

慢性阻塞性肺疾病加重的流行病学研究进展

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摘要: 慢性阻塞性肺疾病加重 (exacerbations of chronic obstructive pulmonary disease, ECOPD) 是慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD) 预后不良的关键因素之一, 对患者健康与生命产生重要影响, 给家庭和社会造成了严重的经济负担。全球 ECOPD 患病率呈持续上升趋势, 病死率处于较高水平, 因此加强对 ECOPD 的预防与控制刻不容缓。在不同国家、不同时间、不同人群中, ECOPD 的患病率与死亡率均存在差异, 且受多种因素影响。本文主要从 ECOPD 的流行特征、危险因素、预防措施等方面加以综述, 旨在提升对 ECOPD 的认知, 为有效防控 ECOPD 发生提供科学参考。

关键词: 慢性阻塞性肺疾病加重; 流行病学特征; 危险因素; 预防措施

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Research progress on epidemiology of exacerbations of chronic obstructive pulmonary disease

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Abstract: **Objective** Exacerbations of chronic obstructive pulmonary disease (ECOPD) represent a critical prognostic factor for COPD patients, significantly impacting health outcomes and imposing substantial economic burdens on families and society. This review aims to summarize current knowledge on ECOPD epidemiology to inform prevention and control strategies. **Methods** We conducted a comprehensive literature review focusing on the epidemiological characteristics, risk factors, and preventive measures of ECOPD. **Results** Global ECOPD prevalence shows a persistent upward trend with consistently high mortality rates. Significant variations exist across countries, time periods, and populations, influenced by multiple factors including environmental exposures, comorbidities, and healthcare accessibility. Key risk factors include smoking, air pollution, respiratory infections, and poor medication adherence. Effective preventive strategies encompass smoking cessation, vaccination programs, air quality improvement, and optimized disease management. **Conclusion** ECOPD remains a major public health challenge requiring urgent attention. Enhanced understanding of its epidemiological patterns and risk factors is crucial for developing targeted interventions to reduce disease burden and improve patient outcomes.

Keywords: Exacerbations of chronic obstructive pulmonary disease; Epidemiological characteristics; Risk factors; Preventive measures

慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD) 是全球的主要致死原因之一, 造成的社会经济负担不断加重, 已成为全球性的公共卫生问题^[1]。慢性阻塞性肺疾病加重 (exacerbations of chronic obstructive pulmonary disease, ECOPD) 指急性呼吸道症状恶化的发作, 可导致肺功能不可逆加速恶化、下肢肌肉功能、身体活动和健康相关生活质量的加速下

降^[2], 是 COPD 高死亡率、高复发率与高医疗支出^[3-4]的主要原因, 对患者健康与医疗资源的合理利用构成极大威胁。ECOPD 作为评估 COPD 严重程度与结局的关键环节, 近年来引起临床广泛关注。掌握 ECOPD 的流行特征及其危险因素, 对于控制疾病的发生发展有重要意义。本文主要从 ECOPD 的流行特征、危险因素、预防措施等方面进行文献综述, 旨在提升对 ECOPD 的预防控制能力, 为开展相关工作提供参考。

1 ECOPD 概述

ECOPD 指 COPD 患者 14 d 内加重的呼吸困难和 (或) 咳嗽咳痰为特征的事件, 可伴有呼吸急促和

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(或)心动过速,常与感染、污染或其他气道损伤引起的局部或全身炎症相关联^[5]。ECOPD 的主要临床表现为气道炎症、粘液增加和气体潴留引起的呼吸困难加重,其他症状包括痰脓、痰量增多及咳嗽和喘息加重^[6],通常持续 7~10 d,但也存在持续时间更长的情况。Seemungal 等^[7]认为,ECOPD 发生 8 周时,约 20% 患者无法恢复至发生前状态,且恢复缓慢人群的病情更易加速进展。《慢性阻塞性肺疾病全球倡议》(Global Initiative For Chronic Obstructive Lung Disease, GOLD)将 ECOPD 患者分为三级:轻度(仅用短效支气管扩张剂治疗)、中度(经短效支气管扩张剂和口服皮质激素 ± 抗生素治疗)及重度(需要住院或急诊)^[8]。

2 ECOPD 的流行病学特征

2.1 时间分布 美国 SPIROMICS 队列研究发现,ECOPD 每年发病率波动性较大,7.4% 的患者存在每年发病的情况,2.1% 的患者每年发病二次以上^[9];一项随访研究发现,ECOPD 发病不稳定,相当部分病例由频繁发病转为不频繁发病,反之亦然^[10]。但 Donaldson 等^[11]对伦敦 COPD 患者进行 6 年随访,结果显示 ECOPD 发病率在研究期间基本保持一致。

ECOPD 全年均可发病,但冬季发病率较高,恢复时间较长。基于伦敦 COPD 队列的 14 年随访发现,冬季 ECOPD 发生 1 052 次,而春夏季只发生 676 次,相较于春夏季,冬季 ECOPD 发生次数增加了 55.6%^[12];一项针对北半球的大型多中心季节研究发现,夏季的 ECOPD 月发病率为 3.53%,冬季为 7.63%,相比之下冬季的 ECOPD 风险超出 116%^[13]。虽然南北半球均有冬季高发特点,但南北半球冬季发病率略有不同。一项气候研究分析了全球 ECOPD 发病的季节性变化,相比于夏季,北半球冬季加重率为 80%,南半球冬季加重率为 71%,略低于北半球^[14]。在热带地区,ECOPD 发病不受季节因素影响,呈现全年平稳发病^[14]。此外,季节性因素对患者的恢复时间也有影响,对伦敦 COPD 队列的 14 年随访研究表明,冬季 ECOPD 需要 10 d 恢复,而夏季仅需要 9 d^[12]。

2.2 地区分布 ECOPD 是全球性的问题,但各国发病率有所不同。中国实现和改善稳定期 COPD 管理 (REAL) 研究显示,我国 ECOPD 年发病率为 0.56 次/人^[15]。我国西北地区 ECOPD 程度最严重,重度 ECOPD 发病率为 0.45,高于中南部(0.41 次/人, 95% CI: 0.37~0.45) 和北部 (0.13 次/人, 95% CI: 0.11~0.16)^[16]。覆盖 30 个国家 COPD 患者的 UPLIFT 队列研究^[17]报道总队列 ECOPD 年发病率为 0.85 次/人,其中亚洲地区的年发病率为 0.92 次/人,高于全球平均水平;日本队列发病率低于总体队列和亚洲队

列,平均年发病率为 0.61 次/人^[17]。在北美、欧洲和新西兰进行的 ECLIPSE 研究报道的年加重率为 1.21 次/人^[18],在英国进行的 Salford Lung^[19]研究报道的年加重率为 2.0 次/人,而德国 DACCORD^[20]研究报道 ECOPD 的年发病率为 0.384 次/人。一项针对 12 个中低收入国家的研究发现,严重 ECOPD 的年平均发病率为 20.1%,且随着严重发作次数的增加,连续发作的时间间隔缩短,对低收入和中等收入人群,预防 ECOPD 发生是降低疾病负担的主要措施^[21]。

ECOPD 发病率有显著的城乡差异,城市 ECOPD 发病率高于郊区。北京市的流行病学显示,2013—2020 年城区女性 ECOPD 患者的总体和每日住院人次均高于郊区,城市西部、中心城区和东北部住院人次密度较高,近郊区相对偏低^[22]。中国 REAL 研究报道,我国中南部地区 ECOPD 年发病率最高,为 0.84 次/人(95% CI: 0.78~0.90),北部地区最低,为 0.27 次/人(95% CI: 0.24~0.31),农村为 0.52 次/人(95% CI: 0.49~0.55),略低于城市的 0.59 次/人(95% CI: 0.57~0.62)^[16]。虽然农村地区 ECOPD 发病率低于城市,但 ECOPD 恶化程度显著高于城市地区。从 REAL 研究的医院分布上看,二级医院的总体 ECOPD 发病率和严重 ECOPD 发病率都高于三级医院(总体 ECOPD 发病率: 0.66 vs. 0.47; 严重 ECOPD 发病率: 0.44 vs. 0.18)。REAL 研究中二级医院的大多数患者来自农村地区,而三级医院的患者更多来自城市地区,虽然农村地区 ECOPD 发病率略低于城市地区,但农村地区患者的病情恶化度较高,常导致住院治疗,这可能反映出农村对疾病的认识和管理较差^[16]。

2.3 人群分布 我国青岛的一项研究发现,职业粉尘暴露者一年内发生 ECOPD 住院超过二次的风险是非职业粉尘暴露者的 1.83 倍^[23]。SPIROMICS 队列探究吸烟者职业暴露与 COPD 的关联结果也表明,与无职业暴露的人群相比,职业暴露人群报告了更高的 ECOPD 发病占比 (0.49 vs. 0.33),职业暴露使男性 ECOPD 发病风险增加,但与女性无关^[24]。韩国的 KOLD 队列研究表明,与无职业暴露的人群相比,曾接触过异氰酸酯、甲苯二异氰酸酯、焊接溶剂、小麦粉、谷物粉尘、毛发持久性药物和其他化学物质的职业暴露人群 ECOPD 发病率更高 (OR=1.418, 95% CI: 1.027~1.956)^[25]。对 COPD 患者的前瞻性队列研究估计了职业暴露于蒸汽、气体、灰尘或烟雾 (vapours, gas, dust, or fumes, VGDF) 和因呼吸导致的离职(呼吸相关工作残疾)与健康之间的关联,同时接触 VGDF 和呼吸相关工作残疾的急诊就诊 (OR=3.9, 95% CI: 1.4~10.5) 和住院 (OR=7.6, 95% CI: 1.8~32.1) 风险更高^[26]。ECOPD 与特殊职业暴露相关,一项综述认为,消防工

作涉及反复接触刺激性气体、烟雾、蒸汽等多类型吸入性暴露,在长期接触野火的过程中,烟雾暴露对消防员呼吸系统健康产生不利影响,从而导致较高的 ECOPD 发病率^[27]。

3 ECOPD 的危险因素

3.1 感染 呼吸道感染是 ECOPD 的最常见病因,包括细菌感染和病毒感染。细菌感染的病原体以流感嗜血杆菌和肺炎链球菌最为常见,其他病原体如卡他莫拉菌、副流感嗜血杆菌、革兰阴性肠杆菌和假单胞菌也占一定比例。Monso 等^[28]将病情加重的患者与病情稳定的患者匹配进行比较,发现在病原体阳性(加重组 52%vs. 稳定组 25%)和细菌浓度负荷超过 10 000 CFU/ml(加重组 24%vs. 稳定组 5%)比例方面均存在显著差异,患者体内最常见的细菌是流感嗜血杆菌和肺炎链球菌。但西班牙一项前瞻性研究在 ECOPD 患者体内分离出不同的细菌性病原体,其中最常见的是铜绿假单胞菌^[29]。由于在没有发生 ECOPD 的情况下,细菌在气道中也存在定植,给确定细菌在 ECOPD 进程中作用时造成阻碍,但大多数研究发现患者细菌培养阳性和高细菌负荷的患者比例在 ECOPD 期间有所增加,流感嗜血杆菌是 ECOPD 最常见的细菌。

ECOPD 相关的常见病毒包括鼻病毒、甲型流感病毒、呼吸道合胞病毒和副流感病毒等,不同国家和地区的主要病原体有地理差异性。病毒感染患者常出现明显的痰量、脓量增加、呼吸困难、咳嗽、声音嘶哑。除呼吸道症状外,病毒加重患者的发热、肌肉疼痛等非呼吸道症状更为常见,症状缓解时间也较长^[30]。韩国的研究发现 ECOPD 住院患者中有 28.1% 出现病毒感染,其中鼻病毒最为常见(38.8%),呼吸道合胞病毒(14.1%)、冠状病毒(11.8%)、甲型流感病毒(10.6%)、副流感病毒(8.2%)、腺病毒(8.2%)和偏肺病毒(8.2%)也占一定比例^[31];欧洲和北美的研究发现病毒感染与 ECOPD 密切相关,其中人鼻病毒、冠状病毒和流感病毒是引发 ECOPD 的主要病毒病原体^[32];澳大利亚的研究者在 58% 的 ECOPD 患者中发现了病毒阳性,最常见的病毒是甲型流感病毒(31%)、鼻病毒(24%)和呼吸道合胞病毒 A/B(17%),且 ECOPD 病例中存在病毒和细菌的同时感染^[33];伊朗的研究证实在病毒感染的 ECOPD 患者中存在双重病毒同时感染^[30],这表明多种病毒和细菌在 ECOPD 中可能同时发生作用。

3.2 温度 短期暴露于极端温度可能会引发 ECOPD。中国台湾的研究报道,气温每降低 1℃, ECOPD 发病率增加 0.8%;气温每降低 5℃时,长期

低温使 ECOPD 风险增加 11.1%,且老年患者在平均气温下降 5℃时更易发生 ECOPD^[34]。2013—2016 年在北京进行的一项大规模的人群研究显示短期暴露于低温会增加 ECOPD 住院的风险,与温度的第 25 百分位数相比,极低的气温和体感温度(温度的第 1 百分位数)的相对风险(relative risk,RR)分别为 1.55(95%CI: 1.21~2.00)和 2.08(95%CI: 1.44~3.01),且这种低温的不利影响持续到暴露后数周,65 岁以下患者更易受到低温变化的影响,但该研究未显示高温与 ECOPD 风险存在关联^[35]。也有研究表明,在平均气温较高的日子里,由于病情加重而住院的人数增加,英国的研究报道气温在 23.2℃以上时,气温每增加 1℃,COPD 住院风险增加 1.47%^[36]。除了极端温度对 ECOPD 的影响,短期温度变化对 ECOPD 也有影响。Wang 等^[37]基于中国南方 21 个城市的荟萃分析显示,日温度变化(日温度变化的第 75 百分位数相对于第 25 百分位数)是 ECOPD 住院的危险因素(RR=1.11, 95%CI: 1.08~1.12),日温度变化幅度增大,ECOPD 的相对危险度相应增加。

3.3 空气污染物 越来越多的研究显示空气污染物对 ECOPD 的发生发展起重要作用,短时间暴露于空气污染会显著增加 ECOPD 风险。一项 meta 分析指出,PM₁₀ 每增加 10 μg/m³,COPD 住院的人数增加 2.7%^[38]。西班牙的一项关于空气污染物与 COPD 急诊的研究发现,SO₂ 每增加 10 μg/m³,COPD 急诊室就诊人数约增加 5%,NO 每增加 10 μg/m³,COPD 患者的急诊就诊风险增加 3.3%^[39]。与 ECOPD 风险增加相关的空气污染物主要有 O₃、CO、NO₂、SO₂、颗粒物等,其中作用最显著的是 O₃ 和 NO₂^[40],这种风险效应在温暖季节中作用更加显著^[41]。恶劣气候引起的室外空气污染与室内空气污染对 ECOPD 发病均有影响。中国香港的一项研究发现,沙尘暴发生后 2 d,因 COPD 而急诊住院的人数显著增加,与非沙尘暴日相比,每 10 μg/m³ PM₁₀ 的 RR 为 1.05(95%CI: 1.01~1.09)^[42];Hansel 等^[43]认为室内空气污染也是 ECOPD 的重要危险因素,室内 PM_{2.5} 浓度每增加 10 μg/m³,发生严重 ECOPD 的风险增加 38%。

3.4 既往加重史与 COPD 严重程度 研究显示,既往加重史和住院史是 ECOPD 住院后 30 d 和 90 d 再入院的重要危险因素^[44]。一项回顾性队列研究发现,既往 COPD 的严重性与 ECOPD 风险升高有关(OR=3.86, 95%CI: 1.50~9.93)^[45]。Hurst 等^[18]发现 22% 的 2 期、33% 的 3 期和 47% 的 4 期 COPD 患者出现频繁加重,ECOPD 发病率随着 COPD 严重程度升高,推测既往加重史可预测 ECOPD 的发生。

3.5 心血管疾病 R. ChadWade 等^[46]开展的 BLOCK-

COPD 试验研究表明, COPD 患者的肺动脉高压易引起 ECOPD 发生; 服用心血管疾病药物与 ECOPD 风险增高有关, 如在存在肺型 p 波(提示右心功能障碍)的患者中, 服用美托洛尔显著增加 ECOPD 风险, 且美托洛尔增加了严重 ECOPD 需要住院治疗的风险和呼吸症状恶化的风险^[47]。心血管疾病不仅增加 ECOPD 发病风险, 也会加重 ECOPD 严重程度。一项 COPD 队列中关于心血管疾病与加重率和死亡率的研究发现, 患有心血管疾病的 COPD 患者有 51% 发生严重恶化, 需要住院治疗^[48]。

3.6 焦虑与抑郁 最近的研究发现, 焦虑和抑郁与 ECOPD 风险存在正相关。与非抑郁或焦虑患者相比, 抑郁症患者出现中重度恶化的风险较高 ($IRR=1.57$, $CI: 1.17 \sim 2.11$), 焦虑患者出现中重度加重 ($IRR=1.52$, $CI: 1.03 \sim 2.27$) 和重度加重 ($IRR=2.13$, $CI: 1.09 \sim 4.15$) 的风险也明显高于非焦虑患者。与没有焦虑和抑郁症的患者相比, 抑郁症患者 ECOPD 发病率相对更高, 症状相对更加严重^[49]。

4 ECOPD 的预防

4.1 戒烟 戒烟是预防 ECOPD 的重要措施。吸烟会显著加重 ECOPD 的风险^[50], 低于 10 包/年的低吸烟暴露量仍会增加 ECOPD 发病风险, 吸烟量增加会导致发病风险增加^[51]。戒烟者发生 ECOPD 的风险显著降低, 其降低程度与戒烟的持续时间有关^[52], 短期戒烟患者也可在一定程度上降低 ECOPD 发病风险^[53]。美国一项研究发现二手烟暴露也会增加 COPD 急诊就诊与住院次数^[54]。杜绝烟草暴露对 ECOPD 症状减轻和健康促进有重要影响。

4.2 疫苗注射 疫苗注射可以显著降低 ECOPD 风险^[55], 具有较高的成本-效益。大多数 ECOPD 由病毒和(或)细菌感染引发, 流感和肺炎球菌感染是引起患者住院和死亡的两个重要原因, 针对这两种病原体接种疫苗能够有效预防 ECOPD。既往研究表明, 流感灭活疫苗能够减少 ECOPD 的发生^[56], 肺炎球菌疫苗接种对 COPD 患者有益^[57]。此外, 联合接种对 ECOPD 预防有益, 肺炎球菌疫苗与流感疫苗同时接种可降低 ECOPD 发病风险^[58], N-乙酰半胱氨酸联合肺炎球菌疫苗可有效控制 ECOPD 发病并改善肺功能^[59]。

4.3 预防短期复发 ECOPD 的恢复是缓慢的, 且复发率高。一项研究表明, ECOPD 的恢复是不完全的, 只有 75% 的 ECOPD 患者在 5 周时肺功能能够恢复至基线水平, 14% 的患者在 ECOPD 发生 5 周时症状持续存在^[7]。伦敦的一项研究发现, 大约三分之一的 ECOPD 是复发性的, 27% 的 ECOPD 患者在 8 周内出现第二次复发^[60], 因此对于短期复发的关注与预

防是必要的, 抗生素应用^[61]、早期肺康复^[62]和家庭无创通气治疗^[63](noninvasive ventilation)可以有效预防 ECOPD 短期复发。

利益冲突声明 本研究不存在任何利益冲突

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