DOI: 10.16781/j.CN31-2187/R.20230162

·专题报道·

凝血功能改变与新型冠状病毒感染后发生急性缺血性脑卒中相关

呼延梅华△，陈　蕾△，袁　绘，杨　洁，姜　一，吴　涛，邓本强，张永巍*
海军军医大学（第二军医大学）第一附属医院脑血管病中心，上海 200433

［摘要］ **目的**　比较新型冠状病毒感染（COVID-19）与非COVID-19的急性缺血性脑卒中患者的临床特点、炎症指标及凝血功能，探讨COVID-19后发生急性缺血性脑卒中的危险因素。**方法**　采用单中心回顾性研究设计，纳入2022年11月5日至2023年2月5日于我院接受治疗且完善COVID-19病毒核酸检测的急性缺血性脑卒中患者187例，其中COVID-19患者75例（COVID-19组）、未发生COVID-19患者112例（非COVID-19组）。分析两组患者的一般临床资料、炎症和凝血功能指标，包括中性粒细胞/淋巴细胞比值（NLR）、D-二聚体、纤维蛋白原（FIB）等。采用多因素logistic回归模型分析COVID-19后发生急性缺血性脑卒中的独立危险因素。**结果**　COVID-19组的NLR［3.62（2.31，6.71）vs 2.64（1.87，5.04），P=0.014］、D-二聚体［0.70（0.32，2.27）mg/L vs 0.37（0.27，0.76）mg/L，P=0.001］、FIB［4.21（3.26，5.17）g/L vs 3.25（2.77，3.87）g/L，P<0.001］高于非COVID-19组，淋巴细胞计数［1.40（1.03，1.71）×10^9/L vs 1.61（1.09，2.21）×10^9/L，P<0.05］低于非COVID-19组。多因素logistic回归分析结果表明，既往脑卒中史（OR=5.430，95% CI 1.538～19.175，P=0.009）、D-二聚体（OR=1.425，95% CI 1.104～1.840，P=0.007）及FIB（OR=2.405，95% CI 1.683～3.437，P<0.001）是COVID-19后发生急性缺血性脑卒中的独立危险因素。**结论**　COVID-19后急性缺血性卒中患者的炎症和凝血功能的血清生物标志物NLR、D-二聚体、FIB水平升高。COVID-19后缺血性脑卒中的发病与高凝状态相关。

［关键词］ 新型冠状病毒感染；急性缺血性脑卒中；中性粒细胞/淋巴细胞比值；D-二聚体；纤维蛋白原
［引用本文］ 呼延梅华，陈蕾，袁绘，等. 凝血功能改变与新型冠状病毒感染后发生急性缺血性脑卒中相关［J］. 海军军医大学学报，2023，44（9）：1045-1049. DOI: 10.16781/j.CN31-2187/R.20230162.

Changes of coagulation function are associated with acute ischemic stroke after coronavirus disease 2019

HUYAN Meihua△, CHEN Lei△, YUAN Hui, YANG Jie, JIANG Yi, WU Tao, DENG Benqiang, ZHANG Yongwei*
Neurovascular Center, The First Affiliated Hospital of Naval Medical University (Second Military Medical University), Shanghai 200433, China

［**Abstract**］ **Objective**　To compare the clinical characteristics, inflammatory indexes and coagulation function of patients with acute ischemic stroke complicated with coronavirus disease 2019 (COVID-19) and those without COVID-19, and to explore the risk factors of acute ischemic stroke after COVID-19. **Methods**　A single-center retrospective study was conducted in 187 patients with acute ischemic stroke who were treated in our hospital from Nov. 5, 2022 to Feb. 5, 2023 and were tested for COVID-19, including 75 patients with COVID-19 (COVID-19 group) and 112 patients without COVID-19 (non-COVID-19 group). The general clinical data, inflammation and coagulation function indexes (neutrophil-lymphocyte ratio［NLR］, D-dimer, and fibrinogen［FIB］) of the 2 groups were analyzed. Multivariate logistic regression was used to analyze the independent risk factors of acute ischemic stroke after COVID-19 infection. **Results**　NLR (3.62［2.31, 6.71］vs 2.64［1.87, 5.04］, P=0.014), D-dimer (0.70［0.32, 2.27］mg/L vs 0.37［0.27, 0.76］mg/L, P=0.001) and FIB (4.21［3.26, 5.17］g/L vs 3.25［2.77, 3.87］g/L, P<0.001) of COVID-19 group were markedly higher than those of non-COVID-19 group, and lymphocyte count (1.40［1.03, 1.71］×10^9/L vs 1.61［1.09, 2.21］×10^9/L, P<0.05) was lower than that of non-COVID-19 group. Multivariate logistic regression analysis showed that the previous stroke history (odds ratio［OR］=5.430, 95% confidence interval［CI］1.538-19.175, P=0.009), D-dimer (OR=1.425, 95% CI 1.104-1.840, P=0.007) and FIB (OR=2.405, 95% CI 1.683-3.437, P<0.001) were independent risk factors for acute ischemic stroke after COVID-19.

［收稿日期］ 2023-03-31　［接受日期］ 2023-06-25
［作者简介］ 呼延梅华，硕士，住院医师. E-mail: huhuhu942665274@163.com；陈　蕾，博士，主治医师. E-mail: gloria_leilei@163.com
△共同第一作者（Co-first authors）.
*通信作者（Corresponding author）. Tel: 021-31161940, E-mail: zhangyongwei@163.com

Conclusion　Serum biomarkers of inflammation and coagulation function (NLR, D-dimer, and FIB) are increasesd in patients with acute ischemic stroke after COVID-19, and the incidence of ischemic stroke after COVID-19 is related to hypercoagulability.

［**Key words**］ coronavirus disease 2019; acute ischemic stroke; neutrophil-lymphocyte ratio; D-dimer; fibrinogen

［**Citation**］ HUYAN M, CHEN L, YUAN H, et al. Changes of coagulation function are associated with acute ischemic stroke after coronavirus disease 2019［J］. Acad J Naval Med Univ, 2023, 44(9): 1045-1049. DOI: 10.16781/j.CN31-2187/R.20230162.

新型冠状病毒感染（coronavirus disease 2019，COVID-19）以传播速度快、并发症复杂为主要特征。缺血性脑卒中是COVID-19的主要并发症之一[1-3]。一项纳入108 571例COVID-19患者的meta分析表明，COVID-19患者急性心血管疾病的发病率为1.4%，其中缺血性脑卒中占87.4%，但COVID-19对卒中的影响及原因仍不清楚，且无法用传统的缺血性脑卒中的病因学分型来解释；此外，与非COVID-19患者相比，COVID-19患者年龄更小，梗死灶累及多个部位且隐源性病因增加[4]。因此，COVID-19状态下脑卒中的发病机制及有效的干预措施迫切需要研究。有研究证实COVID-19后脑卒中患者存在高凝状态，凝血功能指标异常和内皮功能障碍是COVID-19患者常见微血栓形成和血栓形成的原因[5]。尽管COVID-19引起凝血功能异常已在多项研究中得到证实，在脑卒中人群中探寻指标差异仍具有一定意义。有研究表明COVID-19后脑病患者中存在高炎症状态[6]，但炎症反应在COVID-19后急性脑梗死患者中的变化仍不太明确。既往对COVID-19后卒中炎症因子的研究多集中在CRP等[7]。中性粒细胞/淋巴细胞比值（neutrophil-lymphocyte ratio，NLR）被认为是全身炎症反应的良好标志物，有研究证明NLR是评估COVID-19患者预后的指标[8]，但目前尚未见有关NLR与COVID-19后卒中发病机制关系的报道。本研究比较了有无COVID-19的急性缺血性脑卒中患者的临床特点、凝血功能和炎症指标，探讨炎症因子与凝血功能在COVID-19后急性缺血性脑卒中发病中的作用。

1　资料和方法

1.1　*研究对象*　本研究为单中心回顾性观察研究。纳入2022年11月5日至2023年2月5日在我院进行诊疗的急性缺血性脑卒中患者196例，根据有无COVID-19分为COVID-19组和非COVID-19组。急性缺血性脑卒中定义为由MRI上细胞毒性水肿（弥散加权成像信号增加和表观扩散系数降低）证实的脑缺血性损伤引起的急性神经功能障碍。合并COVID-19组纳入标准：（1）18岁以上急性缺血性脑卒中（发病2周内）患者；（2）行头颅MRI平扫检查；（3）入院COVID-19病毒核酸检测阳性或胸部CT平扫存在病毒性肺炎的影像学特征。非COVID-19组纳入标准：因急性缺血性脑卒中住院治疗但未合并COVID-19的患者，COVID-19病毒核酸检测结果为阴性。两组排除标准：既往存在自身免疫病、血管炎，院前明确恶性肿瘤，近3个月内有心肌梗死、手术或创伤、心力衰竭、肾功能衰竭、外周血管严重狭窄或闭塞等病史。本研究通过我院伦理委员会审批。

1.2　*研究方法*

1.2.1　*临床资料收集*　收集患者年龄、性别、BMI、卒中高危因素（糖尿病史、高血压史、血脂异常、吸烟史、脑卒中史、冠心病史、心房颤动史），以及入院后48 h内血常规、凝血功能［D-二聚体、纤维蛋白原（fibrinogen，FIB）］等数据。

1.2.2　*影像学资料收集*　采用德国西门子公司Siemens Magnetom Avanto 3.0 T磁共振仪完善包括T1、T2加权成像及弥散加权成像等在内的头部检查。

1.3　*统计学处理*　应用SPSS 26软件对数据进行统计学分析。经正态性检验发现计量资料均不服从正态分布，以中位数（下四分位数，上四分位数）表示，组间比较采用Mann-Whitney U检验；计数资料以例数和百分数表示，最小期望值均>5，组间比较采用χ^2检验。将单因素分析中$P<0.15$的因素都纳入多因素logistic回归分析。检验水准（α）为0.05。

2　结　果

2.1　*一般临床资料*　5例患者合并恶性肿瘤、1例患者合并心功能衰竭、1例患者合并肾功能衰竭、

2例患者相关信息缺失排除，共187例急性缺血性脑卒中患者入组，其中COVID-19组75例、非COVID-19组112例。两组患者在年龄、性别、BMI、高血压史、高脂血症史、糖尿病史、冠心病史、心房颤动史、既往脑卒中史和吸烟史等方面差异均无统计学意义（P均＞0.05）。见表1。

2.2　炎症及凝血功能指标　与非COVID-19组相比，COVID-19组急性缺血性脑卒中患者NLR、D-二聚体、FIB水平较高，淋巴细胞计数较低，差异有统计学意义（P均＜0.05）。见表1。

表1　两组急性缺血性脑卒中患者一般资料比较

Tab 1　General information of patients with acute ischemic stroke in 2 groups

Characteristic	All patients N＝187	Non-COVID-19 N＝112	COVID-19 N＝75	Statistic	P value
Gender, n (%)				χ^2＝1.270	0.260
Male	131 (70.05)	75 (66.96)	56 (74.67)		
Female	56 (29.95)	37 (33.04)	19 (25.33)		
Age/year, M (Q_L, Q_U)	69.00 (60.00, 75.00)	68.00 (60.00, 73.50)	70.00 (62.00, 76.00)	Z＝－1.827	0.068
BMI/(kg•m^{-2}), M (Q_L, Q_U)	24.22 (20.88, 26.26)	22.81 (20.83, 26.05)	24.49 (21.05, 26.56)	Z＝－0.761	0.370
Hypertension, n (%)	153 (81.82)	90 (80.36)	63 (84.00)	χ^2＝0.401	0.527
Dyslipidaemia, n (%)	33 (17.65)	21 (18.75)	12 (16.00)	χ^2＝0.234	0.629
Diabetes mellitus, n (%)	78 (41.71)	42 (37.50)	36 (48.00)	χ^2＝2.037	0.154
Smoking, n (%)	56 (29.95)	33 (29.46)	23 (30.67)	χ^2＝0.031	0.860
Atrial fibrillation, n (%)	24 (12.83)	14 (12.50)	10 (13.33)	χ^2＝0.028	0.867
Coronary artery disease, n (%)	24 (12.83)	11 (9.82)	13 (17.33)	χ^2＝2.266	0.132
Prior stroke, n (%)	16 (8.56)	6 (5.36)	10 (13.33)	χ^2＝3.653	0.056
Neutrophil/(L^{-1}, ×10^9), M (Q_L, Q_U)	4.65 (3.58, 6.83)	4.52 (3.46, 6.16)	5.06 (3.96, 7.20)	Z＝－1.821	0.069
Lymphocyte/(L^{-1}, ×10^9), M (Q_L, Q_U)	1.47 (1.07, 2.00)	1.61 (1.09, 2.21)	1.40 (1.03, 1.71)	Z＝－2.156	0.031
NLR, M (Q_L, Q_U)	2.86 (1.98, 5.69)	2.64 (1.87, 5.04)	3.62 (2.31, 6.71)	Z＝－2.462	0.014
D-dimer/(mg•L^{-1}), M (Q_L, Q_U)	0.44 (0.28, 1.04)	0.37 (0.27, 0.76)	0.70 (0.32, 2.27)	Z＝－3.206	0.001
Fibrinogen/(g•L^{-1}), M (Q_L, Q_U)	3.49 (2.87, 4.33)	3.25 (2.77, 3.87)	4.21 (3.26, 5.17)	Z＝－5.109	＜0.001
Multi-territorial infarction, n (%)	14 (7.49)	7 (6.25)	7 (9.33)	χ^2＝0.617	0.432

COVID-19: Coronavirus disease 2019; BMI: Body mass index; NLR: Neutrophil-lymphocyte ratio; M (Q_L, Q_U): Median (lower quartile, upper quartile).

2.3　病灶分布情况　头颅MRI平扫检查显示，COVID-19组和非COVID-19组分别有9.33%（7/75）和6.52%（7/112）的患者存在颅内多病灶，组间差异无统计学意义（P＝0.432，表1）。

2.4　多因素logistic回归分析　纳入年龄、冠心病史、既往脑卒中史、中性粒细胞计数、淋巴细胞计数、NLR、D-二聚体和FIB，构建多因素logistic回归模型。分析结果显示，既往脑卒中史、D-二聚体、FIB是COVID-19后发生急性缺血性脑卒中的独立危险因素。见表2。

表2　COVID-19后发生急性缺血性脑卒中的多因素logistic回归分析

Tab 2　Multivariate logistic regression analysis of acute ischemic stroke after COVID-19

Variable	b	SD	OR (95% CI)	P value
Age	－0.130	0.014	0.987 (0.960, 1.014)	0.346
Coronary artery disease	0.214	0.571	1.239 (0.404, 3.797)	0.708
Prior stroke	1.692	0.644	5.430 (1.538, 19.175)	0.009
Neutrophil	0.083	0.107	0.920 (0.745, 1.136)	0.438
Lymphocyte	0.026	0.337	1.026 (0.530, 1.987)	0.938
NLR	0.030	0.070	1.030 (0.897, 1.182)	0.674
D-dimer	0.354	0.130	1.425 (1.104, 1.840)	0.007
Fibrinogen	0.878	0.182	2.405 (1.683, 3.437)	＜0.001

COVID-19: Coronavirus disease 2019; NLR: Neutrophil-lymphocyte ratio; b: Regression coefficient; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval.

3 讨　论

国内外 COVID-19 后缺血性脑卒中的发生率存在一定的差异，为 0.5%～4.5%[1,9-11]。我国武汉一项包含 214 例 COVID-19 住院患者的研究发现约有 3% 发生了缺血性脑卒中[1]；意大利米兰 388 例 COVID-19 患者中有 2.5% 确诊了缺血性脑卒中[9]；美国费城 3 家医院的 844 例 COVID-19 患者中有 2.4% 出现了缺血性脑卒中[10]；2022 年美国一项研究针对当地医院收治 COVID-19 患者的特征、危险因素、实验室指标等建立了一个示意模型，结果显示在 6 381 例 COVID-19 住院患者中，缺血性脑卒中的发生率为 0.5%[11]。

本研究分析结果显示 COVID-19 组与非 COVID-19 组患者在性别、BMI、高血压史、高脂血症史、糖尿病史、心房颤动史及吸烟史等方面差异均无统计学意义，年龄（P＝0.068）、冠心病史（P＝0.132）及既往卒中史（P＝0.056）的比较显示有差异趋势。既往一项回顾性队列研究比较了 COVID-19 和流感患者缺血性脑卒中的发生率，结果显示 COVID-19 患者发生急性缺血性脑卒中的风险高于流感患者，且也多发生在老年和有传统脑卒中危险因素的患者[12]。本研究中 COVID-19 组急性缺血性脑卒中患者的炎症和凝血标志物（NLR、D- 二聚体和 FIB）水平均高于非 COVID-19 组，这与既往报道的 COVID-19 后炎症因子水平升高并伴有凝血功能紊乱的特点[3,13-16]是一致的。既往研究中 COVID-19 后缺血性脑卒中患者的血清 CRP、IL-6、D- 二聚体、FIB 和铁蛋白的水平均有所升高[17-18]，分析其机制可能是病毒与表达血管紧张素转换酶 2 和跨膜丝氨酸蛋白酶 2 受体的细胞（例如肺泡上皮细胞和血管内皮细胞）结合引发了一系列反应。COVID-19 患者细胞释放一组细胞因子和趋化因子，招募巨噬细胞和单核细胞，产生更多的促炎细胞因子，最终形成细胞因子风暴。细胞因子风暴激活中性粒细胞和其他免疫细胞上的组织因子，从而与凝血因子Ⅶ相互作用，刺激外源性凝血级联反应发生[19-20]，生成凝血酶。在高炎症状态下，局部激活的血小板诱导被组织因子覆盖的中性粒细胞，也会导致凝血酶形成[21]。此外，内皮细胞本身也表达血管紧张素转换酶 2 和跨膜丝氨酸蛋白酶 2，使其成为病毒直接入侵、病毒增殖和激活 / 损伤的目标[20-23]。内皮细胞激活本身也是血栓形成和脑卒中发生的主要始动因素。高炎症反应还可独立导致血小板活化和内皮细胞损伤，这两者都可促进血栓形成。因此，炎症因子与高凝状态对 COVID-19 后卒中发生均有一定作用，且促炎因子可能通过影响凝血功能导致 COVID-19 后卒中的发生。

本研究通过构建多因素 logistic 回归模型发现，NLR 并不是 COVID-19 后急性缺血性脑卒中发生的独立影响因素，说明主要是凝血机制在 COVID-19 后卒中的发生中起作用，炎症机制在 COVID-19 后急性缺血性脑卒中发病中的作用尚不明确。本研究中 COVID-19 组与非 COVID-19 组均以单一病灶梗死为主，且 2 组多发性梗死患者比例差异无统计学意义，相关结论与可能机制仍有待进一步探讨。

综上所述，本研究结果表明，COVID-19 后急性缺血性卒中患者的炎症和凝血功能的血清生物标志物 NLR、D- 二聚体、FIB 升高，COVID-19 后急性缺血性脑卒中的发病与高凝状态相关。从临床角度来看，COVID-19 后患者具有较高的缺血性脑卒中发生风险。由于本研究为单中心回顾性观察研究，COVID-19 病例数较少，实验室指标较单一，不足以得出完全可靠的结论，仍需更多的队列研究进一步证实。

[参 考 文 献]

[1] MAO L, JIN H, WANG M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China[J]. JAMA Neurol, 2020, 77(6): 683-690. DOI: 10.1001/jamaneurol.2020.1127.

[2] LI Y, LI M, WANG M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study[J]. Stroke Vasc Neurol, 2020, 5(3): 279-284. DOI: 10.1136/svn-2020-000431.

[3] KATSANOS A H, PALAIODIMOU L, ZAND R, et al. The impact of SARS-CoV-2 on stroke epidemiology and care: a meta-analysis[J]. Ann Neurol, 2021, 89(2): 380-388. DOI: 10.1002/ana.25967.

[4] NANNONI S, DE GROOT R, BELL S, et al. Stroke in COVID-19: a systematic review and meta-analysis[J]. Int J Stroke, 2021, 16(2): 137-149. DOI: 10.1177/1747493020972922.

[5] BONAVENTURA A, VECCHIÉ A, DAGNA L, et al. Endothelial dysfunction and immunothrombosis as key

pathogenic mechanisms in COVID-19[J]. Nat Rev Immunol, 2021, 21(5): 319-329. DOI: 10.1038/s41577-021-00536-9.

[6] MUCCIOLI L, PENSATO U, CANI I, et al. COVID-19-associated encephalopathy and cytokine-mediated neuroinflammation[J]. Ann Neurol, 2020, 88(4): 860-861. DOI: 10.1002/ana.25855.

[7] HAUTECLOQUE G, KEMPF C, STAN C, et al. Multifocal and microvascular involvement in ischemic stroke during COVID-19: a cohort study with comparison with non-COVID-19 stroke[J]. Front Neurol, 2021, 12: 732194. DOI: 10.3389/fneur.2021.732194.

[8] LIU Y, DU X, CHEN J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19[J]. J Infect, 2020, 81(1): e6-e12. DOI: 10.1016/j.jinf.2020.04.002.

[9] LODIGIANI C, IAPICHINO G, CARENZO L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy[J]. Thromb Res, 2020, 191: 9-14. DOI: 10.1016/j.thromres.2020.04.024.

[10] ROTHSTEIN A, OLDRIDGE O, SCHWENNESEN H, et al. Acute cerebrovascular events in hospitalized COVID-19 patients[J]. Stroke, 2020, 51(9): e219-e222. DOI: 10.1161/STROKEAHA.120.030995.

[11] MBONDE A A, O'CARROLL C B, GRILL M F, et al. Stroke features, risk factors, and pathophysiology in SARS-CoV-2-infected patients[J]. Mayo Clin Proc, 2022, 6(2): 156-165. DOI: 10.1016/j.mayocpiqo.2022.01.003.

[12] MERKLER A E, PARIKH N S, MIR S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza[J]. JAMA Neurol, 2020, 77(11): 1-7. DOI: 10.1001/jamaneurol.2020.2730.[Online ahead of print]

[13] BENUSSI A, PILOTTO A, PREMI E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy[J]. Neurology, 2020, 95(7): e910-e920. DOI: 10.1212/WNL.0000000000009848.

[14] TAN Y K, GOH C, LEOW A S T, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature[J]. J Thromb Thrombolysis, 2020, 50(3): 587-595. DOI: 10.1007/s11239-020-02228-y.

[15] YAGHI S, ISHIDA K, TORRES J, et al. SARS-CoV-2 and stroke in a New York healthcare system[J]. Stroke, 2020, 51(7): 2002-2011. DOI: 10.1161/STROKEAHA.120.030335.

[16] HELMS J, TACQUARD C, SEVERAC F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study[J]. Intensive Care Med, 2020, 46(6): 1089-1098. DOI: 10.1007/s00134-020-06062-x.

[17] ZHOU P, YANG X L, WANG X G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin[J]. Nature, 2020, 579(7798): 270-273. DOI: 10.1038/s41586-020-2012-7.

[18] AGBUDUWE C, BASU S. Haematological manifestations of COVID-19: from cytopenia to coagulopathy[J]. Eur J Haematol, 2020, 105(5): 540-546. DOI: 10.1111/ejh.13491.

[19] DINICOLANTONIO J J, MCCARTY M. Thrombotic complications of COVID-19 may reflect an upregulation of endothelial tissue factor expression that is contingent on activation of endosomal NADPH oxidase[J]. Open Heart, 2020, 7(1): e001337. DOI: 10.1136/openhrt-2020-001337.

[20] BAUTISTA-VARGAS M, BONILLA-ABADÍA F, CAÑAS C A. Potential role for tissue factor in the pathogenesis of hypercoagulability associated with in COVID-19[J]. J Thromb Thrombolysis, 2020, 50(3): 479-483. DOI: 10.1007/s11239-020-02172-x.

[21] SKENDROS P, MITSIOS A, CHRYSANTHOPOULOU A, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis[J]. J Clin Invest, 2020, 130(11): 6151-6157. DOI: 10.1172/JCI141374.

[22] TEUWEN L A, GELDHOF V, PASUT A, et al. COVID-19: the vasculature unleashed[J]. Nat Rev Immunol, 2020, 20(7): 389-391. DOI: 10.1038/s41577-020-0343-0.

[23] NISHIGA M, WANG D W, HAN Y, et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives[J]. Nat Rev Cardiol, 2020, 17(9): 543-558. DOI: 10.1038/s41569-020-0413-9.

[本文编辑]　杨亚红，孙　岩