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新冠病毒感染后肺纤维化诊治研究进展

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摘　要

新冠病毒(COVID-19)感染对人类健康造成了极大的危害。虽然大流行已经得到控制，但COVID-19感染带来的长新冠综合征依然影响着出院后患者的健康和生活质量，涉及呼吸、心血管、神经等多个系统。COVID-19感染后肺纤维化(PCPF)是呼吸系统方面的常见问题，具有很高的发生率。但是目前，临床对PCPF的诊断、治疗、疾病转归等方面的研究尚较少。本文就相关文献资料进行综述，期望对PCPF的临床诊治提供参考借鉴。

关键词

COVID-19感染，肺间质纤维化，临床特征，诊断治疗

Research Progress in the Diagnosis and Treatment of Pulmonary Fibrosis after Novel Coronavirus Infection

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Abstract

COVID-19 infection has caused great harm to human health. Although the pandemic has been brought under control, the long COVID syndrome caused by COVID-19 infection still affects the

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health and quality of life of patients after discharge, involving multiple systems such as respiratory, cardiovascular, and neurological. Post-COVID-19 pulmonary fibrosis (PCPF) is a common respiratory problem with a high incidence. However, at present, there are few clinical studies on the diagnosis, treatment, and disease outcome of PCPF. This article reviews the relevant literature and expects to provide reference for the clinical diagnosis and treatment of PCPF.

Keywords

COVID-19 Infection, Pulmonary Interstitial Fibrosis, Clinical Features, Diagnosis and Treatment

1. 背景

COVID-19 给全球带来广泛的人群感染和死亡，并且可导致 200 多种不同程度的后遗症，其中肺纤维化和肺损伤是呼吸系统最常见和直接的表现[1]。研究显示，大约 20%的 COVID-19 患者有肺纤维化的证据，并在 1 年的随访中持续存在[2]。在重症 COVID-19 患者出院后的 3 个月和 6 个月，仍有 78%和 48%的患者存在肺纤维化。因此，加强对新冠病毒感染后肺纤维化的机制和临床诊治研究是临床重要问题。

2. 发病机制

COVID-19 感染后持续性肺损伤、上皮来源的炎症因子的持续释放以及巨噬细胞分泌大量促纤维化因子被认为是肺纤维化的几个主要原因[3]。在 COVID-19 感染的进展阶段，免疫细胞通过表面高表达的 TLR1 受体识别并结合病毒的结构蛋白 E 和 M，引发剧烈的炎症反应激活[4]。同时，结合了 TLR1 的病毒可以通过内吞被带入免疫细胞内部。这种“顿挫感染”的模式会导致病毒无法形成复制转录复合物 RTC 来转录病毒的亚基因组 RNA，但是促炎蛋白 NSP14 却可以直接通过基因组 RNA 进行翻译[5]。由于仅 NSP14 的表达而没有 ORF6 的表达，炎症反应被进一步放大，免疫细胞释放大量炎症因子，炎症因子风暴产生，损害II型肺泡上皮细胞并激活成纤维细胞等细胞成分，促进肺间质纤维化的形成[6]。

病毒感染引起免疫介导的损伤可诱导肺纤维化，常见的变化是 MMP2、MMP8 和组织蛋白酶上调，E-钙粘蛋白下调[7]。这些因子诱导成纤维细胞增殖分化为肌成纤维细胞，肌成纤维细胞分泌更加无序的细胞外基质(ECM)，ECM 成分过度沉积，导致肺泡壁增厚。另外，感染会降低 ACE2 表达，增加 AngII，使 NF-κB 和 ROS 表达增加，激活肺纤维化通路[8]。自噬抑制可导致成纤维细胞的大量增殖，促进肺纤维化的形成。据报道，SARS-CoV-2 通过阻碍自噬体–溶酶体融合来阻止自噬进展[9]。Hill 等人认为，自噬抑制诱导肺泡上皮细胞的 EMT (上皮–间质转化)，并通过异常的上皮–成纤维细胞串扰促进肺纤维化[10]。

3. 临床表现及诊断

3.1. 临床表现

(1) 症状：PCPF 患者的主要临床表现是咳嗽、胸闷及呼吸困难[11]-[13]。咳嗽是新冠病毒感染最常见的症状，平均持续时间为 2~8 周甚至更长。咳嗽的特点是伴有咽部异物感，咽部发痒，需要用力咳嗽来缓解不适感。20%~30%患者存在刺激性的咳嗽，且呈阵发性加重。PCPF 一般表现为活动后的气短和胸

闷不适，患者往往感觉到行动费力，有力不从心感，在青壮年主要表现为登山、爬楼梯、跑步、负重等体能活动受限。

(2) 影像学表现：PCPF 患者胸部 CT 表现为肺呼吸部结构扭曲、磨玻璃和网格影、牵拉性支气管扩张和蜂窝肺等[14]。大部分患者肺纤维化改变随时间推移病变可完全消退，症状后 3 个月左右 50%~60%完全消退，6 个月左右 60%~70%，12 个月左右 75%。病变消退主要在症状后 6 个月以内，6 个月后残留病变消退较慢或持续存在，罕见遗留蜂窝影[15] [16]。一般情况下，影像学改变的程度往往与临床表现严重程度相关，但由于患病个体的异质性，部分患者可以表现出持续的呼吸道症状，而没有影像学或实验室检查异常的证据[17]。

(3) 其他辅助检查：肺功能异常最常见表现为一氧化碳弥散功能降低和限制性通气功能障碍。大多数重症康复患者在出院 6 个月后仍存在疑似肺纤维化引起的限制性通气功能障碍和弥散功能障碍[18]。相关研究显示，约 40%的 COVID-19 幸存者在出院一年后仍存在肺功能障碍，可能与肺纤维化有关[19]。然而肺功能异常可随着时间推移而改善，在随访 12 个月时，患者肺功能较 3 个月和 6 个月时会有所好转[20] [21]。在实验室检查方面，PCPF 患者炎症标志物水平较高，如 c 反应蛋白(CRP)、白细胞介素-6 (IL-6)、血清乳酸脱氢酶和 D-二聚体[22]，此外还可能会出现淋巴细胞计数减少[23]。

3.2. 诊断

来自不同国家的研究表明，新冠后肺纤维化风险较高的患者特征为高龄、男性、吸烟，且有糖尿病、肺部和心血管疾病等[24]-[26]。此外，有无呼吸困难、住院时长、重症监护病房的住院时长、高流量氧支持的使用、机械通气的需要、急性感染的严重程度和 ARDS 的发展，也都与新冠病毒肺间质纤维化的高风险相关[27] [28]。在随访过程中，上述患病风险较高的患者很可能会出现 PCPF。

当具有上述高危因素的患者出现呼吸困难、咳嗽、运动能力下降等可疑长新冠症状时，应详细询问病史并进行体格检查，完善血气电解质分析、咳痰采样、肺功能检测(PFT)和 6 分钟步行试验(6MWT)等相关检查后初步判断，同时进一步完善胸部 CT 检查。一般在感染病变的高峰期，即在患者症状出现后的 10~11 天[22]进行肺部 CT 扫描就会有纤维样病变出现，而且随着病程变化而改变。结合临床症状、检查结果、COVID-19 导致的严重 ARDS 病史，同时排除其他疾病后可作出肺间质纤维化的诊断[29]。

4. 评价指标

4.1. 影像学指标

肺纤维化的严重程度可采用 Camiciottoli 提出的影像评分方法进行评估[30]：分为两部分，一部分是病变类型，另一部分是病变范围。病变类型分为毛玻璃状混浊、线性混浊、小叶间隔增厚、网状、蜂窝状和支气管扩张改变，评分分别为 1、2、3、4、5 分等级。然后对每种病变类型按照叶段的范围进行评分，1~3、4~9 或大于 9 个肺节段，分别评分为 1、2、3 分。肺间质纤维化定量总评分等于所有病变类型的评分加上每种病变类型的范围评分。总评分范围为 0~30 分。例如，如果 1~3 个肺节段有毛玻璃混浊，肺纤维化评分为 1 + 1 = 2 分。根据总分将肺间质纤维化分为轻度(0~10)、中度(11~20)和重度(21~30)三个不同级别的组。

此外，相关研究显示人工智能炎症评分与定量肺间质纤维化评分有着良好的一致性，表明人工智能辅助胸部 HRCT 技术可以通过量化肺部炎症间接反映肺间质纤维化的程度。国内相关研究机构开发的“人工智能(AI)辅助肺炎诊断系统”软件将卷积神经网络与阈值法相结合，根据左右肺解剖病变范围，及检测到的炎症区域，计算肺炎症量(PIV)、全肺容积(WLV)、患病肺百分比(PIV/WLV)以及定量参数给予综合赋分，用以判定肺间质纤维化的程度[31]。

4.2. 其他指标

肺纤维化严重程度及是否进展还可以通过临床表现、肺功能及六分钟步行试验来反映。当患者出现体力活动后呼吸困难程度加重或出现慢性咳嗽加重，在排除其他原因后表明疾病较重或病情进展。使用六分钟步行试验，将患者的步行距离及血氧水平同之前相比较，以判断疾病进展情况。研究发现，对出院后患者 6 个月随访，约 1/4 患者 6 min 步行距离的中位数低于正常参考值[32]。

5. 治疗及管理

PCPF 潜在的治疗方式包括抗纤维化药物、皮质类固醇激素、其他抗炎和免疫抑制药物、螺内酯、N-乙酰半胱氨酸、抗酸药物、间充质干细胞和肺移植[14]。

(一) 药物治疗

1、吡非尼酮和尼达尼布

吡非尼酮一种是一种吡啶酮类口服活性小分子化合物[33]，具有抗炎、抗纤维化和抗氧化特性[34]-[36]。不良反应为光过敏、乏力、皮疹、胃部不适和厌食，但总体症状轻微，且大部分患者可以耐受，很少会因不良反应而停止服药[32]。尼达尼布是一种多靶点酪氨酸激酶抑制剂，作用于表皮生长因子受体、血管内皮生长因子受体和血小板源性生长因子受体[37]-[39]。尼达尼布最常见的不良反应是腹泻[40]，与食物同服即可减少药物对胃肠道的刺激。尼达尼布同样具有较好的安全性和耐受性[41]。

抗纤维化药物吡非尼酮和尼达尼布，可减缓肺纤维化患者的肺功能下降速度。一项前瞻性研究[42]将 30 名 PCPF 患者随机分为两组，分别给予吡非尼酮和尼达尼布治疗 12 周，结束后发现与基线相比，吡非尼酮和尼达尼布组的肺功能参数、六分钟步行测试(6MWT)距离及血氧饱和度均有所提高，而心率和放射学评分水平则有所下降($p < 0.05$)。对于轻、中型 PCPF 患者不倾向加用抗纤维化药物，可随访监测。对于重症或危重症患者可加用抗纤维化药物治疗，但需要基于肺纤维化病变的范围、药物副作用、超适应症等问题，与患者协商后个体化决定[43]。

2、皮质类固醇激素

研究发现，糖皮质激素不仅能通过减少肺部炎症来改善 PCPF 的症状，而且可以降低 PCPF 的风险或严重程度[44]。Myall 等人研究纳入 30 名通过多学科团队方法确诊为 PCILD 并表现为组织型肺炎的患者，结果显示，泼尼松龙(剂量为 0.5 mg/kg)可改善患者的肺功能、症状和影像学表现[45]。另一项研究将 120 例患者随机分为高剂量激素(40 mg/d)与低剂量激素(20 mg/d)组，两组疗程均为 6 周，结果显示两组中 80%以上患者的症状及影像学均有所改善，但疗效未见明显差异[46]。在大剂量和长期使用的情况下，皮质类固醇存在许多副作用，包括肥胖、免疫抑制、抑郁症和骨质疏松症[47]。因此，需要进一步的对照试验评估皮质类固醇激素在 PCPF 的疗效及用药时机，同时解决皮质类固醇的风险问题。

3、IL-6 抑制剂(如托珠单抗)

白细胞介素-6 抑制剂如托珠单抗可抑制 STAT 通路的激活，从而抑制促纤维化细胞因子如 TIMP1、PAI-1、CTGE、TGP、TGFBRI 和 PGDF 上调。在美国和全球的观察性研究中发现托珠单抗似乎可改善 COVID-19 肺炎患者的预后[48]。一项全球性的三期临床试验 EMPACTA 表明，与安慰剂相比，托珠单抗可降低未接受机械通气的 COVID-19 肺炎住院患者进展为机械通气或死亡的可能性，从而预防 PCPF [49]。未来我们需要进一步的试验来评估托珠单抗在预防或减轻 PCPF 方面的影响[44]。

4、其他药物

多份报告指出，使用螺内酯对预防纤维化具有重要意义[50]。醛固酮主要影响肺上皮细胞，导致细胞外基质转化增加[50] [51]，进而引起纤维化。螺内酯是一种抗醛固酮物质[52] [53]，经研究证实，这种药物不仅可以减少肺泡中淋巴细胞、中性粒细胞等白细胞浸润，还可有效治疗急性肺损伤[54]。可在严重

COVID-19 相关的高炎症反应中发挥潜在作用，预防或减轻 PCPF。N-乙酰半胱胺酸(NAC)是一种重要的抗氧化药物，可清除自由基、抑制炎症细胞过量释放活性氧以及减轻细胞损伤。通过抑制 γ 干扰素的活性，阻断核因子 κB 信号转导，从而抑制炎症反应引起的肺纤维化。单药治疗可改善患者的咳痰症状，联合吡非尼酮可用于重症患者的治疗。在 COVID-19 中使用间充质干细胞的潜在目标是防止免疫细胞和细胞因子的释放和激活，降低肺纤维化发生和进展的风险[55]-[57]。此外，间充质干细胞在逆转或减轻 PCPF 方面具有潜在作用[57]。对于预防和治疗 COVID-19，目前此种治疗方法还未获得批准，需要进行进一步的临床试验。

(二) 外科治疗

肺移植可以作为 PCPF 患者最后的治疗手段。若 COVID-19 患者发生严重肺纤维化，经积极内科治疗 1 月以上，如病情无好转，此时患者 1 个月内死亡风险大于 50%，根据国际肺移植指南，可行肺移植手术，根据相关研究表明术后 90 天的生存率可提高至 80%以上[58]。

(三) 呼吸支持及肺康复治疗

PCPF 患者可表现为不同程度的呼吸困难，因此，有必要进行长期氧疗。持续氧疗可改善患者的低氧血症、活动能力和生活质量。对氧饱和度在 92%或以下需要吸氧的患者进行监测，使血氧饱和度达到 94%~98% [59]。肺康复治疗为基于个性化评估和治疗的多学科干预，包括但不限于运动训练、教育和行为改正，旨在改善 PCPF 患者的身心状况。通过肺康复可以缓解患者活动耐量下降的症状，提高生活质量。此外，呼吸锻炼可以使呼吸模式正常化并提高呼吸肌(包括横膈肌)的效率，从而减少能量消耗和气道刺激，改善疲劳和呼吸困难[59]。

6. 总结及展望

COVID-19 感染后肺损伤、炎症因子的释放及大量促纤维化因子的分泌是 PCPF 的发生机制。临床通过胸部 CT、肺功能及六分钟步行试验等方法诊断及评估疾病进展。对于确诊的 PCPF 患者，可采用药物治疗，辅以呼吸支持及肺康复治疗，必要时可进行肺移植手术。不同于慢性纤维化的进行性发展，PCPF 也有一部分患者可出现持续性肺纤维化，但大部分患者的病灶通常可随着时间的推移部分吸收或趋于稳定[43]。到目前为止，PCPF 患者的临床数据及相关研究仍需要进一步深化，同时对患者进行长期随访和专科评估，促进患者整体康复、改善生活质量是主要的临床目标。

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