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慢性阻塞性肺疾病急性加重患者严重程度的评估及预测

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[摘 要] 慢性阻塞性肺疾病急性加重(acute exacerbation of chronic obstructive pulmonary disease，AECOPD)是慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)患者临床过程中常见的重要事件，是COPD患者预后的主要决定因素。AECOPD常常导致患者额外的治疗和生活质量严重下降，且病死率升高，因而对于AECOPD的早期预测和严重程度的评估显得尤为重要。目前主要根据AECOPD患者加重前的用药史、症状、体征、动脉血气分析、肺功能等相关指标评估严重程度。近年来随着诊断技术的发展，各种新型预后预测评估模型和生物标志物越来越多。通过生物标志物进行评估具有操作简单、方便快捷的优点，通过评分进行评估兼具简单、可靠性高且易操作的优点，通过肺功能检查进行评估则具有便捷、无创、安全性高的优点。临床医生在诊疗过程中，根据患者的具体情况合理应用评估工具，在AECOPD发生初期进行精准评估及预测，及时调整用药方案并实施个体化治疗，对患者预后具有十分重要的意义。

[关键词] 慢性阻塞性肺疾病急性加重；生物标志物；评分

Severity assessment and prediction in patients with acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common and important event in the clinical process of patients with chronic obstructive pulmonary disease (COPD), and is the main determinant of the prognosis in patients with COPD. Its occurrence often leads to serious of additional treatment and decline in quality of life and increase in mortality. Therefore, it is particularly important to predict and evaluate the severity of AECOPD in the early stage. At present, the severity of AECOPD patients is mainly evaluated according to their medication history, symptoms, signs, arterial blood gas

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analysis, pulmonary function and other relevant indicators before aggravation. In recent years, with the development of diagnostic technology, there are more and more new prognostic prediction evaluation models and biomarkers. The operation of biomarkers is easy, convenient and fast, scoring is simple, reliable and easy to operate, and lung function test is convenient, non-invasive and safe. In the process of diagnosis and treatment, clinicians should reasonably apply evaluation tools according to the specific conditions of patients, accurately evaluate and predict the initial stage of AECOPD, and timely adjust the drug regimen and implement individualized treatment, which are of great significance to the prognosis of patients.

KEY WORDS　acute exacerbation of chronic obstructive pulmonary disease; biomarker; score

慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)是一种以不完全可逆的气流阻塞为特征，严重影响患者劳动和生活能力的慢性肺病。随着老龄化社会的到来，COPD的发病率将持续上升[1]。2017年全球COPD的时点患病率为3.92%(95% CI：3.52%~4.32%)，COPD的病死率估计为42/100 000(占所有原因死亡的4.72%)，到2030年COPD将成为全球第三大死亡原因[2-3]。其频繁而严重的急性加重不仅使患者生活质量下降，同时增加了患者的经济负担[4]。2022慢性阻塞性肺疾病全球倡议(Global Initiative for Chronic Obstructive Lung Disease，GOLD)指南[5]提及因慢性阻塞性肺疾病急性加重(acute exacerbation of chronic obstructive pulmonary disease，AECOPD)的临床表现不同，因此应根据患者的临床症状来判断病情的严重程度，将其分为AECOPD I级(无呼吸衰竭)、AECOPD II级(急性呼吸衰竭-无生命危险)、AECOPD III级(急性呼吸衰竭-有生命危险)。COPD诊治指南(2021年修订版)[1]明确指出AECOPD的诱发因素和临床表型的异质性，其严重程度的评估主要依据加重前的临床症状、体征、肺功能指标、动脉血气分析及一般实验室检查指标。本文总结近年来对AECOPD严重程度评估的研究，主要从生物标志物、评分、肺功能相关指标对病情评估及预后预测方面进行综述。

1 传统生物标志物

1.1 急性时相反应类

降钙素原(procalcitonin，PCT)和C反应蛋白(C-reactive protein，CRP)作为呼吸系统最常见的生物标志物，在各种呼吸系统疾病中被广泛运用。有研究[6-7]已证实AECOPD患者外周血CRP和PCT水平的升高与AECOPD密切相关。Zhou等[8]回顾性分析167名AECOPD患者，发现感染组的CRP、PCT水平显著高于未感染组(P<0.05)；受试者操作特征(receiver operator characteristic，ROC)曲线结果显示CRP、PCT水平在AECOPD并发肺部感染患者的诊断中具有较高的临床价值[(均曲线下面积 (area under the curve，AUC)>0.7)]。Hoult等[9]在此基础上进一步研究，发现PCT水平>0.5 ng/mL和“阳性CRP”均与痰培养阳性有关，而PCT水平<0.5 ng/mL与非细菌性AECOPD密切相关。

1.2 心血管活性物质类

既往N-末端脑利钠肽前体(N-terminal pro-brain natriuretic peptide，NT-proBNP)被认为是心血管疾病的有效生物标志物。随着研究的深入，研究者发现NT-proBNP在COPD中也能作为预测因子。Chen等[7]研究发现：NT-proBNP升高是AECOPD住院患者早期死亡的强有力的预测因子，且与其他已知预后指标无关。AECOPD患者NT-proBNP的升高与较差的预后相关，增加了住院时间和重症监护的需求，可用于对这些患者进行风险分层[10]。由于COPD患者的疾病负担导致总病死率增加，对这些患者进行早期风险评估以及对高危患者进行分层是至关重要的。

1.3 纤溶系统类

D-二聚体是纤溶酶活化和水解交联纤维蛋白，产生的纤维蛋白降解产物(fibrin degradation product，FDP)主要反映纤维蛋白溶解功能。*D*-二聚体的升高提示体内高凝状态和继发性纤溶亢进。AECOPD合

并呼吸衰竭的患者因高凝状态*D*-二聚体普遍升高，可用于反映病情变化[11]。一项对COPD急性加重期的前瞻性研究[12]证明*D*-二聚体/纤维蛋白原比值和出院后复发的急性加重可能对90 d病死率有重要影响，且当*D*-二聚体≥985 ng/L，其危险分层明显升高(*P*<0.05)。*D*-二聚体的表达水平与临床分期密切相关，可作为评估COPD严重程度的参数[13]。所以，*D*-二聚体可以作为AECOPD有效的预测指标，在AECOPD的诊疗中具有一定的参考意义。

1.4 细胞因子类

炎症细胞因子在COPD早期至关重要，如肿瘤坏死因子α(tumor necrosis factor α，TNF-α)、白细胞介素(interleukin，IL)-6和IL-8。炎症细胞因子释放后，炎症细胞集中在炎症部位介导免疫反应[14]。IL-8水平与AECOPD发作频率呈正相关[15]。IL-6测量值≥14.030 pg/mL是次年COPD急性加重≥2次的危险因素[16]。研究[17]发现miR-146a和miR-146b与炎症细胞因子水平负相关，可能是预测稳定期COPD患者和健康个体AECOPD风险的有希望的生物标志物。Zhang等[18]研究表明血清可溶性白细胞介素-2受体(soluble interleukin-2 receptor，sIL-2R)浓度升高与AECOPD不良结局的风险相关，它可以成为AECOPD患者不良结局诊断和评估的预测因素。CD64作为一项新的炎症指标，越发受到广泛关注，在COPD的发展中起至关重要的病理作用。Fei等[19]将85名存在肺部感染的COPD患者作为肺部感染组纳入研究，采用流式细胞术测定中性粒细胞CD64指数，发现肺部感染组的中性粒细胞CD64指数明显高于对照组(无肺部感染的COPD患者)。临床工作中可以利用细胞因子的水平来评估病情严重程度。

2 血细胞相关的生物标志物

中性粒细胞与淋巴细胞比值(neutrophil-to-lymphocyte ratio，NLR)、血小板与淋巴细胞比值(platelet-to-lymphocyte ratio，PLR)是临床上简单、廉价且易于获得的生物标志物，NLR和PLR与AECOPD患者的28 d病死率相关，这些比值可作为预后生物标志物，用来评估AECOPD住院患者短期病死率[20]。Lv等[21]研究发现血液嗜酸性粒细胞百分比的不同临界值是有用的生物标志物，用于预测AECOPD住院患者的病情严重程度和预后。此外，2022 GOLD指南提出把外周血嗜酸性粒细胞加入到COPD的生物标志物中，以帮助评估在AECOPD患者常规支气管扩张剂治疗中加入吸入糖皮质激素的必要性，用于COPD患者急性加重风险的评估及预测，在COPD的治疗中有一定指导价值[5]。

3 新型生物标志物

Vögeli等[22]研究发现血清不对称二甲基精氨酸(asymmetric dimethylarginine，ADMA)是AECOPD患者长期全因死亡的独立危险因素，ADMA和对称二甲基精氨酸(symmetric dimethylarginine，SDMA)与COPD急性期病情严重程度相关[23-24]。Lin等[25]把120例AECOPD患者纳入AECOPD组。与对照组(COPD缓解组)相比，COPD缓解组血清中血清淀粉样蛋白A(serum amyloid A，SAA)、空腹血糖(fasting blood glucose，FBG)、TNF-α和干扰素γ诱导蛋白-10(interferon-γ inducible protein-10，IP-10)水平显著升高(*P*<0.05)。AECOPD患者血清SAA、FBG、TNF-α和IP-10水平升高，与1秒用力呼气容积(forced expiratory volume in 1 second，FEV_1)和FEV_1/用力肺活量(forced vital capacity，FVC)呈负相关，这可能损害肺功能。SAA可用作AECOPD诊断和治疗的有效指标。Wei等[26]研究证明：在AECOPD期间，SAA水平显著升高，有效预测了AECOPD的进展，是影响AECOPD患者的危险因素。

Chen等[27]探索了一种新的circRNA0001859，它可能作为治疗COPD和AECOPD的潜在生物标志物。Shi等[28]通过整合AECOPD不同阶段免疫调节介质的基因组学和蛋白质组学特征，结合临床信息学，探索了一种新的疾病特异性生物标志物评估方案的可行性和可靠性。该研究发现了4种候选AECOPD特异性免疫调节介质，其中触珠蛋白(haptoglobin，HP)的表达通过骨桥蛋白(osteopontin，OPN)依赖的信号上调，以响应刺激。内源性和外源性OPN均可通过PI3K/Akt通路过度生产HP。AECOPD特异性免疫调节介质的复杂网络将有利于制订精确或个性化的医疗策略。

4 评 分

4.1 BAP-65评分和CURB-65评分

BAP-65评分是基于信息容易获得(血尿素氮升高、精神状态改变、脉搏>109次/min、年龄>65岁)，可作为急诊临床医生简单、快速的风险分层工具。BAP-65评分已在美国因AECOPD入院的住院患者队列中得到推广和验证，并显示出良

好的准确性，可预测住院期间的死亡风险和机械通气的使用[29]。

CURB-65评分指标包括5项，满足1项得1分：意识障碍，尿素>7 mmol/L，呼吸频率≥30次/min，收缩压<90 mmHg(1 mmHg=0.133 kPa)或舒张压≤60 mmHg，年龄≥65岁。0~1分为低危，2分为中危，3~5分为高危，可用来根据死亡风险的增加对患者进行分层[30]。Gayaf等[31]研究表明CURB-65评分是预测COPD加重30 d和90 d病死率的简单和可行的评分，可常规用于所有COPD加重住院患者。但Shiroshita等[32]研究发现BAP-65、CURB-65在AECOPD的住院死亡中显示出较低的预测性能。有必要进行包括更多变量在内的进一步大规模研究。

4.2 DECAF评分和v-DECAF评分

DECAF(呼吸困难、嗜酸性粒细胞减少、肺实变、酸血症、房颤)评分用于预测急性或反复加重的住院患者的病死率，该评分被广泛使用，效果良好。与其他评分系统相比，DECAF评分最显著的特点是简单，可在床边使用常规入院信息指数。Ahmed等[30]研究表明DECAF评分比CURB-65评分在预测AECOPD患者住院病死率上更具特异性(分别为86.25%和68.75%)。Shen等[33]研究表明DECAF评分预测COPD急性加重患者住院病死率的整体敏感性和特异性分别为74%(95% CI：67%~79%)和76%(95% CI：68%~82%)；30 d病死率分别为72%(95% CI：59%~82%)和83%(95% CI：67%~93%)。DECAF评分可以预测住院和30 d病死率，具有令人满意的敏感性和特异性。

有研究[34]发现呼吸机-DECAF(ventilator-DECAF，v-DECAF)评分在预测AECOPD病死率方面优于DECAF评分，且v-DECAF评分具有良好的鉴别力，尤其在预测需要使用有创机械通气的AECOPD患者的90 d全因病死率方面表现突出。本组建议结合评分系统来预测COPD急性加重的住院病死率，该评分系统基于适当性、设施的可及性和临床医生的偏好。

4.3 GCS评分和改良GCS评分

格拉斯哥昏迷量表(Glasgow coma scale，GCS)是用于客观描述所有类型的急性内科和创伤患者意识障碍程度的常用工具。该量表根据睁眼反应、言语反应和肢体运动反应3个方面评估患者[35]。有创机械通气是AECOPD患者的主要治疗选择，尤其是昏迷患者[36]。气管插管患者即使意识清醒也不能说话，因此，在考虑切换到无创呼吸支持时，应考虑意识的变化。

改良GCS评分是对COPD重症呼吸衰竭患者在疾病各阶段整体和身体状况进行动态评估的客观指标。研究[37]证实：采用改良GCS评分≥13作为切换至无创通气的标准，与采用改良GCS评分≥10相比，有创通气时间更短，可明显改善AECOPD合并呼吸衰竭患者的预后。综上所述，改良GCS评分是一种更客观、定量地评估插管患者意识水平的方法，有利于早发现危重患者并及时处理。

4.4 NEWS评分和NEWS 2All COPD

2012年，英国皇家内科医师学会制订了国家早期预警评分(National Early Warning Score，NEWS)，有助于迅速识别因各种疾病住院的患者的临床恶化，它由床边指标(呼吸频率、血氧饱和度、收缩压、脉搏、意识水平、体温)组成，具有明确的阈值，指示临床反应的紧迫性。NEWS等[38]早期预警评分，应在住院期间反复进行，以监测患者病情变化。虽然NEWS在英国被广泛使用，但有两个关键的限制已经凸显出来。首先，COPD和慢性低氧血症患者会引起误报，这可能会导致警惕疲劳。其次，在严重AECOPD患者中，过量氧气与通气需求增加与病死率相关[39-40]。Echevarria等[41]改编了英国NEWS 2，采用NEWS 2评分的第二种血氧饱和度量表(血氧饱和度88%~92%)，命名为NEWS 2All COPD，专门用于AECOPD患者。与NEWS和NEWS 2相比，NEWS 2All COPD降低了12.6%的错误预警，若不考虑不恰当的吸氧评分，则降低了16.1%。NEWS 2All COPD不仅降低了错误预警，更降低了患者的病死率，尤其是降低了没有高碳酸血症的AECOPD患者氧气供应过量所致的病死率。NEWS 2All COPD评分由各项可在床旁获得的指标构成，操作简单，无论是急诊患者还是住院患者，NEWS 2All COPD评分均能评估及预测患者病情，实时监测住院患者的病情，及时捕捉病情变化的相关信息处理。

5 一氧化碳弥散量

Choi等[42]研究发现在AECOPD中，一氧化碳弥散量(diffusing lung capacity for carbon monoxide，DL_{CO})可以预测病死率、需要使用机械通气和ICU护理。通过ROC曲线分析住院病死率、机械通气及ICU护理3种预后因素时，所有DL_{CO}患者的AUC均>0.68。相比之下，FEV_1的AUC在所有3个

预后因素中均低于0.68，表明在使用ROC曲线分析敏感性和特异性时，DL_{CO}的预测能力优于FEV_1。2022 GOLD指南强调肺功能检查中弥散功能指标对评估及预测COPD发生、发展的价值。肺量计是诊断COPD的重要检查手段，采用单次呼吸法测定DL_{CO}以反映肺弥散功能可以更好地评估COPD。在对COPD患者的研究中，DL_{CO}较低(如DL_{CO}<60%预计值)提示运动能力下降、症状加重、健康状况较差以及死亡风险增加。而当DL_{CO}<80%预计值时，提示随着时间的推移，没有气流受限的吸烟者发生COPD的风险增加[5]。对呼吸困难症状与气流阻塞程度不成比例的COPD患者，需多年跟踪随访，监测DL_{CO}，方能发现DL_{CO}有意义的变化。

6 结 语

综上所述，COPD是一种存在多种表型的异质性疾病，患者对现有治疗方案的反应也各有不同，感染性因素通常是AECOPD最常见的原因，所以应及时发现患者临床症状、体征等的变化，并联合相关的炎症生物标志物，以期早期诊断、动态监测、评估及预测AECOPD的严重程度，更好地反映COPD患者的不同临床表型。现已有对COPD患者预测死亡风险很完备的评估工具，但较难准确评估AECOPD住院患者的严重程度，实用的、简便的评估模型在临床工作中至关重要，仍需进一步研究确定AECOPD的特异性生物标志物、评分、肺功能指标或开发新的模型，客观、精准地评估病情，以指导临床医生对AECOPD患者的个体化管理。

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