood inflammatory markers and acute ischemic stroke

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[Abstract] **Objective** To explore the relationships between peripheral blood inflammatory markers and acute ischemic stroke (AIS). **Methods** A total of 80 AIS patients in Neurovascular Center of The First Affiliated Hospital of Naval Medical University (Second Military Medical University) from Aug. to Dec. 2022 were enrolled. According to the National Institutes of Health stroke scale (NIHSS) score, the patients were categorized into mild AIS group (NIHSS<4, n=50) or moderate-to-severe AIS group (NIHSS≥4, n=30). According to the 90-day modified Rankin scale (mRS) score, the patients were categorized into favorable outcome group (mRS 0-2, n=74) or unfavorable outcome group (mRS 3-6, n=6). The basic clinical data, peripheral blood inflammatory markers (including monocyte to lymphocyte ratio [MLR], neutrophil to lymphocyte ratio [NLR], platelet to lymphocyte ratio [PLR], systemic immune-inflammation index [SII], and systemic inflammatory response index [SIRI]), and other laboratory data of the patients in each group were collected and compared. **Results** Compared with the mild AIS group, the moderate-to-severe AIS group had a significantly higher proportion of hyperlipidemia history (43.3%[13/30]vs 18.0%[9/50], P=0.014) and significantly higher NLR (2.81[1.93,5.97] vs 2.01[1.64,3.37], P=0.028). Compared with the favorable outcome group, the unfavorable outcome group had a significantly higher proportion of hyperlipidemia history (83.3%[5/6] vs 23.0%[17/74], P=0.007), but there were no differences in MLR, NLR, PLR, SII, or SIRI (all P>0.05). **Conclusion** Moderate-to-severe AIS patients have higher NLR.

[Key words] acute ischemic stroke; inflammatory markers; neutrophil to lymphocyte ratio; severity of the disease; prognosis

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脑卒中具有高致残率和高致死率, 其中急性缺血性脑卒中 (acute ischemic stroke, AIS) 占大部分, 是危害人民生命和健康的主要疾病之一, 给社会和家庭造成沉重的负担^[1-6]。越来越多的研究表明, 炎症反应在 AIS 的病理生理过程中扮演着重要角色^[7-9]。近年来, 外周血单核细胞与淋巴细胞比值 (monocyte to lymphocyte ratio, MLR)、中性粒细胞与淋巴细胞比值 (neutrophil to lymphocyte ratio, NLR)、血小板与淋巴细胞比值 (platelet to lymphocyte ratio, PLR)、系统免疫炎症指数 (systemic immune-inflammation index, SII)、全身炎症反应指数 (systemic inflammatory response index, SIRI) 作为新兴的炎症生物标志物^[10-15]受到广泛关注。然而, 目前有关新兴外周血炎症标志物与 AIS 的研究较少。本研究通过回顾 AIS 患者的基本临床资料、实验室检查结果, 初步探讨外周血炎症标志物与 AIS 之间的关系, 以期为 AIS 的早期评估和干预提供新的思路和理论基础。

1 资料和方法

1.1 研究对象 回顾性分析 2022 年 8 月至 12 月海军军医大学 (第二军医大学) 第一附属医院脑血管病中心收治的 80 例 AIS 患者的病例资料。本研究通过海军军医大学 (第二军医大学) 第一附属医院伦理委员会审批。

1.2 纳入与排除标准 纳入标准: (1) 符合《中国急性缺血性脑卒中诊治指南 2018》诊断标准^[16], 并经头颅 CT 或 MRI 检查证实为 AIS; (2) 年龄 ≥ 18 岁; (3) 发病至入院时间 < 14 d。排除标准: (1) 患有精神分裂症或精神发育迟滞等; (2) 患有恶性肿瘤或心、肝、肺、肾功能衰竭; (3) 意识障碍; (4) 入院前 2 周有感染史; (5) 临床资料不完整、无 90 d 改良 Rankin 量表 (modified Rankin scale, mRS) 评分。

1.3 研究方法

1.3.1 临床资料收集 收集患者的人口学资料 (年龄、性别、受教育年限、BMI) 及血管危险因素 (高血压病史、糖尿病史、高脂血症病史、冠心

病史、脑卒中家族史、吸烟史、饮酒史), 入院时收缩压和舒张压, 入院 24 h 内美国国立卫生研究院卒中量表 (National Institutes of Health stroke scale, NIHSS) 评分^[17-18], 牛津郡社区卒中规划 (Oxfordshire Community Stroke Project, OCSP) 分型^[19], 以及 Org 10172 急性脑卒中治疗试验 (Trial of Org 10172 in Acute Stroke Treatment, TOAST) 分型^[20]。

1.3.2 实验室检查资料收集及外周血炎症标志物指标计算 患者入院次日采集空腹外周静脉血, 检测白细胞计数、中性粒细胞计数、单核细胞计数、淋巴细胞计数、血小板计数、空腹血糖、总胆固醇、甘油三酯、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇等实验室指标。计算患者的外周血炎症标志物指标, 具体如下: $MLR = \text{单核细胞计数} / \text{淋巴细胞计数}$, $NLR = \text{中性粒细胞计数} / \text{淋巴细胞计数}$, $PLR = \text{血小板计数} / \text{淋巴细胞计数}$, $SII = (\text{血小板计数} \times \text{中性粒细胞计数}) / \text{淋巴细胞计数}$, $SIRI = (\text{中性粒细胞计数} \times \text{单核细胞计数}) / \text{淋巴细胞计数}$ 。

1.3.3 分组 NIHSS 评分范围为 0~42 分, 分值越高表明神经功能缺损越严重。根据 NIHSS 评分将所有患者分为轻度脑卒中组 (NIHSS 评分 < 4 分)、中重度脑卒中组 (NIHSS 评分 ≥ 4 分)。根据 90 d mRS 评分结果, 将患者分为预后良好组 (mRS 评分为 0~2 分) 和预后不良组 (mRS 评分为 3~6 分), 其中 mRS 评分 6 分为死亡。

1.4 统计学处理 应用 SPSS 26.0 软件进行统计学分析。呈正态分布的计量资料以 $\bar{x} \pm s$ 表示, 组间比较采用 t 检验; 呈偏态分布的计量资料以中位数 (下四分位数, 上四分位数) 表示, 组间比较采用 Mann-Whitney U 检验。计数资料以例数和百分数表示, 组间比较采用 χ^2 检验。所有检验均为双侧检验, 检验水准 (α) 为 0.05。

2 结 果

2.1 轻、中重度 AIS 患者临床资料比较 共纳入 80 例 AIS 患者, 年龄为 27~84 岁, 男 58 例、女 22 例, 其中轻度脑卒中组 50 例、中重度脑卒中组

30例。与轻度脑卒中组相比, 中重度脑卒中组有高脂血症病史的患者比例较高, 差异有统计学意义($P=0.014$)。两组患者的年龄、性别、受教育年限、BMI、高血压病史、糖尿病史、冠心病史、脑

卒中家族史、吸烟史、饮酒史、入院时收缩压、入院时舒张压、OCSP分型、TOAST分型差异均无统计学意义(均 $P>0.05$)。见表1。

表1 轻、中重度 AIS 患者临床资料比较

Tab 1 Comparison of clinical data between mild and moderate-to-severe AIS patients

Factor	Mild AIS N=50	Moderate-to-severe AIS N=30	Statistic	P value
Demographic				
Age/year, $\bar{x} \pm s$	62.38±10.48	59.27±13.72	$t=1.143$	0.256
Male, n (%)	34 (68.0)	24 (80.0)	$\chi^2=1.354$	0.245
Education level/year, M (Q_L, Q_U)	9.0 (9.0, 12.0)	9.0 (9.0, 15.0)	$Z=-0.215$	0.830
BMI/(kg·m ⁻²), $\bar{x} \pm s$	25.06±2.69	25.09±3.69	$t=-0.042$	0.967
Vascular risk factor, n (%)				
Hypertension	36 (72.0)	20 (66.7)	$\chi^2=0.254$	0.614
Diabetes mellitus	19 (38.0)	8 (26.7)	$\chi^2=1.077$	0.299
Hyperlipidemia	9 (18.0)	13 (43.3)	$\chi^2=6.036$	0.014
Coronary heart disease	7 (14.0)	6 (20.0)	$\chi^2=0.153$	0.696
Family history of stroke	12 (24.0)	11 (36.7)	$\chi^2=1.469$	0.226
Smoking	25 (50.0)	15 (50.0)	$\chi^2=0.000$	1.000
Drinking	21 (42.0)	14 (46.7)	$\chi^2=0.166$	0.684
Blood pressure on admission/mmHg				
SBP, $\bar{x} \pm s$	146.42±21.38	142.17±20.32	$t=0.877$	0.383
DBP, M (Q_L, Q_U)	85.00 (78.75, 93.75)	80.00 (72.50, 90.25)	$Z=-1.759$	0.079
OCSP classification, n (%)				
Total anterior circulation infarct	1 (2.0)	4 (13.3)		
Partial anterior circulation infarct	33 (66.0)	15 (50.0)		
Posterior circulation infarct	11 (22.0)	10 (33.3)		
Lacunar circulation infarct	5 (10.0)	1 (3.3)		
TOAST classification, n (%)				
Large-artery atherosclerosis	13 (26.0)	7 (23.3)		
Cardioembolism	3 (6.0)	2 (6.7)		
Small vessel occlusion	29 (58.0)	15 (50.0)		
Other determined etiology	3 (6.0)	2 (6.7)		
Undetermined etiology	2 (4.0)	4 (13.3)		

1 mmHg=0.133 kPa. AIS: Acute ischemic stroke; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OCSP: Oxfordshire Community Stroke Project; TOAST: Trial of Org 10172 in Acute Stroke Treatment; M (Q_L, Q_U): Median (lower quartile, upper quartile).

2.2 轻、中重度 AIS 患者实验室检查结果比较 与轻度脑卒中组相比, 中重度脑卒中组 AIS 患者NLR较高($P=0.028$) ; 而MLR、PLR、SII、SIRI在两组间差异均无统计学意义(均 $P>0.05$)。两组患者的空腹血糖、总胆固醇、甘油三酯、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇差异均无统计学意义(均 $P>0.05$)。见表2。

2.3 预后良好、预后不良 AIS 患者临床资料比较 随访90 d发现, 80例AIS患者中预后良好者有74例, 预后不良者6例。与预后良好组相比, 预后不良组有高脂血症病史的患者比例较高($P=0.007$)。两

组患者的年龄、性别、受教育年限、BMI、高血压病史、糖尿病史、冠心病史、脑卒中家族史、吸烟史、饮酒史、入院时收缩压、入院时舒张压、OCSP分型、TOAST分型差异均无统计学意义(均 $P>0.05$)。见表3。

2.4 预后良好、预后不良 AIS 患者实验室检查结果比较 与预后良好组相比, 预后不良组 AIS 患者MLR、NLR、PLR、SII、SIRI差异均无统计学意义(均 $P>0.05$)。两组患者的空腹血糖、总胆固醇、甘油三酯、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇差异均无统计学意义(均 $P>0.05$)。见表4。

表2 轻、中重度AIS患者实验室指标比较

Tab 2 Comparison of laboratory data between mild and moderate-to-severe AIS patients

Index	Mild AIS N=50	Moderate-to-severe AIS N=30	Statistic	P value
FBG/(mmol·L ⁻¹), M(Q _L , Q _U)	5.9 (5.0, 7.3)	5.6 (5.2, 7.8)	Z=-0.114	0.909
TC/(mmol·L ⁻¹), $\bar{x} \pm s$	4.67±1.15	4.62±1.11	t=0.185	0.854
Triglyceride/(mmol·L ⁻¹), M(Q _L , Q _U)	1.44 (1.10, 2.00)	1.48 (1.01, 1.90)	Z=-0.323	0.747
HDL-C/(mmol·L ⁻¹), M(Q _L , Q _U)	1.19 (1.05, 1.33)	1.09 (0.94, 1.36)	Z=-1.089	0.276
LDL-C/(mmol·L ⁻¹), $\bar{x} \pm s$	2.95±1.04	2.87±0.95	t=0.310	0.757
MLR, M(Q _L , Q _U)	0.26 (0.22, 0.35)	0.31 (0.24, 0.47)	Z=-1.908	0.056
NLR, M(Q _L , Q _U)	2.01 (1.64, 3.37)	2.81 (1.93, 5.97)	Z=-2.196	0.028
PLR, M(Q _L , Q _U)	115 (96, 163)	143 (97, 221)	Z=-1.451	0.147
SII/(L ⁻¹ , ×10 ⁹), M(Q _L , Q _U)	472 (343, 780)	658 (350, 1252)	Z=-1.381	0.167
SIRI/(L ⁻¹ , ×10 ⁹), M(Q _L , Q _U)	1.06 (0.78, 1.55)	1.44 (0.85, 2.89)	Z=-1.848	0.065

AIS: Acute ischemic stroke; FBG: Fasting blood glucose; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; MLR: Monocyte to lymphocyte ratio; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; M(Q_L, Q_U): Median (lower quartile, upper quartile).

表3 预后良好、预后不良AIS患者临床资料比较

Tab 3 Comparison of clinical data between favorable outcome and unfavorable outcome AIS patients

Factor	Favorable outcome N=74	Unfavorable outcome N=6	Statistic	P value
Demographic				
Age/year, $\bar{x} \pm s$	60.73±12.10	67.17±4.67	t=-1.289	0.201
Male, n (%)	54 (73.0)	4 (66.7)	$\chi^2=0.000$	1.000
Education level/year, M(Q _L , Q _U)	9.0 (9.0, 12.0)	10.0 (7.5, 13.0)	Z=0.000	1.000
BMI/(kg·m ⁻²), $\bar{x} \pm s$	25.01±3.12	25.85±2.67	t=-0.642	0.523
Vascular risk factor, n (%)				
Hypertension	51 (68.9)	5 (83.3)	$\chi^2=0.077$	0.781
Diabetes mellitus	24 (32.4)	3 (50.0)	$\chi^2=0.182$	0.670
Hyperlipidemia	17 (23.0)	5 (83.3)	$\chi^2=7.341$	0.007
Coronary heart disease	10 (13.5)	3 (50.0)	$\chi^2=3.079$	0.079
Family history of stroke	19 (25.7)	4 (66.7)	$\chi^2=2.771$	0.096
Smoking	37 (50.0)	3 (50.0)	$\chi^2=0.000$	1.000
Drinking	32 (43.2)	3 (50.0)	$\chi^2=0.000$	1.000
Blood pressure on admission/mmHg				
SBP, $\bar{x} \pm s$	144.50±20.14	148.83±31.61	t=-0.330	0.754
DBP, M(Q _L , Q _U)	82.00 (78.00, 91.25)	86.50 (65.00, 97.00)	Z=-0.046	0.963
OCSP classification, n (%)				
Total anterior circulation infarct	4 (5.4)	1 (16.7)		
Partial anterior circulation infarct	45 (60.8)	3 (50.0)		
Posterior circulation infarct	19 (25.7)	2 (33.3)		
Lacunar circulation infarct	6 (8.1)	0		
TOAST classification, n (%)				
Large-artery atherosclerosis	19 (25.7)	1 (16.7)		
Cardioembolism	5 (6.8)	0		
Small vessel occlusion	39 (52.7)	5 (83.3)		
Other determined etiology	5 (6.8)	0		
Undetermined etiology	6 (8.1)	0		

1 mmHg=0.133 kPa. AIS: Acute ischemic stroke; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OCSP: Oxfordshire Community Stroke Project; TOAST: Trial of Org 10172 in Acute Stroke Treatment; M(Q_L, Q_U): Median (lower quartile, upper quartile).

表 4 预后良好、预后不良 AIS 患者实验室指标比较

Tab 4 Comparison of laboratory data between favorable outcome and unfavorable outcome AIS patients

Index	Favorable outcome N=74	Unfavorable outcome N=6	Statistic	P value
FBG/(mmol·L ⁻¹), M(Q _L , Q _U)	5.8 (5.0, 7.5)	6.5 (6.0, 7.8)	Z=-1.279	0.201
TC/(mmol·L ⁻¹), $\bar{x} \pm s$	4.65 ± 1.16	4.63 ± 0.80	t=0.061	0.951
Triglyceride/(mmol·L ⁻¹), M(Q _L , Q _U)	1.45 (1.10, 1.94)	1.60 (0.82, 2.38)	Z=-0.046	0.964
HDL-C/(mmol·L ⁻¹), M(Q _L , Q _U)	1.18 (1.00, 1.31)	1.14 (0.87, 1.73)	Z=-0.183	0.855
LDL-C/(mmol·L ⁻¹), $\bar{x} \pm s$	2.93 ± 1.03	2.78 ± 0.72	t=0.364	0.717
MLR, M(Q _L , Q _U)	0.28 (0.22, 0.36)	0.31 (0.29, 0.50)	Z=-1.516	0.129
NLR, M(Q _L , Q _U)	2.22 (1.77, 3.57)	3.92 (2.34, 11.33)	Z=-1.681	0.093
PLR, M(Q _L , Q _U)	124 (99, 177)	112 (80, 282)	Z=-0.219	0.826
SII/(L ⁻¹ , ×10 ⁹), M(Q _L , Q _U)	510 (343, 873)	579 (416, 2589)	Z=-0.804	0.422
SIRI/(L ⁻¹ , ×10 ⁹), M(Q _L , Q _U)	1.11 (0.79, 1.83)	1.83 (1.28, 4.63)	Z=-1.863	0.062

AIS: Acute ischemic stroke; FBG: Fasting blood glucose; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; MLR: Monocyte to lymphocyte ratio; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; M (Q_L, Q_U): Median (lower quartile, upper quartile).

3 讨 论

本研究结果显示,与轻度脑卒中组相比,中重度脑卒中组AIS患者中有高脂血症病史的比例较高,外周血炎症标志物NLR较高,差异均有统计学意义(均P<0.05)。与预后良好组相比,预后不良组有高脂血症病史的患者比例较高,差异有统计学意义(P=0.007),但预后良好组与预后不良组患者的外周血炎症标志物差异均无统计学意义(均P>0.05)。

大量研究表明,炎症反应在缺血性脑卒中的发生、发展和预后中起着重要作用^[21-26]。脑缺血后,受损的脑细胞产生大量炎症细胞因子、趋化因子、活性氧(reactive oxygen species, ROS)等神经毒性物质,介导血脑屏障破坏和炎症级联反应,同时引导免疫炎症细胞进入脑组织,进一步介导继发性神经元损伤,加重神经功能障碍^[27]。中性粒细胞是最早侵入缺血脑组织的血源性免疫细胞,其到达缺血区域后,释放促炎介质、蛋白酶、ROS和细胞外基质金属蛋白酶(matrix metalloproteinase, MMP),对缺血组织造成二次损伤^[28]。单核细胞作为MMP-9的来源,可浸润至梗死灶区并加重脑损伤^[29]。单核细胞计数增加已被证明是卒中预后不良的独立预测因素^[30-31]。当发生AIS时,血小板的过度激活和聚集可导致血栓形成和血管阻塞,进而导致血管事件^[32-33]。然而,淋巴细胞被认为在炎症诱导的神经保护中起关键作用,是AIS后主要的脑保护免疫调节剂^[7,34]。

既往研究表明,外周血炎症标志物MLR、

NLR、PLR、SII、SIRI与AIS患者的功能预后相关^[11,35-38]。然而关于外周血炎症标志物与脑卒中严重程度的研究不多^[39]。本研究发现中重度脑卒中组AIS患者外周血炎症标志物NLR高于轻度脑卒中组,与既往研究结果^[40]一致。此外,本研究结果显示预后良好组和预后不良组外周血炎症标志物虽有一定的差异,但差异无统计学意义(均P>0.05)。考虑可能是样本过少的原因,预后不良组仅有6例,未来需加大样本量进一步研究。总之,MLR、NLR、PLR、SII和SIRI作为外周血复合炎症指标,较单一的炎症指标更能反映卒中后机体的免疫炎症反应状态。更重要的是,这5种新的炎症复合标志物仅通过血常规检查便可计算得出,具有费用低、时效快等优点,便于临床应用推广。

本研究为单中心、小样本、回顾性分析,未来需开展多中心、大样本、随访研究验证本研究结果,进一步探索外周血炎症标志物与AIS的关系,从而为AIS的早期评估和干预提供新的策略。

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