

血浆致动脉粥样硬化指数与冠心病相关性研究进展及其作为预测指标的优势与局限

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摘要

冠状动脉粥样硬化性心脏病(coronary heart disease, CHD)的发病机制与脂质沉积形成粥样斑块致血管狭窄或闭塞相关, 血浆致动脉粥样硬化指数(atherogenic index of plasma, AIP)作为新型血脂代谢综合指标, 在反映脂质代谢状态、评估抗动脉粥样硬化潜力方面优于传统血脂指标, 为冠心病风险评估提供重要参考。然而, 其临床应用仍面临局限: 易受多种生理和病理因素的干扰, 且与其他生物标志物联合应用的适配性仍存在争议。本文旨在探讨AIP与冠心病发生发展的关联机制, 剖析其作为预测指标的优势与局限, 为未来的研究方向提供有益见解, 以推进临床应用发展, 为冠心病的早期预防、精准评估及临床决策提供更具价值的理论依据。

关键词

冠心病, 血脂, 血浆致动脉粥样硬化指数

Research Progress on the Association between AIP and the Risk of Coronary Heart Disease Onset, as Well as Its Advantages and Limitations as a Predictive Indicator

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Abstract

The pathogenesis of coronary heart disease (CHD) is linked to vascular stenosis or occlusion caused by atherosclerotic plaque formation secondary to lipid deposition. As a novel lipid indicator, the plasma atherogenic index (AIP) demonstrates superior efficacy compared to traditional lipid markers in reflecting lipid metabolism status and anti-atherosclerotic capacity, providing a crucial reference for CHD risk assessment. However, its clinical application faces limitations, including susceptibility to various physiological and pathological factors, as well as controversies regarding its compatibility when combined with other biomarkers. This study aims to investigate the underlying mechanisms linking AIP to the onset and progression of CAD, critically analyzing its advantages and limitations as a predictive marker. By doing so, we aim to provide valuable insights for future research directions, thereby advancing clinical applications and offering robust theoretical foundations for the early prevention, precise assessment, and clinical decision-making regarding CAD.

Keywords

Coronary Heart Disease, Lipid, Atherogenic Index of Plasma

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1. 前言

冠状动脉粥样硬化性心脏病(coronary heart disease, CHD)是全球致死致残的首要原因之一[1]。我国心血管疾病死亡率居高不下, 2021 年数据显示我国农村和城镇占比分别高达 48.98%和 47.35%, 每 5 例中约有 2 例归因于心血管疾病(cardiovascular disease, CVD) [2], 构成严峻的公共卫生挑战。冠心病为全球主要致死病因, 其发病机制复杂且多因素交织[3]。动脉粥样硬化是其发病的主要潜在因素[4]。脂质代谢紊乱在动脉粥样硬化的启动与进展中发挥关键作用。中国成人血脂异常患病率已攀升至 40.40%, 呈大幅度增长趋势, 预计 2010 年至 2030 年期间每年因胆固醇升高导致的心血管事件将增加 50% [5] [6]。值得注意的是, 2012 年全国儿童和青少年调查显示, 5.4%的儿童青少年有高胆固醇血症(TC > 5.2 mmol/L), 较 10 年前升高约 1.5 倍[7]。血脂异常低龄化趋势加剧了未来心血管疾病负担。传统血脂指标长期用于评估动脉粥样硬化风险[8]及临床药物治疗的靶点[9]。然而, 已有多项研究表明, 即使低密度脂蛋白胆固醇(LDL-C)达标, 但仍有 60%~80%的心血管事件发生, 提示富含甘油三酯的脂蛋白(triglyceride-rich lipoproteins, TRL)、残粒胆固醇(residual cholesterol, RC)以及脂蛋白(a) [lipoprotein(a), Lp(a)]等构成的“剩余风险”不容忽视。这些因素共同构成了异常脂质代谢中的重要心血管危险因素, 对全面评估和管理患者的心血管疾病风险具有重要意义[10]。在此背景下, 能够综合反映脂质代谢失衡状态的新型生物标志物备受关注[11]。2001 年, Dobiášová 和 Frohlich 首次引入了 AIP 的概念, 其计算公式为 $\log_{10}(\text{TG}/\text{HDL-C})$ (mmol/L) [12], 可综合反映富含个体发生动脉粥样硬化的风险[13]。其计算方法基于血脂水平, 可有效反映富含甘油三酯脂蛋白与抗动脉粥样硬化脂蛋白的相对比例, 评估个体动脉粥样硬化风险。研究发现, AIP 与糖尿病、高血压等高危人群的心血管疾病风险显著相关[14] [15]。但目前 AIP 在不同人群中的适用性、测量标准化、与其他标志物的协同作用等问题尚存争议, 其从风险预测指标向治疗靶点转化的研究也较为匮乏[16] [17], 此外, AIP 的临床应用也面临着一定的挑战, 包括个体差异、测量标准化等问题, 这些因素可能会影响其

作为预测指标的有效性和准确性[18][19]。本综述旨在系统阐述 AIP 的生物学机制、临床应用价值及局限性, 为其在心血管疾病领域的规范化应用及后续研究提供参考。

2. AIP 的核心病理机制

AIP 升高的核心病理生理学机制根植于高 TG 血症(Triglyceride, TG)和低 HDL-C (high-density lipoprotein cholesterol, HDL-C)失衡状态介导的小而密低密度脂蛋白(sdLDL)生成, 后者作为关键病理中介质, 通过级联放大效应介导下游氧化应激激活、炎症反应募集及血管内皮功能损伤等系列病理过程, 最终构成具有 AIP 特征性的精准致动脉粥样硬化病理通路。Berneis 等证实, 富含 TG 的脂蛋白(如 VLDL)经肝脂肪酶和脂蛋白脂酶脱脂水解为中间密度脂蛋白(IDL), 并进一步代谢成为 LDL [20]。LDL 易被肝脂酶(HL)修饰为小而密 LDL (sdLDL), 这类颗粒粒径小、清除率低, 易穿透血管内皮并被氧化, 且其对 LDL 受体的亲和力更低, 既诱发内皮功能障碍, 其氧化产物还会被清道夫受体识别, 促使巨噬细胞与平滑肌细胞吞噬氧化的 LDL 后形成泡沫细胞, 启动动脉粥样硬化的发展。尽管 sdLDL 水平与冠心病风险呈明确正相关且存在因果关联, 但 sdLDL 的测量检测技术复杂, 成本高昂, 难以适用于常规临床实践, 而 AIP 与 sdLDL-C 颗粒直径密切相关, 可作为评估 sdLDL 相关动脉粥样硬化风险的替代指标。此外, 载脂蛋白 M (ApoM)与 AIP 呈负相关, 是 HDL 的关键抗炎成分[21], ApoM 通过结合鞘氨醇-1-磷酸(S1P)激活 S1P 受体 1 (S1PR1), 形成 ApoM-S1P 复合物, 抑制 NF- κ B 和 MAPK 通路, 减少促炎因子产生, AIP 升高会削弱这一抗炎机制, 进一步加剧血管炎症损伤。针对糖尿病患者的实验验证, 氧化应激的激活主要依赖 NADPH 氧化酶通路[22]。过量 ROS 可氧化修饰 sdLDL-C 形成氧化型 LDL (ox-LDL), 后者滞留于内皮下并被巨噬细胞吞噬, 共同促进泡沫细胞形成及动脉粥样硬化进展[23], 同时, ox-LDL 具有细胞毒性, 可直接诱导内皮细胞凋亡, 抑制内皮细胞增殖和修复能力, ROS 还会氧化内皮型一氧化氮合酶(eNOS), 降低一氧化氮的生成和生物活性, 导致内皮依赖性舒张功能受损进而引发内皮功能障碍[24]。且 ROS 可促进血小板活化, 诱导血小板聚集及血管收缩物质(如内皮素-1)的释放, 加剧血管舒缩功能失衡, 加速动脉粥样硬化进展[25]。除此以外, sdLDL 及 ROS 还可通过多途径激活内皮细胞和巨噬细胞中的核因子- κ B (NF- κ B)通路, 上调血管细胞黏附分子-1 (如 VCAM-1、ICAM-1)和促炎细胞因子(如 TNF- α 、IL-6)的表达, 促进单核细胞向血管壁募集与浸润, 形成“脂质-炎症”正反馈循环[26]。此外, AIP 升高引发的高 TG 血症可引发脂毒性。脂毒性与 IR 密切相关, 其可干扰内膜细胞胰岛素信号传导, 导致 PI-3-激酶活化的磷酸化受损, 影响一氧化氮合酶功能, 增加血管阻力, 进而加速动脉粥样硬化斑块沉积, 诱发炎症和血脂异常[27]。高 TG 血症还可通过脂蛋白脂酶(LPL)水解 TG 释放游离脂肪酸(FFA), FFA 蓄积抑制肝细胞自噬活性, 激活 NF- κ B 并诱导 NLRP3 炎性小体, 触发肝细胞炎症反应[28], 同时有研究表明, CREBZF 转录因子在巨噬细胞中特异性高表达, 可结合炎症因子的启动子区域, 促进促炎因子转录、抑制抗炎因子表达, 打破炎症平衡并加剧局部组织的慢性低度炎症。巨噬细胞大量分泌的促炎因子进一步损伤脂肪细胞与肝细胞的胰岛素信号传导, 引发胰岛素抵抗[29], 而胰岛素抵抗进一步加剧脂质代谢紊乱, 最终形成脂质紊乱-炎症-IR 的恶性循环。这也提示我们巨噬细胞 CREBZF 或可成为 IR 和 T2DM 的潜在治疗靶点, 抑制其表达或活性可通过缓解炎症反应来改善代谢紊乱。综上, AIP 整合 TG 与 HDL-C 核心要素, 是评估血脂异常状态的理想、综合量化指标, 可有效识别存在“高残余心血管风险”的个体。

3. AIP 在冠心病及相关疾病中的临床应用价值

3.1. 冠心病发病风险预测

大量观察性研究、系统评价和荟萃分析一致证实, AIP 是冠心病发病风险的独立预测因子, 预测效能优于传统血脂指标[30]-[32]。Wu 等的研究表明, AIP 每升高 1 个标准差, 冠心病的发病风险增加 2.10

倍(95% CI: 1.51~2.93, $P < 0.001$) [33]。针对 1535 名 ST 段抬高型心肌梗死患者的研究发现, AIP 是预测介入前 TIMI 血流状态的独立因素, 其不同 TIMI 血流等级间差异显著($P < 0.001$), 且预测血管通畅性的曲线下面积(AUC)优于其他脂质参数, 凸显其在心血管疾病预测中的潜在价值[34]。另一项纳入 51 项观察性研究的荟萃分析表明, AIP > 0.24 者冠心病发病风险为正常人群的 2.79 倍(95% CI: 1.75~4.45, $P < 0.00001$), 且发生冠脉钙化(OR: 2.28, 95% CI: 1.74~3.00, $P < 0.00001$)、多血管冠心病(OR: 2.04, 95% CI: 1.50~2.77, $P < 0.00001$)和斑块进展(OR: 1.49, 95% CI: 1.17~1.91, $P = 0.001$)的风险均显著增加。该关联在急性冠状动脉综合征患者(HR: 1.59, 95% CI: 1.33~1.89, $P < 0.00001$)和稳定型 CAD 患者(HR: 1.65, 95% CI: 1.15~2.37, $P = 0.007$)中也是一致的[31], 表明 AIP 对 CAD 的发生、进展以及预后均具有良好的预测价值。Wang 等[35]的研究进一步证实, AIP 与 CAD 发病风险及 SYNTAX 评分相关, 提示其可有效评估 CAD 患病风险及冠脉病变的复杂程度。

3.2. 评估冠脉病变的严重程度及复杂性

冠脉病变数量通常指冠状动脉中存在显著狭窄($\geq 50\%$)的血管数量, 是评估冠心病严重程度的核心指标。多项研究表明, AIP 与冠脉病变严重程度密切相关, 且与冠状动脉钙化评分、Gensini 评分及 SYNTAX 评分均呈正相关[36]。2025 年一项荟萃研究表明, AIP 升高患者的冠状动脉钙化风险显著增减(OR: 2.28, 95% CI: 1.74~3.00, $P < 0.00001$)、多血管冠心病发病风险升高 2.04 倍(OR: 2.04, 95% CI: 1.50~2.77, $P < 0.00001$), 斑块进展亦显著增高(OR: 1.49, 95% CI: 1.17~1.91, $P = 0.001$) [31]。印度一项纳入 260 名参与者的横断面研究发现, AIP 与冠脉受累数呈正相关, 且随冠脉累及数的增加呈升高趋势($P < 0.05$), 提示其对评估冠脉病变有一定预测价值[37]。同时, AIP 也与 SYNTAX 评分相关。我国一项纳入 144 例冠心病患者的前瞻性队列研究显示, AIP 与 SYNTAX 评分相关系数达 0.422 ($r = 0.422$, $P < 0.001$) [38]。另一项涵盖 1826 例冠心病病人的分析亦证实, AIP 随 SYNTAX 评分升高而增加, 其评估冠脉病变严重程度效能优于传统单项血脂指标[30]。综上, AIP 可作为评估冠脉病理解剖学特征的有效量化指标, 为临床制定血运重建策略提供参考, 具有重要的临床应用价值和实践指导意义。

3.3. 预测不良心血管事件的发生

AIP 是预测冠心病患者发生主要不良心血管事件(MACE)的有力工具。一项前瞻性队列研究证实, 基线 AIP 水平升高的患者, 长期随访期间 MACE 发生率显著更高, AIP 与 1 年内 MACE 事件发生呈显著正相关, 是独立预测因子, Q4 组(AIP 最高组) 1 年内 MACE 发生风险较 Q1 组升高 2.35 倍(95% CI: 1.52~3.63, $P < 0.001$), 且 AIP 每升高 0.1 个单位, MACE 风险增加 18% (HR = 1.18, 95% CI: 1.09~1.28, $P < 0.001$) [39]。一项社区前瞻性队列研究发现, AIP 升高与心血管事件风险显著增加相关, 且该关联独立于传统心血管风险因素, 其与卒中发生的相关性在老年人群中尤为显著(HR = 1.69, 95% CI: 1.17~2.45, $P = 0.005$) [40]。Qin 等针对糖尿病患者 PCI 术后预后的研究显示, 高 AIP 组的预后显著劣于低 AIP 组(HR: 1.614, 95% CI: 1.303~2.001, $P < 0.001$), 且该关联独立于 LDL-C 的水平, 提示动态监测 AIP 对优化此类患者的预后评估具有重要的临床价值[41]。

3.4. 预测其他代谢性疾病的价值

代谢综合征并非一种单一的疾病, 而是一组同时出现的代谢异常疾病的集合, 主要累及心血管与肾脏系统、内分泌与生殖系统、消化系统等。代谢综合征因其不断上升的患病率在全球范围内引起了极大的关注, 给全球卫生保健系统带来了沉重的负担[42]。其病理生理均来自于脂质代谢失衡、炎症激活、胰岛素抵抗及内皮功能障碍的交互作用。AIP 的核心价值不仅在于其为血脂衍生指标, 而是通过量化方式

反映整体代谢状态的核心指标。

3.4.1. 高血压

高血压与 AIP 的密切关联本质是脂质代谢失衡对血管重构的驱动效应, AIP 升高所代表的高 TG、低 HDL-C 状态, 通过诱导 sdLDL 生成、激活氧化应激通路, 损伤血管内皮完整性并加剧血管平滑肌增殖, 打破血管舒缩平衡, 这与高血压的核心病理机制高度契合[22]-[25][43][44]。高血压为冠心病的核心危险因素之一, 2023 WHO 高血压报告显示, 全球高血压患病人数已超 10 亿, 但其诊断率仅 54%、治疗率 42%、有效控制率仅 21%, 仍是有待解决的重要公共卫生难题[45]。AIP 可作为识别高血压的早期生物标志物, 有助于易感人群的早期筛查。NHANES 数据库一项研究证实, AIP 与高血压之间存在显著关联(OR: 1.89, 95% CI: 1.11~3.22, $P = 0.019$)。ROC 曲线显示, AIP 对高血压的发生具有良好的预测效能($AUC = 0.652$), 且预测效能女性和 BMI 正常人群中关联更强[46]-[48]。Zhang 等[49]的研究进一步证实, AIP 与血压失调显著正相关, 校正的 Logistic 回归模型显示, AIP 升高对应高血压前期/高血压风险显著增加, (OR = 1.69, 95% CI: 1.38~2.07, $P < 0.001$), 性别分层分析提示女性相关性更显著, AIP 每升高一个单位, 风险增加 1.79 倍(OR: 1.79, 95% CI: 1.35~2.38, $P = 0.001$)。这提示在代谢紊乱早期, AIP 即可捕捉到代谢异常的信号, 为高血压易感人群的早期筛查提供了代谢层面的量化依据。

3.4.2. 糖尿病

在 1999 年, 世界卫生组织(WHO)确定胰岛素抵抗是代谢综合征主要的潜在因素[50]。胰岛素抵抗(IR)是指对胰岛素作用敏感性和反应性降低的状态, 与各种代谢紊乱的发生相关, 易导致心血管疾病的不良结局[51][52]。胰岛素抵抗是冠心病的重要危险因素, 与脂质代谢紊乱相互促进。AIP 升高导致的高 TG 血脂可引发脂毒性。糖尿病患者的 AIP 水平通常较高, 其与内脏脂肪指数(VAI)、脂质积累产物(LAP)一些新兴脂质标志物类似, 在预测代谢紊乱(如糖尿病(DM))及相关微血管并发症(尤其糖尿病肾病(diabetic kidney disease, DKD)、糖尿病视网膜病变(DR))的预测中具有潜在价值。IR 是 CVD 的独立危险因素, AIP 是众多用于衡量胰岛素抵抗的简单辅助指标之一, 来自 CHARLS 数据库队列研究比较 9 项胰岛素抵抗辅助指标与 CVD 发病的关联, 结果显示, AIP 每增加一个标准差, CVD 风险显著升高(HR = 1.08, 95% CI: 1.03~1.13), 证实其为简单易操作、临床可行性强的 CVD 早期风险预测工具[53]。前瞻性研究进一步拓展了 AIP 的应用场景: 其与妊娠期糖尿病呈显著正相关($P < 0.001$), AIP 预测妊娠期糖尿病的曲线下面积(AUC)为 0.629。除此以外, DR 患者的 AIP 水平显著高于无 DR 患者(-0.009 ± 0.226 vs. 0.186 ± 0.261 , $P < 0.001$), AIP 预测 DR 的 AUC 达 0.697 (95% CI: 0.652~0.741)[54]。通过量化代谢紊乱的核心失衡, AIP 成为评估糖尿病患者代谢负荷与靶器官损伤风险的便捷工具。

3.4.3. AIP 与非酒精性脂肪肝

非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)是代谢综合征的核心组分, 其病理基础与脂质代谢紊乱相关, AIP 作为脂质代谢的综合指标, 与非酒精性脂肪肝的发生及进展密切相关。一项纳入 8 项观察性研究的 Meta 分析显示, AIP 预测 NAFLD 的总体 AUC 达 0.764, 且在男女之间存在显著差异(男性 0.761、女性 0.733)。另一项研究结果显示, AIP 在校正后是代谢功能障碍相关脂肪变性肝病的独立危险因素(OR = 5.2, 95% CI: 3.9~7.0), 其 AUC 达 0.733 (95% CI: 0.718~0.747)[55][56]。上述研究提示, AIP 可作为 NAFLD 筛查的便捷临床指标, 或可成为连接肝脏代谢异常与心血管风险的桥梁指标, 为跨系统风险评估提供参考。

4. AIP 的临床干预与未来展望

血脂异常是导致动脉粥样硬化及冠心病发生发展的关键危险因, AIP 作为简便易测、成本低廉的新

型血脂代谢综合指标, 在冠心病风险评估中具有显著优势: 其不仅能精准量化致动脉粥样硬化性血脂异常, 更可深刻地反映内皮功能障碍、炎症反应及氧化应激等核心病理生理过程。截至目前, 鲜有以 AIP 为主要终点评估生活方式或药物干预效果的大型随机对照试验, 但鉴于其临床实用性, AIP 未来有望作为常规血脂检查的附加指标, 应用于普通人群体检或具有高危心血管疾病危险因素患者的早期识别。AIP 领域的研究方兴未艾, 未来需在以下几个方面重点突破: 1) 构建多模态智能预测模型: 将 AIP 与冠状动脉 CT 血管成像(CCTA)衍生的影像学标志物(如 CACS、斑块特征)相结合, 利用人工智能和机器学习算法构建更精准的个体化风险预测模型。2) 开展腔内影像纵向研究: 利用血管内超声(IVUS)或光学相干断层成像(OCT)等先进腔内影像技术, 探究 AIP 动态变化与冠状动脉易损斑块特征(如薄纤维帽、大坏死核心)的关联性, 明确其在斑块进展监测中的价值。3) 深化因果关系与机制研究: 需开展大规模的孟德尔随机化研究验证 AIP 与冠心病间的因果关系, 结合动物模型和人体样本开展转化医学研究, 阐明 AIP 调控内皮功能、炎症和氧化应激的具体分子通路。4) 推进干预性临床试验: 设计以降低 AIP 为主要目标的 RCT, 评估饮食、运动干预及新型调脂药物对 AIP 的影响, 验证 AIP 作为治疗靶点改善冠心病患者临床结局的可行性。5) 优化联合预测体系: 联合其他具有预测价值的炎症因子构建多指标协同预测模型, 提高预测效能。

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