

long COVID 的症状、可能机制、危险因素及治疗

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【摘要】 COVID-19对患者健康的长期影响尚不明确。目前,有研究表明,相当一部分COVID-19康复患者仍存在多个器官和系统的长期影响,称为long COVID,包括疲劳、呼吸困难、嗅觉味觉障碍、心血管异常、认识功能障碍等。本文主要综述了long COVID的流行病学情况、症状及可能机制、危险因素、潜在的治疗方法,以期为COVID-19的康复治疗提供更多参考。

【关键词】 COVID-19; long COVID; 预后; 综述

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Symptoms, Possible Mechanisms, Risk Factors and Treatment of Long COVID ZENG Yang¹, WANG Qian²

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【Abstract】 The long-term impact of COVID-19 on patients' health is still unclear. At present, studies have shown that a significant number of patients who recover from COVID-19 have long-term effects on multiple organs and systems, known as long COVID, including fatigue, dyspnea, olfactory and gustatory dysfunction, cardiovascular abnormalities, cognitive dysfunction, and more. This paper intends to review the epidemiology, symptoms, possible mechanisms, risk factors, and possible treatment plans of long COVID, in order to provide more reference for the rehabilitation treatment of COVID-19.

【Key words】 COVID-19; long COVID; Prognosis; Review

SARS-CoV-2引起的COVID-19疫情全球大流行给人类造成了巨大的疾病负担,截至2022-05-19,全球COVID-19确诊人数已达5亿多,死亡人数超过600万^[1]。COVID-19患者有多种肺内和肺外表现,包括发热、干咳、乏力、鼻塞、流涕、咽痛、嗅觉味觉减退或丧失、结膜炎、肌痛和腹泻,重症患者可出现呼吸困难和/或低氧血症,甚至发生急性呼吸窘迫综合征、脓毒症休克、多器官功能衰竭等^[2]。COVID-19患者平均恢复时间为2~3周^[3],其中20%的患者症状持续时间超过5周,10%的患者症状可持续12周甚至更长^[4]。HUANG等^[5]研究结果显示,随访2年长期存在1种及以上COVID-19症状的患者比例高达55%。

近年随着COVID-19持续流行和康复患者数量增多,越来越多的证据表明,COVID-19可能对多个器官和系统产生长期影响,被称为long COVID^[5-7]。多项队列研究指出,COVID-19对机体的影响可能持续1年,可表现为不同程度的疲劳、肌痛、胸闷、心悸、失眠、焦虑抑郁,或肺弥散功能、生活质量降低等^[6, 8-9]。目前,COVID-19的自然病程尚不明确,其对机体的长期影响仍需要重点关注。本文主要综述了long COVID的流行病学情况、症状及可能机制、危险因素、潜在的治疗方法,以期为COVID-19的康复治疗提供更多

参考。

1 long COVID的概念

long COVID由意大利伦巴第大区的Elisa Perego于2020-05-20首次提出^[10],之后有专业人员呼吁将此概念用于专业医学期刊和同行评议^[11-12],但目前该定义尚未达成共识^[4]。英国国家健康与临床卓越研究所(National Institute for Health and Care Excellence, NICE)将long COVID定义为COVID-19急性期后症状持续或进一步发展,且无法通过其他疾病解释,包括SARS-CoV-2感染后4~12周症状持续和12周后出现的COVID-19症状综合征^[13]。美国国立卫生研究院使用的是美国疾控中心对long COVID的定义:初始感染后超过4周的后遗症^[14]。

2 long COVID的流行病学情况

目前,因受到人口学基数、诊断准确率、疾控报告系统和医疗机构等因素的影响,long COVID患者数量难以估计。此外,各流行病学报告显示,long COVID数据也存在差异,其原因主要与随访时间、病情严重程度、自我报告的准确性、辅助检查方法及症状评估标准不同有关。全球多个国家的流行病学报告显示,不同随访时间的long COVID发生率不同,包括60 d的32.6%^[15]、60 d的87%^[16]、6个月的76%^[17]、12个月的49.0%^[6]、24个月的68%^[5]。上述数据提示,许多COVID-19患者可能存在long COVID,故需要长期治疗,而这增加了医疗资源和社会资源的消耗。

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3 long COVID的症状及可能机制

3.1 疲劳及可能机制 疲劳是一种主观上疲乏无力的不适感觉,持续疲劳会降低患者的注意力、精力和活力,其是病毒感染后的常见症状之一。既往有关SARS的研究结果显示,多达60%的SARS患者急性期康复后12个月内仍持续存在疲劳症状^[18]。英国国家统计局估计,COVID-19患者确诊5周后疲劳发生率为11.9%^[4]。一项横断面研究显示,分别有92.9%的住院COVID-19患者和93.5%的非住院COVID-19患者发病后79 d仍存在持续疲劳^[19]。多项研究表明,无论COVID-19急性期病情多严重,疲劳均是患者康复后最常见的临床症状^[5-6, 20-21]。综上,疲劳是long COVID的主要症状。

研究表明,SARS-CoV-2感染后的慢性疲劳可能是炎症反应通路信号传导错误的结果^[22]。一项横断面研究发现,在伴有持续疲劳的COVID-19患者中,促炎标志物与长期疲劳之间可能没有关联^[20]。中枢-周围神经系统和心理因素可能在COVID-19后疲劳中发挥作用,嗅觉神经元损伤会导致筛状板对脑脊液引流的阻力增加,导致中枢神经系统内淋巴系统充血和之后的毒性积聚,进而可能导致患者出现疲劳症状^[23]。额叶和小脑低代谢也与COVID-19患者的疲劳有关,其原因可能是全身炎症和细胞介导的免疫机制所致,但尚不清楚这一发现是否持续存在^[24]。因COVID-19疫情全球大流行导致的负面情绪和社会因素也与患者的慢性疲劳有关^[25]。再者,骨骼肌直接感染SARS-CoV-2会导致其肌肉纤维和神经肌肉接头受损、虚弱、发炎,进而可能导致疲劳^[26]。总之,可能有多个因素在COVID-19患者长期疲劳中发挥作用。

3.2 呼吸困难及可能机制 呼吸急促是long COVID的常见症状。英国国家统计局估计,无论COVID-19急性期病情多严重,COVID-19发病后5周患者呼吸急促患病率约为4.6%^[4]。COVID-19住院患者1个月后行肺功能检查发现,其一氧化碳弥散功能、总肺活量、第1秒用力呼气容积、用力肺活量和小气道功能异常,提示COVID-19患者肺功能恢复可能需要较长时间^[27]。多项研究发现,呼吸困难是COVID-19的常见症状^[28-29]。有研究报道,43.4% (62/143)的COVID-19患者发病60 d后仍存在呼吸困难症状^[16]。一项纳入27项long COVID症状研究的Meta分析结果显示,COVID-19患者发病后4周呼吸困难发生率为32% [95%CI (18%, 47%)]^[30]。国内一项纳入1 191例COVID-19患者的队列研究发现,随访6个月时,存在呼吸困难(mMRC评分≥1分)的患者比例高达26%,随访2年时存在该症状的患者比例降至14%^[5]。

COVID-19是一种传染性疾病,其病毒SARS-CoV-2在内皮细胞复制可对肺脏和呼吸道造成严重损伤,从而导致内皮细胞损伤及强烈的免疫反应和炎症反应^[31]。研究发现,COVID-19治愈患者可能长期伴有肺部影像学检查异常^[32],且伴有呼吸困难高风险(老年人、急性呼吸窘迫综合征、住院时间长和既往有慢性肺部疾病史等)的COVID-19患者容易出现肺纤维化样改变^[33],重症COVID-19患者肺栓塞和深静脉血栓形成发生率较高,这可能均是患者长期伴有呼吸困难

的原因^[34]。

3.3 嗅觉和味觉障碍及可能机制 嗅觉和味觉障碍是COVID-19患者的常见症状。据报道,COVID-19康复患者仍然存在嗅觉和味觉异常。英国国家统计局估计,COVID-19患者确诊5周后嗅觉丧失和味觉丧失发生率分别为7.9%和8.2%^[4]。有队列研究发现,COVID-19患者急性期后嗅觉和味觉障碍患病率为11.0%~45.1%^[35-36]。一项关于long COVID症状的荟萃分析结果显示,COVID-19患者发病后4周嗅觉改变、味觉改变的发生率分别为14% [95%CI (11%, 18%)]和7% [95%CI (4%, 10%)]^[30]。

SARS-CoV-2的功能宿主受体是血管紧张素转换酶2(angiotensin converting enzyme 2, ACE2)受体,而ACE2受体的非神经元表达可使SARS-CoV-2进入嗅觉支持细胞、干细胞和血管周围细胞,进而引起局部感染,而这种局部感染可能引起炎症反应,从而降低嗅觉感觉神经元功能;此外,SARS-CoV-2还可以破坏负责局部水和电解质平衡的支持细胞,间接减少感觉神经元到大脑的信号传导,从而导致嗅觉丧失^[37]。ACE2受体在人体口腔黏膜和舌头上也有表达,故SARS-CoV-2可以直接感染口腔细胞,进而导致细胞损伤和功能障碍^[38]。此外,SARS-CoV-2还可能与唾液酸受体结合,导致味觉阈值增高,加速味觉颗粒降解,进而导致味觉障碍^[39]。味觉障碍的另一种可能机制是味觉和嗅觉之间的功能联系,即由于嗅觉障碍,味觉感知也会随之降低^[40]。

3.4 心血管异常及可能机制 心脏损伤和肌钙蛋白水平升高可明显增加COVID-19患者死亡风险^[41]。一项队列研究显示,许多COVID-19患者确诊后71 d仍存在心脏受累、持续的心肌炎症和血清肌钙蛋白水平升高^[42]。一项大型病例系列研究纳入143例COVID-19患者,结果显示,21.7%的患者确诊COVID-19 2个月后报告了胸痛,表明胸痛是long COVID的常见症状^[16]。有研究者在年轻人、运动员等COVID-19低重症风险人群中发现,COVID-19患者康复后很长时间内仍有残余心肌炎表现^[43]。除心脏疾病外,由于自主神经功能障碍,COVID-19康复患者还新发了体位性心动过速综合征(postural tachycardia syndrome, POTS),主要表现为心悸、眩晕、高血压/低血压、恶心、焦虑等^[44-45]。

ACE2受体在心脏呈高表达^[46],这为SARS-CoV-2提供了直接的感染途径。研究表明,被SARS-CoV-2感染的心肌细胞会发生肌节破裂和碎裂、去核、转录变化和强烈的局部免疫反应^[47]。急性心脏损伤和病毒性心肌炎的病理反应,如内皮细胞损伤和微血栓形成可导致凝血障碍^[48],而慢性缺氧和肺动脉压增高可能进一步加速COVID-19患者心脏损伤^[49]。此外,持续的免疫激活可导致纤维化改变和桥粒蛋白迁徙,可能导致心律失常^[50]。研究表明,ACE2受体在神经元上表达,故SARS-CoV-2可能对自主神经系统产生直接的负面影响^[51]。而感染、自主神经系统调控的炎症反应和自身免疫反应均可能导致自主神经功能障碍和POTS^[45]。

3.5 认知功能降低及可能机制 既往研究表明,SARS-CoV-2

可引起感染性脑病、非免疫效应(如低血压、缺氧和血栓形成)及免疫效应(如适应性免疫、小胶质细胞激活等)^[52]。此外, COVID-19患者还可能出现一系列相关症状, 包括脑病、认知障碍、脑血管事件、癫痫发作、缺氧性脑损伤、皮质脊髓束征、执行障碍综合征、精神状态改变^[52-54]。已发表的long COVID相关文献将这些症状描述为“脑雾”^[55]。

危重疾病、急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)和长期使用呼吸机会对患者长期认知功能产生不良影响。一项纳入1 040例在ICU治疗的COVID-19患者的回顾性研究发现, 住院期间出现呼吸衰竭或休克的患者中71%存在谵妄, 且谵妄持续至出院后约4个月^[56]。另外一项类似研究发现, 在ICU治疗的COVID-19患者中, 出院后3个月约40%的患者老年人认知减退知情者问卷(Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE)评分与中度创伤性脑损伤患者相似, 26%的患者IQCODE评分与轻度阿尔茨海默病患者相似^[57]。

研究表明, 包括SARS-CoV-2在内的冠状病毒可以通过血行或神经元逆行神经途径侵袭中枢神经系统^[58], 这可能是COVID-19患者中枢神经炎发生率高的原因之一; SARS-CoV-2感染与神经退行性病变、精神疾病密切相关^[58-59]。此外, SARS-CoV-2还可能影响血-脑脊液屏障通透性, 这可使外周细胞因子和其他血液衍生物进入中枢神经系统并进一步导致神经炎症^[60]。血栓炎症通路可能是COVID-19患者卒中发病率升高的原因之一^[61], 而“脑雾”可能源自创伤后应激障碍或危重疾病、侵入性治疗后的失能^[62]。有研究表明, 病毒性脑炎、全身性炎症、外周器官功能障碍和脑血管变化可能导致COVID-19患者后遗症的发生^[63]。

3.6 其他表现及可能机制 《新型冠状病毒感染肺炎诊疗方案(试行第九版)》^[2]指出, COVID-19可导致多器官功能损伤。尽管尚未完全阐明COVID-19对肾脏的长期影响, 但有研究表明, COVID-19康复出院患者仍存在急性肾损伤^[64], 35%的COVID-19患者出院后6个月仍存在肾功能下降^[17]。LIU等^[65]在COVID-19患者中发现了由SARS-CoV-2感染引发的胰腺炎。COVID-19对脾脏的影响包括淋巴滤泡萎缩、T淋巴细胞和B淋巴细胞减少及脾梗死等^[66]。HUSAIN-SYED等^[67]研究表明, 肝脏、胃肠道、肌肉和血管等器官/组织可表达ACE2受体, 故容易受到SARS-CoV-2的直接损伤和全身炎症反应的间接损伤。此外, 还有研究者观察到, 部分患者感染SARS-CoV-2后还出现了肠道微生物群改变^[68]和亚急性甲状腺炎^[69]。

COVID-19患者发生肾损伤的可能机制包括败血症和肺损伤, 二者均可导致血流动力学变化和低氧血症。ACE2受体虽在胰腺呈高表达^[70], 但胰腺损伤是由胰腺内SARS-CoV-2感染还是全身炎症反应引起尚不清楚^[71]。有研究者发现, COVID-19患者脾脏中有ACE2受体表达, 推测SARS-CoV-2直接攻击可能是其发生脾损伤的主要原因^[72]。

4 long COVID的危险因素

目前, 关于long COVID的危险因素尚存在争议, 高龄、男性、肥胖、糖尿病、心血管疾病、呼吸系统疾病、高血压

史等是COVID-19重症和死亡的危险因素^[19, 73]。有研究报道, 免疫抑制可能对long COVID具有保护作用^[74], 但也有研究结果相反^[75], 故免疫抑制是否与long COVID相关尚不清楚。

一项横断面研究显示, COVID-19急性期病情严重程度与long COVID呈正相关^[21]。一项队列研究显示, COVID-19急性感染期存在5种症状的患者出现long COVID的风险更高^[76]。但另外一项评估COVID-19康复患者的前瞻性队列研究没有发现基线特征与long COVID相关^[77]。研究表明, 男性、年龄及既往病史(包括肥胖、糖尿病和心血管病)与long COVID的风险无关, 但哮喘史与long COVID的风险明显相关[OR=2.14, 95%CI(1.55, 2.96)]^[76]。

5 long COVID症状的潜在治疗方法

WHO和long COVID论坛小组一致认为, long COVID患者的临床症状对治疗方案的选择非常重要^[78]。抗组胺药可能是治疗COVID-19的有效药物, 一项细胞实验表明, H1拮抗剂能够通过抑制SARS-CoV-2进入表达ACE2受体的细胞而降低COVID-19发生率^[79]。有系统评价和分子研究表明, H1拮抗剂和H2拮抗剂是COVID-19进一步临床试验的候选药物^[80-81]。但抗组胺药是否具有治疗long COVID的作用还有待观察。一项针对伴抑郁症的COVID-19患者的荟萃分析表明, 抗抑郁药可降低患者外周炎症标志物^[82], 因其具有减轻炎症的作用, 故被提出可用来减少long COVID的症状。

此外, 探索高压氧、孟鲁司特和去吡非尼酮治疗long COVID效果的临床试验正在进行^[83]。一项系统评价结果显示, 补充维生素C可能有助于治疗long COVID患者的疲劳症状, 静脉注射高剂量维生素C可能是一种有益的治疗^[83]。LOVIT-COVID(NCT04401150)是一项正在进行的临床试验, 旨在评估静脉注射高剂量维生素C对COVID-19住院患者的影响^[84]。此外, 还有多项关于long COVID治疗的研究正在进行, 如膳食补充烟酰胺核苷可以通过调节促炎因子来减轻认知症状和疲劳^[85], 补充益生菌减轻long COVID的炎症, 利用褪黑素的抗氧化和抗炎作用治疗long COVID^[86]。

6 小结

随着COVID-19疫情在全球大流行, 其长期影响越来越受到关注。目前, long COVID仍是个未解之谜, 且SARS-CoV-2变异可能对long COVID的发生率和严重程度产生影响, 故继续探索COVID-19患者康复后的长期症状具有重要的临床意义。

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· 新进展 ·

基于中医“治未病”思想拓展 COVID-19 无症状感染者的防治策略

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王岗, 张丹, 陈新

【摘要】 随着奥密克戎毒株的流行、核酸检测效率的提高和大规模的疫苗接种, COVID-19无症状感染者数量明显增加, 其具有传播隐匿性、症状主观性、发现局限性的特征, 给疫情防控带来了巨大挑战。本文结合中医“治未病”思想的“三防理论”和当前COVID-19无症状感染者的特点, 提出“未病先防”需养护正气、避其毒气, “既病防变”需防止传变、扶正祛邪, “瘥后防复”需除邪务尽、扶正防复, 以期COVID-19无症状感染者的防控提供新思路。

【关键词】 COVID-19; 无症状感染者; 治未病

【中图分类号】 R 563.12 **【文献标识码】** A **DOI:** 10.12114/j.issn.1008-5971.2022.00.301

Expanding the Prevention and Treatment Strategies for Asymptomatic Infections of COVID-19 Based on the Idea of "Preventive Treatment of Disease" in Traditional Chinese Medicine WANG Gang, ZHANG Dan, CHEN Xin

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【Abstract】 With the prevalence of Omicron strains, the improvement of nucleic acid detection efficiency and large-scale vaccination, the number of asymptomatic infections of COVID-19 has increased significantly. It has the characteristics of hidden transmission, subjective symptoms, and limited detection, which has brought great challenges to epidemic prevention and control. Combining the "three prevention theories" of the idea of "preventive treatment of disease" in traditional Chinese medicine and the characteristics of current asymptomatic infections of COVID-19, this paper proposes that "prevention before disease" requires maintaining the righteousness and avoiding its poisonous gas, "prevention of disease progression" needs to prevent the spread of change and support the righteous but evil, and "prevent recurrence after recovery" needs to eliminate evil, strengthen the righteousness and prevent recovery, in order to provide new ideas for the prevention and control of asymptomatic infections of COVID-19.

【Key words】 COVID-19; Asymptomatic infections; Preventive treatment of disease

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