

急性冠脉综合征的研究进展

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摘要

根据世界卫生组织的调查发现, 全球每年有1500人死于心脑血管疾病, 其中半数以上死于急性冠脉综合征。随着生活方式的改变, 我国ACS患者呈逐年上升趋势。从2004年至今, 心脑血管疾病及其相关性死亡居我国城乡居民总死亡原因的首位, 高于肿瘤和其他疾病, 占居民疾病死亡构成的40%以上。因此, 早预测早管理成为了预防急性冠脉综合征发生的重要措施, 越来越多的生物标志物被提及。

关键词

急性冠脉综合征, 单生物指标, 多生物指标组合, 综述

Research Progress in Acute Coronary Syndrome

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Abstract

According to the survey of the World Health Organization, there are 1500 people with cardio cerebral vascular disease in the world every year, and more than half of them die of acute coronary syndrome. With the changes in daily lifestyle, ACS patients in China are showing an increasing trend year by year. Since 2004, the death of cardio cerebral vascular disease and its related diseases has ranked first among the total causes of death of urban and rural residents in China, higher than tumors and other diseases, accounting for more than 40% of the death of residents. Therefore, early prediction and management have become important measures to prevent the occur-

rence of acute coronary syndrome, and more and more biomarkers have been mentioned.

Keywords

Acute Coronary Syndrome, Single-Indicator, Combinations of Multiple Indicators, Review

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1. 引言

急性冠状动脉综合征(Acute coronary syndrome, ACS)是一种严重的心血管不良事件,是一组急性心肌梗死导致的临床综合征,主要病理基础是冠状动脉斑块破裂或者糜烂导致的完全或不完全闭塞性血栓形成,具有起病急、病情变化快、病死率高等特点,主要包括 ST 段抬高型心肌梗死(STEMI)、非 ST 段抬高型心肌梗死(NSTEMI)和不稳定性心绞痛(UA),前两者合称急性心肌梗死(AMI) [1]。根据相关报道[2],中国城乡居民总死亡原因占比最大为心血管疾病(cardiovascular disease, CVD),其中 ACS 占据 CVD 的半数以上。大量研究指出 ACS 相关的传统危险因素包括吸烟[3]、高血压[4]、高脂血症[5]、糖尿病[6]等。近年来,中性粒细胞/淋巴细胞比值、同型半胱氨酸、25-羟维生素 D、胱抑素 C、纤维蛋白原以及平均血小板体积与淋巴细胞比值等生物指标引起了国内外学者的关注。

2. 单生物指标

2.1. 同型半胱氨酸(Homocysteine, Hcy)

同型半胱氨酸(homocysteine, Hcy)是一种含羟基氨基酸,由肝脏,肌肉和某些其他组织中蛋氨酸的去甲基化产生。它主要由肾脏和肝脏通过两种途径代谢:甲基化或硫酸化为蛋氨酸。血浆 Hcy 是 65~72 岁人群心血管和非心血管死亡率的有力预测指标[7]。一项 Hcy 水平与心血管疾病的荟萃分析表明,Hcy 每增加 5 $\mu\text{mol/L}$, MACE 的风险就会增加约 20%。正常血浆 Hcy 浓度为 5~15 $\mu\text{mol/L}$,其中约 70%~80%与血浆蛋白(主要是白蛋白)结合,约 1%以游离硫醇的形式存在于循环血液中,约 20%~30%与 Hcy 二聚体本身结合或与其他硫醇的混合二硫化物结合,如半胱氨酸形成 Hcy-Cys [8]。其可能致病机制:1) Hcy 升高抑制 NO 的产生,损害血管内皮功能[9]。2) Hcy 升高导致血管平滑肌细胞增殖导致血管舒张功能减弱,形成动脉粥样硬化的病理基础。3) Hcy 升高导致血小板粘附增加,加速血栓形成[10]。4) Hcy 可以影响细胞信号调节通路增加高灵敏度 C 反应蛋白的产生,从而催进血管动脉粥样硬化的进程[11]。

2.2. 25-羟维生素 D (25-Hydroxy Vitamin D)

维生素 D 是一种维持钙稳态的激素前体。25-羟基维生素 D 的血液水平被确定为维生素 D 状态的最佳估计值[12]。多项研究表明,低血 25-羟基维生素 D 水平正在成为 CAD 患者心血管或全因死亡率和 MACE 的预测生物标志物,维生素 D 缺乏容易导致发病率、死亡率和复发性心血管事件增加[13] [14] [15]。低维生素 D 可以激活肾素-血管紧张素-醛固酮系统的活性[16];其次,维生素 D 缺乏可能伤害 CAD 患者通过增强炎症[17] [18]。最后,25-羟基维生素 D 水平低与经皮冠状动脉介入治疗后无回流现象的发生密切相关和 CAD 的严重程度。低血 25-羟基维生素 D 水平可能是 CAD 患者心血管或全因死亡率和 MACE 的独立预测指标。基线 25-羟基维生素 D 水平可为 CAD 患者提供有用信息。

2.3. 胱抑素 C (CystatinC, CysC)

胱抑素 C 是体内胱氨酸代谢产物, 经肾脏排出, 不受饮食、情绪、性别、年龄的影响, 被认为是一般人群心血管和全因死亡率的独立预测指标。一项包含了 10 份研究数据库的 meta 分析评估中肯定了基线循环胱抑素 C 水平在急性冠脉综合征(ACS)患者中的预后价值, 证明高胱抑素 C 水平与 ACS 患者的死亡风险和 MACE 显著相关[19]。另一项研究表明, 胱抑素 C 水平的最高类别与最低类别的 MACE 风险和全因死亡率相关, 基线时胱抑素 C 水平升高与 ACS 患者 MACE 和全因死亡率风险增加密切相关且独立[20]。因此, 胱抑素 C 可以纳入风险分层模型, 以指导高危 ACS 患者的治疗。

2.4. 纤维蛋白原(Fibrinogen, FIB)

纤维蛋白原是由肝脏合成的具有二聚体分子结构的血清糖蛋白[21], 在炎症和凝血级联反应中起重要作用, 纤维蛋白原有助于加强全身或局部血管炎症、继发性血管内皮损伤, 有助于 CAD 的发展和进展, 并通过与其他炎症细胞, 内皮和血栓前分子的相互作用促进急性冠脉综合征的形成。一项我国观察性研究表明, 纤维蛋白原 ≥ 3.17 g/L 的入院是 CAD 患者全因死亡率和心脏死亡率的独立预测指标; Fib 水平与中国 CAD 患者的死亡风险独立相关, 表明 Fib 水平可能在中国 CAD 的二级预防中发挥作用[22]。据国外报道, 高纤维蛋白原水平是 CAD 存在和严重程度的独立预测指标[23]。Tabakcı 等人的研究表明, 血浆纤维蛋白原是一种易于测量的全身炎症标志物, 在冠状动脉患者中与冠状动脉的严重程度和复杂性独立相关, 纤维蛋白原浓度增加与动脉粥样硬化血栓性疾病的发生或存在有关[24]。

3. 多生物指标组合

3.1. 中性粒细胞/淋巴细胞比值(Neutrophil/Lymphocyte Ratio, NLR)

中性粒细胞和淋巴细胞(NLR)之间的比率是炎症因子之一, 可以挑选出未来心血管事件风险的个体。在总白细胞计数(WBC)及其亚型中, NLR 似乎对急性冠脉综合征(ACS)患者的死亡和主要不良心血管事件(MACE)具有最大的预测价值[25], 与 NLR 低的患者相比, 入院时 NLR 高与 STEMI 患者的总体死亡率较高相关和非 ST 段抬高型心肌梗死患者。在 NLR 高的 STEMI 患者中发现 MACE (重大心血管不良事件)风险增加。对于近期 ACS 患者, 治疗前 NLR 值升高可有效预测死亡/MACE 风险, NLR 值 5.0 可能是 ACS 风险的临界值[26]。NLR 可作为廉价且有用的标志物, 在 ACS 患者中具有很强的预后意义, 尤其是 NLR 高的患者时。

3.2. 平均血小板体积与淋巴细胞比值(MPVLR)

炎症和血小板活化是 AMI 的两种主要病理生理机制[27], 具有高止血活性的血小板在冠状动脉疾病(CAD)的病理生理学中起重要作用, 平均血小板体积(MPV)已被提出作为血小板反应性的指标。血小板活化和高反应性在发生 ST 段抬高型心肌梗死(STEMI)的血管内血栓中起关键作用。MPVLR 与 Gensini 评分和 Grace 评分呈正相关。MPVLR 或 MHR 水平高的患者发生 AMI 的风险增加[28]。HudzikB 等人的研究表明 MPVLR 升高是 STEMI 后早期和晚期死亡的独立危险因素。它在预测院内死亡率方面与 PLR 具有相似的价值, 在预测长期死亡率方面比 PLR 具有更好的价值[29]。血小板与淋巴细胞比(PLR)已成为炎症和血栓形成之间严重程度的新标志, PLR 升高是全因死亡率和 CV 事件的预测指标[30]。

3.3. 单核细胞与高密度脂蛋白胆固醇比值(MHR)

炎症、氧化应激和受损的内皮功能障碍在冠状动脉血流缓慢(SCF)的发生中起重要作用[31]。单核细胞与高密度脂蛋白胆固醇比(MHR)是最近出现的炎症和氧化应激指标, 较高的 MHR 表明炎症和氧化应

激增强, 与 SCF 的存在显著且独立相关。此外, MHR 作为全身炎症的常规标志物, 与血清 hsCRP 水平呈正相关[32]。冠心病患者血清中 MHR 较高, MHR 与冠状动脉病变严重程度密切相关, 是冠心病的独立危险因素[33]。

3.4. 中性粒细胞与高密度脂蛋白比值(NHR)

脂质相关生物标志物的重要性与急性心肌梗死(AMI)的病理过程和预后有关。一项有 528 名研究对象的实验分析结果是: 高 NHR、高 MHR 和高 LDL-C/HDL-C 组的死亡率和 RMI 率高于相应的低风险组, NHR 是一种新型实验室标志物, 可能是老年 AMI 患者长期临床结局的预测指标, 其优于 MHR 和 LDL-C/HDL-C。且证明 NHR 与 Gensini 评分呈正相关, 表明 NHR 在一定程度上与冠状动脉的严重程度相关[34]。NHR 是一种简单、廉价、现成且无创的基于血液的参数[35]。Lamichhane 等人从多个数据库中筛选出与 NHR 相关的文章及数据库进行回顾性分析, 研究发现 NHR 用于预测不良事件, 包括死亡率的敏感性和特异性极高, 与急性冠脉综合征相关[36]。因此, NHR 可用于临床心血管医学用于风险分层和预测 MACE 的短期和长期结果。

3.5. 纤维蛋白原与白蛋白比值(Fibrinogen-to-Albumin Ratio, FAR)

纤维蛋白原与白蛋白比值(FAR)目前已成为预测慢性疾病炎症的新型炎症标志物。血清白蛋白是维持血浆胶体渗透压的主要成分, 也参与急性炎症反应。血清白蛋白的生理水平抑制血管细胞粘附分子-1 的表达, 增加氧自由基的消除, 从而减少炎症反应和内皮细胞凋亡, 提示白蛋白是一种抗炎和抗氧化因子[37]。FAR 可作为一种方便、有效且无创的生物标志物, 用于指示 CAD 的严重程度, 预测预后, FAR 与 CAD 的严重程度和 STEMI 患者的不良结局有关。Karahan 等人表明, 在预测 STEMI 患者 CAD 严重程度方面, FAR 与 SYNTAX 评分显著相关[38]。Zhao 等人表明, 入院 FAR 对识别接受原发性 PCI 的 STEMI 患者的血管造影无回流和短期死亡率具有较高的敏感性和特异性[39]。Xiao 等人表明, 术前 FAR 与 C 反应蛋白、GRACE 评分和死亡率呈正相关, 提示 FAR 可作为接受原发性 PCI 的 STEMI 患者的预后指标[40]。Desai 等人的荟萃分析结果表明, FAR 可用于预测 PCI 后人群的 MACE、心脏死亡率、无血流风险或血运重建需求[41]。

3.6. 低密度脂蛋白胆固醇/高密度脂蛋白胆固醇比值(LDL-C/HDL-C, LHR)

有证据表明, LDL-C/HDL-C 比值可能是动脉粥样硬化性心血管疾病发生风险的新指标, 因为 LDL-C/HDL-C 比值可同时评估 LDL-C 和 HDL-C 水平[42]。一项最近的回顾性研究发现, ACS 患者入院时急诊 NLR、LDL-C/HDL-C 比值与 Gensini 评分存在显著相关性, 对 ACS 患者冠状动脉狭窄严重程度具有一定的预测价值, 可作为评估冠状动脉疾病严重程度的预测指标[43]。

3.7. 甘油三酯葡萄糖(TyG)指数

甘油三酯葡萄糖(TyG)指数是胰岛素抵抗的一种新的替代指标, 也是冠状动脉疾病患者的危险因素, 其计算公式为: $\text{Ln}[\text{空腹甘油三酯}(\text{mmol/L}) \times \text{空腹葡萄糖}(\text{mmol/L})/2]$ 。高 TyG 指数已被证明与糖尿病和 CVD 患者的不良心血管事件有关, 例如 ACS [44]。一项近期 meta 分析报道, 较高的 TyG 指数可能与一般人群中 CAD (中等质量)、MI (极低质量)和 CVD (极低质量)的发生率增加有关[45]。TyG 指数升高与 MINOCA 后预后不良独立相关。常规评估 TyG 指数可改善 MINOCA 患者的风险分层并促进决策[46]。另一项研究表明, 在基线时没有 ASCVD 的人群中, 较高的 TyG 指数可能与较高的 ASCVD、CAD 和卒中的发病率较高独立相关[47]。

3.8. 全身免疫炎症指数(SII)

SII 是一种基于血小板、中性粒细胞和淋巴细胞计数的新炎症指数,反映了宿主的炎症和免疫状态,计算为(中性粒细胞 × 血小板)/淋巴细胞。它可以相对全面地反映宿主炎症和免疫状态之间的平衡[48]。最近的研究表明, SII 可能与 CVD 的预后和死亡率有关,具有较高全身免疫炎症指数(SII)的个体患心血管疾病(CVD)的风险增加[49]。CVD 发病时的全身免疫炎症指数显著高于一般人群, YeZ 等人的研究发现 SII 水平高的人群患 CVD 的风险明显更高;在几乎所有类型的 CVD 中都可以观察到这种风险。SII 值在各种 CVD 开始时也显著增加[50]。该项指标可以通过全血细胞计数的常规血液检查轻松获得,也临床实践中最常用的测试。

4. 总结

高危人群的健康管理极为重要,长期不健康的饮食、缺乏身体活动、烟草使用和长久饮酒可能会导致血压和(或)血糖和(或)血脂的升高以及超重肥胖,从而导致心绞痛、心梗事件的发生。告知高危人群停止吸烟,减少饮食中的盐分,多吃水果和蔬菜,定期进行体育锻炼和戒酒,必要时给予药物治疗。上述生物标志物可以帮助患者进行早发现早诊断,给予患者及时的治疗,进而减少心脑血管疾病的发生,尽可能的降低对相关脏器的严重损害。

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