电子、语音版

·综述·

血清炎症标志物与出血性脑小血管病的相关性

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摘　要：内皮损伤被认为是造成脑小血管病（CSVD）的主要原因，而炎症可导致内皮损伤。越来越多的证据表明，炎症与CSVD的发病及其进展存在关联。血清炎症标志物水平可以直接反映CSVD相关脑卒中的血管内皮损伤程度。然而，目前的研究主要集中在血清炎症标志物与缺血性CSVD的关系上。该文旨在评估血清炎症标志物与出血性CSVD之间的相关性。研究结果表明，与全身炎症标志物相比，血管／内皮功能障碍相关炎症标志物和氧化应激相关炎症标志物与出血性CSVD之间的关联更密切。炎症因子在缺血性和出血性脑卒中中可能有不同的分布模式。该文扩展了对炎症和CSVD之间关系的了解，并提示不同的CSVD表型间可能有不同的潜在机制。

关键词：脑卒中；脑小血管病；炎症；内皮损伤；血脑屏障

中图分类号：R743　　**DOI**:10. 16636/j. cnki. jinn. 1673-2642. 2025. 01. 013

Association between serum inflammatory markers and hemorrhagic cerebral small vessel disease

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Abstract: Endothelial injury is considered the main cause of cerebral small vessel disease (CSVD), and inflammation can lead to endothelial injury. An increasing number of evidence has shown that inflammation is associated with the development and progression of CSVD. Serum inflammation markers can directly reflect the degree of vascular endothelial injury leading to CSVD - related stroke. However, current studies mainly focus on the association between serum inflammatory markers and ischemic CSVD. This article aims to investigate the association between serum inflammatory markers and hemorrhagic CSVD. Research findings have confirmed that compared with systemic inflammation, vascular/endothelial dysfunction - related inflammatory markers and oxidative stress - related inflammatory markers have a closer association with hemorrhagic CSVD. Inflammatory factors may have different distribution patterns in ischemic and hemorrhagic stroke. This article expands our knowledge in the association between inflammation and CSVD and suggests

基金项目：湖南省重点研发计划（2023SK2019）；国家自然科学基金（82371343）；湖南省自然科学基金（2023JJ30966）。
收稿日期：2024-08-21；**修回日期：**2024-11-05
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that different phenotypes of CSVD may have different potential mechanisms.

Keywords: stroke; cerebral small vessel disease; inflammation; endothelial injury; blood-brain barrier

脑小血管病(cerebral small vessel disease, CSVD)是一种弥漫性的脑血管疾病,可通过磁共振成像(magnetic resonance imaging, MRI)影像标志物反映,包括白质高信号(white matter hyperintensities, WMH)、假定血管源性的腔隙、脑出血(intracerebral hemorrhage, ICH)和脑微出血(cerebral microbleed, CMB)等[1]。CSVD造成了全球约30%的缺血性脑卒中、85%的出血性卒中和45%的痴呆患者,加剧了脑血管疾病的社会和经济负担[2]。血管内皮细胞(vascular endothelial cells, VEC)功能障碍在CSVD神经血管单元的损伤中起着关键作用[3-4]。血管内皮损伤、动脉硬化、血管壁增厚、管腔狭窄甚至闭塞,造成慢性脑缺血性改变。此外,血管通透性增加导致血管成分外渗到周围组织中,表现为脑出血性改变。然而,不同CSVD表型(缺血性或出血性、CMB或ICH)的表达机制仍然未知,其中部分原因可能是因为不同的炎症因子参与[5]。越来越多的证据表明,血清炎症标志物与缺血性CSVD的影像标志物(例如WMH和腔隙)或出血性CSVD的影像标志物(例如CMB和ICH)之间存在关联[6]。然而,不同研究间的结论存在巨大差异,关于血清炎症标志物与CSVD其他出血标志物(如皮质表面铁沉着和凸面蛛网膜下腔出血)之间关系的研究很少。

血清炎症标志物可分为全身系统炎症、血管/内皮功能障碍相关炎症以及氧化应激相关炎症,主要分类如下[7]。①全身系统炎症标志物:超敏C-反应蛋白(high sensitivity C-reactive protein, hs-CRP)或C-反应蛋白(C-reactive protein, CRP)、白细胞介素-6(interleukin-6, IL-6)、单核细胞趋化蛋白-1(monocyte chemotactic protein-1, MCP-1)、肿瘤坏死因子-α(tumor necrosis factor alpha, TNF-α)、肿瘤坏死因子受体2(tumor necrosis factor receptor 2, TNFR2)和纤维蛋白原;②血管/内皮功能障碍相关炎症标志物:细胞间黏附分子-1(intercellular adhesion molecule-1, ICAM-1)、血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)、CD40配体(CD40 ligand, CD40L)、E-选择素、P-选择素、脂蛋白相关磷脂酶-A2(lipoprotein-associated phospholipase A2, Lp-PLA2)、总同型半胱氨酸(total homocysteine, tHcy)、血管内皮生长因子(vascular endothelial growth factor, VEGF)和基质金属蛋白酶(matrix metalloproteinases, MMP);③氧化应激相关炎症标志物:活性氧(reactive oxygen species, ROS)和髓过氧化物酶(myeloperoxidase, MPO)。

本研究旨在探究血清炎症标志物与出血性CSVD标志物之间的关联,并试图评估缺血性和出血性CSVD标志物之间关于血清炎症标志物的差异。由于关于皮质表面铁沉着和凸面蛛网膜下腔出血的研究有限,我们将只关注出血性CSVD的两种关键影像标志物,即ICH和CMB。

1　方法

1.1　检索策略和选择标准

在PubMed、Embase和Cochrane图书馆中检索了从数据库建立到2023年4月16日用英语发表的相关人群研究,检索词如下:("small vessel disease" OR "SVD" OR "cerebral microbleed" OR "CMB" OR "cerebral microhemorrhages" OR "CMH" OR "intracerebral hemorrhage" OR "ICH") AND ("neuroinflammation" OR "inflammation" OR "interleukin-6" OR "IL-6" OR "C-reactive protein" OR "CRP" OR "tumor necrosis factor" OR "TNF-α" OR "tumor necrosis factor receptor 2" OR "TNFR2" OR "fibrinogen" OR "intercellular adhesion molecule 1" OR "ICAM-1" OR "vascular cell adhesion molecule-1" OR "VCAM-1" OR "CD40" OR "E-selectin" OR "P-selectin" OR "lipoprotein-associated phospholipase A2" OR "Lp-PLA2" OR "homocysteine" OR "vascular endothelial growth factor" OR "VEGF" OR "matrix metalloproteinase" OR "MMP" OR "reactive oxygen species" OR "ROS" OR "myeloperoxidase") AND ("healthy" OR "community" OR "dementia" OR "Alzheimer's" OR "cognitive impairment" OR "stroke")。由于参考文献有限,本研究没有使用("SVD" AND "CMB")或者("SVD" AND "ICH")检索词,并将CMB和ICH限制在CSVD患者中。这有助于发现缺血性和出血性CSVD在血清炎症标志物方面可能存在的差异。

审查相关研究的参考文献进行补充。排除病例报道、论文综述和没有全文的文献;排除继发性ICH相关的研究、遗传学研究和病理组织学研究。王鸿独立完成文献的审查、筛选工作。

1.2　数据分析

对数据进行了描述性评价和分析。

2　结果

2.1　文献纳入情况

本研究检索到了1 214篇文献,从中筛选出了符合标准的94篇。因其中有30篇研究的血清炎症标志物临床上应用较少,相关研究也相对较少(例如血清Netrin-1蛋白、S100A12蛋白、YKL-40因子等),因此,本研究仅讨论了64篇常见的血清炎症标志物。本研究文献筛选的流程图如图1所示。

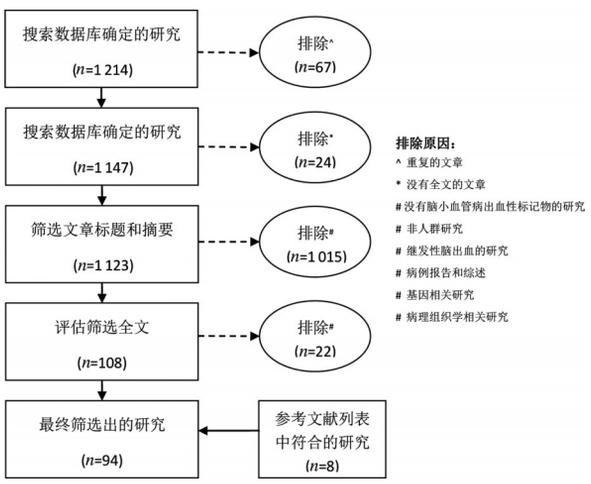

图1　文献筛选程序流程图

在纳入的94篇文献中,有9篇(9.6%)的研究人群为社区居民,62篇(66.0%)为脑血管病患者,1篇(1.1%)为有血管危险因素的患者,1篇(1.1%)为其他神经退行性疾病患者,20篇(21.3%)为脑血管病患者和社区居民组成的队列,1篇(1.1%)为脑血管病患者和血管危险因素患者组成的队列。其中23项是关于CMB的研究,71项是关于ICH的研究。

2.2　血清炎症标志物与ICH/CMB的相关性

如表1所示,大多数研究显示,血管/内皮功能障碍相关炎症标志物[8,10-24,26-29]和氧化应激相关炎症标志物[7,31]与ICH/CMB之间存在正相关。然而,有一项中国人群队列的研究显示,任何血清炎症标志物与CMB之间没有关联[9]。全身炎症标志物和ICH特征(包括ICH体积、血肿扩张和血肿周围水肿体积)关联性研究的结论存在不一致[15,18,32-35,37-39,44-48,50-54,66,69]。在伴随血管危险因素和脑血管病患者中,血管/内皮功能障碍相关炎症与氧化应激相关炎症与出血性CSVD标志物之间的相关性更为常见[8,10-13,15-18,20-24,26-31,55-59]。有研究观察到,ICH与sCD40L呈正相关[21]。而另一项研究没有观察到CMB与sCD40L相关[9]。同时,也有研究发现,MPO与ICH、CMB均呈正相关[7,31]。

2.3　血清炎症标志物与ICH临床结局的相关性

由于CMB是慢性病理过程,并且在短时间内对临床结果几乎没有直接影响[70]。所以本研究只总结了ICH患者急性期血清炎症标志物与临床结局之间的相关性(表2)。

表1　血清炎症标志物与ICH和CMB的相关性

炎症标志物	与ICH呈正相关	与ICH呈负相关或无关	与CMB呈正相关	与CMB呈负相关或无关
血管/内皮障碍相关炎症				
sICAM-1			(+)[8]	(−)[9]
VCAM-1				(−)[9]
VEGF	(+)[10-11]	(−)[12]	(+)[13-15]	
MMP2		(−)[16]		(−)[9]
MMP3		(−)[12]	(+)[16]	(−)[9]
MMP9	(+)[10,16-18]	(−)[12]	(+)[19-20]	(−)[9]
sCD40L	(+)[21]			(−)[9]
E-选择素			(+)[22]	(−)[9]
Lp-PLA2	(+)[23]		(+)[24]	(−)[9,25]
Hcy/tHcy	(+)[26]		(+)[27-29]	(−)[9,30]
氧化应激相关炎症				
MPO	(+)[31]		(+)[7]	
全身系统炎症				
IL-6	(+)[18,32-35]		(+)[19,36]	(−)[9]
CRP/hsCRP	(+)[32,35,37-38]	(−)[39]	(+)[19-20,36,40-41]	(−)[9,42-43]
TNF/TNFR	(+)[15,18,44]		(+)[7]	(−)[9]
WCC	(+)[45-46]	(−)[47-48]		
ANC/NC	(+)[45-46]	(−)[48]		(−)[49]
AMC	(+)[48]	(−)[45-46]		
ALC		(−)[48]		
NLR	(+)[50-54]	(−)[15]		(−)[49]

注:(+)表示两者呈正相关,(−)表示两者呈负相关或无关,(+)和(−)后的数字序号表示该结果的文献来源;空白处表示炎症标志物与ICH或CMB的相关性尚未见文献报道;ICH=脑出血;CMB=脑微出血;sICAM-1=可溶性细胞间黏附分子-1;VCAM-1=血管细胞间黏附分子-1;VEGF=血管内皮生长因子;MMP=基质金属蛋白酶;sCD40L=可溶性CD40配体;Lp-PLA2=脂蛋白相关磷脂酶-A2;Hcy=同型半胱氨酸;tHcy=总同型半胱氨酸;MPO=髓过氧化物酶;IL-6=白细胞介素-6;CRP=C反应蛋白;hsCRP=超敏CRP;TNF=肿瘤坏死因子;TNFR=肿瘤坏死因子受体;WCC=白细胞计数;ANC=中性粒细胞绝对计数;NC=中性粒细胞计数;AMC=单核细胞绝对计数;ALC=淋巴细胞绝对计数;NLR=中性粒细胞与淋巴细胞比值。

表2　血清炎症标志物与ICH临床结局的相关性

炎症标志物	与ICH不良结局呈正相关	与ICH不良结局呈负相关或无关
血管/内皮障碍相关炎症		
VEGF	严重程度(NIHSS评分)[11] 严重程度(NDS)[15]	3个月mRS评分[11,55]
MMP2		CAA-ICH复发率[16] 认知障碍[16]
MMP3	3个月mRS评分[12,56]	严重程度(GCS评分和NIHSS评分)[12]
MMP9	3个月mRS评分[12] 深部ICH神经功能障碍(GCS评分)[17] 3个月病死率[10,57]	严重程度(GCS评分和NIHSS评分)[12]
MMP10	3个月mRS评分(女性)[56]	
sCD40L	严重程度(NIHSS评分)[21] 6个月mRS评分[21] 7 d和6个月病死率[21]	
E-选择素	3个月mRS评分[57]	
Lp-PLA2	严重程度(NIHSS评分)[23] 3个月mRS评分[23]	严重程度[58]
Hcy/tHcy	ICH复发率[59] 3个月病死率[57]	6个月mRS评分[26]
氧化应激相关炎症		
MPO	严重程度(NIHSS评分)[31] 6个月mRS评分和病死率[31]	
全身系统炎症		
IL-6	严重程度(GCS评分)[34] 90 d的mRS评分[33] 30 d病死率[32]	
IL-11	严重程度(NDS评分)[15]	
CRP/hsCRP	早期神经功能障碍(GCS评分)和30 d病死率[38] 严重程度和住院病死率[60] 30 d病死率[61] 30 d的GCS评分和病死率[37] 3个月病死率[57] 入院和出院时mRS评分;入院、90 d和1年的病死率(WCC和CRP共同升高时)[62]	30 d的GCS评分[61] 6个月GOS评分[63] 总生存率[63]
TNF-α	严重程度(NDS评分)[15]	
WCC	ICH复发率[64] 90 d的mRS评分[65] 90 d病死率[65]	30 d的GCS评分[61] 6个月GOS评分[63] 30 d病死率[46] 1个月和1年病死率[47] 总生存率[63]
ANC/NC	90 d的mRS评分[65] 90 d病死率[65]	30 d病死率[46]
AMC	30 d病死率[45-46]	
NLR	严重程度(NIHSS评分)[52] 90 d的mRS评分[52,65-67] 住院病死率[52,68] 30 d病死率[50,53,67-68] 90 d病死率[65,67]	3个月mRS评分和病死率[51]

注:ICH=脑出血;VEGF=血管内皮生长因子;MMP=基质金属蛋白酶;sCD40L=可溶性CD40配体;Lp-PLA2=脂蛋白相关磷脂酶-A2;Hcy=同型半胱氨酸;tHcy=总同型半胱氨酸;MPO=髓过氧化物酶;IL=白细胞介素;CRP=C反应蛋白;hsCRP=超敏CRP;TNF=肿瘤坏死因子;WCC=白细胞计数;ANC=中性粒细胞绝对计数;NC=中性粒细胞计数;AMC=单核细胞绝对计数;NLR=中性粒细胞与淋巴细胞比值;NIHSS=美国国立卫生研究院卒中量表;NDS=神经功能障碍评分;mRS=改良的Rankin量表;GCS=格拉斯哥昏迷量表;CAA-ICH=脑淀粉样血管病-脑出血;GOS=格拉斯哥结局量表;空白处表示炎症标志物与ICH临床结局的相关性尚未见文献报道。

本研究发现,与全身系统炎症相比[15,32-34,37-38,45-46,50,52-53,57,60-62,64-68],ICH的临床结果与血管/内皮功能障碍相关炎症[10-12,15,17,21,23,56-57,59]或氧化应激相关炎症[31]存在更为密切的相关性。MMP家族作为关键的血管/内皮功能障碍相关炎症标志物,主要由小胶质细胞/巨噬细胞产生[71],之前已在ICH患者中进行了广泛研究。大多数研究显示,MMP3、MMP9和MMP10与ICH不良结局呈正相关(定义为在ICH后3或6个月时的改良的Rankin量表评分>2/3分)[10,12,17,56-57]。相比之下,较高水平的MMP2与较低的脑淀粉样血管病-脑出血复发率和认知障碍风险降低显著相关,独立于年龄和ICH体积[16]。一些小样本研究未能检测到Lp-PLA2或Hcy与ICH患者不良预后相关[26,58]。作为氧化应激相关炎症的典型标志物,MPO水平与ICH的严重程度和预后相关[7,31]。全身系统炎症标志物(如IL-6、CRP、TNF、白细胞计数、中性粒细胞计数、单核细胞计数和中性粒细胞与淋巴细胞比值)与ICH不良预后或病死率的关联性仍存在争议。一些研究发现其中一些炎症标志物与ICH不良结局或病死率之间可能存在正相关[15,32-34,37-38,45-46,50,52-53,57,60-62,64-68],但另一些研究发现可能存在负相关或不相关[46-47,51,61,63]。

2.4　出血性和缺血性CSVD的不同血清炎症标志物特征

E-选择素和VEGF是内皮功能障碍相关的两个重要炎症标志物,与CMB相关,但与CSVD的其他标志物(即WMH、腔隙和血管周围间隙扩大)无关[6]。有研究显示,与出血性CSVD标志物(CMB)相比,缺血性CSVD〔定义为无症状性脑梗死和(或)广泛WMH〕患者有较高水平的循环ICAM-1、Lp-PLA2质量和较低水平的循环MPO[7]。此外,有研究比较了缺血性脑卒中和出血性脑卒中患者的血清炎症标志物,与缺血性脑卒中患者相比,ICH患者的Lp-PLA2质量水平更高[58],而Hcy/tHcy和IL-6可能通过多种机制参与CSVD的发生和发展,与ICH的相关性弱于缺血性脑卒中[59,72]。

3　讨论

本研究证实了血清炎症标志物与出血性CSVD存在密切关联。与全身系统炎症标志物相比,血管/内皮功能障碍相关炎症标志物与氧化应激相关炎症标志物和出血性CSVD之间的关联更密切。炎症因子谱的差异提示缺血性和出血性卒中、ICH和CMB可能在炎症通路上存在不同的潜在机制,需要进一步深入研究。

血管/内皮功能障碍相关炎症标志物与出血性CSVD之间呈正相关,这支持了CSVD开始时即存在潜在病理生理机制的假设,如内皮功能障碍[73]。在使用脂多糖诱导形成的CMB动物模型中,Sumbria等[74]确定了血清炎症标志物在CMB发病机制中的作用,包括神经炎症的诱导、VEC的激活和血脑屏障的破坏。因此,作为在VEC上表达的糖蛋白,ICAM-1可作为内皮功能障碍相关的血清炎症标志物。ICAM-1与其他黏附分子(例如选择素和VCAM-1)一起吸附白细胞,并帮助其进入脑组织,活化小胶质细胞和星形胶质细胞,从而产生炎症细胞因子(如TNF-α、IL-1β和IL-6),进而进一步放大炎症环境[75-77]。当膜结合的ICAM-1发生裂解时,其以可溶性ICAM-1(soluble ICAM-1, sICAM-1)的形式释放到血液中,因此可定量其血清水平[78]。有研究发现,在缺血性脑卒中患者中,血清sICAM-1与CMB水平和出血转化风险增加呈正相关[8]。这表明sICAM-1可能成为梗死后出血转化的临床实用标志物。

与血管/内皮功能障碍相关炎症或氧化应激相关炎症的标志物相比,全身系统炎症标志物与出血性CSVD之间的关联不太密切,这一发现与先前报道的炎症与CSVD缺血标志物(例如WMH和腔隙)相关性研究[6]的结论一致。尽管有证据表明,全身系统炎症标志物在ICH后的继发性损伤中起着至关重要的作用[79],但目前尚不确定全身系统炎症标志物是否与不良临床结局有关。据研究报道,白细胞计数[64-65]、NLR[50,52-53,65-68]和IL-1β[80-81]表达增加是ICH后不良结局的预测因子。然而,在一项纳入26 927名无卒中受试者的前瞻性队列研究中,白细胞总数(total leukocyte count, TLC)和中性粒细胞计数升高与脑梗死发生率增加呈正相关,而TLC升高与ICH呈负相关,与病死率无关[47]。这些研究结论的差异可能部分是因为研究样本种族、样本量和其他混杂因素(例如纳入标准和统计方法)的不同导致,也可能表明全身系统炎症在ICH的发生发展过程中不如在缺血性脑卒中重要。

CRP和hsCRP作为常见的全身炎症标志物,在ICH和CMB中的研究已经相当广泛[9,19-20,32,35-43,57,60-63,72]。然而,CRP与出血性CSVD之间的关系仍有待充分研究。一些研究表明,较高的CRP水平与CMB之间的关联可能与CMB的位置有关[40-41]。其中一项研究观察到CRP水平升高与脑叶微出血相关,但与深部微出血无关[40]。然而,另一项则结论相反[41]。

除了TLC之外,我们还观察到,在ICH和缺血性脑卒中患者中Lp-PLA258、Hcy[59]和IL-6[72]等血清炎症标志物水平也不同。Lp-PLA2是一种由循环巨噬细胞分泌的酶,可水解氧化磷脂,并参与炎症和低密度脂蛋白胆固醇的代谢[82]。传统观点认为,Lp-PLA2是缺血性心脑血管疾病的危险因素[83]。然而,据报道,与缺血性脑卒中患者相比,ICH患者的Lp-PLA2水平更高[58]。一种可能的解释是高Lp-PLA2可能会降低胆固醇水平,从而增加红细胞的渗透脆性和血管坏死,进而导致出血事件[84-87]。这些研究提示,这些血清炎症标志物可能在不同卒中表型中发挥不同作用,其是否可用于预测缺血性或出血性脑卒中值得深入研究。目前,关于CMB与Lp-PLA2[23-25,58]和

Hcy[26-30,59]关系的研究结论存在不一致。鉴于Lp-PLA2[88]和Hcy[89]与缺血性CSVD密切相关(如WMH和腔隙),这些血清炎症标志物相对大血管来说是否与CSVD(包括出血性CSVD)的关系更为密切,需要进一步研究来证实。

4　总结与展望

血清炎症标志物与CMB和ICH密切相关,其间参与的炎症因子可能不同,但确切的病理机制仍有待阐明。与全身炎症相比,血管/内皮功能障碍相关炎症和氧化应激相关炎症与出血性CSVD的相关性更密切。血清炎症因子在缺血性和出血性脑卒中患者中可能具有不同的分布模式,这可能意味着不同CSVD表型可能存在不同的潜在的炎症机制。目前的研究存在一定局限性,如多是横断面研究、小样本量和特定种族群体的研究,因此需要更多大样本量、前瞻性、随机临床研究。此外,需要更多的研究来确定炎症对CSVD不同表型的影响,这可能有助于出血性CSVD的早期预测和诊断。

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