脑白质病变严重程度与缺血性脑血管病介入治疗预后不良有关

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摘要 目的:探讨脑白质病变(WMLs)严重程度与缺血性脑血管病患者介入治疗预后不良的关系。方法:选取收治的 102 例缺血性脑血管病患者为研究对象,收集一般资料和临床指标,并根据介入治疗的预后情况分为预后不良组(43 例)和预后良好组(59 例)。通过单因素和多因素分析影响患者预后的独立危险因素,并通过拟合曲线及相关性分析探究 WMLs 与患者预后的关系。依据影响因素构建列线图预测模型,并对模型进行验证。结果:与预后良好组比较,预后不良组年龄更大,糖尿病及高血脂的患者比例更多,体重指数(BMI)、治疗前美国国立卫生研究院卒中量表(NIHSS)、治疗后即刻 NIHSS、术后 24h MAP、WMLs 评分、超敏 C 反应蛋白(hs-CRP)、白介素(IL)-1、IL-6、IL-8、尿酸(UA)、肌肝(Scr)及糖化血红蛋白(HbAc1)更高(P 均 <0.05)。多因素 Cox 回归分析显示,治疗后即刻 NIHSS 评分、WMLs 评分、hs-CRP 及 IL-6 为患者介入治疗预后不良的独立危险因素(P 均 <0.05)。曲线拟合发现,随着 WMLs 评分的升高,患者介入治疗后预后不良的概率呈上升趋势。Pearson 相关性分析显示,WMLs 评分与治疗后即刻 NIHSS 评分、hs-CRP 及 IL-6 呈显著正相关(P 均 <0.05)。用以上因素构建列线图预测模型,其一致性指数(C-index)为 0.815(95% *CI*:0.794 ~ 0.826),受试者工作特征曲线(ROC)曲线下面积(AUC)为 0.832(95% *CI*:0.814 ~ 0.843),具有较好的区分度。结论:WMLs 严重程度为缺血性脑血管病患者介入治疗预后不良的独立危险因素。

关键词 缺血性脑血管病;脑白质病变;介入治疗;预后
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Relationship between the severity of white matter lesions and poor prognosis of interventional treatment in patients with ischemic cerebrovascular disease

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Abstract Objective: To explore the relationship between the severity of white matter lesions (WMLs) and poor prognosis of interventional treatment in patients with ischemic cerebrovascular disease. Methods: A total of 102 patients with ischemic cerebrovascular disease were selected as the research objects. The general data and clinical indicators of the patients were collected, and the patients were divided into poor prognosis group (n = 43) and good prognosis group (n = 59) according to the prognosis of patients after interventional therapy. The independent risk factors influencing the prognosis of patients were analyzed by univariate and multivariate analysis, and the relationship between WMLs and prognosis was explored by fitting curve and correlation analysis. The nomograph prediction model was constructed according to the influencing factors, and the model was verified. Results: The poor prognosis group had a higher mean age, a larger proportion of patients with diabetes and hyperlipidemia, and higher values of body mass index (BMI), National Institute of Health Stroke Scale(NIHSS) before treatment, NIHSS immediately after treatment, mean arterial pressure (MAP) 24 h postoperatively, WMLs score, high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-1, IL-6, IL-8, uric acid (UA), serum creatinine (Scr), and glycosylated hemoglobin (HbA1c) than the good prognosis group (all $P<0.05$). Multivariate Cox regression analysis revealed that NIHSS immediately after treatment, WMLs score, hs-CRP, and IL-6 were independent risk factors for poor prognosis in patients undergoing interventional therapy (all $P<0.05$). Curve fitting showed that the probability of poor prognosis after interventional therapy increased with higher WMLs scores. Pearson correlation analysis indicated a significantly positive correlation between WMLs score and NIHSS immediately after treatment, hs-CRP, and IL-6 (all $P<0.05$). A nomogram prediction model was constructed using these independent influencing factors, with a concordance index (C-index) of 0.815 (95% *CI*: 0.794-0.826) and an area under the receiver operating characteristic (ROC) curve (AUC) of 0.832 (95% *CI*: 0.814-0.843), demonstrating good discrimination. Conclusion: The severity of WMLs may be an independent risk factor of poor prognosis following interventional treatment in patients with ischemic cerebrovascular disease.

Key words Ischemic cerebrovascular disease; White matter lesions; Interventional therapy; Prognosis

缺血性脑血管病包括大血管狭窄脑梗死、椎动脉或锁骨下动脉狭窄所致后循环缺血、慢性大血管闭塞等。主要发病机制为脑部供血动脉狭窄或闭塞引起脑组织不同程度的缺氧、缺血,最终导致脑组织

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坏死,造成持久性损害[1~3]。介入治疗是临床针对老年缺血性脑血管病常用的治疗方法,可有效改善患者症状、延缓病情发展、促进脑供血恢复[4]。脑白质是中枢神经系统的重要组成部分,其中中枢神经细胞的髓鞘损害会引起脑白质病变(white matter lesions, WMLs)[5,6]。脑部动脉粥样硬化是 WMLs 的主要原因,WMLs 严重程度与颈动脉内中膜厚度和颈动脉粥样硬化斑块病变程度密切相关。WMLs 可能是缺血性脑血管病治疗后预后不良的危险因素。本研究通过探讨缺血性脑血管病患者介入治疗预后不良的危险因素,分析 WMLs 与患者预后的关系。

资料与方法

1. 研究对象:选取 2020 年 1 月-2022 年 6 月如皋市人民医院神经内科收治的 102 例缺血性脑血管病患者为研究对象,其中男 52 例,女 50 例,患者年龄 49 ~ 81 岁,平均(66.5 ± 7.2)岁。根据介入治疗预后情况分为预后不良组(43 例)和预后良好组(59 例),2 组相关临床资料见表 1。

纳入标准:①符合缺血性脑血管病的诊断标准[7];②经影像学检查[动脉造影、磁共振成像(MRI)、电子计算机断层扫描(CT)]确诊;③符合介入治疗适应证[8]。排除标准:①排除其他疾病(如中毒、代谢性疾病等)引起的 WMLs;②肝肾功能障碍者;③自身免疫性疾病者;④交流障碍、精神障碍者。本研究经医院伦理委员会批准(批号:20190937),所有患者或家属均知情并签署同意书。

2. 观察指标:收集患者性别、年龄、体重指数(body mass index,BMI)、既往病史、治疗前后美国国立卫生研究院卒中量表(National Institute of Health Stroke Scale,NIHSS)评分、发病至入院时间(onset-to-door time,ODT)、入院至治疗时间(door-to-needle time,DNT)、术后 24 h 平均动脉压(mean arterial pressure,MAP)等临床资料。患者入院后 24 h 内空腹采集外周血标本 5 mL,离心检测总胆固醇(total cholesterol,TC)、甘油三酯(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)、空腹血糖(fasting plasma glucose,FPG)、同型半胱氨酸(homocysteine,Hcy)、尿酸(uric acid,UA)、纤维蛋白原(fibrinogen,FIB)、尿素氮(blood urea nitrogen,BUN)、肌酐(Scr)、糖化血红蛋白(glycated hemoglobin,HbA1c)、白细胞计数(WBC)、超敏 C-反应蛋白(hs-CRP)、白细胞介素(IL)-6、IL-1 及 IL-8。

3. WMLs 评估:将脑白质分为侧脑室旁脑白质和皮质下深部脑白质分别进行评分[9],后将两部分得分相加,总分越高 WMLs 越严重,见图 1。侧脑室旁脑白质评分标准:①未见病变为 0 分;②侧脑室旁可见帽状或者铅笔样薄层病变为 1 分;③侧脑室周围病变呈光滑的晕圈为 2 分;④不规则的脑室旁高信号,延伸到深部白质为 3 分。皮质下深部脑白质评分标准:①未见病变为 0 分;②点状病变为 1 分;③病变开始融合为 2 分;④病变大面积融合为 3 分。

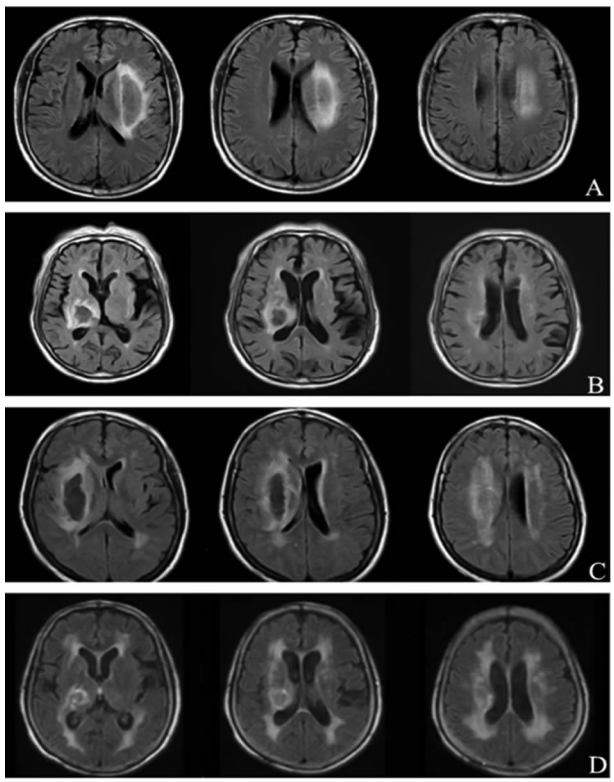

图 1 WMLs 程度(A 为无 WMLs;B 为轻度 WMLs;C 为中度 WMLs;D 为重度 WMLs)

4. 治疗方法:本研究所有患者均行自膨胀式支架介入治疗,治疗前对患者进行维持稳定颅内压、调节血脂、稳定粥样硬化斑块等治疗措施。患者口服 100 mg 阿司匹林肠溶片,连续用药 4 d。治疗过程中行全脑血管造影检查,测量并详细评估脑血管的病变情况,包括但不限于血管狭窄、闭塞、扩张、畸形(如动脉瘤、动静脉瘘)、血管壁钙化、血栓形成以及血流速度、方向和分布等异常改变病变。患者全身麻醉,将导管放置再狭窄病变的近心端,微导丝通过狭窄血管,选择合适球囊,在微导丝引导下通过狭窄部位,确认球囊对病变部位进行覆盖后完成 1 ~ 2 次扩张,去除球囊;选择合适的自膨胀式支架,沿着导

丝到达病变部位。治疗后患者常规口服氯吡格雷和阿司匹林。

5. 预后评估:患者于术后 3 个月再次行全血管造影,血管狭窄率 <30% 为预后良好,血管狭窄率≥30% 为预后不良。

6. 统计学分析:采用 SPSS 23.0 统计学软件,计量资料以($\bar{x} \pm s$)表示,组间比较采用 t 检验;计数资料以百分数(%)表示,组间比较采用 χ^2 检验;采用多因素 Cox 回归分析患者预后不良的危险因素;采用 Pearson 法分析 WMLs 评分与各危险因素的相关性;采用 rms 程序包依据危险因素建立列线图模型,采用 Bootstrap 自抽样法进行验证,采用受试者工作特征(receiver operating characteristic,ROC)曲线评价模型的区分度、准确性和有效性。以 $P<0.05$ 为差异有统计学意义。

结 果

1. 介入治疗预后的单因素分析:与预后良好组比较,预后不良组年龄更大,糖尿病、高血脂的患者比例更多,BMI、治疗前 NIHSS、治疗后即刻 NIHSS、术后 24 h MAP、WMLs 评分、hs-CRP、IL-1、IL-6、IL-8、UA、Scr 及 HbAc1 更高(P 均 <0.05),见表 1。

表 1 介入治疗预后的单因素分析

变量	预后不良组(n=43)	预后良好组(n=59)	统计值	P 值
男性[例(%)]	22(51.16)	30(50.85)	<0.001	0.994
年龄(岁,$\bar{x} \pm s$)	69.1±14.0	60.5±14.2	3.041	0.003
BMI(kg/m^2,$\bar{x} \pm s$)	27.13±3.90	24.53±3.25	3.665	<0.001
吸烟[例(%)]	19(44.19)	26(44.07)	0.001	0.991
饮酒[例(%)]	17(39.53)	23(38.98)	0.210	0.647
高血压[例(%)]	25(58.14)	31(52.54)	0.315	0.575
糖尿病[例(%)]	23(53.49)	15(25.42)	8.381	0.004
高血脂[例(%)]	26(60.47)	24(40.68)	3.897	0.048
冠心病[例(%)]	17(39.53)	22(37.29)	0.053	0.818
房颤[例(%)]	14(32.56)	19(32.20)	0.001	0.970
缺血部位[例(%)]			0.030	0.862
前循环	32(74.42)	43(72.88)		
后循环	11(25.58)	16(27.12)		
治疗前 NIHSS 评分(分,$\bar{x} \pm s$)	16.35±3.76	13.91±4.12	3.063	0.003
治疗后即刻 NIHSS 评分(分,$\bar{x} \pm s$)	10.07±1.64	7.25±1.33	9.579	<0.001
ODT(min,$\bar{x} \pm s$)	114.52±12.53	113.79±12.85	0.286	0.775
DNT(min,$\bar{x} \pm s$)	42.38±8.07	42.16±7.96	0.137	0.891
术后 24 h MAP(mmHg,$\bar{x} \pm s$)	116.93±13.28	103.94±11.83	5.200	<0.001
WMLs[例(%)]	24(55.81)	22(37.29)	3.448	0.063
WMLs 评分(分,$\bar{x} \pm s$)	3.28±1.45	2.02±0.27	12.020	<0.001
TG(mmol/L,$\bar{x} \pm s$)	1.80±0.30	1.74±0.27	1.057	0.293
TC(mmol/L,$\bar{x} \pm s$)	4.12±0.02	4.09±0.13	1.498	0.137
HDL-C(mmol/L,$\bar{x} \pm s$)	1.09±0.14	1.12±0.12	1.162	0.248
LDL-C(mmol/L,$\bar{x} \pm s$)	4.20±0.29	4.16±0.27	0.716	0.476
FPG(mmol/L,$\bar{x} \pm s$)	5.52±1.34	5.50±1.48	0.07	0.944
hs-CRP(mg/L,$\bar{x} \pm s$)	18.46±2.50	5.46±1.57	32.198	<0.001
WBC($\times 10^9$/L,$\bar{x} \pm s$)	21.33±2.74	20.57±2.76	1.377	0.171
IL-1(ng/L,$\bar{x} \pm s$)	17.02±1.49	6.22±0.97	44.302	<0.001
IL-6(ng/L,$\bar{x} \pm s$)	28.36±2.63	11.38±1.36	45.459	<0.001
IL-8(ng/L,$\bar{x} \pm s$)	24.75±3.17	14.57±2.84	17.020	<0.001
BUN(mmol/L,$\bar{x} \pm s$)	5.62±1.41	5.60±2.43	0.048	0.962
UA(μmol/L,$\bar{x} \pm s$)	301.28±84.15	265.39±78.76	2.208	0.030
Scr(μmol/L,$\bar{x} \pm s$)	69.31±12.75	62.73±13.45	2.494	0.014
FIB(g/L,$\bar{x} \pm s$)	2.80±0.50	2.78±0.47	0.207	0.827
Hcy(μmol/L,$\bar{x} \pm s$)	11.73±3.84	10.84±1.53	1.615	0.109
HbAc1(%,$\bar{x} \pm s$)	6.15±0.39	5.70±0.32	6.392	<0.001

2. 介入治疗预后的多因素分析：将单因素分析中差异有统计学意义（$P<0.05$）的因素作为自变量，患者预后情况（预后不良 =1，预后良好 =0）为因变量，进行 Cox 多因素分析，结果显示治疗后即刻 NIHSS 评分、WMLs 评分、hs-CRP 及 IL-6 为患者介入治疗预后不良的独立危险因素（P 均 <0.05），见图 2。

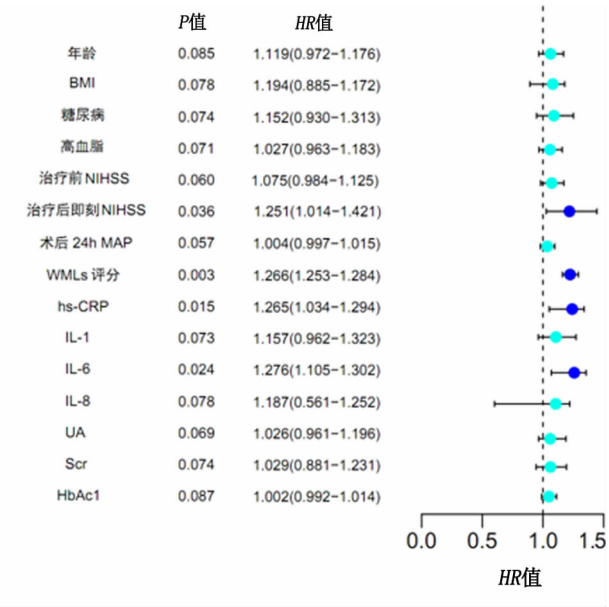

图 2　患者介入治疗预后不良的影响因素森林图

3. WMLs 评分与患者预后的相关性分析：调整治疗后即刻 NIHSS 评分、hs-CRP 和 IL-6 等，曲线拟合及阈值效应分析发现，随着 WMLs 评分的升高，预后不良的发生率呈上升趋势，见图 3。Pearson 相关性分析显示，WMLs 评分与治疗后即刻 NIHSS 评分、hs-CRP 和 IL-6 呈显著正相关（r = 0.73、0.74、0.68，P 均 <0.05），见图 4。

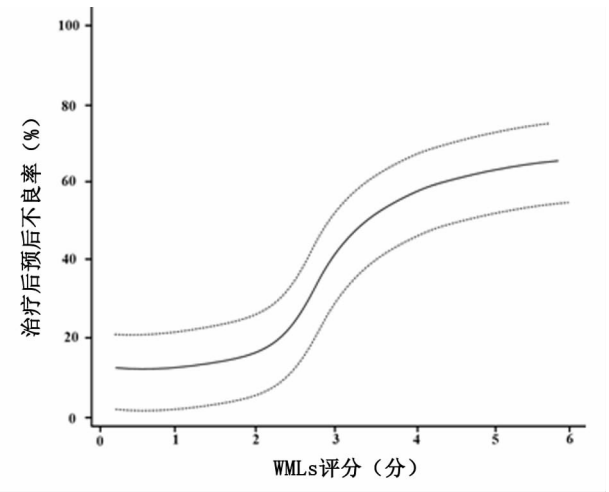

图 3　WMLs 评分与患者预后的拟合曲线

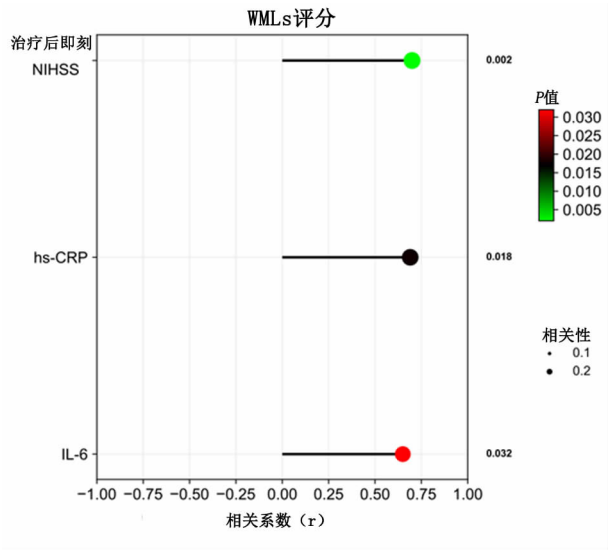

图 4　WMLs 评分与患者预后的拟合曲线

4. 预测模型的构建：将多因素分析结果中影响患者预后的危险因素纳入，构建列线图预测模型发现，治疗后即刻 NIHSS 及 WMLs 评分、hs-CRP、IL-6 的得分分别为 52.31、62.49、56.42、55.36 分，所得总分（226.58 分）对应概率即为列线图模型预测患者治疗后预后不良的概率（80.35%），见图 5。

5. 模型分析：采用 Bootstrap 自抽样法进行内部验证，该预测模型 C-index 计算结果为 0.815（95% *CI*：0.794 ~ 0.826），ROC 曲线下面积（area under the curve，AUC）为 0.832（95% *CI*：0.814 ~ 0.843），提示该风险预测模型的区分度尚可，见图 6。

讨　论

WMLs 是临床常见的影像学表现，主要表现为脑室旁或皮质下白质病变，其发生发展往往预示着神经功能、认知功能障碍以及颅内外缺血事件的发生[10~12]。在缺血性脑卒中患者中，WMLs 的发生率为 45.16%，且不同病情严重程度的患者的 WMLs 程度也有所不同[13]。研究显示，WMLs 可导致缺血性脑卒中患者病情加重，是病情再发、早期梗死灶扩大的独立预测因素[14]。本研究中有 46 例（45.10%）存在不同程度的 WMLs。介入治疗后预后不良的患者 WMLs 评分显著高于预后良好患者。通过多因素 Cox 分析可知 WMLs 评分为缺血性脑血管病患者介入治疗后预后不良的独立危险因素。本研究通过曲线拟合发现，随着 WMLs 评分升高，患者介入治疗后预后不良的概率呈上升趋势。本研究推测 WMLs 是由脑小动脉病变所致，而脑小动脉病

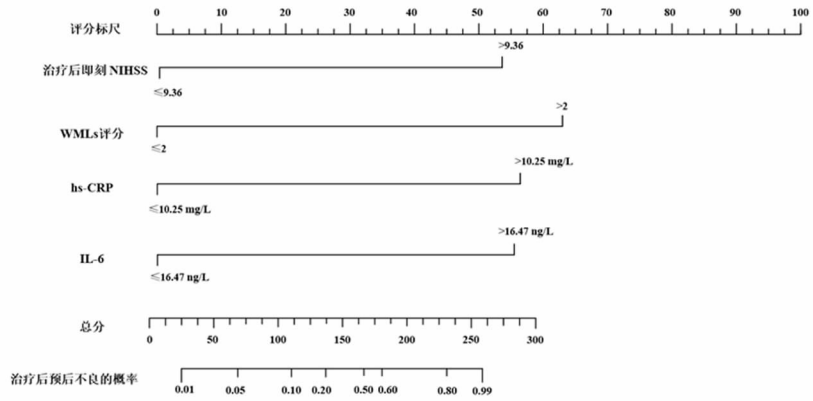

图 5 预测患者预后的列线图模型

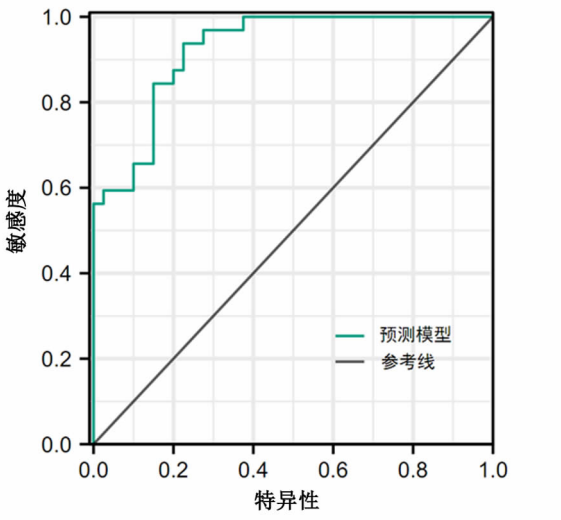

图 6 列线图模型的区分度评价

变导致的动脉粥样硬化会使血管狭窄和闭塞加重[15]，使脑组织中的血流灌注降低，增加颅内血肿量，进而影响患者预后。有研究显示，大脑半球内或半球间完整的联络系统在缺血性脑血管病的恢复过程中扮演着关键角色，WMLs 的发生使髓鞘蛋白与卵磷脂减少，导致神经网络的功能失调，随着 WMLs 的发展，脑组织对缺血缺氧的耐受性不足，血肿周围神经元受损，再生能力降低，进而导致预后不理想[16]。本研究通过多因素 Cox 分析确定治疗后即刻 NIHSS 评分、hs-CRP 和 IL-6 为介入治疗后预后不良的独立危险因素。NIHSS 评分一直是缺血性脑血管疾病预后的重要影响因素，NIHSS 评分高往往预示着预后不良。大量研究表明，炎症因子与缺血性脑血管病之间存在密切联系[17-19]。IL-6 作为参与炎症反应的主要因子之一，可在血栓形成过程中直接作用于血管内皮细胞，影响血管通透性[20]，加重血管堵塞，且其水平越高，患者的神经功能缺损程度越严重，预后越差。而 hs-CRP 是一种急性时相反应蛋白，可参与机体各种的炎性反应过程[21]，表达水平升高提示患者病情较重，预后不良的风险较高。

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