

营养状态与心血管疾病关系的研究进展

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摘要

营养不良与多种疾病的不良预后相关, 近些年在心血管疾病中也有许多研究发现营养不良与心血管疾病预后相关, 但目前心血管疾病并无公认的营养不良金标准, 本文梳理了营养不良与心血管疾病之间的关系, 并且探讨了多种营养不良评估工具目前在心血管疾病关系的研究, 特别是客观营养状态评分工具COUNT、GNRI及PNI评估为营养不良的患者在多种心血管疾病预后不佳, 同时部分营养状态评分意义仍有争议。

关键词

营养状态, COUNT, GNRI, PNI, 心血管疾病, 研究进展

Advances in Research on the Relationship between Nutritional Status and Cardiovascular Diseases

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Abstract

Malnutrition is associated with adverse prognoses across a spectrum of diseases. In recent years, a growing body of research has established links between malnutrition and outcomes in cardiovascular diseases (CVDs). However, a universally accepted gold standard for diagnosing malnutrition in the context of CVDs is still lacking. This article synthesizes the current understanding of the relationship between malnutrition and CVDs, and examines the application of various malnutrition assessment

tools in CVD-related research. Notably, patients identified as malnourished via objective nutritional status scoring tools—including the Controlling Nutritional Status (CONUT), Geriatric Nutritional Risk Index (GNRI), and Prognostic Nutritional Index (PNI)—exhibit poor prognoses across multiple CVD subtypes. Concurrently, the clinical significance of certain nutritional status scores remains a subject of debate.

Keywords

Nutritional Status, COUNT, GNRI, PNI, Cardiovascular Diseases, Research Progress

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1. 心血管疾病现状

心血管疾病是全球头号死因，2017 更新的一份关于冠心病及卒中的统计，全球每年死于心血管疾病的人约有 1730 万，占全球所有死亡人口的 31.5% [1]。根据世界卫生组织 2021 年的报道，2019 年全球心血管疾病死亡人数已上升至 1790 万，占全球总死亡人数的 32.0%，同时因心血管疾病死亡的患者主要集中于中等收入及低收入国家，约占总死亡人口的四分之三 [2]。我国情况更不容乐观，2017 年我国死因构成比中，心血管疾病占 45.91% [3]。2020 年我国死因构成仅心脏病导致的死亡仍位于我国死因构成首位 [4]。目前已经在多种心血管疾病中发现患者营养不良与不良预后相关。目前临床上有许多营养状态评分，根据各评估工具纳入的评估因素大体上可以分为主观营养状态评分及客观营养状态评分，仍无公认的适用于心血管疾病的营养状态评估工具，本文将根据现有研究结果对营养不良与心血管疾病的关系及目前在心血管疾病患者中研究较多的营养状态评分进行简要阐述。

2. 营养状态与心血管疾病之间的关系

动脉粥样硬化是一种慢性炎症疾病，是导致心血管疾病的主要发病因素和死亡因素。动脉粥样硬化主要涉及低密度脂蛋白沉积于动脉内膜，沉积的脂质可引起内皮功能的障碍，进一步加剧脂质沉积同时促进慢性炎症的发生、脂质池的形成、内膜结构的破坏及纤维帽形成，病变严重的可能导致纤维斑块坏死、溃疡破裂，最终导致动脉血栓形成和心肌梗死 [5]-[7]。其发生和发展过程中与多种炎症因子和炎症细胞相关，如白介素-1、白介素-6、肿瘤坏死因子- α 、C-反应蛋白、淋巴细胞、巨噬细胞等相关，有相关研究表明氧化应激及全身炎症反应与营养状态相关 [8]-[11]。也有相关研究发现，免疫系统在参与动脉粥样硬化的发生和发展的过程中起到双向调节作用，在粥样硬化开始时起到促进作用，达到一定程度后起到限制斑块进展的作用 [12]。

细胞自噬是一种保守的细胞质量控制系统，越来越多的证据指出，细胞自噬通过维持细胞稳态在许多生物学过程中发挥着重要的作用，如炎症和器官重构 [13]。在衰老的过程中，细胞通过自噬作用不断清除受损的组成部分并合成新的分子替代，以确保细胞的稳态从而延缓衰老，但是在应激状态下细胞自噬会被强烈激活 [14]。过度激活的自噬可能会消耗细胞正常生存所必需的分子及细胞器，从而导致细胞的死亡 [15]。心肌梗死后由于急性缺血缺氧打击，细胞自噬也在其发生发展中起重要作用，适度的自噬可产生三磷酸腺苷供能促进心肌细胞的存活 [16] [17]。在心力衰竭的患者中自噬通过多种形式发挥作用，很多形式的心力衰竭与错误折叠蛋白的积累相关，自噬能够在缺血、饥饿等刺激下去除错误折叠或异常的蛋白

质和受损的细胞结构来保护心肌细胞[18]。虽有证据证明细胞自噬在维持心脏稳态方面起着重要积极作用,但是过度自噬也会加剧心脏疾病。因此营养不良、肌肉分解代谢增加和自噬增强可导致心脏损伤,必要时补充足够的必需氨基酸可以达到心肌保护作用[19]。

心脏恶病质是以蛋白质-卡路里营养不良伴有肌肉萎缩和周围水肿为特点的疾病,其是营养不良的进展与加重[20]。Aquilani 等人的研究揭示了营养不良和恶病质之间的相互作用。他们评估了门诊非肥胖、临床稳定的心衰患者的饮食,发现 54% 的患者存在卡路里营养不良、蛋白量营养不良或者两者均有。恶病质组与对照组能量摄入相当,但恶病质组静息能量消耗增加,这表明恶病质组的能量代谢更强,却未能得到补充。还有研究发现对于心衰患者纠正蛋白能量营养不良补充必需氨基酸效果要强于单纯补足能量,这说明补充能量的种类和质量同样重要[21]。总的来说心力衰竭可能通过肠道水肿引起营养吸收不良、细胞因子产生的厌食及疲劳和呼吸功能增加引起的进食限制或障碍等机制引起营养不良,严重地导致心脏恶病质。反过来,心脏恶病质导致的机体及心脏所需必要宏观及微观营养素缺乏,又进一步加重了心脏功能的恶化、骨骼肌的损失,进一步降低运动耐力[22]。这种心力衰竭和营养不良及恶病质的相互促进,及时纠正营养不良,打破恶性循环尤为重要。

3. 营养状态评估工具分类及临床应用

由于体重、白蛋白、血脂等单一指标不能相对全面客观地代表患者的整体营养状态,依赖医生的主观目测和临床经验,导致大量患者被漏诊。营养不良筛查工具应运而生。

现使用较广的主观营养状态评分有营养风险筛查 2002 (Nutrition Risk Screening 2002, NRS 2002)、微型营养评定表(Mini Nutritional Assessment, MNA)、主观整体评估(Subjective Global Assessment, SGA)、营养不良通用筛查工具(Malnutrition Universal Screening Tool, MUST)。主观营养状态评分工具通常包含近期食纳情况、体重变化、BMI 变化、疾病情况等,部分包含肌肉变化指标及精神状态[22]-[26]。食纳、体重、BMI 等均为营养状况宏观体现,肌肉状态及精神状态是营养状态在功能层面的表现。但其包含部分主观评估项目需要专业医师与患者相互配合以保证评估的准确性,一定程度上限制了它们在临床上的应用。目前主观营养状态评分广泛用于老年患者及肿瘤患者营养状态的评估。并与多种疾病的临床预后相关[27]-[29]。主观营养状态评分在心血管疾病应用相对较少。

客观营养状态主要有控制营养状态评分(Controlling Nutritional Score, COUNT)、营养风险指数(Nutritional Risk Index, NRI)和营养风险指数(prognostic nutritional index, PNI) [30]-[32]。COUNT 评分由 Ulibarrie 等人开发并最早于 2005 年用于临床评估患者营养状况,其包含血清白蛋白、淋巴细胞数和胆固醇指标,根据这些指标进行赋分,按照总分划分患者无、轻、中及重度营养不良。NRI 评分是 Buzby 等人最初用于术前全肠外营养患者评估,患者体重和血清白蛋白,计算公式为 $NRI = 1.519 \times \text{血清白蛋白(g/l)} + 41.7 \times [\text{当前体重(kg)}/\text{既往体重(kg)}]$ 。因其既往体重不易获得,根据洛伦兹变换将既往体重使用理想体重替代得到老年营养风险指数(GNRI),其计算公式为 $GNRI = 1.489 \times \text{血清白蛋白(g/l)} + 41.7 \times [\text{当前体重(kg)}/\text{理想体重(kg)}]$,男性: $\text{身高(cm)} - 100 - [(\text{身高(cm)} - 150)/4]$,女性: $\text{身高(cm)} - 100 - [(\text{身高(cm)} - 150)/2.5]$ [33]。更改后的评分包含患者身高、体重、血清白蛋白指标,替换了既往体重使得 GNRI 在临床上使用变得简便易行。PNI 评分最早是 Onodera 等人开发,用于癌症患者胃肠外科手术术前进行风险分层,其包含血清白蛋白及淋巴细胞计数两个临床指标,计算公式为 $PNI = 10 \times \text{血清白蛋白(g/dl)} + 0.005 \times \text{淋巴细胞计数(mm}^3\text{)}$ 。客观营养状态评分计算数据易获取、计算简单、无需评估经验,易于推广,已有很多心血管疾病的相关研究。

肌肉组织是人体最丰富的组织。肌少症表现为肌肉力量、质量和功能的进行性丧失,与死亡风险增加、跌倒、残疾、住院和独立性丧失相关[34]。同时营养不良在肌少症病理生理中发挥重要作用[35]。ESPEN

强调营养不良与肌少症的紧密联系,指出肌肉质量下降是营养不良的核心表现之一[36]。骨骼肌质量指数是诊断肌少症的常用指标,通常可通过双能 X 射线吸收测量、磁共振成像和计算机断层扫描检测。人体肌肉质量测量、生物电阻抗分析、握力及肌力检查对于肌少症诊断及分级重要意义[37]。

4. 营养状态评估工具在心血管疾病中的应用

主观营养状态评分中 MNA 在心血管疾病患者中研究相对较多,在 Kinugasa 等人的研究中迷你营养评估简表(MNA-SF: MNA 评分的简化版,可适用于青年人)、老年营养风险指数(GNRI)和控制营养状况(CONUT)对心衰患者进行营养评估,发现 MNA-SF 对心衰患者营养不良诊断能力最高[38]。Besler 等人的研究在经导管三尖瓣置换术(TTVR)的患者中使用 MNA 行营养状态评估,发现 TTVR 患者中有 94% 的患者存在营养不良风险,同时营养不良的患者相较于营养正常的患者手术效果差。在后期的随访中可见营养状况改善的患者六分钟步行实验改善,而营养状况恶化的病人在再院率及因心力衰竭死亡风险均增加[39]。在另一项研究中,使用 MNA、COUNT、GNRI、预后营养指数(PNI)评分对心力衰竭患者进行营养评估,发现 MNA 和 GNRI 与心衰患者全因死亡相关性最强[40]。MNA 在心衰及 TTVR 术后的患者中有良好的营养风险鉴别及不良预后的预测能力。

客观营养状态在心力衰竭中的研究非常广泛,并与患者预后相关。Prausmüller 等人的关于慢性心力衰竭的患者的营养不良患病率及预后意义的研究 4021 例患者,分别使用 COUNT、GNRI 和 PNI 评分对患者进行营养评估。其研究结果表明,在心力衰竭的患者中中重度营养不良患者占 7%至 10%。任何评分均评为无营养不良的患者占 42%。与营养状态正常的患者相比,营养不良的患者 NT-proBNP 更高、死亡风险更高,他们研究认为 GNRI 评分相较于 COUNT 和 PNI 评分是更好的营养不良筛查工具,对不良预后预测价值最高,同时营养不良对预后的价值高于 BMI [41]。Sze 等人也在心力衰竭患者中做了相似的研究,他们使用的营养评估工具更丰富,包括 GNRI、COUNT、PNI、MUST、MNA-SF 和 SGA。他们发现任何营养状态评分评估的营养不良均与患者全因住院率和死亡率风险增加有关。但是他们发现白蛋白这个单一指标与营养不良筛查工具有着相似的预后价值。他们认为白蛋白可能反应心力衰竭患者的综合营养状态,可以替代相对复杂的营养不良筛查工具[42]。

客观营养状态评分与冠心病患者预后相关。Arero 等人的一项关于 COUNT 评分预测冠状动脉疾病患者预后的荟萃分析中发现,根据 COUNT 评分评估的结果,轻、中、重度营养不良患者全因死亡风险是正常患者的 1.25、1.62 和 2.49 倍。中、重度营养不良的患者主要心血管不良事件风险为营养正常患者的 1.71 和 2.66 倍。此外,每当 COUNT 评分增加 1 分,都会增加患者 20%到 23%的全因死亡和不良心血管事件风险[43]。在 Raposeiras 等人关于急性冠脉综合征患者的营养状态及预后的研究中,他们使用 COUNT、NRI 和 PNI 评分对患者进行营养状态评估,发现营养不良在急性冠脉综合征患者中很常见,71.8%被至少一种营养状态评分评估为营养不良,中重度营养不良患者占 8.9%至 39.5%。同时营养不良患者全因死亡与不良心血管事件风险均增加。三种评分中 COUNT 评分对患者不良预后预测能力最强,但都弱于 GRACE 评分,将营养不良评分与 GRACE 评分联合均能提高对患者不良预后的预测能力,但是这种提高非常有限[44]。在心肌梗死的患者中,Abe 等人的研究发现 GNRI 评分与急性心肌梗死患者全因死亡和不良心血管事件相关[45]。Chen 等人在 PCI 术后的 STEMI 患者中使用 PNI 进行营养评估,也发现了相似的结果[46]。Wu 等人的研究发现 COUNT 和 GNRI 评分与急性心肌梗死后新发心房颤动相关[47]。

在高血压方面,Cao 等人发现,高 GNRI 评分与高血压风险提高相关,并发现 GNRI 通过血清白蛋白和 BMI 的路径起到了血清尿酸与高血压之间的中介作用,相同的血清尿酸水平下,营养状态正常的患者高血压风险降低 17.77% [48]。Cai 等人的研究发现 GNRI 与老年高血压患者的卒中发生率相关,当 GNRI 低于 103 时患者卒中风险明显增加[49]。

在心房颤动方面,有研究结果显示在非瓣膜性心房颤动患者中使用 COUNT 进行营养状态评估,超过三分之一的患者存在中重度营养不良。同时这些营养不良的患者一年死亡率更高[50]。Wang 等人在非瓣膜性心房颤动患者发现 $\text{PNI} \leq 48.0$ 的患者左心房血栓/自发超声显影较 $\text{PNI} > 48.0$ 的患者高 2.57 倍[51]。Kim 等人在接受导管消融的心房颤动患者中使用 COUNT 评分评估, $\text{COUNT} \geq 2$ 的患者导管消融术后并发症发生风险是营养状态正常的 2.87 倍[52]。

客观营养状态评分在特发性扩张型心肌病及肥厚梗阻性心肌病中也有也就,这两项研究均使用 PNI 评分进行营养状态评估,在特发性扩张型心肌病患者中,当 PNI 评分 ≤ 44.0 ,患者的全因死亡率及不良心血管事件发生率明显增加。在肥厚梗阻性心肌病的研究中,这一界值为 $\text{PNI} < 48.8$ [53] [54]。

客观营养状态评分与心脏瓣膜病的研究主要集中于患者术后的临床结局方面。近期的一项关于经导管主动脉瓣膜植入术的荟萃分析发现,使用 COUNT、GNRI 和 PNI 评分进行营养状态评估,营养不良与患者术后一年全因死亡风险增高相关。在校正结果的 meta 分析中,低 GNRI 仍与高 1 年全因死亡率独立相关[55]。在 Caneiro-Queija 等人的关于二尖瓣经导管缘对缘修复术后患者的研究中,使用 COUNT 评分,发现有 74.4% 的患者被评估为营养不良。同时中重度营养不良的患者因心力衰竭再入院率和全因死亡率更高[56]。

在其他心血管疾病中,有两项研究使用 PNI 评分对川崎病和 A 型主动脉夹层患者进行营养评估,发现低 PNI 与患者高心血管并发症发生率和院内死亡率独立相关。

肌少症与心血管疾病进展加速、死亡率升高、跌倒风险增加及生活质量下降相关,尤其在老年人群中更为显著。肌少症是导致心衰患者长期反复住院和死亡风险增加的独立风险因素[57] [58]。因肌少症与冠脉病变有相似的发病机制,既往有相关研究表明,老年肌少症患者与冠脉硬化相关[59] [60]。也有研究表明,肌少症患者心脏手术后不良事件及长期死亡率更高[61] [62]。

5. “肥胖悖论”及营养状态评分的局限性

在心血管疾病中,体重及体重指数与患者预后研究结果并不统一。部分研究中认为持续性的肥胖可能通过血液游离脂肪酸沉积于心肌,引起脂毒性、心肌细胞凋亡,从而导致进行性的心脏损伤、心肌重构、心功能障碍及心力衰竭,从而导致超重及肥胖的患者死亡率明显高于体重正常及偏瘦的患者[63]。也有持反对结论的研究,De Paola 等人进行荟萃分析发现体重过轻的患者死亡率更高,他们的研究认为高体重指数是心肌梗死患者的保护因素,他们认为肥胖患者有更大的能量储备,对于心肌梗死后应急状态及负氮平衡状态有更强的适应性及承受力。同时肥胖可能通过调节白介素-10 等炎症因子对抗因肥胖引起的促进心血管疾病的有害炎症[64]。也有相关研究认为体重指数与预后呈“U”型曲线关系,肥胖与高血压、高血脂、胰岛素抵抗等多种有害因素相关,同时肥胖也与较低的心血管有害炎症相关。两者处于动态平衡,过高及过低的 BMI 都可能打破平衡从而增加死亡风险[65]。

血清白蛋白是人体中含量最丰富的蛋白质。其与多种生理病理过程相关。既往研究发现其与糖尿病发病率、白介素及 C 反应蛋白等炎症指标相关,具有抗炎、抗氧化等作用,同时低白蛋白与血栓形成相关[66]-[70]。

总胆固醇目前认为是动脉硬化的重要危险因素。有研究表明,胆固醇参与动脉粥样硬化全过程,并且与斑块不稳定及血栓形成相关[71]。多项研究表明,高胆固醇会增加心梗复发风险、增加全因死亡率。降低胆固醇水平可使冠心病患者明显那受益[72] [73]。但在 Yousufuddin 等人的研究发现 $\text{LDL-C} \geq 100 \text{ mg/dL}$ 的急性心肌梗死患者长期死亡率更低,中位生存时间更长[74]。

淋巴细胞在心血管疾病中扮演着双重角色,即促进炎症反应促进斑块的形成、发展、破裂,但同时 CD8^+ 调节 T 细胞也同时发挥着限制有害炎症的作用,体现出血管保护作用[12]。

可以看出,目前营养评价的相关指标在心血管疾病的发生发展及预后中均有双向作用,但是在如COUNT、GNRI、PNI等评价标准中,只能体现出相关指标的单一作用,并不能客观体现出相关营养指标的真实影响。

6. 总结与展望

营养状态是患者整体蛋白储备、能量储备、炎症水平等多方面的复杂的综合状态。营养不良被认为与多种心血管疾病不良预后独立相关。主观营养状态评分因需要专业评估医师和患者积极配合完成,临床使用可能受限。客观营养状态评分数据获取方便、计算简单,同时普通临床医师即可进行评估,可在临床上推广使用。但是目前还未见根据营养状态评分进行营养干预的大规模前瞻性临床研究。故根据营养状态评分进行营养干预是否能使患者受益还不清楚。同时目前也无公认的营养状态金标准。目前肌少症与心血管疾病相关研究发现其与进展加速、死亡率升高相关。同时肌少症与营养不良显著相关,是营养不良在功能层面的重要体现。结合目前患者就医的过程中影像学如胸部CT等检查的普及化,结合快速发展的AI技术快速评估患者某一断层或多断层的肌肉治疗,为进一步开发包含BMI、血脂、白蛋白、淋巴细胞计数及影像学肌肉质量评估的新模型,可更加准确评估患者营养状态,同时排除患者主观因素的不确定性。同时此类指标临床容易获取,可操作性更强。同时需要进一步结合临床营养指导、营养支持等相关研究,使营养风险评估具有临床营养治疗等指导作用。

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