·临床研究·

中老年体检人群颈动脉易损斑块的影响因素及列线图模型的建立

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【摘 要】 目的 分析中老年体检人群颈动脉易损斑块的相关危险因素,并构建列线图预测模型。**方法** 回顾性分析2021年9月至12月于苏州大学附属第一医院健康管理中心行颈部血管彩超检查的1 612例体检者的体检资料。根据颈部血管彩色多普勒超声检查分为易损斑块组(287例)及非易损斑块组(1 325例),统计分析2组一般资料、血常规及生化等实验室指标。采用单因素分析及多因素logistic回归分析筛选发生易损斑块的危险因素,联合各独立因素构建发生易损斑块的列线图预测模型,并对模型的预测性和区分度进行验证。采用SPSS(26.0)及R Studio(4.0.2)软件进行统计分析及图形绘制。根据数据类型,组间比较分别采用t检验及χ^2检验。**结果** 与非易损斑块组比较,易损斑块组患者年龄更大,男性、高血压及糖尿病史占比更高,差异均有统计学意义(均$P<0.05$);易损斑块组患者中性粒细胞计数、单核细胞计数、中性粒细胞/淋巴细胞比值、空腹血糖、肌酐较非易损斑块组患者升高,易损斑块组患者血小板计数、血小板/淋巴细胞比值、白蛋白、总胆固醇、低密度脂蛋白胆固醇较非易损斑块组患者降低,差异均有统计学意义(均$P<0.05$)。多因素logistic回归分析结果显示年龄($OR=1.099$,95%CI 1.078~1.120,$P<0.001$)、高血压($OR=1.848$,95%CI 1.351~2.527,$P<0.001$)、糖尿病($OR=3.757$,95%CI 2.614~5.400,$P<0.001$)、中性粒细胞/淋巴细胞比值($OR=2.025$,95%CI 1.055~3.885,$P=0.034$)是颈动脉易损斑块的独立危险因素。利用上述指标构建回归方程并绘制列线图预测模型,对发生易损斑块的列线图模型进行内部验证,C检验参数为0.778,校准曲线显示,模型一致性较好,受试者工作特征曲线下面积为0.781(95%CI 0.752~0.809)。**结论** 中老年体检者发生颈动脉易损斑块的列线图预测模型预测能力和区分能力较好,可用于中老年体检人群颈动脉易损斑块的预测。

【关键词】 体检人群;易损斑块;列线图;模型
【中图分类号】 R543.4 **【文献标志码】** A **【DOI】** 10.11915/j.issn.1671-5403.2022.12.198

Influencing factors of and a nomogram model formulation for vulnerable carotid artery plaques in middle-aged and elderly patients

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【Abstract】 Objective To analyze the risk factors of the vulnerable carotid artery plaques in the middle-aged and elderly people undergoing physical examination and to formulate a predictive nomogram model. **Methods** A retrospective analysis was performed of the physical-examination data of 1 612 patients who underwent cervical vascular Doppler ultrasonography at Health Management Center of the First Affiliated Hospital of Soochow University from September 2021 to December 2021. According to ultrasonographic findings, the patients were divided into vulnerable plaque group ($n=287$) and non-vulnerable plaque group ($n=1\ 325$). Statistical analysis were done of the general data, results of routine blood test, biochemical and other laboratory indicators of the two groups. The risk factors for the occurrence of vulnerable plaques were screened with univariate analysis and multivariate logistic regression, and a predictive nomogram model for the occurrence of vulnerable plaques was formulated by combining the independent factors, and the predictiveness and discrimination of the model were verified. SPSS 26.0 and R Studio 4.0.2 were used for statistical analysis and graphics. Depending on the data type, t-test and χ^2 test were used for comparison between groups. **Results** Compared with the non-vulnerable plaque group, the patients in vulnerable plaque group were older with a higher proportion of males, hypertension and diabetes history, the differences being statistically significant ($P<0.05$ for all). The vulnerable plaque group were higher than the non-vulnerable plaque group in neutrophil count, monocyte count, neutrophil to lymphocyte ratio, fasting plasma glucose and creatinine, but lower in platelet count, platelet-to-lymphocyte ratio, albumin, total cholesterol and low-density lipoprotein cholesterol, all with statistically significant difference ($P<0.05$ for all). Multivariate logistic regression analysis showed that age ($OR=1.099$, 95%CI 1.078-1.120, $P<0.001$), hypertension ($OR=1.848$,

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95%*CI* 1.351-2.527, *P*<0.001), diabetes mellitus (*OR*=3.757, 95%*CI* 2.614-5.400, *P*<0.001), and neutrophil count/lymphocyte count ratio (*OR*=2.025, 95%*CI* 1.055-3.885, *P*=0.034) were independent risk factors of vulnerable carotid plaque. The above indicators were used to formulate a regression equation and draw a predictive nomogram for the occurrence of vulnerable plaque, and an internal verification of it was performed. With a parameter of 0.778 for C test, the calibration curve showed good consistency of the model with an area under the receiver operating characteristic curve of 0.781 (95%*CI* 0.752-0.809). **Conclusion** The predictive histogram model for the occurrence of vulnerable carotid plaque in middle-aged and elderly patients is good. The predictiveness and discrimination can be used to predict vulnerable carotid plaque in middle-aged and elderly people undergoing physical examination.

【Key words】 physical examination population; vulnerable plaque; column chart; model

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脑卒中是我国成年人致死、致残的首位病因,具有发病率、致残率、死亡率及复发率高的特点。近年来,我国居民脑卒中的发病率呈不断上升趋势[1]。相对于其他类型的脑卒中而言,颈动脉及颅内动脉粥样硬化引起的脑梗死是脑卒中患病率最高的一种类型[2,3]。而不稳定的颈动脉易损斑块相比斑块造成的狭窄是更危险的因素[4]。研究显示年龄是颈动脉易损斑块的独立危险因素,随着年龄增长,颈动脉粥样硬化斑块不稳定性明显增加[5]。相比 50 岁以下,50 岁以上居民颈动脉斑块形成率及中重度狭窄率更高[6]。因此,本研究旨在探索中老年体检人群颈动脉易损斑块形成的影响因素并建立预测模型,为人群中大动脉粥样硬化型缺血性脑卒中的预防提供理论依据。

1 对象与方法

1.1 研究对象

本研究为横断面研究,选取 2021 年 9 月至 12 月于苏州大学附属第一医院健康管理中心进行颈部血管彩色多普勒超声检查的体检者为研究对象。纳入标准:(1)年龄≥50 岁;(2)参加体检并完成内外科门诊问诊、常规检查、实验室检查和影像学检查;(3)上述检查结果资料完整。排除标准:(1)严重肝、肾功能障碍;(2)体质量指数(body mass index,BMI)、生化检查等重要数据缺失或记录错误导致与实际情况不符的体检者。最终纳入研究对象 1 612 例,其中男性 1 161 例,女性 451 例;平均年龄(63.38±7.78)岁。根据颈部血管彩色多普勒超声检查结果分为易损斑块组(287 例),非易损斑块组(1 325 例)。本研究经过医院伦理委员会审核批准[(2022)伦研批第 395 号)]。

1.2 方法

1.2.1 一般检查及实验室检查 所有体检者均禁食 8 h 以上,于清晨参加体检,包括询问高血压、糖尿病等相关病史,测量身高、体质量,并计算 BMI,分别抽取肘静脉血 3~5 ml 用于测定血常规及生化指标。

1.2.2 颈部血管超声检查方法 检查仪器为 GE LOGIQ e7/8 彩色多普勒超声诊断仪,参数设置为线阵探头频率 9~3 MHz、凸阵探头 5~2 MHz。患者取仰卧位,头后仰稍偏向检查侧对侧,分别沿颈动脉走行自近心端至远心端扫查双侧颈总动脉、颈动脉分叉、颈内动脉颅外段及椎动脉,测量颈动脉的内-中膜厚度(intima-media thickness, IMT)、内径,观察有无斑块,并记录斑块的大小、表面形态及内部回声。

1.2.3 判断标准 斑块的界定[7]为当 IMT≥1.5 mm,凸出于血管腔内,或局限性内膜增厚高于周边 IMT 的 50%。易损斑块为低回声及不均质回声斑块(内部见大的极低回声即“脂核”,形态不规则,纤维帽薄且不完整)、溃疡型斑块(表面缺损或内见血流信号);非易损斑块为硬斑或扁平斑(内部回声均匀,形态规则,表面光滑,纤维帽完整)。

1.3 观察指标

本研究通过回顾颈动脉易损斑块相关的医学指南、系统综述、预测模型类文献及咨询专家意见等决定观察 22 个因素,主要包括常规项目:年龄、性别、是否有高血压病史、糖尿病病史及 BMI;血常规:中性粒细胞计数、淋巴细胞计数、单核细胞计数、血小板计数(platelet, PLT)、中性粒细胞/淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)、血小板/淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)等;生化指标:空腹血糖(fasting plasma glucose, FPG)、肌酐(creatinine, CRE)、尿酸(uric acid, UA)、白蛋白(albumin, ALB)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、门冬氨酸氨基转移酶(aspartic acid aminotransferase, AST)、总胆红素(total bilirubin, TBil)、甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)及高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)等。

1.4 统计学处理

采用 SPSS 26.0 及 RStudio 软件(4.0.2)进行统计分析及图形的绘制。计量资料用均数±标准差($\bar{x}\pm s$)表示,2 组比较采用独立样本 t 检验;计数资

料用例数(百分率)表示,采用χ^2检验。将候选变量纳入logistic回归分析,以确定颈动脉易损斑块的影响因素。基于多因素logistic回归分析的结果建立预测模型。将独立影响因素导入RStudio软件中使用rms数据包绘制列线图,并通过区分度和校准度对模型进行评价。以受试者工作特征曲线程序数据包绘制受试者工作特征(receiver operating characteristic curve, ROC)曲线和计算C检验参数(C-index)评估模型的区分度,C-index≥0.7表明模型具有参考价值,C-index<0.7表明模型不具有价值或无效;校准度采用校准曲线(Calibration Plot)检验进行评价。采用Bootstrap法重复抽样1 000次,对预测模型进行内部验证。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者的临床资料比较

与非易损斑块组比较,易损斑块组患者年龄更大,男性、高血压及糖尿病史占比更高,差异均有统计学意义(均$P<0.05$);易损斑块组患者中性粒细胞计数、单核细胞计数、NLR、FPG、CRE较非易损斑块组患者升高,易损斑块组患者PLT、PLR、ALB、TC、LDL-C较非易损斑块组患者降低,差异均有统计学意义(均$P<0.05$;表1)。

2.2 多因素logistic回归分析颈动脉易损斑块的独立危险因素

将表1中筛选的单因素和其他潜在影响因素作为协变量,以是否出现颈动脉易损斑块作为因变量进行二元logistic回归分析,结果显示:年龄、高血压史、糖尿病史、空腹血糖及NLR是颈动脉易损斑块的危险因素($P<0.05$;表2)。考虑到空腹血糖易受饮食、情绪及睡眠等多种因素影响常不稳定,本研究最终将年龄、高血压、糖尿病及NLR作为预测因子纳入模型。

2.3 预测模型的构建以及列线图的展示

上述结果显示中老年体检人群颈动脉易损斑块的影响因素为:年龄、高血压病、糖尿病及NLR,以此构建回归方程为:$Logit(P)=-8.097+0.097\times X_1+0.631\times X_2+1.104\times X_3+0.274\times X_4$,其中$X_1$=年龄,$X_2$=高血压病,$X_3$=糖尿病,$X_4$=NLR。并绘制列线图,详见图1。列线图的使用方法:根据列线图每个预测因子的赋值情况,即年龄及NLR为定量资料为具体的数值,高血压及糖尿病为定性资料为1=有,0=无,各预测因子对应到"Point"轴上可以得到相应的分数,将分数加起来的合计分数对应到"Total Points"便可得出个体颈动脉易损斑块发生的概率。

表1 易损斑块及非易损斑块患者临床资料比较

Table 1 Comparison of clinical data between patients with vulnerable and non-vulnerable plaques

Clinical indicator	Non-vulnerable plaque group(n=1 325)	Vulnerable plaque group(n=287)	χ^2/t	P value
Age(years, $\bar{x}\pm s$)	62.14±6.89	69.13±8.99	−12.403	<0.001
Male[n(%)]	928(70.0)	233(81.2)	14.547	<0.001
Hypertension[n(%)]	530(40.0)	183(63.8)	54.003	<0.001
Diabetes mellitus[n(%)]	176(13.3)	94(32.8)	64.130	<0.001
BMI (kg/m^2, $\bar{x}\pm s$)	24.74±3.08	24.97±3.28	−1.165	0.244
N($\times10^9$/L, $\bar{x}\pm s$)	3.29±1.05	3.47±1.06	−2.694	0.007
L($\times10^9$/L, $\bar{x}\pm s$)	1.94±0.59	1.99±0.79	−1.028	0.305
M($\times10^9$/L, $\bar{x}\pm s$)	0.43±0.13	0.46±0.14	−4.130	<0.001
PLT($\times10^9$/L, $\bar{x}\pm s$)	215.60±50.31	206.68±52.34	2.702	0.007
NLR($\bar{x}\pm s$)	1.81±0.74	1.93±0.90	−2.092	0.037
PLR($\bar{x}\pm s$)	118.65±39.53	112.38±40.40	2.424	0.015
FPG(mmol/L, $\bar{x}\pm s$)	5.93±1.33	6.15±1.29	−2.612	0.009
CRE(μmol/L, $\bar{x}\pm s$)	70.92±14.78	75.80±17.38	−4.429	<0.001
UA(μmol/L, $\bar{x}\pm s$)	382.31±88.91	387.86±88.85	−0.959	0.338
ALB(g/L, $\bar{x}\pm s$)	45.71±2.36	45.36±2.39	2.186	0.029
ALT(U/L, $\bar{x}\pm s$)	24.12±25.59	25.25±27.74	−0.668	0.504
AST(U/L)	24.60±14.46	26.10±12.81	−1.632	0.103
TBil(μmol/L, $\bar{x}\pm s$)	16.85±7.65	17.04±7.06	−0.398	0.691
TG(mmol/L, $\bar{x}\pm s$)	1.71±1.15	1.67±1.30	0.464	0.643
TC(mmol/L, $\bar{x}\pm s$)	5.17±1.03	4.79±1.12	5.342	<0.001
LDL-C(mmol/L, $\bar{x}\pm s$)	3.14±0.93	2.80±1.01	5.109	<0.001
HDL-C(mmol/L, $\bar{x}\pm s$)	1.24±0.33	1.21±0.33	1.487	0.137

BMI: body mass index; N: neutrophil; L: lymphocyte; M: monocyte; PLT: platelet; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; FPG: fasting plasma glucose; CRE: creatinine; UA: uric acid; ALB: albumin; ALT: alanine aminotransferase; AST: aspartic acid aminotransferase; TBil: total bilirubin; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

表 2 中老年体检人群颈动脉易损斑块的 logistic 回归分析

Table 2 Logistic regression analysis of carotid vulnerable plaque in middle-aged and elderly people undergoing physical examination

Variable	*B*	*SE*	Wald	*OR*	95%*CI*	*P* value
Gender (male)	0.372	0.230	2.605	1.451	0.923-2.279	0.107
Age	0.094	0.010	94.395	1.099	1.078-1.120	<0.001
Hypertension	0.614	0.160	14.785	1.848	1.351-2.527	<0.001
Diabetes mellitus	1.324	0.185	51.140	3.757	2.614-5.400	<0.001
BMI	0.018	0.026	0.482	1.018	0.968-1.072	0.487
N	-0.389	0.203	3.676	0.678	0.455-1.009	0.055
L	0.219	0.200	1.194	1.244	0.841-1.842	0.274
PLT	0.006	0.004	2.507	1.006	0.999-1.014	0.113
NLR	0.705	0.332	4.504	2.205	1.055-3.885	0.034
PLR	-0.012	0.007	3.356	0.988	0.975-1.001	0.067
FPG	-0.176	0.063	7.826	0.839	0.742-0.949	0.005
CRE	0.008	0.006	2.094	1.008	0.997-1.020	0.148
UA	-0.001	0.001	1.370	0.999	0.997-1.020	0.242
ALB	-0.033	0.032	1.065	0.968	0.909-1.030	0.302
TC	-.0.093	0.322	0.084	0.911	0.485-1.712	0.772
TG	0.060	0.134	0.203	1.062	0.817-1.380	0.653
LDL-C	-.0.054	0.315	0.300	0.947	0.511-1.756	0.863
HDL-C	0.405	0.437	0.859	1.499	0.637-3.527	0.354

BMI: body mass index; N: neutrophil; L: lymphocyte; PLT: platelet; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; FPG: fasting plasma glucose; CRE: creatinine; UA: uric acid; ALB: albumin; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

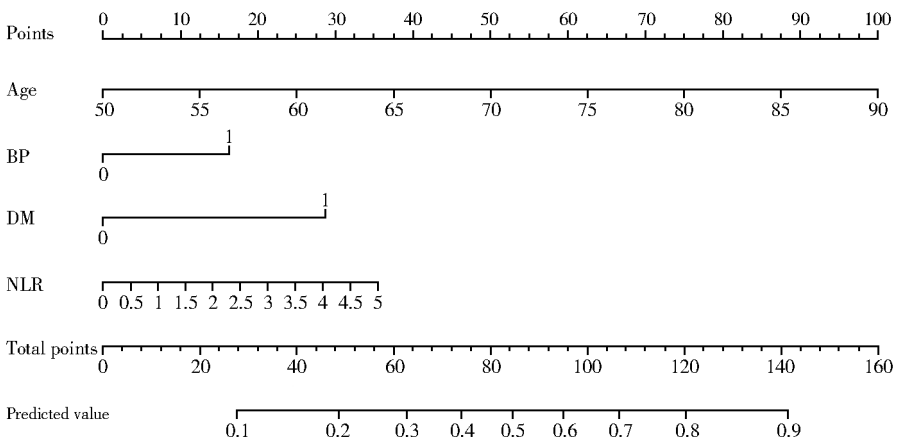


图 1 中老年体检人群颈动脉易损斑块预测模型列线图

Figure 1 Column diagram of prediction model of vulnerable carotid plaques in middle-aged and elderly physical examination population

BP: blood pressure; DM: diabetes mellitus; NLR: neutrophil-to-lymphocyte ratio.

2.4 验证列线图模型对易损斑块的预测能力

为进一步验证列线图模型的临床预测能力，我们首先利用 ROC 曲线，评估基于列线图模型获得的每位患者的总分数与易损斑块发生的关系。结果发现，基于列线图模型的总分数可以有效地预测易损斑块的发生（AUC = 0.781，95% *CI* 0.752~0.809；图 2）。校准曲线分析显示校准曲线与预测概率和实际概率完全相等的理想曲线之间具有良好的一致性（图 3）。此外，预测模型内部验证得到的 C 检验参数为 0.778，校准曲线显示，模型一致性较好（图 4）。

3 讨 论

目前颈动脉粥样硬化及斑块的检查已成为研究大血管病变的窗口，相对于颈动脉狭窄，颈动脉易损斑块被认为更易导致缺血性卒中的发生[8]，并且与缺血性卒中的预后密切相关。因此，如果能在卒中发生的前期或早期对颈动脉易损斑块进行预测，将对脑卒中的预防及控制病情的进展具有重要意义。

研究表明，高血压史、糖尿病史为脑卒中患者颈动脉易损斑块发生的独立危险因素[9,10]。女性、高 HDL-C 是颈动脉斑块及易损斑块形成的保护因素[11]。

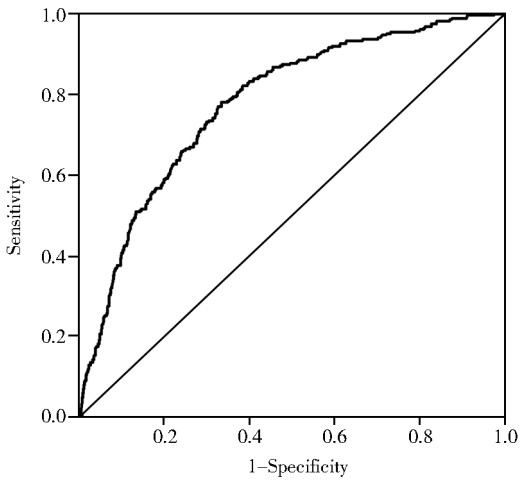


图 2 中老年体检人群颈动脉易损斑块预测模型的 ROC 曲线

Figure 2 ROC curve of carotid vulnerable plaque prediction model in middle-aged and elderly physical examination population

ROC: receiver operating characteristic.

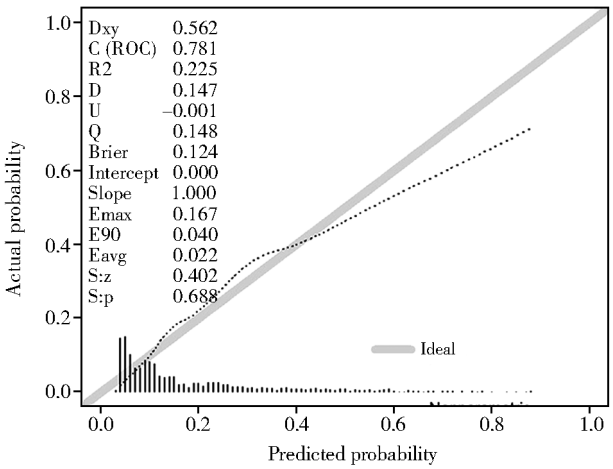
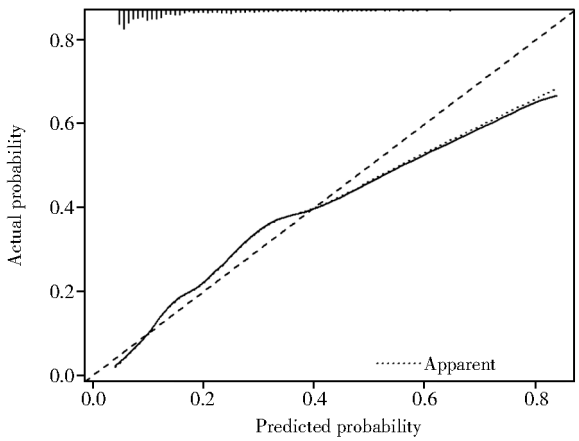


图 3 中老年体检人群颈动脉易损斑块预测模型的校准曲线

Figure 3 Calibration curve of carotid vulnerable plaque prediction model in middle-aged and elderly physical examination population



B=1 000 repetitions, boot mean absolute error=0.022, n=1 612

图 4 中老年体检人群颈动脉易损斑块预测模型的内部校准图

Figure 4 Internal calibration diagram of carotid vulnerable plaque prediction model in middle-aged and elderly physical examination population

高峰等[12]研究表明,年龄>60 岁是颈动脉易损斑块形成的危险因素。本研究通过单因素分析显示,与非易损斑块组比较,易损斑块组患者年龄更大,男性、高血压史及糖尿病史占比更大,多因素 logistic 回归分析进一步证实年龄、高血压史、糖尿病史为颈动脉易损斑块发生的独立危险因素,与上述研究结果基本一致。

研究表明,颈动脉易损斑块发生的主要原因是斑块内新生血管的形成[13]。斑块内新生血管通常为仅由内皮细胞组成的管道,周围无支撑结构及基底膜,斑块容易破裂、出血;且新生血管可能是炎症细胞和脂质成分进入斑块的通路。中性粒细胞是斑块内主要的炎症细胞,是炎症反应的关键因素。一方面,中性粒细胞可以通过增加巨噬细胞募集,并与抗原提呈细胞相互作用来加强炎症反应。另一方面,中性粒细胞通过分泌炎症介质参与急性组织损伤。例如,中性粒细胞通过蛋白水解酶释放花生四烯酸衍生物和超氧自由基,使形成的斑块更加脆弱。淋巴细胞凋亡进一步增加动脉硬化,淋巴细胞与颈动脉易损斑块呈负相关[14]。本研究结果发现易损斑块组患者中性粒细胞计数、NLR 较非易损斑块组患者升高,多因素 logistic 回归分析进一步证实 NLR 为预测颈动脉易损斑块发生的独立危险因素,与张娟等[15]研究结果一致。研究表明,斑块不稳定性的风险随着 NLR 的增加而增加[16]。NLR 是反映人体炎症状态以及炎症激活因子和调节因子之间平衡的生物标志物[17]。因此,NLR 相对于单独研究中性粒细胞及淋巴细胞意义更大。

本研究中易损斑块组总胆固醇及 LDL-C 较非易损斑块组偏低,与既往研究结果相反[15]。可能原因为本研究的研究对象为健康体检无症状人群,并不处于急性卒中发病期,临床患者多因血脂偏高而导致斑块易损诱发卒中,而体检者一经发现颈动脉易损斑块,本中心便会将其纳入重要异常结果来进行管理,告知卒中风险并建议减少胆固醇摄入以及使用他汀类降脂药,从而降低了总胆固醇和 LDL-C 水平。

血糖水平升高可引起人体大血管壁发生慢性炎症改变,高糖诱发的氧化应激反应可加速动脉粥样硬化进程[18,19]。本研究经过多因素 logistic 回归分析建立的颈动脉易损斑块预测模型中去除了容易受饮食、情绪等因素影响的空腹血糖,纳入了比较客观的年龄、高血压、糖尿病病史以及 NLR。经过内部验证,此列线图模型得出的预测结果与实际观察值有较好的一致性,且 ROC 曲线证实此模型有较高的诊断价值。本研究所构建的预测模型将复杂的回归方程进行可视化处理,可以更加简单有效地对患者

发生颈动脉易损斑块风险进行个体化预测。

综上,本研究通过对颈动脉易损斑块临床相关指标的分析,得出了颈动脉易损斑块的独立危险因素,并构建了颈动脉易损斑块的列线图预测模型,该预测模型预测能力和区分能力较好。但本研究也存在样本量较小,未对模型进行外部验证等缺点,在后期可以通过大样本的多中心的前瞻性研究进一步验证此模型的有效性,从而更加精准地进行脑卒中危险分层和风险评估,更有效地识别、管理和干预脑卒中的危险人群。

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