

· 临床研究 ·

核心梗死体积对大血管闭塞性急性缺血性脑卒中早期临床预后后的预测价值

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[摘要] 目的:探讨核心梗死体积对大血管闭塞性急性缺血性脑卒中预后的影响。方法:回顾性分析南京医科大学第一附属医院急诊医学中心2020年1月1日—2021年12月31日行血管内治疗和/或静脉溶栓的大血管闭塞性急性缺血性脑卒中患者的相关临床和影像学资料。根据入院时和治疗72 h后美国国立卫生研究院卒中量表(NIHSS)评分改变值分为预后良好组和预后不佳组,分别比较两组基线资料特征,采用单因素和多因素回归分析预后不佳的危险因素。构建受试者工作特征(receiver operating characteristic, ROC)曲线,分析核心梗死体积对不良预后的预测能力。绘制核心梗死体积和预后不佳的概率以及优势比(odds ratio, OR)之间的关系曲线,分析预后不佳随核心梗死体积变化的趋势。结果:共计纳入131例患者,预后良好组83例,预后不佳组48例。基线资料显示,预后良好组核心梗死体积显著小于预后不佳组($P=0.041$),预后良好组血管内治疗高于预后不佳组($P=0.040$)。预后不佳的单因素回归分析显示,核心梗死体积($OR=1.012, 95\%CI: 1.004\sim 1.021, P=0.006$)、出血并发症($OR=2.296, 95\%CI: 1.028\sim 5.181, P=0.043$)、血管内治疗($OR=0.310, 95\%CI: 0.106\sim 0.851, P=0.025$)、桥接($OR=0.443, 95\%CI: 0.203\sim 0.930, P=0.035$)有统计学意义。多因素回归分析结果显示,核心梗死体积($OR=1.013, 95\%CI: 1.005\sim 1.022, P=0.003$)是预后不佳的独立危险因素。ROC曲线提示核心梗死体积($AUC=0.60, 95\%CI: 0.50\sim 0.71$)对预后不佳有较好的预测价值。非线性曲线表明,核心梗死体积 ≤ 31 mL,预后受核心梗死体积影响较小;核心梗死体积 > 31 mL,预后受核心梗死体积影响较大。结论:核心梗死体积是大血管闭塞性缺血性脑卒中患者预后的独立危险因素。

[关键词] 急性缺血性脑卒中;大血管闭塞;CT灌注成像;核心梗死体积;早期预后**[中图分类号]** R743.3**[文献标志码]** A**[文章编号]** 1007-4368(2022)12-1716-07**doi:** 10.7655/NYDXBNS20221212

Predictive value of core infarct volume in early clinical prognosis of acute ischemic stroke with large vessel occlusion

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[Abstract] **Objective:** To investigate the influence of core infarct volume on the prognosis of acute ischemic stroke with large vessel occlusion. **Methods:** Clinical and imaging data of patients with acute ischemic stroke who underwent endovascular therapy and/or intravenous thrombolysis from January 1, 2020 to December 31, 2021 in the Emergency Medicine Center of the First Affiliated Hospital of Nanjing Medical University were retrospectively analyzed. According to the change value of the National Institutes of Health Stroke Scale (NIHSS) score at admission and 72 hours after treatment, the patients were divided into the good prognosis group and the poor prognosis group. The characteristics of baseline data of the two groups were compared, and the risk factors for poor

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prognosis were analyzed by univariate and multivariate regression. The receiver operating characteristic (ROC) curve was constructed to analyze the predictive ability of core infarct volume on adverse prognosis. The relationship between core infarction volume and the probability of poor prognosis as well as odds ratio (OR) was plotted, and the trend of poor prognosis with core infarction volume was analyzed. **Results:** A total of 131 patients were enrolled, 83 in the good prognosis group and 48 in the poor prognosis group. Baseline data showed that the core infarct volume in the good prognosis group was significantly smaller than that in the poor prognosis group ($P=0.041$), and endovascular therapy in the good prognosis group was higher than that in the poor prognosis group ($P=0.040$). Univariate regression analysis of poor prognosis showed that core infarction volume (OR=1.012, 95% CI: 1.004~1.021, $P=0.006$), bleeding complications (OR=2.296, 95% CI: 1.028~5.181, $P=0.043$), endovascular therapy (OR=0.310, 95% CI: 0.106~0.851, $P=0.025$) and bridging (OR=0.443, 95% CI: 0.203~0.930, $P=0.035$) were statistically significant. Multivariate regression analysis showed that core infarct volume (OR=1.013, 95% CI: 1.005~1.022, $P=0.003$) was an independent risk factor for poor prognosis. ROC curve indicated that core infarct volume (AUC=0.60, 95% CI: 0.50~0.71) had a good predictive value for poor prognosis. The non-linear curve showed that the prognosis was less affected by the volume of core infarction ≤ 31 ml. The prognosis was significantly affected by the volume of core infarction > 31 mL. **Conclusion:** Core infarct volume is an independent risk factor for prognosis of ischemic stroke patients with occlusive large vessels.

[Key words] acute ischemic stroke; large vessels occlusion; CT perfusion imaging; core infarct volume; early prognosis

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大血管闭塞性(large vessel occlusion, LVO)脑卒中占急性缺血性脑卒中的30%~38%^[1],这类患者往往因为病变累及脑供血范围大,病情较重,有较高比例的致残和病死率,给患者、家庭和社会带来经济、心理等多重影响。近年来随着影像技术的发展,单纯血管内治疗或联合静脉溶栓,最短时间内开通血管、恢复脑血流,已经成为大血管闭塞性脑卒中的标准化治疗方式^[2]。血管内治疗前行静脉溶栓,可降低微血管血栓形成的频率,减少术中实现血管再通所需的次数,从而达到良好预后。

有关大血管闭塞性脑卒中患者临床预后的相关因素,目前研究较多的有年龄、入院前美国国立卫生研究院卒中量表(NIHSS)评分、高血压、房颤、Alberta卒中项目早期CT评分(alberta stroke program early CT score, ASPECTS)等^[3-5]。计算机断层扫描灌注成像(computed tomography perfusion imaging, CTP)可定量评估缺血脑组织的血流情况。目前临床常用的自动化分析软件多以相对脑组织血流量(cerebral blood flow, CBF)值小于30%对侧正常脑组织CBF值的区域定义为脑梗死^[6]。既往研究表明,核心梗死体积大小对患者的临床预后具有重要的临床预测价值^[7-8]。本文通过回顾性分析探讨基于CTP的核心梗死体积在预测大血管闭塞性急性缺血性脑卒中早期临床预后中的作用。

1 对象和方法

1.1 对象

回顾性分析南京医科大学第一附属医院急诊

医学中心2020年1月1日—2021年12月31日经脑卒中绿色通道行血管内治疗和/或静脉溶栓的急性缺血性脑卒中患者,收集患者基线资料。患者纳入标准:①入院头颅CT平扫提示无出血;②多模影像显示大血管急性闭塞(包括颈内动脉、大脑中动脉M1/M2段、大脑前动脉A1段、椎基底动脉、大脑后动脉P1段);③CTP图像质量良好,满足后续自动化软件分析要求;④年龄 ≥ 18 岁;⑤发病时间在4.5 h内;⑥接受血管内治疗和/或静脉溶栓;⑦成功再灌注,即改良脑梗死溶栓评分(modified thrombolysis in cerebral infarction, mTICI)达到2b。排除标准:①各种原因未行多模式CT检查;②临床资料不全。研究方案经南京医科大学第一附属医院伦理委员会批准。

1.2 方法

最终共计纳入131例患者,收集患者相关临床资料:年龄、性别、发病到CTP时间、入院时NIHSS评分、核心梗死体积、治疗方式(静脉溶栓、血管内治疗、桥接)、既往史(高血压、糖尿病、冠心病、脑卒中、房颤)、病变血管(前循环、后循环)、出血并发症、吸烟史、饮酒史。所有患者入院后均行多模CT扫描:头颅CT及CTP,CTP检查后根据RAPID软件得出CBF值,将相对CBF值 $< 30\%$ 对侧正常脑组织CBF值的区域定义为脑梗死。CTP重建CT血管造影(CT angiography, CTA)后观察大血管闭塞情况。对符合静脉溶栓适应证的患者,在头颅CT平扫排除颅内出血后征得患者及家属同意后给予重组人组织型纤溶酶原激活物(rt-PA)行静脉溶栓治疗。总量按0.9 g/kg计算,其中前10%剂量静脉推注

10 min,后90%剂量静脉维持1 h,过程中观察有无并发出血、神志改变、症状加重等,如有改变,立即复查头颅CT,如无异常,常规6 h后复查头颅CT。对符合血管内治疗的患者,征得患者及家属同意后给予血管内治疗。术后24 h常规复查头颅CT排除有无出血。

所有患者于入院时及治疗72 h后由2名卒中医生评估NIHSS值。72 h NIHSS较入院NIHSS下降 ≥ 4 分,定为预后良好。72 h NIHSS较入院NIHSS下降 < 4 分或较入院NIHSS升高,定义为预后不佳^[9]。

1.3 统计学方法

所有数据均采用SPSS 25.0软件进行统计学分析。计量资料采用中位数(四分位数)[$M(P_{25}, P_{75})$]表示。所有计量资料通过Shapiro-Wilk正态性检验确定是否服从正态分布,不服从的变量利用Mann-Whitney U 检验比较(最后正态性检验结果显示所有的计量资料均不服从正态分布)。计数资料采用计数和百分比表示。除了病变血管由于格子理论频数小于5,所以使用Yate's连续性校正后卡方检验,其他变量均使用卡方检验。对预后良好组和预后不佳组先进行单因素分析,后使用多元Logistic回归模型分析预后不佳的独立危险因素,后对核心梗死体积及患者基线信息进行Logistic逐步回归分析,根

据最小赤池信息准则(Akaike information criterion, AIC)确定最后引入模型的变量为:核心梗死体积、入院NIHSS评分、高血压史,分析预后不佳的独立危险因素。构建受试者工作特征(receiver operating characteristic, ROC)曲线,通过比较曲线下面积(area under curve, AUC)对核心梗死体积以及其他指标对不良预后的预测能力进行评价,AUC的95%CI通过bootstrap获得。拟合限制立方样条,节点数设为3,绘制核心梗死体积和患者发生不良预后的概率以及优势比(odds ratio, OR)之间的关系曲线,观察预后随核心梗死体积变化的趋势。 $P < 0.05$ 为差异有统计学意义。

2 结果

本研究共计纳入131例患者,依据前文定义的72 h NIHSS改变值,分为预后良好组(83例)和预后不佳组(48例)。两组间比较见表1,预后良好组核心梗死体积明显小于预后不佳组[20.00(9.00, 44.50)mL] vs. 28.00(15.00, 81.75)mL, $P=0.041$];血管内取栓治疗情况,预后良好组高于预后不佳组[76(91.6%) vs. 37(77.1%), $P=0.040$]。年龄、性别、发病到CTP时间、入院时NIHSS评分、静脉溶栓、桥接、高血压、糖尿病、冠心病、脑卒中、房颤、病变血管、出

表1 预后良好组和预后不佳组患者基本资料比较

Table 1 Comparison of the basic characteristics of poor outcome group and good outcome group

临床资料	预后良好($n=83$)	预后不佳($n=48$)	P 值
年龄[岁, $M(P_{25}, P_{75})$]	71.00(65.00, 77.50)	71.00(65.00, 81.00)	0.670
男性[$n(\%)$]	47(56.6)	25(52.1)	0.748
核心梗死体积[mL, $M(P_{25}, P_{75})$]	20.00(9.00, 44.50)	28.00(15.00, 81.75)	0.041
发病到CTP时间[h, $M(P_{25}, P_{75})$]	3.18(1.86, 3.97)	3.26(1.86, 3.85)	0.956
入院NIHSS评分[分, $M(P_{25}, P_{75})$]	16.00(11.50, 20.50)	16.00(9.50, 21.00)	0.702
静脉溶栓[$n(\%)$]	47(56.6)	25(52.1)	0.748
血管内治疗[$n(\%)$]	76(91.6)	37(77.1)	0.040
出血并发症[$n(\%)$]	16(19.3)	17(35.4)	0.066
桥接[$n(\%)$]	40(48.2)	14(29.2)	0.051
高血压史[$n(\%)$]	57(68.7)	39(81.2)	0.173
糖尿病史[$n(\%)$]	15(18.1)	12(25.0)	0.471
冠心病史[$n(\%)$]	13(15.7)	10(20.8)	0.609
脑卒中史[$n(\%)$]	16(19.3)	11(22.9)	0.786
房颤史[$n(\%)$]	30(36.1)	20(41.7)	0.660
病变血管[$n(\%)$]			0.971
前循环	81(97.6)	46(95.8)	
后循环	2(2.4)	2(4.2)	
饮酒史[$n(\%)$]	16(19.3)	8(16.7)	0.890
吸烟史[$n(\%)$]	18(21.7)	7(14.6)	0.444

血并发症、吸烟、饮酒在两组间均无差异($P > 0.05$)。

预后不佳的单因素分析见表2,核心梗死体积大(OR=1.012, 95%CI: 1.004~1.021, $P=0.006$)、出血并发症(OR=2.296, 95%CI: 1.028~5.181, $P=0.043$)、未行血管内治疗(OR=0.310, 95%CI: 0.106~0.851, $P=0.025$)、未行桥接(OR=0.443, 95%CI: 0.203~0.930, $P=0.035$)可作为预后不佳的重要影响因素。根据逐步 Logistic 回归结果,将核心梗死体积、入院NIHSS评分、高血压史纳入预后不佳的多元 Logistic 回归模型(表3),可见核心梗死体积(OR=1.013, 95%CI: 1.005~1.022, $P=0.003$)有统计学意义,可作为预后不佳的独立危险因素。进一步校正发病到CTP时间、入院NIHSS评分、病变血管(前循环、后循环)、脑卒中史、糖尿病史、高血压史、冠心病史以及房颤史,发现核心梗死体积(OR: 1.017, 95%CI 1.008~1.028, $P=0.001$)仍然有统计学意义,是预后不佳的独立危险因素(表4)。

ROC曲线(图1)提示核心梗死体积对预后有良好的预测价值(AUC=0.60,95%CI:0.50~0.71)。采用

表2 影响预后不佳的单因素分析

因素	OR	95%CI	P值
年龄	1.000	0.971~1.031	0.990
性别(女性 vs. 男性)	1.201	0.587~2.458	0.615
核心梗死体积	1.012	1.004~1.021	0.006
发病到CTP时间	1.006	0.755~1.342	0.969
入院时NIHSS评分	0.985	0.941~1.030	0.522
病变血管(前循环 vs. 后循环)	1.761	0.206~15.075	0.578
高血压史	1.977	0.860~4.882	0.121
糖尿病史	1.511	0.631~3.570	0.347
脑卒中史	1.245	0.513~2.943	0.620
房颤史	1.262	0.606~2.614	0.531
冠心病史	1.417	0.557~3.528	0.455
吸烟史	0.617	0.223~1.550	0.322
饮酒史	0.838	0.315~2.086	0.710
出血并发症	2.296	1.028~5.181	0.043
血管内治疗	0.310	0.106~0.851	0.025
静脉溶栓	0.833	0.407~1.703	0.615
桥接	0.443	0.203~0.930	0.035

表3 影响预后不佳的多元回归分析

因素	OR	95%CI	P值
核心梗死体积	1.013	1.005~1.022	0.003
入院NIHSS评分	0.960	0.911~1.008	0.115
高血压史	2.217	0.908~5.896	0.092

表4 核心梗死体积和不良预后之间关系敏感性分析

Table 4 Sensitivity analysis of the relationship between core infarction volume and poor prognosis

模型	OR	95%CI	P值
model1	1.012	1.004~1.021	0.006
model2	1.012	1.004~1.021	0.005
model3	1.017	1.008~1.028	0.001

model1: 只纳入核心梗死体积的单变量模型; model2: 校正年龄、性别、吸烟史以及饮酒史; model3: 进一步校正发病到CTP时间、入院NIHSS评分、病变血管(前循环、后循环)、脑卒中史、糖尿病史、高血压史、冠心病史以及房颤史。

多因素 Logistic 回归模型对核心梗死体积和入院时NIHSS评分、高血压史联合建模, AUC=0.61, 95%CI: 0.55~0.75。考虑到核心梗死体积和预后之间的关系可能是非线性,所以拟合限制立方样条,节点数设为3,绘制核心梗死体积和不良预后的概率以及OR之间的关系曲线,可以看出在核心梗死体积较小(≤ 31 mL)时,对发生不良预后的贡献相对平稳;在31 mL以后,贡献明显升高(图2)。

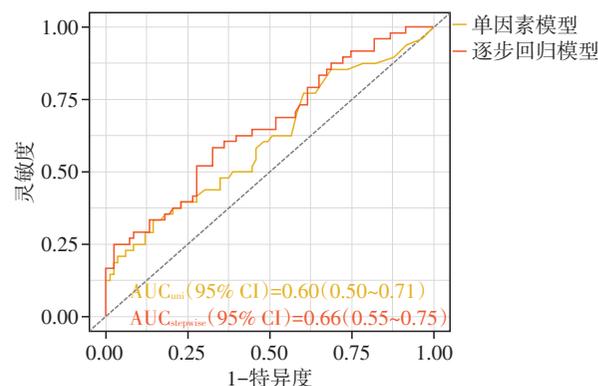


图1 核心梗死体积预测预后的ROC曲线

Figure 1 Receiver operating characteristic curve of the prognosis prediction of core infarction volume

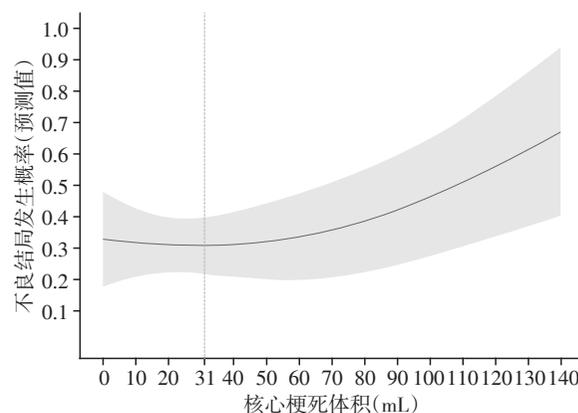


图2 核心梗死和预后不佳的非线性关系

Figure 2 Nonlinear relationship between core infarction and poor prognosis

3 讨论

大血管闭塞导致的急性缺血性脑卒中病情严重、进展迅速、致死率及致残率高、临床预后差,治疗这类脑卒中的关键是快速有效开通闭塞脑血管,恢复脑血流有效循环。如临床救治不及时,将快速出现脑细胞缺血缺氧不可逆性死亡。但即使时间窗内的患者,经积极开通血管治疗,临床结局仍存在不确定性。早期识别预后不佳的危险因素将有助于临床医生对病情进行早期判断和后期严密观察。既往研究发现,高龄、基础NIHSS评分高、侧支循环差、缺血再灌注损伤、核心梗死体积大、高血糖等因素可能影响患者血管再通率及临床预后^[10]。有研究通过回顾性分析发现,动脉取栓后,核心梗死体积小是良好预后的独立危险因素^[11-12]。本文研究结果与之相一致,本中心在校正了相关单因素后,证实核心梗死体积是大血管闭塞性缺血性脑卒中预后的独立危险因素。这与良好的侧支循环及小核心梗死相关,从而带来良好预后^[13-15]。Song等^[16]研究发现,尽管做了静脉溶栓或介入取栓治疗,核心梗死体积大的患者仍然不能有良好预后,作者分析认为核心梗死体积大的患者侧支循环差。良好的侧支可通过软脑膜侧支循环、Willis循环等对缺血区域提供代偿性血流,在脑梗死出现缺血相对较长时间内仍能维持核心梗死区周边组织的血流,从而有效减少梗死区体积;相反,侧支循环差可导致梗死区域代偿性血流少,组织灌注减少,梗死灶扩大,加速缺血半暗带受损组织快速转变为不可逆核心梗死区,从而导致患者不良预后。此外,在安全性方面,大核心梗死与症状性脑出血和恶性水肿相关。有研究证实,随着核心梗死体积增大,症状性出血风险增高^[17-18]。Nawabi等^[19]的一项荟萃分析显示,大核心梗死患者取栓术后恶性水肿率显著升高。本文预后良好和预后不佳组比较结果显示,除核心梗死体积外,预后良好组血管内治疗比例明显高于预后不佳组;单因素分析结果提示,除核心梗死体积外,血管内治疗、桥接是预后不佳的保护因素。这与既往研究结果一致^[20],对大血管闭塞性缺血性脑卒中患者,尽早开通病变血管、挽救缺血半暗带脑组织将带来良好预后可能。同时联合静脉溶栓的桥接治疗较单纯血管内治疗,能降低新发梗死的发生率,降低患者病死率。

目前时间窗内的卒中患者是否应该采用CTP进行评估尚存在争论,Dhillon等^[21]发现窗内使用

CT灌注评估患者核心梗死体积大小与良好预后明显相关,这与本研究结果相一致。然而有研究表明CT灌注成像存在高估核心梗死体积的现象,尤其是时间窗内且发病到CTP成像时间短的患者,梗死核心被过度评估的可能性越高^[22]。另一方面,CTP也存在辐射剂量较大,含碘造影剂用量较多,对患者配合、图像后处理要求高以及可能延误再通时间等现实缺陷,这些因素都在一定程度上限制了时间窗内患者使用CTP进行临床决策^[22]。本研究发现核心梗死体积对预后有较大预测价值,但表现为非线性曲线。当核心梗死体积 <31 mL时,患者治疗后的预后改善情况与其相关性较小;但当核心梗死超过31 mL时,其与预后相关性近乎线性增加。这与Chen等^[23]的研究结论一致,分析原因,考虑可能因为,小核心梗死患者病变血管多为M2等末梢血管,并且拥有良好侧支循环,而大核心梗死患者病变血管多为颈内动脉或者MI近端血管。虽然核心梗死体积大可能会存在治疗后预后不佳,但积极血管内治疗仍显著提高患者90 d良好预后,并且不增加症状性出血发生率^[24]。HERMES研究显示,虽然大核心梗死(≥ 70 mL)患者病死率要高于小核心梗死患者(<70 mL),但是接受血管内治疗的患者较保守治疗患者良好预后率更高,病死率更低^[25]。基于多模影像不断拓宽缺血性卒中的治疗窗,挽救更多的病患是目前卒中救治领域的方向。2022年新奥尔良国际卒中大会上,日本研究者公布了RESCUE-JAPAN LIMIT试验结果,表明大核心梗死患者行血管内治疗,在功能结局方面优于单纯药物保守治疗^[26]。但治疗不应止步于开通血管,早期对于病情客观准确评估,更加有利于卒中患者的早期全面救治,提高良好预后率。结合本研究结果我们认为,即使在大血管病变治疗窗内的患者,当核心梗死体积较大时,积极开通血管后患者仍有预后不佳的可能,临床应该更严密地进行治疗后的病情观察和治疗方案的及时调整。

本研究存在局限性,尽管目前已在多项研究中验证了RAPID软件用于评估核心梗死的准确性,但扫描机器的异质性和CTP方案的略有不同,会导致梗死核心体积的量化差异。其次,所有机构都可以应用功能性影像学对急诊卒中患者进行分诊,并且时间窗内使用CTP评估患者脑组织血流动力学可能有一定程度的假阳性率,这些都限制了本研究结果的泛化。最后,本研究的样本量较少,未能得到预后良好和预后不佳的其他单因素差异,在后续研

究中,将扩大样本量,寻找更多的预后不佳的危险因素。本文选取的时间窗为发病4.5 h内,但在实际临床中,还有更多患者发病于醒后或没有十分清楚的发病时间,希望基于CTP的核心梗死体积对预后的预测价值能扩展应用到此类患者,从而使更多患者受益。

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