doi: 10.13241/j.cnki.pmb.2021.13.027

不同类型缺血性脑血管病血清 VCAM-1、MMP-2、TIMP-1 的表达及与神经功能缺损的关系分析 *

赵锦程[1] 王 星[2] 吴 磊[1] 韩 莹[1] 李起超[1] 张明乐[3]

（1 秦皇岛市第一医院神经外二科 河北 秦皇岛 066000;2 秦皇岛市第一医院内分泌二科 河北 秦皇岛 066000;
3 河北医科大学附属第二医院妇产科 河北 石家庄 050000）

摘要 目的:探讨不同类型缺血性脑血管病血清血管细胞粘附分子 -1(VCAM-1)、基质金属蛋白酶 -2(MMP-2)、基质金属蛋白酶抑制剂 1(TIMP-1)的表达及与神经功能缺损的关系。**方法:**选择 2016 年 1 月至 2020 年 1 月我院接诊的 98 例缺血性脑血管病患者为本研究对象,其中脑梗死 55 例设为脑梗死组,短暂性脑缺血发作组 43 例,并选择我院同期体检中心健康者 50 作为对照组,分析三组血清 VCAM-1、MMP-2、TIMP-1 水平之间的差异及不同神经缺损程度血清 VCAM-1、MMP-2、TIMP-1 水平、美国国立卫生研究院卒中量表(NIHSS)评分变化情况,及其之间的相关性。**结果:**脑梗死组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于短暂性脑缺血发作组和对照组，差异显著（$P<0.05$）；短暂性脑缺血发作组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于对照组,差异显著($P<0.05$);重度神经缺损组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于中度神经缺损组和轻度神经缺损组,差异显著($P<0.05$);中度神经缺损组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于轻度神经缺损组,差异显著($P<0.05$);相关性分析结果中显示,血清 VCAM-1、MMP-2、TIMP-1 均和 NIHSS 评分呈正相关(r=0.603, 0.915, 0.778,$P<0.05$)。**结论:**血清 VCAM-1、MMP-2、TIMP-1 在缺血性脑血管病患者中表达异常,神经缺损越严重血清 VCAM-1、MMP-2、TIMP-1 表达越高。

关键词:不同类型;缺血性脑血管病;血管细胞粘附分子 -1;基质金属蛋白酶 -2;基质金属蛋白酶抑制剂 1;神经功能缺损

中图分类号:R743 **文献标识码:**A **文章编号:**1673-6273(2021)13-2531-04

Analysis of the Expression of vCAM-1, MMP-2 and TIMP-1 in Serum of Different Types of Ischemic Cerebrovascular Diseases and Their Relationship with Nurological Impairment*

ZHAO Jin-cheng[1], WANG Xing[2], WU Lei[1], HAN Ying[1], LI Qi-chao[1], ZHANG Ming-le[3]

*(1 The Second Department of Neurosurgery, Qinhuangdao First Hospital, Qinhuangdao, Hebei, 066000, China;
2 Department of Endocrinology, Qinhuangdao First Hospital, Qinhuangdao, Hebei, 066000, China; 3 Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050000, China)*

ABSTRACT Objective: To study Analysis of theexpression of Vascular cell adhesion molecule-1 (VCAM-1), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-1 (TIMP-1) in serum of different types of ischemic cerebrovascular diseases and their relationship with neurological impairment. **Methods:** 98 cases of patients with ischemic cerebrovascular disease in our hospital from January 2016 to January 2020 were selected as the research objects, including 55 cases of cerebral infarction as cerebral infarction group, 43 cases of transient ischemic attack group, and 50 healthy people in the physical examination center of our hospital at the same period as the control group. The differences of serum VCAM-1, MMP-2, TIMP-1 levels and serum VCAM-1, MMP-2, TIMP-1 levels in three groups were analyzed TIMP-1 level, NIHSS score changes, and their correlation. **Results:** The serum levels of VCAM-1, MMP-2, TIMP-1 and NIHSS scores in cerebral infarction group were significantly higher than those in TIA group and control group($P<0.05$). The serum levels of VCAM-1, MMP-2, TIMP-1 and NIHSS score in TIA group were significantly higher than those in control group ($P<0.05$). Serum VCAM-1, MMP-2, TIMP-1 and NIHSS scores in severe nerve defect group were significantly higher than those in moderate nerve defect group and mild nerve defect group, the differences were significant($P<0.05$). The serum levels of VCAM-1, MMP-2, TIMP-1 and NIHSS score in moderate nerve defect group were significantly higher than those in mild nerve defect group($P<0.05$). Correlation analysis results showed that serum VCAM-1, MMP-2, TIMP-1 were positively correlated with NIHSS score (r=0.603,0.915,0.778, $P<0.05$). **Conclusion:** Serum VCAM-1, MMP-2 and TIMP-1 were abnormally expressed in patients with ischemic cerebrovascular disease, and the more serious the nerve defect was, the higher the expression of VCAM-1, MMP-2 and TIMP-1 was.

* 基金项目:河北省医学适用技术跟踪项目(GZ2020087)

作者简介:赵锦程(1987-),男,硕士研究生,主治医师,研究方向:脊柱退行性变,髓内肿瘤,脑血管病,颅脑肿瘤,
电话:13603359113,E-mail: xinbadazhao@126.com

(收稿日期:2020-12-27 接受日期:2021-01-23)

Key words: Different types; Ischemic cerebrovascular disease; Vascular cell adhesion molecule-1; Matrix metalloproteinase-2; Matrix metalloproteinase inhibitor 1; Neurological impairment

Chinese Library Classification(CLC): R743 Document code: A

Article ID: 1673-6273(2021)13-2531-04

前言

缺血性脑血管病又称脑血性疾病，是神经科常见疾病，主要是由于供血功能障碍引起的脑组织缺血缺氧，引起脑组织损伤，从而导致的神经功能异常，可分为短暂性脑缺血发作、脑梗死等，病死率较高，已成为我国致残和死亡的主要原因[1-3]。有研究显示，缺血性脑血管病的发生受 VCAM-1、MMP-2、TIMP-1 的影响[4]。VCAM-1 在正常情况下无表达，在炎性刺激下表达升高，参与血管内皮发生的过程，有研究显示，VCAM-1 在缺血性脑卒中中表达较高，参与了脑血管疾病的发展[5]。MMP-2 是基质金属蛋白酶(MMP)基因家族的成员，参与了脑组织损伤的病理过程；TIMP-1 是重要的生物活性因子，是引起脑部微循环损伤的主要成分，可加重脑缺血再灌注损伤，可成为预测脑梗死的危险因素[6,7]。目前已有研究证实 VCAM-1、MMP-2、TIMP-1 水平与缺血性脑血管病的发生有密切关系[8]，但不同类型缺血性脑血管病与 VCAM-1、MMP-2、TIMP-1 的关系缺乏相关报道，因此，本研究观察不同类型缺血性脑血管病血清 VCAM-1、MMP-2、TIMP-1 水平变化，并分析与神经功能缺损的关系。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月至 2020 年 1 月我院接诊的 98 例缺血性脑血管病患者，其中脑梗死 55 例设为脑梗死组，男 38 例，女 17 例，年龄 35~81 岁，平均(52.35± 3.25)岁，短暂性脑缺血发作组 43 例，男 22 例，女 21 例，年龄 33~78 岁，平均(52.28± 3.31)岁；将两组患者根据美国国立神经缺损评分分为重度神经缺损 19 例(31~42 分)，中度神经缺损 52 例(16~30 分)，轻度神经缺损 27 例（0~15 分）；选择我院同期体检中心健康者 50 作为对照组，其中男性 28 例，女性 22 例；年龄 36~79 岁，平均年龄(52.35± 3.41)岁。两组患者在性别、年龄等一般资料无明显差异，具有可比性。

参照《中国缺血性脑血管病血管内介入诊疗指南 2015》[9]：昏迷；肌张力减弱或消失；血管造影确诊。

纳入标准：(1)符合上述诊断标准；(2)首次发病；(3)发病时间小于 3 d；(4)家属签署知情同意书。排除标准：(1)出血性疾病者；(2)沟通障碍者；(3)合并恶性肿瘤者；(4)日常生活能力丧失，完全依赖；(5)无法言语交流者；(6)依从性较差者；(7)近 1 月未使用糖皮质激素；(8)严重肝肾疾病者；(9)感染性疾病者；(10)头颅外伤者。

1.2 方法

采集治疗前、治疗 7 d 后肘静脉血 4 mL，3500 r·min^{-1} 离心 10 min，提取血清，采用双抗体夹心酶联免疫吸附法测定血清 VCAM-1、MMP-2、TIMP-1，仪器和试剂都是罗氏公司的 cobas702 生化分析仪及配套试剂，cobas601 型全自动免疫分析仪及配套试剂。

1.3 统计学分析

以 SPSS 18.0 软件包处理，计量资料用均数± 标准差($\bar{x}\pm s$)表示，t 检验，多组分析采用方差分析，相关性分析使用 Spearman 相关系数，P<0.05 为差异具有统计学意义。

2 结果

2.1 不同类型缺血性脑血管病血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分比较

脑梗死组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于短暂性脑缺血发作组和对照组，差异显著（P<0.05）；短暂性脑缺血发作组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于对照组，差异显著(P<0.05)见表 1。

表 1 不同类型缺血性脑血管病血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分比较($\bar{x}\pm s$)

Table 1 Comparison of serum VCAM-1, MMP-2 and TIMP-1 levels in different types of ischemic cerebrovascular diseases($\bar{x}\pm s$)

Groups	n	VCAM-1(mg/L)	MMP-2(ng/mL)	TIMP-1(μg/L)	NIHSSscore(points)
Cerebral infarction group	55	4.56± 1.03	951.26± 102.52	278.97± 65.35	22.31± 2.35
Transient ischemic attack group	43	3.49± 0.79	653.63± 191.25	160.13± 31.87	17.59± 2.18
Control group	50	2.35± 0.68	134.26± 52.17	110.25± 36.53	1.01± 0.02
F value		87.366	574.805	209.323	1861.082
P value		0.000	0.000	0.000	0.000

2.2 不同神经功能缺损程度血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分比较

重度神经缺损组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于中度神经缺损组和轻度神经缺损组，差异显著（P<0.05）；中度神经缺损组血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分显著高于轻度神经缺损组，差异显著(P<0.05)见表 2。

2.3 血清 VCAM-1、MMP-2、TIMP-1 与神经功能缺损之间的相关性分析

将神经功能缺损作为因变量，将血清 VCAM-1、MMP-2、TIMP-1 水平分别作为自变量，Logistic 回归分析发现，血清 VCAM-1、MMP-2、TIMP-1 均和 NIHSS 评分呈正相关(r=0.603,0.915,0.778，P<0.05)，见图 1~ 图 3。

表 2 不同神经功能缺损程度血清 VCAM-1、MMP-2、TIMP-1 水平及 NIHSS 评分比较($\bar{x}\pm s$)

Table 2 Comparison of serum LEVELS of VCAM-1, MMP-2 and TIMP-1 with different degrees of neurological impairment($\bar{x}\pm s$)

Groups	n	VCAM-1(mg/L)	MMP-2(ng/mL)	TIMP-1(μg/L)	NIHSSscore(points)
Severe nerve defect group	19	6.15± 1.05	1025.63± 105.69	202.35± 61.25	24.34± 2.35
Moderate nerve defect group	52	5.01± 1.02	896.87± 125.36	172.33± 32.85	19.56± 2.41
Mild nerve defect group	27	3.98± 0.93	718.56± 114.28	145.63± 35.56	18.66± 2.38
F value		26.366	39.506	20.002	86.35
P value		0.000	0.000	0.000	0.000

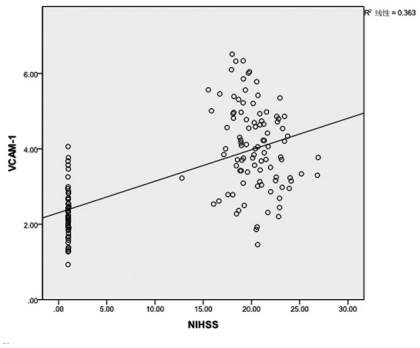

图 1 NIHSS 评分和血清 VCAM-1 的散点图

Fig.1 Scatter plot of NIHSS score and serum VCAM-1

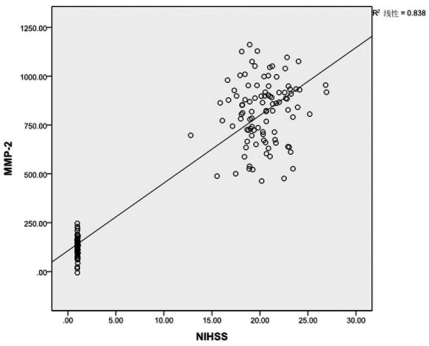

图 2 NIHSS 评分和血清 MMP-2 的散点图

Fig.2 Scatter plot of NIHSS score and serum MMP-2

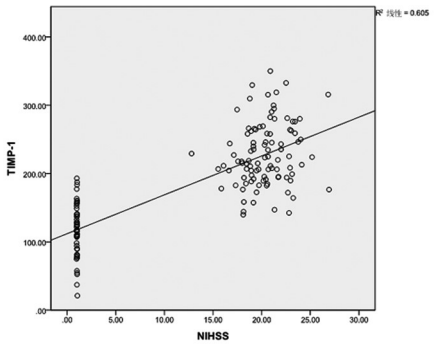

图 3 NIHSS 评分和血清 TIMP-1 的散点图

Fig.3 Scatter plot of NIHSS score and serum TIMP-1

3 讨论

缺血性脑血管疾病是目前全球主要致死性疾病之一,该病是在炎症基础上发生动脉粥样硬化和血管痉挛,导致脑组织缺血缺氧,引发一系列神经缺损症状,致残率及病死率较高,超过50%患者存在不同程度神经系统后遗症[10,11]。急性脑梗死和短暂性脑缺血发作是缺血性脑血管疾病常见的两个类型,短暂性脑缺血发作若得不到及时治疗则可发展为缺血性脑血管疾病,严重威胁患者的生命[12-15]。缺血性脑血管疾病病因复杂导致治疗效果不佳,因此对疾病早期预测具有重要意义。血管造影是诊断脑血管疾病的"金标准",具有直观、特异性高的特点,但部分患者对造影剂过敏,因此寻找无创、快速的检测方法对不同类型缺血性脑血管疾病的早期诊断至关重要[16-19]。有研究显示,检测缺血性脑血管疾病相关因子变化可为了解病理生理变化提供诊疗信息[20]。

内皮细胞的衰老和损伤是血管病变的初始事件,VCAM-1是机体内的一种黏附分子,是血管内皮功能密切相关的因子,广泛分布于血管内皮细胞、巨噬细胞等表面,其水平过高可使白细胞聚集并黏附在内皮细胞上,加剧血管壁的破坏[21-24]。目前有关 VCAM-1 的研究多局限于动物模型,但也有研究显示,VCAM-1 与梗死大小有关,参与缺血后脑组织损伤,与高血压病血压呈正相关[25]。本研究结果显示,脑梗死患者血清 VCAM-1 水平显著高于短暂性脑缺血发作组和健康人群,短暂性脑缺血发作组血清 VCAM-1 水平显著高于对照组;重度神经缺损组血清 VCAM-1 水平显著高于中度神经缺损组和轻度神经缺损组,中度神经缺损组血清 VCAM-1 水平显著高于轻度神经缺损组,进一步相关分析发现,血清 VCAM-1 和神经功能缺损之间呈正相关,提示,VCAM-1 在缺血性脑血管疾病发病过程中起到了重要的作用,其水平越高代表对血管内皮的损伤越大,神经功能缺损程度越高。Barbara D[26]等研究也显示,VCAM-1 在急性缺血性脑卒中表达较高,随着水平的升高患者远期预后越差。分析其原因可能是因为在正常情况下 VCAM-1 含量较低,可促进细胞增殖,参与血管内皮细胞损害后的修复过程,当发生缺血性脑血管疾病时患者机体炎症细胞被激活,而 VCAM-1 与炎症反应相辅相成,随着炎症诱发源持续刺激,导致 VCAM-1 水平升高,加重血管损伤,从而参与了缺血性脑血管疾病的进展。

MMP-2 属于明胶酶家族成员之一,能破坏内皮细胞基膜,调节其他蛋白酶与细胞因子活性,维持细胞外基质的平衡,在炎性疾病及血管病变中发生一定程度的变化[27-30]。有研究显示,MMP-2 能对患者神经系统产生影响,损害患者血脑屏障,导致脑细胞出现损伤[31]。本研究结果显示,脑梗死患者血清 MMP-2 水平显著高于短暂性脑缺血发作组和健康人群,短暂性脑缺血发作组血清 MMP-2 水平显著高于对照组;重度神经缺损组血清 MMP-2 水平显著高于中度神经缺损组和轻度神经缺损组,中度神经缺损组血清 MMP-2 水平显著高于轻度神经缺损组,进一步相关分析发现,血清 MMP-2 和神经功能缺损之间呈正相关,提示 MMP-2 在缺血性脑血管疾病中呈高表达,其中在脑梗死患者中表达更高,且可随着神经功能缺损程度的严重程度而升高,分析其原因可能是因为 MMP-2 水平升高可破坏患者微血管基底膜,造成内皮功能的进一步损伤,增加其通透性,从而加重组织缺血缺氧情况,最终导致病情进一步加重。

TIMP-1 是金属蛋白酶家族调控因子,是基质金属蛋白酶 9 的特异性抑制剂,在细胞外基质降解中发挥重要作用,能阻碍

细胞外介质降解，导致细胞外基质沉积，在人体正常组织中不能检测到 TIMP-1 及基质金属蛋白酶 9 活性，当脑组织缺血缺氧时，基质金属蛋白酶 9 水平升高，为抑制基质金属蛋白酶 9 的过度激活，体内 TIMP-1 也随之增加[32-34]。本研究结果显示，本研究结果显示，本研究结果显示，脑梗死患者血清 TIMP-1 水平显著高于短暂性脑缺血发作组和健康人群，短暂性脑缺血发作组血清 TIMP-1 水平显著高于对照组；重度神经缺损组血清 TIMP-1 水平显著高于中度神经缺损组和轻度神经缺损组，中度神经缺损组血清 TIMP-1 水平显著高于轻度神经缺损组，进一步相关分析发现，血清 TIMP-1 和神经功能缺损之间呈正相关，提示 VCAM-1 在缺血性脑血管疾病中呈高表达，且随着神经功能损伤程度而升高，可作为预测疾病的标志物水平。Mustafa N[35]等研究也显示，当发生脑梗死时，梗死病灶的出现可刺激基质金属蛋白酶大量生成，导致 TIMP-1 释放增多，避免基质金属蛋白酶过度激活，因此其水平直接影响脑梗死的发生。

综上所述，血清 VCAM-1、MMP-2、TIMP-1 在缺血性脑血管病患者中表达异常，且与神经功能损伤程度密切相关，对以上指标进行检测可有效地发现高危患者，并及时给予干预。

参 考 文 献(References)

[1] Brutto V J D, Chaturvedi S, Diener H C, et al. Antithrombotic Therapy to Prevent Recurrent Strokes in Ischemic Cerebrovascular Disease[J]. Journal of the American College of Cardiology, 2019, 74(6): 786-803

[2] Sukmawan Y P. Lumbrokinase Reduced the Fibrinogen Concentration in Ischemic Cerebrovascular Disease Patients: A Systematic Review and Meta-Analysis [J]. Indonesian Journal of Clinical Pharmacy, 2020, 9(1): 43

[3] Chen F Y, Fang X Y, Zhang H. Effect of polydatin on expression of p53 and Notch1 in brain tissue of ischemic cerebrovascular disease[J]. Journal of Biological Regulators & Homeostatic Agents, 2018, 32(1): 133

[4] Yang J, Lyu Y, Ma Y, et al. Relationship between cerebral microbleeds location and cognitive impairment in patients with is chemic cerebrovascular disease[J]. Neuroreport, 2018, 29(14): 1209-1213

[5] Garciasanchez P, Lopezlopez R, Rubiogordon L, et al.Childhood ischemic cerebrovascular disease in a paediatric emergency service: a descriptive study[J]. Revista De Neurologia, 2018, 66(8): 261-267

[6] José Alberto Choreo-Parra, Martha Carnalla-Cortés, Parménides Guadarrama-Ortíz. Ischemic cerebrovascular disease: extensive review of the literature for the first contact physician[J]. Medicina Interna de Mexico, 2019, 35(1): 61-79

[7] Zhu L. Research Status of Three-Dimensional Pseudo-Continuous Arterial Spin Labeling in Ischemic Cerebrovascular Diseases [J]. Radiation Science and Technology, 2018, 4(1): 1

[8] Satoru M, Hideaki I, Nobuhito S. Precision Medicine for Ischemic Cerebrovascular Diseases[J]. Japanese Journal of Neurosurgery, 2018, 27(7): 528-538

[9] The Neurology Branch of The Chinese Medical Association, the brain Vascular Division of the Neurology branch of the Chinese Medical Association, and the neurovascular intervention Cooperative group of the Neurology Branch of the Chinese Medical Association. Chinese Guidelines for endovascular Interventional Diagnosis and Treatment of ischemic cerebrovascular Diseases 2015 [J]. Chinese Journal of Neurology, 2015, 48(010): 830-837

[10] Shuang-Yue, Liu, Yu-Lian, et al. Effect of electroacupuncture on neurological deficit and activity of TLR2/NF-κB signaling in ce-rebral ischemia /reperfusion injury rats[J]. Acupuncture research, 2019, 44(4): 242-247

[11] Zhang J, Wang G, Zhang F, et al. Improvement of postoperative cognitive dysfunction and attention network function of patients with ischemic cerebrovascular disease via dexmedetomidine[J]. Experimental & Therapeutic Medicine, 2018, 15(3): 2968-2972

[12] Hao, Xin, Tan, et al. cerebrovascular diseases% hypothermia therapy%ischemic stroke%medical gas%neuroprotection%normobaric hyperoxia%xenon[J]. Medical gas research, 2019, 8(4): 172-175

[13] Hovland A, Mundal L J, Igland J, et al. Risk of Ischemic Stroke and Total Cerebrovascular Disease in Familial Hypercholesterolemia: A Register Study From Norway[J]. Stroke, 2019, 50(1): 172-174

[14] Kawakita F, Suzuki H. Periostin in cerebrovascular disease[J]. Neural Regeneration Research, 2020, 15(1): 63-64

[15] Daniel, Staub. Duplex ultrasound in cerebrovascular disease - asymptomatic carotid stenosis [J]. Therapeutische Umschau. Revue therapeutique, 2018, 75(8): 489-495

[16] Kim Joon-Tae, Choi Kang-Ho, Park Man-Seok, et al. Clinical Significance of Acute and Serial Platelet Function Testing in Acute Ischemic Stroke[J]. Journal of the American Heart Association, 2018, 7 (11): e008313

[17] Romay M C, Toro C, Iruela-Arispe M L. Emerging molecular mechanisms of vascular dementia[J]. Current Opinion in Hematology, 2019, 26(3): 1

[18] Xiao-Qiang, Yao, Xing-Lan, et al. Effect of scalp acupuncture stimulation on expression of pentraxin 3 in striatum in acute ische-mic cerebrovascular disease rats [J]. Acupuncture research, 2019, 44(11): 793-798

[19] Nordestgaard L T, TybjæRg-Hansen A, Rasmussen K L, et al. Genetic variation in clusterin and risk of dementia and ischemic vascular disease in the general population: cohort studies and meta-analyses of 362,338 individuals[J]. Bmc Medicine, 2018, 16(1): 39

[20] Chun L, Hong S, Guodong X, et al. Mito-Tempo prevents nicotine-induced exacerbation of ischemic brain damage [J]. Journal of Applied Physiology, 2018, 8(1): 49-57

[21] Jiang M, Liu X, Zhang D, et al. Celastrol treatment protects against acute ischemic stroke-induced brain injury by promoting an IL-33/ST2 axis-mediated microglia/macrophage M2 polarization [J]. J Neuroinflammation, 2018, 15(1): 78

[22] Zhang J, Feng L, Hou C, et al. Health benefits on cardiocerebrovascular disease of reducing exposure to ambient fine particulate matter in Tianjin, China [J]. Environmental Science and Pollution Research, 2020, 27(12): 13261-13275

[23] Chi L, Jiao D, Nan G, et al. miR-9-5p attenuates ischemic stroke through targeting ERMP1-mediated endoplasmic reticulum stress[J]. Acta Histochemica, 2019, 121(8): 151438

[24] Skarpengland T, Skjelland M, Kong X Y, et al. Increased Levels of Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 in Ischemic Stroke and Transient Ischemic Attack[J]. Journal of the American Heart Association, 2018, 7(2): e006479

（下转第 2507 页）

[15] Riaz MA, Sak A, Erol YB, et al. Metformin enhances the radiosensitizing effect of cisplatin in non-small cell lung cancer cell lines with different cisplatin sensitivities[J]. Sci Rep, 2019, 9(1): 1282

[16] Li C, Fan K, Qu Y, et al. Deregulation of UCA1 expression may be involved in the development of chemoresistance to cisplatin in the treatment of non-small-cell lung cancer via regulating the signaling pathway of microRNA-495/NRF2 [J]. J Cell Physiol, 2020, 235(4): 3721-3730

[17] 耿帅, 郭宏举. 多西他赛联合顺铂治疗晚期非小细胞肺癌有效性和安全性的 Meta 分析[J]. 河北医学, 2020, 26(4): 620-625

[18] Rose MC, Kostyanovskaya E, Huang RS. Pharmacogenomics of cisplatin sensitivity in non-small cell lung cancer [J]. Genomics Proteomics Bioinformatics, 2014, 12(5): 198-209

[19] Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study [J]. Lancet Oncol, 2016, 17(11): 1497-1508

[20] 郭磊, 王键玮, 李爱洁, 等. 盐酸埃克替尼与多西他赛、培美曲塞不同联合方式对非小细胞肺癌 PC-9 细胞系作用的实验研究 [J]. 现代生物医学进展, 2015, 15(22): 4257-4262

[21] 杨常建, 董海林, 聂改红, 等. 培美曲塞联合顺铂与吉西他滨联合顺铂治疗晚期非鳞非小细胞肺癌的疗效研究[J]. 辽宁医学院学报, 2016, 37(4): 74-76

[22] 彭文潘, 徐泳, 王志超, 等. 金复康口服液含药血清调控肺癌淋巴管新生机制探讨[J]. 中华肿瘤防治杂志, 2020, 27(5): 337-344

[23] 慕晓艳, 白浩然, 周晓辉, 等. 金复康口服液合软化汤联合化疗治疗气阴两虚型ⅢIb～Ⅳ期非小细胞肺癌 [J]. 中国临床研究, 2019, 32(9): 1271-1274

[24] Rafei H, El-Bahesh E, Finianos A, et al. Immune-based Therapies for Non-small Cell Lung Cancer[J]. Anticancer Res, 2017, 37(2): 377-387

[25] 张俊红, 王镓, 崔青荣. 金复康口服液对气阴两虚型非小细胞肺癌患者的疗效和血清 MMP-9 水平的影响 [J]. 中医药信息, 2019, 36(2): 65-68

[26] Fu L, Wang R, Yin L, et al. CYFRA21-1 tests in the diagnosis of non-small cell lung cancer: A meta-analysis [J]. Int J Biol Markers, 2019, 34(3): 251-261

[27] Sun J, Chen X, Wang Y. Comparison of the diagnostic value of CEA combined with OPN or DKK1 in non-small cell lung cancer[J]. Oncol Lett, 2020, 20(3): 3046-3052

[28] Ma L, Xie XW, Wang HY, et al. Clinical Evaluation of Tumor Markers for Diagnosis in Patients with Non-small Cell Lung Cancer in China [J]. Asian Pac J Cancer Prev, 2015, 16(12): 4891-4894

[29] Chen Y, Mathy NW, Lu H. The role of VEGF in the diagnosis and treatment of malignant pleural effusion in patients with non-small cell lung cancer (Review)[J]. Mol Med Rep, 2018, 17(6): 8019-8030

[30] Jafarian AH, Kooshki Forooshani M, Reisi H, et al. Matrix metalloproteinase-9(MMP-9) Expression in Non-Small Cell Lung Carcinoma and Its Association with Clinicopathologic Factors [J]. Iran J Pathol, 2020, 15(4): 326-333

[31] Yang N, Wan R, Dai L, et al. Effect of Osimertinib on the expression of serum mmp-7 and mmp-9 in patients with non-small cell lung cancer[J]. Pak J Pharm Sci, 2020, 33(1(Special)): 499-504

[32] 李超富, 高云姝, 周洲, 等. 富氢水协同金复康口服液阻断硫代乙酰胺诱发大鼠胆管癌上皮癌变的实验研究[J]. 解放军医学院学报, 2019, 40(6): 586-589, 604

[33] 陈石秀, 陈佳蕾, 谢瑞芳, 等. 基于网络药理学的金复康口服液治疗非小细胞肺癌机制[J]. 中成药, 2019, 41(7): 1547-1555

（上接第 2534 页）

[25] Lugovaya A V, Emanuel V S, Kalinina N M, et al. Apoptosis and autophagy in the pathogenesis of acute ischemic stroke (review of literature) [J]. Klinicheskaia laboratornaia diagnostika, 2020, 65 (7): 428-434

[26] Barbara D, Toulis K A, Neil T, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study [J]. Plos Medicine, 2018, 15(1): e1002488

[27] Broocks G, Flottmann F, Ernst M, et al. Computed Tomography-Based Imaging of Voxel-Wise Lesion Water Uptake in Ischemic Brain: Relationship Between Density and Direct Volumetry[J]. Investigative Radiology, 2018, 53(4): 207-213

[28] Tsantilas P, Kuehnl A, Kallmayer M, et al. Risk of Stroke or Death Is Associated With the Timing of Carotid Artery Stenting for Symptomatic Carotid Stenosis: A Secondary Data Analysis of the German Statutory Quality Assurance Database [J]. Journal of the American Heart Association Cardiovascular & Cerebrovascular Disease, 2018, 7 (7): e007983

[29] Bhatia R, Sharma G, Patel C, et al. Coronary Artery Disease in Patients with Ischemic Stroke and TIA[J]. Journal of Stroke and Cerebrovascular Diseases, 2019, 28(12): 104400

[30] Aghamiri H, Paybast S, Lima B S, et al. New Advances in Acute Ischemic Stroke Management: Review Article[J]. International Clinical Neuroscience Journal, 2020, 7(2): 55-60

[31] Singh V, Bajia K K, Ram C, et al. Comparative lipid profile study between ischemic and haemorrhagic stroke [J]. International Journal of Research in Medical Sciences, 2020, 8(2): 544

[32] Garg B, Mehta N, Jaryal A. Larger screw on the concave side of apex pedicle: Friend or foe? Report on a rare cause of neurological deficit in scoliosis surgery[J]. Indian Spine Journal, 2020, 3(1): 114

[33] Fudim M, Liu P R, Shrader P, et al. Mineralocorticoid Receptor Antagonism in Patients With Atrial Fibrillation: Findings From theORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) Registry [J]. Journal of the American Heart Association Cardiovascular & Cerebrovascular Disease, 2018, 7(8): e007987

[34] Aroor A R, Manrique-Acevedo C, Demarco V G. The role of dipeptidylpeptidase-4 inhibitors in management of cardiovascular disease in diabetes; focus on linagliptin[J]. Cardiovascular Diabetology, 2018, 17(1): 59

[35] Mustafa N, Zahoor H, Shamim K. Transcranial Doppler Sonography for Detecting Stenosis or Occlusion of Intracranial Arteries in People with Acute Ischemic Stroke in Neurocritical Care Unit[J]. International Journal of Health Science, 2020, 4(1): 129