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脓毒症预后评估的研究进展

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摘　要

脓毒症是威胁人类健康的急危重症之一，其发病后的死亡率均处于较高水平，早期发现、尽早评估、及时治疗脓毒症可以有效降低这一比例。因此，对脓毒症的早期评估已成为国际共识。目前，有很多临床手段及科学研究在脓毒症的预后评估方面进行了探索，并取得了相应的进展。该文常见的生物标志物、复合临床指标、传统临床评分、基于机器学习构建的临床预测模型等四个方面对脓毒症预后评估进行系统阐述，以期为临床医务工作者提供参考。

关键词

脓毒症，预后评估，预测模型，机器学习

Research Progress in the Prognostic Assessment of Sepsis

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Abstract

Sepsis is one of the acute and critical illnesses that threaten human health, and the mortality rate after its onset is at a high level. Early detection, early evaluation, and timely treatment of sepsis can effectively reduce this rate. Therefore, early assessment of sepsis has become an international consensus. Currently, there are many clinical tools and scientific studies exploring the prognostic assessment of sepsis and making progress accordingly. In this article, the common biomarkers,

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composite clinical indicators, traditional clinical scores, and clinical prediction models constructed based on machine learning are systematically described for the prognostic assessment of sepsis, in order to provide references for clinical medical workers.

Keywords

Sepsis, Prognostic Assessment, Predictive Modeling, Machine Learning

1. 引言

1991 年建立的第一个脓毒症共识定义指出脓毒症是一种患者对感染的全身反应，并且至少有两种或以上的全身炎症反应综合征[1]，2016 年的第 3 版脓毒症及脓毒性休克国际共识将脓毒症定义修订为宿主对感染反应失调所引起的严重危及患者生命的多器官功能障碍的疾病[2]。最新研究估计全球约有 4890 万例脓毒症患者，其中有 1100 万例死于脓毒症及其并发症，约占全球死亡病例的 20% [3]。脓毒症也是重症监护室(Intensive Care Unit, ICU)患者死亡的主要原因之一。国家重症监护(Intensive Care Over Nations, ICON)研究中前瞻性地收集 80 个国家的 730 个医疗中心的数据，结果表明全球范围内脓毒症患者 ICU 死亡率为 25.8%，远高于 ICU 平均死亡率 16.2%。除此之外，脓毒症的住院费用较高，给医疗卫生系统带了巨大的经济负担。有调查显示，脓毒症被列为美国最昂贵的疾病。仅 2017 年，脓毒症患者的总住院费用就高达 382 亿美元[4]。因此，尽早判断脓毒症的严重程度，及时进行干预性治疗，有利于提高患者的生存率，减少住院时间，减轻脓毒症给社会带来的负担。本文从常见的生物标志物、复合临床指标、传统临床评分、基于机器学习构建的临床预测模型等四个方面对脓毒症预后评估的相关研究进行阐述。

2. 常见的生物标志物

为了尽早评估脓毒症的严重程度，关于常见生物标志物对脓毒症的预后价值研究层出不穷。乳酸(Lactic Acid, Lac)、C-反应蛋白(C-Reactive Protein, CRP)、降钙素原(Procalcitonin, PCT)等指标已经在许多研究中出现[5] [6]。CRP 和 PCT 是使用最广泛的两种标志物，CRP 是当病原微生物入侵机体时肝脏合成的一种急性时相反应蛋白，一般在 12~24 小时开始升高，2~3 天达到高峰，其可以激活补体、加强吞噬细胞的吞噬作用[7]。PCT 是一种血浆中的蛋白质，当细菌、真菌感染达到一定的严重程度时，其就会升高，一般在感染后 2~3 小时升高，24 小时达到峰值[8]。尽管这两者的特异性不高，但是它们的存在时间足够长，检测的指标高低可以反应实时的炎症反应，有时也会将二者结合起来预测脓毒症的预后。脓毒症患者 Lac 水平的增高与患者死亡率呈正相关，当机体出现组织灌注不良时体内无氧代谢增加，Lac 生成增多，降低 Lac 水平是治疗中公认的一个目标[9] [10]。Lac > 4.0 mmol/L 是评估重度脓毒症患者的一个重要临界值，连续的 Lac 值可以用来进行危险分层及评估治疗反应[5]。同时连续的 Lac 水平对于评估脓毒症患者发生脓毒性休克也有一定的预测价值[11]。研究表明 Lac 水平可以作为评估患者发生急性肾损伤的独立危险因素，同时 Lac 水平越高，脓毒症相关肾损伤的患者死亡率就越高[12]。IL-6 是在 2 小时内即可达到峰值的一种促炎因子，其可以作用于多种靶细胞(如中性粒细胞、B 细胞及 T 细胞)调节炎症反应，有研究发现 IL-6 在革兰阴性菌患者血液中的水平远远高于革兰阳性菌患者，因此其对致病菌的诊断有一定的帮助作用[13]。

3. 复合临床指标

除了使用常见生物标志物预测脓毒症的严重程度，由多种实验室指标构成的复合临床指标的研究也越来越多，一项荟萃分析显示中性粒细胞/淋巴细胞比值(Neutrophil-Lymphocyte Ratio, NLR)在预测脓毒症患者的生存率时比二者单独预测更可信，NLR 比值过高时患者预后往往较差[14]。患者入院时的血小板/淋巴细胞比值(Platelet-Lymphocyte Ratio, PLR)水平与脓毒症患者的死亡率呈 U 型关系，早期 PLR 越低死亡率越高[15]。除了以上这两种常见的比值，一项回顾性研究指出 Lac/白蛋白可以反应出细胞的缺氧情况及组织的损伤情况，PCT/白蛋白则可以将机体的炎症情况与人体的营养状况结合起来，这两项比值在预测脓毒症患者 28 天的存活率时都有一定的价值[16]。CRP/白蛋白对患有慢性疾病急性加重的老年人及患有败血症的新生儿都具有预测价值，当其比值大于 5 时，脓毒症患者的死亡风险明显升高[17]。全身免疫炎症指数(Severity of Illness Index, SII)是 2019 年在《肠外肠内营养学名词》中新出现的一个词汇，研究表明它可以用来判断脓毒症患者入院后短期内的结局，对于治疗时间较长的脓毒症患者预后价值有限[18]。预后营养指数(Prognostic Nutritional Index, PNI)最开始是外科用来评估患者术前营养状况的一种指标，计算公式为血清白蛋白(g/L) + 5 × 淋巴细胞绝对数($\times 10^9$/L)，后来开始被用于评估实体肿瘤的预后情况。比如 PNI 可被用于胃癌、头颈癌术后死亡风险的预测[19] [20]。近年来研究发现其在脓毒症中也具有一定预后价值，PNI 往往随着脓毒症严重程度的升高而显著降低[21] [22]。但是单个指标往往存在稳定性差、预测性能低等缺点，因此，需要利用多维度、多变量的方法对脓毒症患者进行评估，及时识别死亡风险较高的脓毒症患者，可以帮助 ICU 医生做出最佳的临床决策，从而改善患者预后。

4. 传统临床评分系统

不同的临床评分系统也通常被作为脓毒症的预测脓毒症预后的工具。改良早期预警评分(Modified Early Warning Score, MEWS)是在急诊及 ICU 被广泛应用的一种评分，可以用来预测患者病情恶化的可能性[23]，有研究表明，MEWS 对预测脓毒症死亡率有着较高的特异度[24]。在脓毒症 3.0 中指出当序贯器官衰竭评分(Sequential Organ Failure Assessment, SOFA)上升≥2 分且患者明确或疑似存在感染可以考虑诊断脓毒症[25]，而快速序贯器官衰竭评分(Quick Sequential Organ Failure Assessment, qSOFA)是一种更加快速简洁的评分，它不需要任何实验室检查结果的辅助，具有以下三项中的两项即可认为患者存在器官功能障碍，三项指标包括呼吸频率 ≥ 22 次/分，神志或者精神的改变，收缩压 ≤ 100 mmHg [26]。脓毒症患者如果能够尽早诊断就能显著的缩短住院时间改善患者预后，因此 qSOFA 评分的重要性不言而喻[27]。但是也有许多研究显示 qSOFA 评分的灵敏度不高，他们考虑这可能是由于 qSOFA 没有考虑到体温及心率这两个指标，体温和心率往往是最早发生恶化的两个临床变量[28] [29]。同时我们也必须承认在评估神志或者精神的改变时我们要考虑到环境以及患者最初状态的影响，这都会影响 qSOFA 评分的结果[30]。尤其是最新的指南已不推荐 qSOFA 评分作为筛选脓毒症和脓毒性休克的单一工具[31]。急性生理与慢性健康评分(Acute Physiology and Chronic Health Evaluation, APACHE)是 1985 年 Knaus 在临床研究的基础上提出的可以对患者病情作出定量评价的一种评分，它可以评估各种急危重症患者的病情并预测预后[32]，也可以用于评估脓毒症患者的死亡率[33]。然而，随着对脓毒症病理机制的不断认识，针对脓毒症的治疗措施、技术和理念已经更新。而且多项研究已显示，这些临床评分系统的灵敏度和特异度明显低于建立的临床预测模型[34] [35] [36]。

5. 基于机器学习构建的脓毒症临床预测模型

近年来，新型机器学习技术在医学研究发挥的作用越来越大，运用机器学习技术可以帮助临床医生进行疾病的诊断、疾病死亡率的预测、进行临床决策[37]。机器学习属于人工智能的一个重要分支，该工

具可以处理多维、复杂、大量的数据。Haug CJ [38]等人的研究提出在涉及大量预测因子的复杂问题，机器学习是处理这些问题首选的方法。尤其在重症医学领域，涉及到的疾病较复杂，存在较多的因素影响疾病结局，机器学习被运用到相关疾病的诊断和预后研究中。目前，许多基于机器学习开发的脓毒症临床预测模型已被公开发表，引起了广泛的关注。Giannini HM 等人利用随机森林(Random Forest, RF)算法来预测脓毒症和脓毒性休克的发生，并在多家医院的非 ICU 系统中使用[39]。Zhang L 等人基于 RF 算法的老年脓毒症患者 30 天死亡风险预测预后模型，结果证明它优于传统的 SOFA 等评分系统[40]。一项基于美国多家医疗中心的研究表明，利用自适应增强(Adaptive Boosting, AdaBoost)算法的模型在 ICU 中脓毒症的早期诊断方面表现出色[41]。Eskandari MA 等人[42]基于机器学习构建了三种模型：K 近邻、多层感知机、RF，3 种模型均表现良好，仅通过实验室指标可以早期预测 ICU 患者是否发生脓毒症。Delahanty RJ 等人[43]基于梯度提升树(Gradient Boosting Decision, GBDT)算法对 49 家医疗中心的急诊科患者进行回顾性分析，利用实验室指标和临床体征建立了全新的脓毒症风险模型，该模型可以在 24 小时内识别急诊科的脓毒症患者，模型 AUC 为 0.97，比临床常用的 SOFA 评分更准确。Chen Q 等人[44]基于重症医学信息市场(MedicalInformation Mart for Intensive Care III, MIMIC III)数据库和上海市瑞金医院的数据库，利用机器学习算法，通过迁移学习和集成学习，构建了脓毒症早期预警模型，该模型 AUC 为 0.86~0.9，可以在 5 小时内准确地预测脓毒症。Hou N 等人基于 MIMIC IV 数据库，利用极限阶梯提升(eXtreme Gradient Boosting, XGBoost)算法建立了脓毒症患者 30 天死亡风险的预测模型，该模型 AUC 为 0.857，预测性能良好[45]。一项来自西班牙的研究，基于 MIMIC III 数据库，利用随机梯度提升算法构建了预测脓毒症患者 1 年内死亡率的模型，该模型 AUC 为 0.8039，该算法生成的模型与 SOFA 评分相比，预测效果更准确[46]。Bouza C 等人均利用一种算法建立了预测脓毒症住院死亡率的模型，模型的 AUC 为 0.863 [47]。Zhang G 等人基于 MIMIC IV 数据库，利用七种机器学习算法构建模型，最终 XGBoost 模型在预测脓毒症患者院内死亡风险方面的性能最好[48]。针对不同的疾病及不同人群，所选择最优的机器学习模型可能不同。Wang Z 等人利用机器学习算法建立了 AdaBoost、SVM、XGBoost 三种模型来预测脓毒症预后，其中 AdaBoost 模型明显优于 SVM、XGBoost 模型，显示了优秀的预测能力[49]。而在 Zhang G 等人的研究中，XGBoost 模型则明显优于其他模型[48]。可能与样本的数量、纳入变量等多种因素相关。机器学习所构建的临床预测模型，能够处理大量的临床数据、精准预测脓毒症的严重程度，但是目前研究多数运用国外数据库，基于国内数据库的研究较少，仍需要进一步的探索。

综上，对于脓毒症的预后评估，临床常见的生物标志物和复合临床指标的研究中，往往具有稳定性差、预测性能低等缺点。而传统临床评分系统在一定程度上弥补了单一指标的不稳定性，但其灵敏度和特异度仍远远低于机器学习所构建的临床预测模型。因此，整合更多维度的生物标志物和复合临床指标，结合传统临床评分对于患者病情的动态监测，为临床预测模型的建立提供更多维度的预测因子，将使脓毒症的预后评估更加精准。

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