脓毒症的新型生物标志物研究进展

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关键词 脓毒症；降钙素原；可溶性 CD14 亚型；肝素结合蛋白；可溶性尿激酶型纤溶酶原激活物受体；可溶性髓样细胞触发受体-1；血浆游离 DNA；微小 RNA

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脓毒症是一种具有非特异性临床症状的异质性疾病。脓毒症 3.0 定义为严重感染并引起器官功能障碍,序贯器官功能衰竭评估(sequential organ failure assessment,SOFA)评分≥2 分[1]。早期诊断对脓毒症治疗尤为关键,而传统炎症生物标志物,如白细胞计数、乳酸、C-反应蛋白在预测脓毒症方面的作用有限[2],本文旨在讨论脓毒症的新型生物标志物的研究进展。

蛋白肽类生物标志物

降钙素原 降钙素原(procalcitonin,PCT)是包含 114-116 个氨基酸的无活性前肽,在脓毒症的早期诊断中已被公认为具有重要价值[3]。Samsudian 等[4]认为,PCT 有助于判断脓毒症严重程度和风险分层。PCT 指导的抗生素管理已显示出其超然的优越性,可以减少抗生素使用时间(5.7 d *vs* 8.1 d)从而有效降低抗生素相关副作用的风险(16% *vs* 18%)[5]。2018 年一项 Meta 分析发现,针对脓毒症重症患者,2 252 名 PCT 指导的抗生素管理患者死亡率显著低于 2 230 名对照组患者(21.1% *vs* 23.7%)[6]。将 PCT 指导的抗生素管理应用于临床,有望缓解全球细菌耐药性危机。

可溶性 CD14 亚型 可溶性 CD14 亚型(soluble CD14 subtype,sCD14-ST or Presepsin)是膜标记受体蛋白 CD14 的可溶性氨基端终止区,是脂多糖复合物的特异性高亲和力受体,参与识别多种细菌产物,例如肽聚糖,即革兰阳性细菌的主要细胞壁成分。最近 Presepsin 被描述为新生儿脓毒症的可靠诊断和预后标志物[7]。Memar 等[8]发现,在脓毒症中,Presepsin 水平明显高于无脓毒症患者或全身炎症反应综合征(systemic inflammatory response syndrome,SIRS)患者。Hassan 等[9]证明 Presepsin 在预测脓毒症相关的病死率方面比高敏 C 反应蛋白具有更好的准确性[*AUC*(0.824)95% *CI*(0.646 ~ 0.955) *vs* *AUC*(0.576)95% *CI*(0.395 ~ 0.743)]。一项针对严重脓毒症或脓毒症休克患者的回顾性病例对照研究发现,死亡组早期 Presepsin 水平明显高于生存组[2 269 pg/mL(1 171 ~ 4 300 pg/mL) *vs* 1 184 pg/mL(875 ~ 2 113 pg/mL), $P=0.002$],并且在 Cox 模型中是唯一与 28d 病死率相关的变量,是脓毒症良好的预后标志物[10]。有研究发现,Presepsin 在抗生素治疗过程中逐渐降低,表明其在监测治疗反应、降低短期病死率中的潜在价值[11]。

肝素结合蛋白 肝素结合蛋白(heparin-binding protein,HBP)是一种阳离子抗微生物蛋白,主要存在于中性粒细胞的嗜天青颗粒(含量接近 74%)和分泌小泡(含量接近 18%)中。HBP 参与激活白细胞、增加毛细血管通透性、血管渗漏及有效循环血容量减少等多种脓毒症的病理生理过程,可作为诊断和治疗脓毒症的新型生物标志物[12]。一项前瞻性的多中心研究发现,在进展为脓毒症的感染患者中,78% 的患者出现 HBP 水平升高(>30 ng/mL),是疾病进展为脓毒症的强有力的预测因子[*AUC* 0.8,95% *CI*(0.76 ~ 0.85), $P<0.01$][13]。有研究表明,HBP 在脓毒症出现低血压或器官功能障碍等典型临床症状之前就明显升高,可作为严重脓毒症早期可靠的预测指标[14]。国外学者对 233 例危重症患者进行了前瞻性研究[15],以 HBP 截断值为 15 ng/mL来区分脓毒症与非脓毒症,其敏感度和特异度分别为 87.1% 和 95.1%,AUC 为 0.949。Zhou 等[16]报道 HBP≥28.1 ng/mL 的临界值在诊断脓毒症时的敏感性为 84.9%,特异性为 78.3%。有研究表明,HBP 联合 PCT 诊断脓毒症 ROC 曲线下面积更是高达 0.958,95% CI(0.76 ~ 0.85),具有显著的临床应用价值[17]。然而,在判断脓毒症的严重程度及预后和指导治疗等方面,仍需进一步确认 HBP 在临床的实用性。

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受体类生物标志物

可溶性尿激酶型纤溶酶原激活物受体 尿激酶型纤溶酶原激活物受体(urokinase plasminogen activator receptor,uPAR)是一多配体受体,通过结合尿激酶、整合素、低密度脂蛋白受体等多种配体参与细胞迁移粘附、免疫活化、信号转导、血管生成、组织损伤修复等生理病理过程[18]。当机体受到炎症刺激时,uPAR 经蛋白酶水解后形成可溶性 uPAR(soluble urokinase plasminogen activator receptor,suPAR)。当前,suPAR 作为脓毒症的危险分层及预后性标志物,已基本得到认可。在坏死性软组织感染中,suPAR 水平与 SAPSⅡ(r = 0.52,P < 0.001)和 SOFA 评分(r = 0.64,P < 0.001)显著相关[19]。丹麦的一项大样本(n = 5 992)研究发现,血清 suPAR 水平为脓毒症 30d 死亡的独立预测因子,*AUC* 为 0.85[95% *CI*(0.82,0.87)][20]。Ni 等[21]报道高水平的血浆 suPAR 与高死亡风险相关,总体相对度为 3.37[95% *CI*(2.60,4.38)],预测死亡的总体灵敏度和特异度分别为 70%、72%,*AUC* 为 0.77。国内外的多项前瞻性研究中,均将 suPAR 水平用于危险分层评估[22,23]。

可溶性髓样细胞触发受体 1 髓样细胞触发受体-1(triggering receptor expressed on myeloid cell-1,TREM-1)是属于免疫球蛋白家族的跨膜糖蛋白,表达于中性粒细胞、成熟单核细胞、巨噬细胞等骨髓来源的细胞表面。感染可诱导细胞表面的 TREM-1 表达增加,使其从活化的吞噬细胞膜上脱落,并在血清和体液中以可溶性 TREM-1(sTREM-1)被检测到。sTREM-1 可导致炎性细胞因子的释放和炎性细胞表面上其他受体的表达增加,成为感染中的重要信号受体[24]。在脓毒症患者中,血液或体液中 sTREM-1 水平会显著上升,使其作为脓毒症的新型生物标志物越来越受到关注。研究表明,sTREM-1 是可以单独运用于新生儿脓毒症的早期诊断(最佳截断值为≥767 pg/mL,灵敏度 100%,特异度 86.7%,阳性预测值 84.4%)[25]。Jedynak 等[26]发现 sTREM-1 水平可以早期预测脓毒症患者的 28 d 病死率[*AUC* 0.772;95% *CI*(0.672 ~ 0.871)],Bernner 等[27]认为,sTREM-1 早期诊断脓毒症的价值优于 C 反应蛋白和 PCT,并且还发现其在预测脓毒症患者病死率方面也有一定价值。最近有研究发现,腹腔引流液 sTREM-1 水平对腹部创伤脓毒症具有较高的诊断效能(*AUC* 0.937,95% *CI*:0.890 ~ 0.992),可能与腹部创伤脓毒症严重程度相关[28]。同时,尿 sTREM-1 可以成为脓毒症相关性急性肾损伤早期诊断的新型标志物[29]。

遗传生物标志物

血浆游离 DNA 血浆游离 DNA(circulating Cell-free DNA,cf-DNA)是存在于人体血液循环中、游离于细胞外的微量 DNA 片段,主要包括基因组 DNA 和线粒体 DNA(mitochondrial DNA,mtDNA)两种类型,其来源和释放机制尚未完全明确。Timmermans 等[30]发现,脓毒症患者 cf-DNA 水平明显升高,使其成为在危重病研究领域中备受关注的生物标志物。有研究表明,mtDNA 可能是小儿脓毒症诊断和预后评估的有效生物标志物[31]。黄天宝等[32]报道 cf-DNA 水平与脓毒症的严重程度显著相关,较于 PCT(*AUC* 0.898)和急性生理与慢性健康评估(acute physiology and chronic health evaluation,APACHE-Ⅱ)评分(*AUC* 0.905),cf-DNA 对脓毒症患者的预后判断价值更高[*AUC* 0.961,95% *CI*(0.930 ~ 0.992)],同时 cf-DNA 和 PCT 联合检测可进一步增加判断价值[*AUC* 0.974,95% *CI*(0.950 ~ 0.998)]。尿 mtDNA 水平升高与脓毒症患者的线粒体功能障碍和肾损伤相关[33],使其在脓毒症诱导的急性肾损伤的线粒体靶向治疗方面,具有一定价值。

微小 RNA 微小 RNA(microRNA,miR)是一类长度约为 18 ~ 25 个核苷酸的内源性非编码单链 RNA。其功能主要是直接结合到特定靶基因的 3 非编码区来影响功能基因的表达,从而在炎症反应、免疫细胞分化和凋亡、免疫抑制、血管屏障和内皮功能等不同层面精细地调控着脓毒症的发生、发展和转归[34],见表 1。

表 1 miR 作为脓毒症标志物的意义

miR	作为脓毒症标志物的意义
miR-4270 miR-4321	参与调节脓毒症相关的急性肾损伤[35]
miR-143	与 SOFA 及 APACHEⅡ评分正相关,并鉴别脓毒症、SIRS[36]
miR-155	预测脓毒症患者预后及病死率[37]
miR-10a	与病情严重程度相关,早期预测患者发病及预后[38]
miR-21-3p	诊断并调节脓毒性心肌损伤[39]

展 望

将细胞、分子等不同水平的新型生物标志物应用于脓毒症的诊断及优化治疗,是当前的研究热点。有效的生物标志物将为靶向性、特异性治疗脓毒症及其并发症提供全新的帮助。关于脓毒症,当前尚未出现最佳的、有效的、独立的生物标志物,单一指标诊断效能欠佳,各种新型生物标记物的研究正在蓬勃发展中,其临床效用需通过更多的临床数据来进一步证实。如文中所述,在脓毒症的诊断、预后评估及治疗指导中,联合应用多种生物标志物具有更良好的效能及意义。

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