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# “长新冠”: 事实、证据与机制

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**摘要** 本文回顾了“长新冠”(long COVID)的定义和起源, 总结了人体各器官常见的“长新冠”症状以及检测方法和治疗手段, 并梳理了“长新冠”的影响因子例如年龄、性别、基础疾病、新冠疫苗和重复感染等. 此外, 本文深入探讨了“长新冠”的致病机制, 包括SARS-CoV-2(RNA或蛋白质)的持续存在, 感染后长期免疫失调, 线粒体功能障碍, 血管内皮损伤与凝血障碍, 人体微生物群失调, 潜伏病毒再激活以及激素或神经递质的紊乱等. 最后, 本文还对我国的“长新冠”研究现状进行了讨论和展望, 这些将为广大民众、医护人员和研究者提供针对“长新冠”的全面认识和建议.

**关键词** 新型冠状病毒, “长新冠”, 流行病学, 致病机制, 风险因子

## 1 “长新冠”的起源和定义

“长新冠”(long COVID)一词最早起源并发展于COVID-19患者群体在社交媒体平台的自我发声[1]. 2020年4月来自*New York Times*的记者Fiona Lowenstein在网络平台上公开描述其在新型冠状病毒检测转阴后数周仍存在疲劳、气促、咳嗽不止等诸多症状. 1个月后, 来自英国的Elisa Perego首次在推特使用了“long COVID”一词, 并引发了许多未彻底恢复的COVID-19患者的共鸣, 随后掀起相关热议和研究[1]. “长新冠”的最初提出也曾遭到过诸多质疑和争论, 例如, 早期的“长新冠”讯息主要来自COVID-19患者群体散在的自我报告和社交媒体而非专业的研究机构, 也缺乏科学的研究设计, 因此认可度和影响力有限. 此外, 早期“长新冠”研究缺乏明确的定义, 甚至没有统一的命名, 其症状频率和范围不确定, 且多种常见症状与其他疾病之间存在交集和关联, 容易被误诊[2,3]. 但随着证据和患者人数不断增加, 以及专业研究团体的加入, “长新冠”的证据链逐渐完整. 例如, 2020年5月, 由患者主导的研究合作组织正式发表了他们的研究结果, 描述了60多种长期症状, 包括疲劳、味觉或嗅觉丧失以及认知障碍等[4]. 著名流行病学家Ziyad Al-Aly领导的团队则利用美国退伍军人事务部健康管理局庞大的电子病历档案, 严谨地设计并发表了多项“长新冠”相关研究[4]. 与此同时, 许多针对“长新冠”的回顾性研究、横断面研究、德尔菲调查(Delphi)以及各种大样本的荟萃分析证据使广大研究者、民众、医护人员和政策制定者们对“长新冠”逐渐达成一定的共识, 且不得不正视这一公共卫生问题[2,3,5]. 国内的曹彬教授团队是“长新冠”研究的先行者, 他们在2021年1月发布了2020年1~5月之间出院新冠患者的随访结果, 发现感染后6个

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月仍存在多种长期症状例如疲劳、肌肉无力、睡眠困难、焦虑、抑郁以及部分器官的长期损伤[6]. 此外, 我们团队2020年11月发布的研究表明, 疫情早期病例(2020年3~4月)的细胞代谢和线粒体代谢受损, 蛋白生产加工和免疫被抑制, 且都指向其完全恢复可能需要更长时间[7].

“长新冠”的医学定义应为新型冠状病毒感染后综合征(post-COVID-19 syndrome)或新型冠状病毒急性感染后遗症(post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection), 是指新型冠状病毒(SARS-CoV-2)感染者在经历急性感染后, 仍持续出现一些症状(包括持续、复发或新发), 并且这些症状无法用其他原因解释[2,3]. 不同地区或研究机构目前对“长新冠”的时间定义尚未统一[8]. 世界卫生组织(World Health Organization, WHO)定义为感染新型冠状病毒3个月后还有症状(包括复发或新发), 且至少2个月的症状不能用其他疾病来解释. 美国疾病控制与预防中心(Centers for Disease Control and Prevention, CDC)定义为在新冠感染后4周后检测不到有复制能力的病毒, 但仍然持续有症状或健康问题. 欧洲临床微生物与感染性疾病学会(European Society of Clinical Microbiology and Infectious Diseases, ESCMID)定义为确诊新型冠状病毒肺炎后出现的症状持续或复发超过12周, 且无法用其他原因来解释. 英国国家卫生与临床优化研究所(National Institute for Health and Care Excellence, NICE)将新型冠状病毒感染后的持续症状分为亚急性期症状(4~12周)和新型冠状病毒感染后综合征(超过12周). 最近, 由美国国家科学院、工程院和医学院(美国三院)组成的联盟根据“长新冠”目前的进展给出了最新和较为广泛的定义: 即“长新冠”是一种与感染相关的慢性疾病, 在SARS-CoV-2感染后发生, 持续至少3个月, 表现为影响一个或多个器官系统的持续、复发和缓解或进行性的疾病状态[9].

可见, 尽管不同机构或地区对“长新冠”的定义不完全一致, 但这些定义都共同提到了持续或长期存在的症状, 且无法用其他病因解释, 即都强调了由新型冠状病毒感染导致的长期症状且无论是新发还是复发. “长新冠”定义的分歧主要集中在时间节点选择上, 即从4周到3个月, 且3个月居多. 此外, 美国CDC的定义中将是否检测到病毒复制作为依据之一, 但是这很可能会漏诊“长新冠”患者, 因为很难大范围确诊有长期症状的患者是否还存在病毒复制, 且部分“长新冠”患者体内存在病毒间歇性活跃的现象. 总体而言, 本文比较倾向于美国三院的定义, 因为它能更有效地覆盖那些自身症状感觉明显却难以临床确诊的人群, 且该定义强调了可延迟出现或发病, 无人群倾向, 对生活自理能力和身心造成影响, 可加重或诱发慢性疾病等基本特征[9]. 尽管如此, 正如新定义中指出的, 过分强调3个月的时间节点可能会忽略早期症状的发现和监测[9].

## 2 “长新冠”症状和临床表现

据保守估计, 全球所有感染过SARS-CoV-2的人中, 至少有1.4亿人受到“长新冠”的困扰, 疾病负担从轻到重, 其规模使之成为一个巨大的医疗保健挑战[9~13]. “长新冠”影响范围广泛, 临床症状多达200多种, 症状表现可单一或多种同时出现(图1)[9~13]. 这些症状列表和范围最初是通过对新型冠状病毒阳性感染者的调查报告得出的, 覆盖了人体的多个器官系统, 包括运动、消化、呼吸、泌尿、生殖、内分泌、免疫和神经等系统(表1)[13~15]. 例如, 一项覆盖56个国家的3762名新冠患者的全球调查(2019年12月至2020年5月), 显示大约一半患者在感染后6个月内无法全职工作, 主要症状包括疲劳、劳累后不适和认知功能障碍等[13]. 在143名从COVID-19康复并出院的意大利人中(2020年4~5月), 仅有12.6%参与者在60天后完全没有任何COVID-19相关症状, 而32%有一种或两种症状, 55%有三种或更多症状[16]. 其中, 最常见的症状是疲劳(53.1%)、呼吸短促(43.4%)、关节疼痛(27.3%)和胸痛(21.7%), 不太常见的症状包括皮疹、心悸、头痛和“针刺感”等[16]. 2021年一项涵盖39项“长新冠”研究的系统性回顾强调: 虚弱(41%)、全身不适(33%)、疲劳(31%)、注意力不集中(26%) 和呼吸困难(25%)是最常见的长期症状, 而不常见的症状(低于20%)包括出汗、胸痛、喉咙痛、焦虑和头痛等[17]. 另外, 认知功能障碍(“脑雾”)也是常见症状之一[16,17]. 例如, 陆军军医大学大坪医院神经内科的研究团队发文称, 在对1245名单次感染新冠原始毒株的幸存者和358名未受感染的配偶进行长期随访后发现: 在感染后2.5年内, COVID-19老年幸存者中认知障碍的总体发生率为19.01%, 且重症患者的认知障碍比例更高[18]. 与此同时, 英国牛津大学一项纵向前瞻性队列研究(2020年2月至2021年3月)在对475新冠出院患者进行2~3年随访后发现, 52.1%和24.9%报告了轻度或重度的主观认知下降, 而这通常被认为是阿尔茨海默病的早期阶段[19]. 此外, 儿童也可能出现“长新冠”, 其

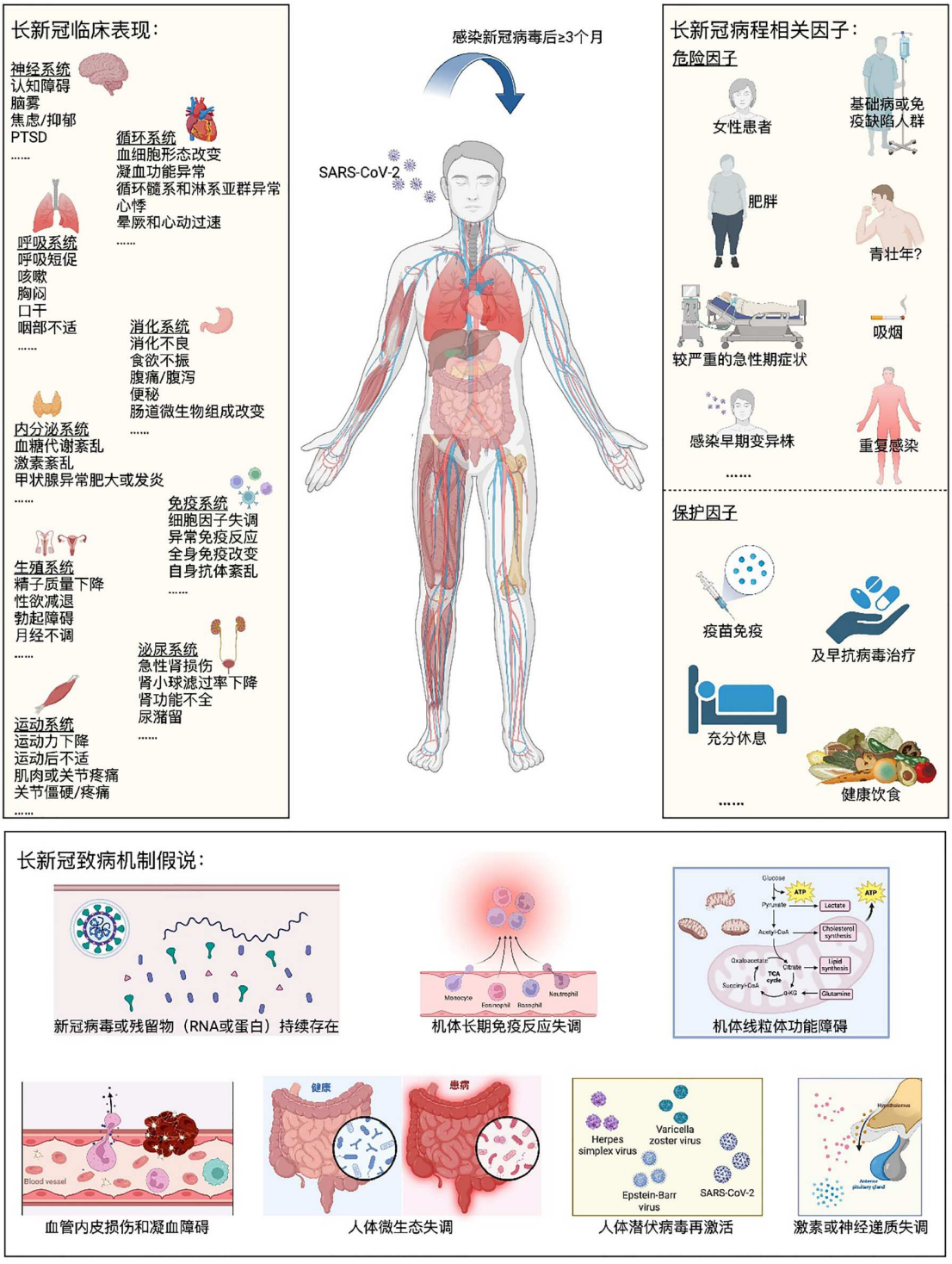


**图 1** “长新冠”的常见症状、病程相关因子和致病机制总结

**Figure 1** Schema summary of common symptoms, disease-related factors and pathogenesis of long COVID (Created with BioRender.com)

大部分症状与成人相似[20,21]，但儿童的症状表现还可能包括脑代谢减退、肝脏受累、肌痛性脑脊髓炎/慢性疲劳综合征(myalgic encephalomyelitis/chronic fatigue syndrome，ME/CFS)和肺部异常等[22,23]. 总之，大量证

**表 1** 人体各大器官系统的“长新冠”临床表现

**Table 1** Clinical symptoms of long COVID in human major organ systems

| 人体系统 | 临床表现 | 文献 |
|---|---|---|
| 运动系统 | 运动力下降、运动后不适、肌肉或关节疼痛或肿胀, 关节角度和曲度变化、不对称步态、关节僵硬、关节疼痛等 | [31~37] |
| 消化系统 | 消化不良、食欲不振、腹痛、腹泻、恶心呕吐、胃酸反流、腹胀、胃灼热、吞咽困难、便秘、肠动力改变和肠易激综合征, 肠道微生物群组成改变, 免疫性肝胆损伤等 | [2,35,38~42] |
| 呼吸系统 | 呼吸短促、咳嗽、喘息、胸闷、口渴、口干、咽部不适、打喷嚏、鼻塞等 | [38,43~45] |
| 泌尿系统 | 急性肾损伤、肾小球滤过率下降、肾功能不全、下尿路症状(膀胱出血、急性尿潴留)等 | [46~52] |
| 生殖系统 | 精子数量或精液量减少、精子形态和精子浓度均受损, 性欲减退、射精困难、勃起功能障碍等; 月经不调、经前症状增加和月经稀少等 | [53~56] |
| 内分泌系统 | 血糖代谢紊乱、激素紊乱、甲状腺异常肥大或发炎等 | [57~60] |
| 免疫系统 | 细胞因子失调、炎症增加、异常免疫反应(如$CD4^+/CD8^+$细胞应答、抗体反应过度)、全身免疫改变、自身抗体紊乱、诱发自身免疫性病症(类风湿性关节炎样表现、纤维肌痛综合征等) | [38,61~65] |
| 神经系统 | 疲劳、认知障碍、记忆减退/丧失、脑雾、头痛、抑郁、焦虑、睡眠紊乱、嗅觉味觉减退(或幻觉)、沟通困难、计划困难、感觉异常、头晕和平衡问题、对光和噪音敏感、自主神经功能障碍, 耳鸣、听力损失和眩晕、视网膜出血 、棉絮斑和视网膜静脉阻塞、创伤后应激障碍综合征、癫痫、痴呆等 | [38,66~70] |
| 循环系统 | 血细胞形态长期改变、凝血功能异常、血栓和栓塞增加、循环髓系和淋系亚群异常、心肌梗死、心律失常、心力衰竭、心悸、中风、低血压、晕厥和心动过速、诱发POTS等 | [71~74] |

据表明“长新冠”是一种真正的多器官、多系统疾病, 其症状表明病理变化超出急性感染期间病毒进入的受体ACE2阳性组织(表1). 尽管不同时期报告的“长新冠”症状和患病率存在一定异质性, 但一些典型症状仍可作为“长新冠”的主要参考指征, 包括运动后不适、疲劳、脑雾、头晕、胃肠道症状、心悸、性欲改变、嗅觉或味觉改变、口渴、慢性咳嗽、胸痛、异常动作和脱发等[24].

“长新冠”症状涉及系统广泛, 不乏难以通过自身辨识而需要临床检查发现的隐匿症状, 因此报道出来的症状可能仅是冰山一角. “长新冠”症状经常出现与其他疾病高度相似或重叠的临床表现, 给临床诊断及分类带来诸多困难和挑战[1~3]. 例如, 部分“长新冠”症状与ME/CFS、体位性心动过速综合征(postural tachycardia syndrome, POTS)和其他急性感染后综合征的症状有重叠难以区分[25~27]. 此外, 研究发现“长新冠”患者与阿尔茨海默病人群的认知障碍极为相似且共享部分生物学致病机理, 如活跃的神经炎症和星形胶质细胞等[18,28]. 对于具有如此多种症状组合重叠的疾病, 如何将“长新冠”患者有效分类面临挑战. 有观点认为, 可对这种异质性疾病进行精细化和个性化管理, 但是相反的观点是其存在很强的主观判断, 可能导致误诊增加. 尽管如此, 一些优化临床分类体系的研究一直在进行. 一项研究使用机器学习将6469名“长新冠”的患者分为6类[29]; 另有研究基于71个国家/地区的1535名参与者的德尔菲调查得出了“长新冠”11项预后核心清单[30]. 虽然承认”长新冠”症状的多样性, 但许多研究仍集中在常见的劳累后不适、疲劳或疲倦、肌痛、呼吸困难、胸痛和认知功能障碍或脑雾上[1,2,14]. 未来, 随着“长新冠”临床分类逐渐共识化, 通过特定的方法或生物标志物来引导聚类, 促进诊断或辨析发病机制与病理的关系仍迫在眉睫.

## 3 “长新冠”发生与病程相关因子

不同研究报道的“长新冠”发病率具有很强的群体和地区异质性, 约5%~60%. 研究群体的背景差异, 甚至社会和经济环境以及心理因素都可能对“长新冠”的最终发病率统计产生影响(图1). 第一, 患有基础病或免疫缺陷人群的“长新冠”发生率更高, 例如多项研究都发现高血压、糖尿病、心脑血管病、呼吸道疾病(哮喘, 慢性阻塞性肺病)、慢性疾病(例如慢性鼻炎, 慢性咽炎)等都是“长新冠”的危险因子[75~77]. 接受免疫抑制治疗的人群可能因为无法有效清除病毒, 因此康复过程可能会更长, 也更容易出现“长新冠”[78]. 第二, 女性相对男性更容易发生“长新冠”, 许多研究都得出相似的结论, 其具体的性别差异机制仍有待阐明[75,76,79]. 第三, 通常认为年龄增长与“长新冠”正相关, 即衰老促进“长新冠”进展, 但也有部分研究发现青壮年的“长新冠”患病率更高[75,76]. 我们近期开展的“长新冠”调查研究也发现在调整混淆因子后, 年龄增长仅是长期肌肉或关

节痛以及睡眠紊乱的危险因子，而对于其他大部分长期症状是保护因子. 因此老年人群体的“长新冠”易感性可能受到其他因素的影响，例如基础病、免疫衰退、经济条件和退休状态等. 第四, 多项研究都报告了肥胖或吸烟是“长新冠”的危险因子，这些群体至少在炎症指标或肺功能存在不同程度的异常，可促进“长新冠”的进展[76,80]. 第五，新冠感染后的急性期症状也是“长新冠”的主要危险因子[6,12,81,82]，急性期重症或病程更长患者的需要更长的时间去恢复. 第六, 重复感染是已知的一年内因新冠死亡或“长新冠”的危险因子，且感染次数越多风险越大[12,81]. 第七, 许多研究都证明急性期和长期症状因感染变异株的毒力而存在一定异质性, 与早期的原型株、Alpha、Beta、Delta等毒株相比，奥密克戎(Omicron)及其子代进化株的毒力显著降低，导致的长期症状也显著减少[75,83,84].

关于保护因子，普遍认为新冠疫苗接种是改善“长新冠”的保护因子. 研究证明，与没有接种新冠疫苗的人群相比，疫苗接种显著减少了感染、急性期病症和“长新冠”的发生，特别是那些接种了加强针的人群(大于3针)，获得了更好的保护[12,76,85]. 其他的“长新冠”保护因子可能还涉及早期有效的抗病毒治疗、健康的生活方式，均衡的营养以及感染后及时且充分地休息等(图1). 总之, 充分认识“长新冠”相关影响因子可协助新冠感染后自我评估，再同时加强自身防护和健康管理, 减少重复感染机会并及时接受治疗和康复，可有效减少“长新冠”的发生并降低其影响.

## 4 “长新冠”检测和治疗

### 4.1 “长新冠”的检测

目前尚无特异性的临床诊断或检测指标用来确诊“长新冠”患者的疾病状态，主要依托针对经典症状涉及的专业问卷调查，随访并辅助一些医学检测例如医学超声检查、CT、MRI和血常规等来判断. 要确定症状是否由“长新冠”引起，首先要排除其他可能引起相同症状的疾病，因此可能需要对各系统开展针对性的检测[86]. 鉴于呼吸系统受累是“长新冠”中较为常见的症状，可通过呼吸功能检查来评估“长新冠”患者的状况. 对肺通气功能、气体交换效率和肺部疾病严重程度的评估可采用静态或运动肺功能检查，如肺容量、通气换气功能、肺弥散功能和氧耗等检查. 对于持续12周以上的呼吸系统症状, 应考虑通过胸部X射线检查肺部是否有实质性病变[87]. 而经检查无肺部实质性病变的呼吸困难等症状，可能是因自主神经功能失调而导致的肺通气调节不当，即POTS(一种自主神经系统疾病)，可通过直立倾斜试验来辅助诊断[88]. “长新冠”患者的生理功能和炎性反应程度也可通过部分实验室检测项目评估，例如血常规、炎症指标和抗体指标等[89]. 淋巴细胞功能评估等免疫学检查有助于对患者的免疫状况进行评估. 研究显示, “长新冠”患者与对照人群在急性感染一年多后存在显著的免疫学差异，“长新冠”患者的循环免疫细胞群发生了显著变化，这包括非经典单核细胞、双阴性B细胞和分泌IL-4/IL-6的$CD4^+$ T细胞数量增加、常规DC1和中枢记忆$CD4^+$ T细胞数量减少等. 研究还发现, “长新冠”患者针对新型冠状病毒、EBV和VZV抗原的抗体水平也更高[62]. 此外, 与“长新冠”的疲劳症状相关的检测指标异常有血浆的D-二聚体和LDH升高及淋巴细胞绝对值减少等；与神经系统症状相关的有血IL-6、MCP-1和TNF-α水平升高；与认知功能障碍相关的则是EBV-DNA和EBV抗体滴度升高；与头痛和持续性神经痛相关的有血浆细胞骨架蛋白、GFAP以及β-葡聚糖水平升高[90]；与嗅觉障碍/味觉障碍相关的则是血清皮质醇降低等[91]. 总之, 尽管“长新冠”对于机体健康的潜在影响程度可通过相关检查来辅助评估，但是其特异性的诊断临床指标或者生物标志物仍有待探究.

### 4.2 “长新冠”的治疗

针对“长新冠”的治疗和临床管理，以专科治疗为主, 必要时多学科会诊, 以对症治疗、营养支持等综合治疗为主，积极治疗基础疾病，并按需给予心理治疗、中医治疗, 以及早期积极康复治疗[92]. 在病程早期给予抗病毒药物可能对治疗急性症状有益，还有助于减少“长新冠”发生[92]. 对“长新冠”综合征呼吸系统症状的治疗，有慢性咳嗽或有明显呼吸道症状的患者可考虑短期使用小剂量激素治疗，有肺纤维化、低皮质醇水平等时可使用小剂量糖皮质激素治疗，支气管扩张症加重时应使用抗菌药物治疗，同时也可考虑使用包括气道清理在内的非抗菌疗法[92]. 有心血管症状的患者以经验性支持治疗和对症处理为主，患者应接受规范的心血管疾病一级或二级预防. “长新冠”综合征的神经精神系统症状，应主要以心理支持、认知行为疗法、分级运动疗法及针灸治疗，以抗焦虑、镇静催眠药物辅助治疗[93,94]. “长新冠”患者的消化系统症状以对症

治疗为主, 建议患者少食多餐, 重点在补充蛋白质和热量, 部分患者如体重严重减轻和持续食欲缺乏者应对症进行营养咨询. 补充乙酰左旋肉碱、羟基酪醇、维生素C和D等具有抗氧化和抗炎活性的食品补充剂, 可在一定程度上缓解“长新冠”患者的长期疲劳和胃肠道症状[95]. 内分泌系统症状的治疗中, 有研究显示与安慰剂相比, 使用二甲双胍治疗可使“长新冠”发病率降低约41%[96]. 对于可能因肾上腺皮质功能减退而出现乏力、食欲减退、恶心、腹泻、体重减轻、低血压、低钠血症等症状的患者, 使用糖皮质激素进行治疗[97]. 有风湿免疫系统症状的“长新冠”综合征患者, 主要通过非甾体抗炎药和激素治疗, 建议对自身抗体阳性患者动态监测抗体, 对自身免疫性疾病确诊者开展专科治疗[98,99]. “长新冠”患者的症状如果符合焦虑、抑郁和/或创伤后应激障碍综合征的, 应由精神科评估症状严重程度并确定治疗方案[100,101]. 对于出现“长新冠”症状的神经退行性疾病患者(如阿尔茨海默病、帕金森病以及多发性硬化症等), 应积极治疗基础疾病并关注早期预防和监测, 治疗方法包括使用药物积极控制病程进展, 同时应努力控制炎症[102]. 总之, 对于“长新冠”患者的治疗的具体方案应该根据其症状的严重程度及功能指标开展综合评估后进行个性化和动态化调整.

## 5 “长新冠”致病机制与相关假说

“长新冠”的致病机理十分复杂, 且不同的“长新冠”症状的产生机理可不同或存在交互影响. 目前的致病机理假说可大致归类如下(图1).

### 5.1 新型冠状病毒或残留物(RNA或蛋白)持续存在

持续存在的新型冠状病毒或病毒残留物(RNA或蛋白)引起的机体异常免疫反应是“长新冠”的驱动因素之一. 早期研究已经报道可在生殖系统、心血管系统、胃肠道、血浆、粪便和尿液等检测到新型冠状病毒蛋白或RNA[103~105]. 尸检组织显示新型冠状病毒可在全身组织中传播和复制, 甚至能长期存在7个多月之久[104]. 在37名“长新冠”患者(12个月)的血液中, 60%能检测到新型冠状病毒S蛋白, 而对照未检出. 另有研究发现92.2%的人(224/243)在初次检测新型冠状病毒后10~72天内再次检出阳性结果, 且高龄群体的阳性率更高[106]. 一名37岁患有风湿疾病的独居女性因鼻咽部间歇性存在病毒抗原超过6个月和明显的“长新冠”症状寻求治疗, 经过为期5天的抗病毒治疗后(奈玛特韦/利托那韦)患者的鼻咽部病毒抗原显著减少且症状基本消失, 但是在停药后的第4周再次出现病毒抗原和症状, 表明新型冠状病毒的再激活[107]. 近期, 中国曹彬教授团队在*The Lancet Infectious Diseases*杂志发表了新型冠状病毒持续性存在的重磅证据[106]. 该研究调查了225名奥密克戎感染后几个月的上百份组织样本, 包括血液、胃、肺、肠道、血管、肾脏、乳腺、甲状腺、肝脏、脑、胰腺、胆囊和阑尾等[108]. 结果发现, 在感染后1、2、4个月, 手术标本中的病毒核酸检出率分别为30%、27%和11%, 病毒载量从几个到几万个拷贝数不等, 且在43%病毒阳性样本中甚至可检测到病毒亚基因组[108]. 研究还发现, 在持续存在的病毒残留物可能导致抗病毒相关基因活性降低和凝血及胆固醇调节相关基因失调[108]. 对于这些报告的病毒残留现象, 重要的未解谜题可能包括是否存在更易于长期携带SARS-CoV-2的特殊群体? SARS-CoV-2是否存在未知机制使细胞内病毒RNA序列或蛋白难以降解甚至发生病毒休眠?

### 5.2 机体长期免疫反应失调

免疫反应失调是“长新冠”患者经常出现的共有特征. 我们之前的研究发现早期的新型冠状病毒感染存在两个阶段: 第一阶段宿主存在明显的免疫抑制、紧密连接受损和代谢紊乱, 第二阶段人体免疫被激活且体内细胞因子风暴或炎症可引发组织器官损伤[7]. 耶鲁大学岩崎明子团队发现与未感染健康对照和感染后的康复者相比, “长新冠”患者的耗竭T细胞、IL-4/IL-6双阳性T细胞、活化B细胞、双阴性B细胞以及非典型单核细胞表现出增加, 而常规树突状细胞减少[62]. 另一项研究也报道“长新冠”患者的耗竭性T细胞增加, 且$CD4^+$和$CD8^+$效应记忆细胞数量减少, 中央记忆细胞的程序性死亡受体(PD1)表达升高, 且可持续1年以上[109]. 细胞毒性T细胞扩增还被发现与长期胃肠道症状有关[89]. 多个细胞因子在“长新冠”人群中异常升高, 例如IFNβ、IFNλ、IL-1β、IL-4、IL-6、CCL4、TNF和IP10等[110~112], 还有研究发现CCL11水平持续升高与认知功能障碍有关[111]. 除了免疫细胞与细胞因子, 研究发现“长新冠”人群的自身抗体水平会异常升高, 包括针对ACE2, β2-肾上腺素受体, 毒蕈碱M2受体和血管紧张素1-7 MAS受体等的抗体[112~115]. 这些抗体可对组织(结缔组织、细胞外基质成分、血管内皮、凝血因子和血小板等)、器官系统(肺、中枢神经系统、皮肤和

胃肠道等)或免疫调节蛋白(细胞因子、趋化因子、补体成分和细胞表面蛋白等)造成损伤[114~117]. 然而, 也有研究得出“长新冠”患者中的自身抗体不显著或不是主要驱动力的结论[1~3]. 总之, 免疫失调驱动“长新冠”是确定的, 但是其失调方向(增加或减少)存在争议, 阐明复杂人群背景和免疫表型的关联仍存在挑战, 需要等待后续更多的研究推动.

### 5.3 机体线粒体功能障碍

线粒体是细胞内的重要细胞器, 正常的线粒体可通过参与干扰素系统和诱导程序性细胞死亡来促进人体免疫进而抵抗感染[118,119]. 新型冠状病毒感染可造成线粒体功能障碍, 包括线粒体膜电位丧失等进而促进自身的生存和复制[2]. 线粒体损伤被发现与新冠感染后长期的乏力、疲惫和虚弱有关[32,120]. 有研究发现“长新冠”患者运动能力下降以及运动后不适(PEM)的病理机制是因为骨骼肌细胞的最大线粒体呼吸减少和线粒体含量降低[31]. 新型冠状病毒也可直接与线粒体蛋白结合, 抑制线粒体基因表达, 诱导线粒体能量产生功能障碍[121,122]. 基于尸检组织的研究发现尽管肺线粒体基因表达已恢复, 但在心脏以及肾脏和肝脏组织中, 线粒体功能仍受抑制[119]. 进一步的研究发现宿主细胞试图通过激活先天免疫防御和线粒体基因表达来进行补偿, 但长期的线粒体功能受损最终导致了严重的COVID-19后遗症[121,122]. 除了影响细胞能量, 线粒体还与细胞因子和炎症存在相互影响. 例如新冠肺炎感染诱导的TNF-α和IFN-γ和IL-10能通过诱导线粒体活性氧(ROS)生成相关基因来增加线粒体氧化, 进一步加剧线粒体功能障碍, 且过度的ROS还会导致血管内皮系统的损伤和凝血系统异常等[123,124].

### 5.4 血管内皮损伤和凝血障碍

新型冠状病毒感染对血管内皮和凝血系统的影响是巨大的. 首先, 新型冠状病毒可通过ACE2受体直接进入并损伤血管内皮细胞, 导致血管通透性增强和功能调节障碍[125,126]. 此外, 新型冠状病毒感染血管内皮会引起全身高凝状态, 导致微血栓或血栓形成, 损害肺、心脏、脑和肾脏等器官[125,126]. 这些急性感染期形成的血管内皮和凝血障碍就像海啸袭击后的残局, 需要很长时间的修复才能完成, 进而伴随着长期症状. 多项研究均在重症出院个体的长期随访中都检出凝血和血管内皮相关指标的长期失调, 包括D-二聚体、IL-6和血管性血友病因子(vWF)升高等[127~131]. 苏黎世大学医院的Onur Boyman团队在对113名新冠感染患者及39名健康对照进行长达一年的随访后, 发现“长新冠”患者的补体激活与血栓炎症相关的蛋白信号显著活化, 且介导长期组织损伤[132]. 研究还发现“长新冠”患者中$CD41^{+}$的单核细胞-血小板聚集体增多[132], 而另一项基于上千份血细胞和血浆样本的大型研究也发现奥密克戎感染引发了白细胞-血小板广泛聚集以及血小板紊乱和血栓形成[133]. 这些研究都共同支持血管内皮细胞损伤和凝血激活是新冠长期症状的主要特征, 且能导致长期疲惫, 呼吸困难, 运动力下降等. 最近, 我们的研究发现即使是那些轻症新冠感染者, 其凝血系统也需要长达6个月的时间才能彻底恢复[134]. 综上, 这些研究表明感染后血管内皮系统的失调或凝血障碍可能导致长期的缺氧, 血栓, 炎症, 栓塞等共同驱动“长新冠”症状的发生.

### 5.5 人体微生态失调

人体携带上千种微生物群落, 包括细菌、真菌、古菌和病毒, 特别是肠道菌群含量最为丰富且与疾病密切相关. 肠道菌群可大致分为益生菌、中性菌和致病菌, 当菌群失调时会引发各种病症. 据统计80种以上的菌群被报道与新冠急性期严重程度或长期症状有关, 且“长新冠”患者体内的有益菌明显减少, 而“恶菌”则明显富集[135,136]. 新型冠状病毒感染后会导致患者出现致病菌(例如瘤胃球菌*Ruminococcus gnavus*、普通拟杆菌*Bacteroides vulgatus*、内氏放线菌*Actinomyces naeslundii*、扭链瘤胃球菌*Ruminococcus torques*等)的富集, 和有益共生菌(例如普拉梭菌*Faecalibacterium prausnitzii*、真杆菌*Eubacterium rectale*、双歧杆菌属*Bifidobacterium spp.* 等)的减少[135,137~140]. 这些肠道菌群的紊乱可通过改变ACE2受体表达、抑制免疫细胞富集, 产生致病菌毒素, 损伤肠黏膜、诱导炎症或细胞因子等机理诱发或加重“长新冠”症状[2,135,136]. 此外, 一项基于142名新冠患者的支气管肺泡灌洗液菌群研究还发现一种口腔共生微生物(唾液支原体*M. salivarium*)与患者的预后显著相关[141], 表明呼吸道部位的菌群紊乱也可能与“长新冠”有关.

有趣的是, 有研究总结发现有益于缓解“长新冠”症状的菌群的共有特征似乎是都可以产生丁酸盐或短链脂肪酸等有益代谢物, 可为基于菌群治疗提供启示[2,135,136]. 香港中文大学黄秀娟团队评估了合生元制

剂(SIM01)对“长新冠”症状缓解情况, 该制剂由3个菌株(青春双歧杆菌、两歧双歧杆菌、长双歧杆菌)和3种益生元(低聚半乳糖、低聚木糖和抗性糊精)组成[142]. 治疗结果显示6个月时SIM01组相比于安慰剂组的肠道菌群多样性显著增加, 并且显著改善了疲劳、记忆丧失、难以集中注意力、胃肠不适等多个“长新冠”症状[142]. 此外, 墨西哥的Pedro Gutiérrez-Castrellón等人也发布了AB21益生菌(含植物乳杆菌和乳酸片球菌)的临床治疗效果, 发现益生菌干预能更好地改善新冠患者症状和病毒清除[143], 还观察到AB21益生菌配方增加了针对SARS-CoV2的特异性IgM和IgG, 提示其可能通过与免疫系统互作来发挥作用[143].

除了肠道菌群, 研究也发现新冠患者肠道中*Pepper mild mottle*病毒(RNA 病毒)和多种噬菌体(DNA病毒)的载量降低, 并且它们与COVID-19的严重程度、血液中的促炎蛋白、白细胞和中性粒细胞的水平呈负相关, 表明肠道常驻病毒可能具有调节宿主对新型冠状病毒感染的免疫反应的能力[144]. 总之, 这些研究表明微生物群落(特别是肠道菌群)及其产物与新冠感染及其后续长期症状密切相关. 改善和干预肠道菌群, 如通过补充益生菌、益生元和菌群代谢产物或可以改善新冠患者的肠道生态、促进免疫恢复、进而预防再感染和改善“长新冠”.

### 5.6 人体潜伏病毒再激活

人体潜伏病毒的重新激活在新冠感染后经常被检测到, 并且被认为可驱动“长新冠”发生. 2022年, James R. Heath团队发现EBV病毒水平可作为“长新冠”的早期风险因素[91]. 重要的是, 由于EBV再激活已经被证明是导致多发性硬化症(一种病因不明的中枢神经系统慢性脱髓鞘疾病)的主要原因[145], 因此“长新冠”的疲劳和神经认知功能障碍被认为可能是新型冠状病毒和EBV共同作用的结果. 2023年耶鲁大学研究人员发现“长新冠”患者(症状持续至少4个月)体内的EBV病毒和其他疱疹病毒(VZV, HHV-6)被重新激活, 并可作为“长新冠”的潜在标志物[62]. 此外, EBV和HHV-6再激活的临床表现还包括单核细胞增多症、乏力、脑雾、睡眠障碍、关节痛、肌痛、咽炎、头痛、发热、胃肠道不适等[146]. 过往研究发现在许多ME/CFS患者中观察到EBV和HSV-1再激活, 且能导致线粒体分解并严重影响能量代谢[147,148]. 可见EBV和HHV再激活并非新冠特有, 并提示新型冠状病毒诱导活化的潜伏病毒可能通过影响线粒体诱导“长新冠”症状. 也有部分研究得出不一致的结果, 例如一项荟萃分析表明新冠和非新冠人群之间的活动性EBV、CMV和HSV感染没有显著差异[149]. 目前, 遗留的谜题是这些潜伏病毒什么时候被再激活仍是不明确的, 因为新冠感染后机体大部分时间处于活跃的抗病毒亢奋状态, 不应有利于潜伏病毒的生存. 然而, 有研究发现新型冠状病毒入侵人体后会在早期抑制宿主免疫状态, 特别是早期抑制干扰素, 而这正是抑制潜伏病毒(HHV)并使其处于潜伏期的重要因子[150~152]. 此外新型冠状病毒感染后也会在特定阶段出现$CD4^+$ T、$CD8^+$ T和自然杀伤细胞(NK)的耗竭, 这也可能成为HHV或其他潜伏病毒再激活的时间窗口[153]. 除了EBV和HHV, 另有研究证据表明新型冠状病毒自身蛋白可激活宿主体内的逆转录病毒, 且直接导致许多病理特征[154~156].

### 5.7 激素或神经递质失调

新型冠状病毒感染后可引起患者的激素或神经递质失调进而引发症状. 例如, 许多流行病学观察到新型冠状病毒感染后糖尿病患者的比例显著增加, 而新冠引发的胰岛素紊乱可能是重要原因[157,158]. 新型冠状病毒可以通过ACE2受体进入胰腺细胞, 从而对胰腺造成损害, 影响胰岛素分泌或者造成胰岛素抵抗[157,158]. 有研究表明与完全康复者相比, 胰岛素抵抗在“长新冠”患者中显著增加, 且可作为“长新冠”慢性疲劳综合征和抑郁相关症状的风险因子[159]. 此外, 与完全康复者相比, “长新冠”患者存在明显的垂体前叶功能缺陷, 且皮质醇水平、胰岛素生长因子-1和生长激素水平都更低[160]. 几项研究均报道了“长新冠”患者血液中的皮质醇含量显著降低, 且该激素缺少与疲劳、肌无力、头晕和情绪变化等症状有关[62,161]. 性激素也与新冠症状有关, 研究发现新型冠状病毒能感染生殖系统, 并影响生殖功能, 导致月经失调和激素紊乱等[162,163]. 研究还发现较高的内源性黄体酮可减少女性新冠患者发展为重症, 推测这种性激素差异可能与“长新冠”的性别偏好性有关[164].

神经递质也被报道与“长新冠”相关, 特别是血清素(又叫做5-羟色胺)[165,166]. 血清素对于认知能力非常重要, 也有助于缓解焦虑、减轻抑郁, 是重要的情绪调节剂[165]. 2023年宾夕法尼亚大学Andrea C Wong等人在比较了“长新冠”患者(3-22个月)和康复者的血清代谢物后发现高达86.7%的“长新冠”患者的血清素显著

下调，且与疲劳、认知困难、头痛、耐力丧失、睡眠问题、焦虑和记忆力减退等长期症状有关[165]. 该研究的小鼠实验还证明了提高血清素水平可改善老鼠的认知能力，并提出了血清素减少的3种可能机制：血清素前体色氨酸的肠道吸收减少，血小板过度活化或减少进而影响血清素储存，血清素代谢酶活性增强导致血清素降解增加[165]. 其中，色氨酸不仅是制造血清素的原料，还是体内合成烟酸和褪黑激素等重要功能分子的原料，这些功能物质的缺乏很可能会加剧人体功能或免疫失调[165]. 重要的是，研究还发现服用类似色氨酸的补充剂甘氨酸-色氨酸双肽和5-羟色胺酸(5-HTP, 血清素的前体物)能有效逆转血清素减少导致的长期症状，且这两种物质的吸收不像色氨酸一样容易受病毒感染的影响[165]. 血清素信号传导还可能会影响血液凝固和胃肠道系统, 例如John W Blackett等人发现感染新型冠状病毒后持续存在心理健康和胃肠道症状患者的肠道微生物的色氨酸代谢和血清素信号传导降低[166]. 综上，这些结果表明新型冠状病毒感染引发的激素或神经递质失调可能驱动“长新冠”的发生发展.

## 6 国内“长新冠”研究现状

“长新冠”已经被多国列为重要的公共卫生问题并被广泛研究，然而我国的“长新冠”研究相对较少. 自2022年底以来, 许多居民经历了新型冠状病毒感染, 但大队列的“长新冠”流行病数据却很少，也缺乏相应地大型联盟或机构收集、监测和发布相关的流行病数据. 我国人群的基线特征、免疫背景和重复感染对“长新冠”影响仍有待探明. 此外，中国长期执行严格的疫情防控和高疫苗覆盖率避免了大量重症和死亡的发生, 也使中国人群具有不同于其他国家的免疫和感染背景, 且一定时间内感染的毒株较为一致，这些对于“长新冠”的流行病学研究是颇有裨益的.

在PubMed上检索以“long COVID”和“China”为关键词进行检索，共发现339篇文献，其中126篇为综述类，单独的“long COVID”检索记录则高达5178份(2024/9/5). 总体而言, 国内已发表的“长新冠”研究选题和内容主要集中以下方面: 第一, 探究“长新冠”的症状频率、范围和持续时间以及不同人群基线特征与“长新冠”症状的关联，这些研究队列主要集中在上海、北京、武汉、广州、香港等城市. 第二，探究或描述“长新冠”患者体内异常生物学过程或分子或菌群等，主要体现在通过转录组、蛋白组或宏基因组手段对“长新冠”患者的血液、尿液或粪便样本开展多组学研究. 需要指出的是，国内的曹彬教授和张文宏教授等团队作为先行者开展了诸多“长新冠”的随访和临床监测研究[6,75,82,167,168]. 值得一提的是曹彬教授团队在2021年1月和8月就陆续发布了疫情早期上千名出院患者长达6-12个月的随访结果，证明了多种长期后遗症的存在[6,82]. 来自中国香港的黄秀娟教授和黄志基教授等团队在“长新冠”机制和干预方面也有深入研究[142,169]. 更重要的是2023年底卢洪洲教授等团队牵头发布了《“长新冠”综合征临床诊治专家共识》，为中国“长新冠”的诊疗奠定了基础[92]. 此外，本团队在2023年初和2024初开展了两次大型的问卷调查，总共获得了超过8万人的新型冠状病毒感染情况和“长新冠”相关数据, 可为认识新冠流行规律提供数据支撑[12,85].

国内与国外“长新冠”研究的节奏仍存在一定差异, 可能存在以下短板. 第一, 国内的“长新冠”流行病研究主要集中在2022以前的新冠毒株(例如BA.1, BA.2或更早的新冠毒株)，这可能难以代表2022年底以来由BA.4、BA.5、BF.7和XBB等变异株导致的感染浪潮. 第二，目前的“长新冠”流行病数据中包含了很多中度和重度的出院患者，恐难以有效代表后续感染浪潮中的绝大部分轻症或没有就医的感染人群. 第三, 过往随访研究的样本量通常较小，且部分研究调查的症状较为单一, 仍需开展对大队列样本的长期监测和调查. 第四, 目前国内的“长新冠”研究多是回顾性研究, 仍缺乏针对“长新冠”致病机制或干预手段的前瞻性研究设计. 最后，国内的“长新冠”致病机制和标志物研究进展缓慢，仍缺乏依托动物疾病模型、细胞模型、人体多组织采样或新型技术手段(例如单细胞测序、免疫组库、时空表达谱和抗体谱分析)等的深入解析和验证.

## 7 展望

“长新冠”从最初的无人问津甚至质疑到现在的广泛关注见证了坚持向科学要答案(特别是案例研究和流行病学研究)的重要性. 尽管已经报告的“长新冠”发病率存在很大的异质性，我们假设常见的10%~30%患病率，也意味着全球几亿人曾经或正在遭受“长新冠”的影响. 这些长期症状可能不仅影响到生命健康, 还会波及全球生产力和经济发展. 正如Eric J. Topol等人指出的参考对ME/CFS和人类寿命关系的研究，如果不采取积极的行动，“长新冠”在未来可能会降低全球平均寿命, 加重医疗负担并引发诸多新的社会问题[2].

未来至少存在以下方面等待解决或努力: 基础研究领域, 需要探索“长新冠”的发病机制, 发现有效的生物标志物和治疗靶点, 为“长新冠”的诊治和药物研发提供有力支持. 此外, 还需关注“长新冠”与基础疾病、年龄、性别甚至心理等因素的关系, 为不同患者制定个性化的治疗方案. 公共卫生领域, 我们需要加强对“长新冠”患者的自我评估和监测管理, 确保他们及时发现病情并得到及时有效的治疗, 这需要积极提高公众对“长新冠”的认识, 引导公众树立科学的防控观念. 社会经济方面, 患者因长期患有症状导致劳动能力下降, 不仅对自身经济收入和劳动力市场造成冲击, 还可能影响企业的正常运转, 给全球产业链带来不稳定因素. 因此, 政府可能需要制定相应的政策和措施, 支持受影响的个人和企业渡过难关. 全球卫生格局方面, “长新冠”可能成为推动全球卫生合作的重要力量, 事实上诸多研究人员都在期待和共享中国的“长新冠”研究数据.

总之, “长新冠”是个值得持续关注和研究的科学问题, 为了面对这一共同挑战, 各国需要在“长新冠”干预药物的研发和防控政策上加强合作和共享, 确保广大民众都能够得到及时的诊治, 共同构建人类卫生健康共同体.

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Summary for "'长新冠': 事实、证据与机制"

# Long COVID: the facts, evidence, and the underlying mechanisms

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The monitoring data showed that the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues and its long-term post-infection effect (long COVID) still affects people's health and lives. The medical definition of long COVID should be termed as post-COVID-19 syndrome or post-acute sequelae of SARS-CoV-2 infection. It refers to the condition where individuals infected with SARS-CoV-2 continue to experience some symptoms (including persistent, recurrent, or new-onset) after the acute infection phase, and these symptoms cannot be explained by other causes. The latest definition also posits that long COVID is a chronic disease related to infection, occurring after SARS-CoV-2 infection, lasting for at least 3 months, and manifesting as a persistent, recurrent, and remitting or progressive disease state affecting one or more organ systems. Long COVID is currently a topic of concern and difficulty in the fields of public health and basic research.

Since the end of 2022, many Chinese residents experienced widespread SARS-CoV-2 infection, but awareness and attention to the long COVID still need to be improved. This article reviews the basic facts, evidence, and underlying mechanisms or hypotheses of long COVID, so as to provide a comprehensive understanding for the general public, clinicians, and researchers, and promote the research and development of prevention, control, diagnosis, and treatment programs for long COVID. Specifically, we reviewed the definition and origin of long COVID, and summarized the common symptoms of long COVID in various organ systems of the human body, as well as the current limited and pending detection methods and treatments. We also listed contributing factors that may affect long COVID, such as age, gender, underlying disease, COVID-19 vaccine, SARS-CoV-2 sub-variants, repeated infection, smoking and drinking habits, etc. In addition, we summarized the pathogenesis mechanisms or hypotheses that may drive long COVID, including the persistence of SARS-CoV-2 (RNA or protein), SARS-CoV-2-induced long-term immune response or autoantibody disorder, mitochondrial dysfunction, vascular endothelial injury and coagulation disorders, human microbiota disorders, latent virus reactivation, hormone or neurotransmitter disorders. Overall, the pathogenic mechanisms of long COVID are highly complex, and the underlying mechanisms of different symptoms may vary or interact with each other.

Finally, we also summarized the current status of long COVID-19 in China, and proposed possible problems and prospects for the future. The main tasks may include timely tracking and updating epidemiological knowledge of long COVID, establishing large-scale disease early warning and monitoring systems based on the internet and artificial intelligence, designing more prospective studies targeting the pathogenic mechanisms or interventions for long COVID, exploring the pathogenic mechanisms or biomarkers of long COVID by leveraging animal disease models, cell models, and novel technological approaches. In addition, the field of public health needs to strengthen self-assessment and monitoring for long COVID patients to ensure timely detection of the condition and access to effective treatment. This requires enhancing public science education to raise awareness and understanding of long COVID. Long-term symptoms may also lead to reduced work capacity, thereby impacting personal income and the labor market. Therefore, it is necessary to implement corresponding measures to support affected individuals and enterprises in overcoming these challenges. On the whole, long COVID is an important scientific issue worthy of continuous attention and research. In order to face this common challenge, countries need to strengthen cooperation and sharing in drug development and strategies for long COVID, so as to ensure that people around the world can get timely diagnosis and treatment and jointly build a community of human health.

**SARS-CoV-2, long COVID, epidemiology, pathogenesis, risk factors**

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