· 综述 ·

颈动脉易损斑块生物标记物与急性缺血性脑卒中研究进展

张燕春[1)] 侯 倩[2)]

1)青海大学研究生院,青海 西宁 810000 2)青海省人民医院,青海 西宁 810007

通信作者:侯倩

【摘要】 近些年来颈动脉粥样硬化及相关循环生物标记物与急性缺血性脑卒中的关系得到越来越多的重视及深入的了解,20%的脑卒中是由动脉粥样硬化病变引起,其中颈动脉斑块不稳定因素是导致缺血性脑卒中的主要病因。大量研究表明,颈动脉粥样硬化斑块可转变为易损斑块,易损斑块破裂后可激活凝血机制,进而形成血栓,这是引起急性缺血性脑卒中的重要病因。临床上探究颈动脉斑块的稳定性对于降低急性缺血性脑卒中发病率具有非常重要的意义和价值。斑块的稳定性可由某些生物标记物预测,为缺血性脑卒中的预防、治疗提供了新的思路。

【关键词】 颈动脉粥样硬化;易损斑块;骨桥蛋白;正五聚蛋白3;基质金属蛋白酶9;视黄醇结合蛋白4;急性缺血性脑卒中

【中图分类号】 R743.33 【文献标识码】 A 【文章编号】 1673-5110(2022)06-0768-04

基金项目:中国卒中学会脑血管病全程管理项目启航基金(编号:2020017)

Progress of carotid vulnerable plaque and related biomarkers and acute ischemic stroke

ZHANG Yanchun, HOU Qian

1) Graduate School of Qinghai University, Xining 810000, China; 2) Qinghai Provincial People's Hospital, Xining 810007 China

Corresponding author: HOU Qian

【**Abstract**】 In recent years, the relationship between carotid atherosclerosis and related circulating biomarkers and acute ischemic stroke has been paid more and more attention and deeply understood. 20% of strokes are caused by atherosclerotic lesions, among which the carotid plaque instability factor is the main cause of ischemic stroke. A large number of studies have shown that the carotid atherosclerotic plaque can transform into a vulnerable plaque, and the vulnerable plaque rupture can activate the coagulation mechanism, and then form thrombosis, which is an important cause of in acute ischemic stroke. It is of great significance and value to explore the stability of carotid artery plaque clinically to reduce the incidence of acute ischemic stroke. The stability of plaque can be predicted by some biomarkers, which provides a new diagnosis and treatment idea for the prevention and treatment of ischemic stroke.

【**Key words**】 Carotid artery atherosclerosis; Vulnerable plaque; Osteopontin; Pentraxin-3; Matrix metalloproteinase-9; Retinol-binding protein; Acute ischemic stroke

脑卒中是位居中国首位、全球第二的致死性疾病,其预后差、致残率高,给全球带来严重的经济负担。因此,了解缺血性脑卒中的病因及其危险因素,对早期识别缺血性脑卒中、预防其发生至关重要[1-3]。脑动脉缺血引起的卒中发病率最高,大样本数据统计可达80%左右,而斑块破裂、脱落引起的卒中仅占

DOI:10.12083/SYSJ.220481

本文引用信息:张燕春,侯倩. 颈动脉易损斑块生物标记物与急性缺血性脑卒中研究进展[J]. 中国实用神经疾病杂志,2022,25(6):768-771. DOI:10.12083/SYSJ.220481

Reference information: ZHANG Yanchun, HOU Qian. Progress of carotid vulnerable plaque and related biomarkers and acute ischemic stroke[J]. Chinese Journal of Practical Nervous Diseases, 2022, 25(6): 768-771. DOI:10.12083/SYSJ.220481

脑卒中发生率的20%[4]。颈动脉作为机体表浅大动脉，其粥样硬化程度可反映全身动脉血管整体硬化的情况，因此可作为全身动脉血管粥样硬化程度的观察窗口。颈动脉内不稳定斑块可引起缺血性脑卒中或短暂性脑缺血发作[5-6]，是急性缺血性脑卒中的独立危险因素之一。研究表明，炎性反应是动脉粥样硬化形成、易损斑块破裂、斑块脱落的关键点[7]。部分研究提出，缺血性脑卒中的发生与颈动脉易损斑块的组成成分相关，而不仅仅指斑块大小及颈动脉的狭窄程度[8-9]，因此，尽早识别导致斑块不稳定的相关因素，针对性采取相应的干预措施，对降低缺血性脑卒中的发生具有深远意义。

1 概述

1.1 易损斑块的定义 关于颈动脉斑块，其形态学、组织学研究提出“易损斑块”的概念，它代表不稳定和易破裂的斑块。易损斑块也被描述为非同源性或者异质性斑块，也可指表面不规则、溃疡的斑块[10]。

1.2 易损斑块的特点 易损斑块的免疫组织学和病理学的特征主要包括以下几点[11-12]：(1)薄壁粥样斑块；(2)斑块内大脂质核心；(3)斑块被大量炎性细胞浸润 (4)斑块内新生血管的情况；(5)斑块内出血；(6)斑块内炎性标志物的增加。

2 生物标记物与颈动脉易损斑块的关系

2.1 骨桥蛋白(osteopontin，OPN) 骨桥蛋白是一种酸性磷酸蛋白酶，带有负电荷，具有细胞黏附、迁移和免疫调节等多种功能，可参与中枢神经系统神经炎症调节[13]。OPN是一种炎性细胞因子，高度表达时可加速动脉粥样硬化斑块进展、导致斑块破裂，干预其表达时可减轻颈动脉内膜的增厚[14]。OPN与CD44蛋白表面受体结合后能够刺激T淋巴细胞趋化、黏附，进一步抑制巨噬细胞释放白细胞介素-10(IL-10)[15]。OPN在体内快速升高时，有加速缺血后新生血管的生成，减轻血管钙化的作用，而缓慢升高则与心血管不良预后相关[16]。血小板源性生长因子、白介素-1 a 可诱导OPN的表达，引起巨噬细胞趋化、血管平滑肌细胞黏附、迁移，加速动脉粥样硬化的进展，引起血栓形成，这都与缺血性脑卒中的发生及发展有密切关联[17]。临床研究表明，缺血性脑卒中患者7 d后OPN水平的升高与脑梗死体积及美国国立卫生研究院卒中量表(NIHSS)评分呈正相关[18]。因此，血清OPN可作为颈动脉易损斑块的生物标记物，对于预防缺血性脑卒中的发生具有重要意义。

2.2 正五聚蛋白3(pentraxin-3，PTX3) PTX3属于pentraxine家族，是由381个氨基酸组成的一种炎性因子，主要由巨噬细胞、活化的内皮细胞、成纤维细胞分泌生成[19-20]。PTX3可参与机体炎症反应和免疫表达，是一种新型中枢神经系统疾病风险预测的生物标记物之一。PTX3在脑血管疾病中能准确反映急性卒中患者的动脉粥样斑块负荷情况，并与卒中患者病情的严重程度相关[21]。PTX3通过抑制粗纤维生长因子生成，削弱斑块纤维帽结构的完整性，介导内皮细胞因子的生成，参与血栓的发生和发展[22]。PTX3有氧化低密度脂蛋白的功能，加速炎症反应，加快动脉粥样斑块的病理进程[23-24]。研究发现，易损斑块组PTX3浓度较稳定斑块组明显增高，提出PTX3可反映动脉粥样硬化斑块的稳定性[25]。还有研究[26]表明，PTX3可能是斑块急性破裂的一种新型炎性生物标记物，可以识别动脉内易损斑块、预测预后，也可用于急性冠脉综合征患者病情的评估。缺血性脑卒中发生时体内PTX3升高明显，循环中高表达的PTX3具有促凝血功能活性，从而加重了缺血性脑卒中的发生、发展[27]。还有研究指出，PTX3水平与NIHSS评分呈正相关，提出PTX3水平可反映脑神经功能缺损程度，可用于临床预测急性脑梗死患者神经功能缺损情况[28]。

2.3 基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9) MMP-9主要是由血管内皮细胞、单核细胞、中性粒细胞分泌的一种基质金属蛋白酶，又称明胶B，其对多种明胶底物具有分解作用[29]。生理条件下，MMP-9在外周血单核细胞表达水平很低，而在病理条件下，许多促炎因子和细胞外基质(extracellular matrix，ECM)上调时，MMP-9表达水平增加。当机体发生炎症时炎性细胞释放大量MMP-9到组织中，然后降解细胞外基质，引起斑块纤维帽变薄，导致斑块不稳定[30]。缺血性脑卒中发生后促炎因子致MMP-9表达增多，MMP-9生成增加可加速降解脑血管基膜中Ⅳ型明胶原蛋白，使血-脑屏障通透性增加，进一步诱导脑水肿、脑出血的发生，而过度降解的细胞外基质可导致动脉粥样硬化斑块中纤维帽变薄，导致粥样斑块向易损斑块转化，使斑块破裂、血栓生成，引起动脉闭塞或狭窄[31-32]。血浆中MMP-9活性增加还可加速脑神经元凋亡，造成脑功能的缺失。多项研究表明，血浆中MMP-9活性与脑梗死的严重程度、梗死体积、不良预后和出血后转化相关[33-34]。

2.4 视黄醇结合蛋白4(retinol-binding protein，RBP4) RBP4主要是由肝细胞和脂肪细胞分泌的

一种新型脂肪因子，是有“脂蛋白折叠”的三级结构，这种结构有利于与脂性小分子结合。RBP4可将维生素A（视黄醇）从肝脏输送到靶组织来调节视黄醇的循环水平，是目前已知仅有的特异性转运蛋白。RBP4还在糖类物质代谢和胰岛素敏感性中起决定性作用[35-37]。部分流行病学研究[38]发现，RBP4水平与缺血性脑卒中的发生呈正相关，原因是血浆中RBP4水平升高，可直接引起线粒体功能障碍和血管内皮氧化损伤，引起血管内皮早期功能障碍。RBP4还可参与血管壁慢性炎性反应，诱导内皮下泡沫细胞形成，促进动脉粥样硬化（atherosclerosis，AS）斑块形成。另外有不少学者提出，RBP4可致动脉斑块不稳定[39-40]。SASAKI等[41]提出RBP4可作为预测AS患者发生脑梗死的重要生物标志物，在急性缺血性脑卒中患者中RBP4水平显著升高，并且与病情严重程度明显相关[42]。外周血中升高的RBP4还可促进血管收缩加重脑缺血，这是大动脉粥样硬化型脑梗死急性期病情进展的重要预测指标[43-44]。

3 总结与展望

急性缺血性脑卒中发病机制十分复杂，大多数研究认为是由动脉血管粥样硬化所致，忽略了易损斑块与缺血性脑卒中的关系。颈动脉粥样硬化易损斑块可导致管腔狭窄、斑块破裂、脱落及血流动力学改变，是颈动脉易损斑块引起缺血性脑卒中的重要发病机制[45-50]。生物标记物可预测颈动脉斑块的稳定性，对缺血性脑卒中的严重性评估及预后发挥重要的作用。缺血性脑卒中作为世界范围内的重大致死、致残性疾病，是中国首要致死病因，且其长期生存率低，因此，尽早识别缺血性脑卒中的病因及危险因素对于预防缺血性脑卒中的发生至关重要，可减轻家庭和社会的经济负担。

4 参考文献

[1] FISHER M, PAGANINI-HILL A, MARTIN A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis [J]. Stroke, 2005, 36(2): 253-257. DOI: 10.1161/01.STR.0000152336.71224.21.

[2] HERPICH F, RINCON F. Management of Acute Ischemic Stroke [J]. Crit Care Med, 2020, 48(11): 1654-1663. DOI: 10.1097/CCM.0000000000004597.

[3] FESKE S K. Ischemic Stroke [J]. Am J Med, 2021, 134(12): 1457-1464. DOI: 10.1016/j.amjmed.2021.07.027.

[4] WANG W, JIANG B, SUN H, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults [J]. Circulation, 2017, 135(8): 759-771. DOI: 10.1161/CIRCULATIONAHA.116.025250.

[5] BRINJIKJI W, HUSTON J R, RABINSTEIN A A, et al. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability [J]. J Neurosurg, 2016, 124(1): 27-42. DOI: 10.3171/2015.1.JNS142452.

[6] 孙海燕. 彩色多普勒超声检测颈动脉斑块对脑血管疾病的防治效果分析[J]. 影像研究与医学应用, 2017, 1(16): 45-47. DOI: CNKI: SUN: YXYY.0.2017-16-023.

[7] ZENG Z, ZHANG Y, LIANG X, et al. Qingnao dripping pills mediate immune-inflammatory response and MAPK signaling pathway after acute ischemic stroke in rats [J]. J Pharmacol Sci, 2019, 139(3): 143-150. DOI: 10.1016/j.jphs.2018.12.009.

[8] BOS D, ARSHI B, VAN DEN BOUWHUIJSEN Q, et al. Atherosclerotic Carotid Plaque Composition and Incident Stroke and Coronary Events [J]. J Am Coll Cardiol, 2021, 77(11): 1426-1435. DOI: 10.1016/j.jacc.2021.01.038.

[9] BARADARAN H, EISENMENGER L B, HINCKLEY P J, et al. Optimal Carotid Plaque Features on Computed Tomography Angiography Associated With Ischemic Stroke [J]. J Am Heart Assoc, 2021, 10(5): e19462. DOI: 10.1161/JAHA.120.019462.

[10] WU J, ZHANG J, WANG A, et al. Association between non-high-density lipoprotein cholesterol levels and asymptomatic vulnerable carotid atherosclerotic plaques [J]. Eur J Neurol, 2019, 26(12): 1433-1438. DOI: 10.1111/ene.13973.

[11] MURGIA A, ERTA M, SURI J S, et al. CT imaging features of carotid artery plaque vulnerability [J]. Ann Transl Med, 2020, 8(19): 1261. DOI: 10.21037/atm-2020-cass-13.

[12] SABA L, SAAM T, JAGER H R, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications [J]. Lancet Neurol, 2019, 18(6): 559-572. DOI: 10.1016/S1474-4422(19)30035-3.

[13] KIM J, AHN M, CHOI Y, et al. Osteopontin is a biomarker for early autoimmune uveoretinitis [J]. Neural Regen Res, 2022, 17(7): 1604-1608. DOI: 10.4103/1673-5374.330614.

[14] ZHU Z, HE Y, SHI M, et al. Plasma osteopontin levels and adverse clinical outcomes after ischemic stroke [J]. Atherosclerosis, 2021, 332: 33-40. DOI: 10.1016/j.atherosclerosis.2021.07.010.

[15] VIANELLO E, KALOUSOVA M, DOZIO E, et al. Osteopontin: The Molecular Bridge between Fat and Cardiac-Renal Disorders [J]. Int J Mol Sci, 2020, 21(15): 5568. DOI: 10.3390/ijms21155568.

[16] LOK Z, LYLE A N. Osteopontin in Vascular Disease [J]. Arterioscler Thromb Vasc Biol, 2019, 39(4): 613-622. DOI: 10.1161/ATVBAHA.118.311577.

[17] 于洋，项广宇，李涛，等. 降纤酶与阿加曲班对急性缺血性脑卒中患者脑血流动力学凝血/纤溶系统及血清GFAP OPN的影响[J]. 中国实用神经疾病杂志, 2020, 23(23): 2061-2067. DOI: 10.12083/SYSJ.2021.04.009.

[18] MESEGUER E, DIALLO D, LABREUCHE J, et al. Osteopontin Predicts Three-Month Outcome in Stroke Patients Treated by Reperfusion Therapies [J]. J Clin Med, 2020, 9(12): 4028. DOI: 10.3390/jcm9124028.

[19] GARLANDA C, BOTTAZZI B, MAGRINI E, et al. PTX3, a Humoral Pattern Recognition Molecule, in Innate Immunity, Tissue Repair, and Cancer [J]. Physiol Rev, 2018, 98(2): 623-639. DOI: 10.1152/physrev.00016.2017.

[20] SHINDO A, TAKASE H, HAMANAKA G, et al. Biphasic roles of pentraxin 3 in cerebrovascular function after white matter stroke [J]. CNS Neurosci Ther, 2021, 27(1): 60-70. DOI: 10.1111/cns.13510.

[21] ZHANG Y, HU H, LIU C, et al. Serum pentraxin 3 as a biomarker for prognosis of acute minor stroke due to large artery atherosclerosis [J]. Brain Behav, 2021, 11(1): e1956. DOI: 10.1002/brb3.1956.

[22] HANSEN C B, BAYARRI-OLMOS R, KRISTENSEN M K, et al. Complement related pattern recognition molecules as markers of

short-term mortality in intensive care patients[J]. J Infect, 2020, 80(4): 378-387. DOI: 10.1016/j.jinf.2020.01.010.
[23] LEIRA Y, IGLESIAS-REY R, GOMEZ-LADO N, et al. Periodontitis and vascular inflammatory biomarkers: an experimental in vivo study in rats[J]. Odontology, 2020, 108(2): 202-212. DOI: 10.1007/s10266-019-00461-3.
[24] KANG Y, YU Y, LU L. The Role of Pentraxin 3 in Aspergillosis: Reality and Prospects[J]. Mycobiology, 2020, 48(1): 1-8. DOI: 10.1080/12298093.2020.1722576.
[25] 许位, 张园园, 高敬华, 等. 急性脑梗死患者血清 sdLDL-C 与 PTX-3 水平与颈动脉粥样硬化斑块性质的关系[J]. 中风与神经疾病杂志, 2019, 36(8): 704-707.
[26] KIMURA S, SUGIYAMA T, HISHIKARI K, et al. Relationship of systemic pentraxin-3 values with coronary plaque components on optical coherence tomography and post-percutaneous coronary intervention outcomes in patients with stable angina pectoris[J]. Atherosclerosis, 2020, 292: 127-135. DOI: 10.1016/j.atherosclerosis.2019.11.022.
[27] KASUDA S, SAKURAI Y, TATSUMI K, et al. Enhancement of Tissue Factor Expression in Monocyte-Derived Dendritic Cells by Pentraxin 3 and Its Modulation by C1 Esterase Inhibitor[J]. Int Arch Allergy Immunol, 2019, 179(2): 158-164. DOI: 10.1159/000496744.
[28] 吴海燕. 急性脑梗死患者糖原合成酶激酶-3β正五聚蛋白 3 水平及意义[J]. 中国实用神经疾病杂志, 2021, 24(1): 60-65. DOI: 10.12083/SYSJ.2020.23.002.
[29] JIANG Y, LIU H, WANG Y, et al. Meta-analysis of matrix metalloproteinase (MMP)-9 C1562T polymorphism and susceptibility to ischemic stroke in the Chinese population[J]. J Int Med Res, 2020, 48(6): 1220725979. DOI: 10.1177/0300060520926427.
[30] LI T, LI X, FENG Y, et al. The Role of Matrix Metalloproteinase-9 in Atherosclerotic Plaque Instability[J]. Mediators Inflamm, 2020, 2020: 3872367. DOI: 10.1155/2020/3872367.
[31] MECHTOUFF L, BOCHATON T, PACCALET A, et al. Matrix Metalloproteinase-9 and Monocyte Chemoattractant Protein-1 Are Associated With Collateral Status in Acute Ischemic Stroke With Large Vessel Occlusion[J]. Stroke, 2020, 51(7): 2232-2235. DOI: 10.1161/STROKEAHA.120.029395.
[32] MASHAQI S, MANSOUR H M, ALAMEDDIN H, et al. Matrix metalloproteinase-9 as a messenger in the cross talk between obstructive sleep apnea and comorbid systemic hypertension, cardiac remodeling, and ischemic stroke: a literature review[J]. J Clin Sleep Med, 2021, 17(3): 567-591. DOI: 10.5664/jcsm.8928.
[33] SALEEM S, WANG D, ZHAO T, et al. Matrix Metalloproteinase-9 Expression is Enhanced by Ischemia and Tissue Plasminogen Activator and Induces Hemorrhage, Disability and Mortality in Experimental Stroke[J]. Neuroscience, 2021, 460: 120-129. DOI: 10.1016/j.neuroscience.2021.01.003.
[34] DAGONNIER M, DONNAN G A, DAVIS S M, et al. Acute Stroke Biomarkers: Are We There Yet?[J]. Front Neurol, 2021, 12: 619721. DOI: 10.3389/fneur.2021.619721.
[35] LIU C, CHE Y. Retinol-Binding Protein 4 Predicts Lesion Volume (Determined by MRI) and Severity of Acute Ischemic Stroke[J]. Neurotox Res, 2019, 35(1): 92-99. DOI: 10.1007/s12640-018-9933-z.
[36] NONO N P, BLUHER M. Retinol-binding protein 4 in obesity and metabolic dysfunctions[J]. Mol Cell Endocrinol, 2021, 531: 111312. DOI: 10.1016/j.mce.2021.111312.
[37] RYCHTER A M, SKRZYPCZAK-ZIELINSKA M, ZIELINSKA A, et al. Is the Retinol-Binding Protein 4 a Possible Risk Factor for Cardiovascular Diseases in Obesity?[J]. Int J Mol Sci, 2020, 21(15): 5229. DOI: 10.3390/ijms21155229.
[38] DOL-GLEIZES F, PAUMELLE R, VISENTIN V, et al. Rimonabant, a selective cannabinoid CB1 receptor antagonist, inhibits atherosclerosis in LDL receptor-deficient mice[J]. Arterioscler Thromb Vasc Biol, 2009, 29(1): 12-18. DOI: 10.1161/ATVBAHA.108.168757.
[39] LIU Y, ZHONG Y, CHEN H, et al. Retinol-Binding Protein-Dependent Cholesterol Uptake Regulates Macrophage Foam Cell Formation and Promotes Atherosclerosis[J]. Circulation, 2017, 135(14): 1339-1354. DOI: 10.1161/CIRCULATIONAHA.116.024503.
[40] SATISH M, SAXENA S K, AGRAWAL D K. Adipokine Dysregulation and Insulin Resistance with Atherosclerotic Vascular Disease: Metabolic Syndrome or Independent Sequelae?[J]. J Cardiovasc Transl Res, 2019, 12(5): 415-424. DOI: 10.1007/s12265-019-09879-0.
[41] SASAKI M, OTANI T, KAWAKAMI M, et al. Elevation of plasma retinol-binding protein 4 and reduction of plasma adiponectin in subjects with cerebral infarction[J]. Metabolism, 2010, 59(4): 527-532. DOI: 10.1016/j.metabol.2009.08.015.
[42] ISIK M, BEYDEMIR S, YILMAZ A, et al. Oxidative stress and mRNA expression of acetylcholinesterase in the leukocytes of ischemic patients[J]. Biomed Pharmacother, 2017, 87: 561-567. DOI: 10.1016/j.biopha.2017.01.003.
[43] ZHOU W, YE S D, WANG W. Elevated retinol binding protein 4 levels are associated with atherosclerosis in diabetic rats via JAK2/STAT3 signaling pathway[J]. World J Diabetes, 2021, 12(4): 466-479. DOI: 10.4239/wjd.v12.i4.466.
[44] KADOGLOU N, KORAKAS E, KARKOS C, et al. The prognostic role of RBP-4 and adiponectin in patients with peripheral arterial disease undergoing lower limb endovascular revascularization[J]. Cardiovasc Diabetol, 2021, 20(1): 221. DOI: 10.1186/s12933-021-01411-6.
[45] SPACEK M, ZEMANEK D, HUTYRA M, et al. Vulnerable atherosclerotic plaque - a review of current concepts and advanced imaging[J]. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2018, 162(1): 10-17. DOI: 10.5507/bp.2018.004.
[46] FABIANI I, PALOMBO C, CARAMELLA D, et al. Imaging of the vulnerable carotid plaque: Role of imaging techniques and a research agenda[J]. Neurology, 2020, 94(21): 922-932. DOI: 10.1212/WNL.0000000000009480.
[47] VRACHATIS D A, PAPAIOANNOU T G, Deftereos S, et al. Hunting the Vulnerable Carotid Plaque: All That Glitters May Not Be Gold[J]. Ultrasound Med Biol, 2020, 46(11): 3168. DOI: 10.1016/j.ultrasmedbio.2020.04.039.
[48] KRAMER C M, TREIMAN G S. Vulnerable Plaque in Carotid Arteries Without "Significant" Stenosis: Unmasking the Hidden Links to Stroke[J]. J Am Coll Cardiol. 2020, 76(19): 2223-2225. DOI: 10.1016/j.jacc.2020.09.531.
[49] SHEN Y, GUO D Q. Predict the Probability of the Presence of Vulnerable Carotid Plaque[J]. Ann Vasc Surg, 2021, 70: e2. doi: 10.1016/j.avsg.2020.08.091.
[50] Schinkel A F L. Hunting the Vulnerable Carotid Plaque: In Search of a Gold Standard[J]. Ultrasound Med Biol, 2020, 46(11): 3169. DOI: 10.1016/j.ultrasmedbio.2020.07.016.