



doi:10.7659/j.issn.1005-6947.250598
http://dx.doi.org/10.7659/j.issn.1005-6947.250598
China Journal of General Surgery, 2026, 35(2):343-349.

· 临床研究 ·

常规血/尿生化指标与胰腺癌风险因果关联的孟德尔随机化分析

贺逸嘉¹, 刘雍容², 张欣³, 吴可柯⁴

(中南大学湘雅三医院 1. 肝胆外科 2. 手术中心 4. 麻醉科, 湖南长沙 410013; 3. 湖南省湘潭市第二人民医院 消化内科, 湖南湘潭 411100)

摘要

背景与目的: 胰腺癌(PC)早期诊断困难, 现有标志物(如CA19-9)难以满足人群筛查需求。常规血/尿生化指标具备可及性强、可重复检测等优势, 但其与PC风险的因果关系尚不明确。本研究基于两样本孟德尔随机化(MR)方法, 系统评估35项常规生化指标与PC风险的潜在因果关联。

方法: 暴露数据来源于英国生物样本库(UK Biobank)相关GWAS汇总数据, 结局数据来自FinnGen R12数据库。以逆方差加权法(IVW)为主要分析方法, 并结合MR-Egger、加权中位数及加权模式方法进行验证, 同时开展异质性、多效性及稳健性分析。

结果: MR分析显示, 肾功能相关指标与PC风险存在稳定因果关联: 遗传预测的血肌酐每升高1个标准差, PC风险增加18% ($OR=1.18$, $95\% CI=1.03\sim 1.36$, $P=0.019$); 估算肾小球滤过率(eGFR)每升高1个标准差, PC风险降低17% ($OR=0.83$, $95\% CI=0.72\sim 0.97$, $P=0.016$)。多种敏感性分析结果一致, 未发现显著异质性或水平多效性。

结论: 本研究提供了肾功能相关指标与PC风险之间的遗传学因果证据, 提示“肾功能轴”可能参与PC发生发展。血肌酐与eGFR有望作为PC风险分层及早期识别的潜在宿主标志物, 仍需进一步机制研究与前瞻性验证。

关键词

胰腺肿瘤; 生物标记; 肌酐; 肾小球滤过率; 孟德尔随机化分析
中图分类号: R735.9

Routine blood and urine biochemical biomarkers in relation to pancreatic cancer risk: a Mendelian randomization analysis

HE Yijia¹, LIU Yongrong², ZHANG Xin³, WU Keke⁴

(1. Department of Hepatobiliary Surgery 2. Surgical Center 4. Department of Anesthesiology, the Third Xiangya Hospital, Central South University, Changsha 410013, China; 3. Department of Gastroenterology, the Second People's Hospital of Xiangtan, Xiangtan, Hunan 411100, China)

Abstract

Background and Aims: Early detection of pancreatic cancer (PC) remains challenging, and conventional biomarkers such as CA19-9 are inadequate for population screening. Routine blood and urine biochemical markers are widely accessible and reflect systemic physiological status; however, their

收稿日期: 2025-10-29; 修订日期: 2026-02-18。

作者简介: 贺逸嘉, 中南大学湘雅三医院本科生, 主要从事胰腺癌基础方面的研究。

通信作者: 吴可柯, Email: 703297196@qq.com

causal relationships with PC risk remain unclear. Therefore, this study aimed to systematically evaluate the potential causal associations between 35 routine biochemical biomarkers and pancreatic cancer risk using a two-sample Mendelian randomization (MR) framework.

Methods: A two-sample MR study was conducted using genome-wide association study (GWAS) summary data from the UK Biobank for 35 biochemical traits. Outcome data for PC were obtained from the FinnGen consortium (release R12). The inverse-variance weighted (IVW) method was used as the primary analysis, complemented by MR-Egger, weighted median, and weighted mode approaches. Sensitivity analyses were performed to assess robustness.

Results: Two kidney function-related traits showed consistent causal associations with PC risk. Genetically predicted higher serum creatinine levels were associated with an 18% increased risk of PC per 1-standard deviation increment ($OR=1.18$, 95% $CI=1.03-1.36$, $P=0.019$), whereas higher estimated glomerular filtration rate (eGFR) was associated with a 17% reduced risk ($OR=0.83$, 95% $CI=0.72-0.97$, $P=0.016$). Sensitivity analyses supported the robustness of these findings, with no evidence of substantial heterogeneity or horizontal pleiotropy.

Conclusions: This MR study provides genetic evidence supporting a potential causal role of kidney function-related pathways in pancreatic cancer. Serum creatinine and eGFR may serve as promising host-related biomarkers for risk stratification and early detection, warranting further mechanistic and prospective validation.

Key words

Pancreatic Neoplasms; Biomarkers; Creatinine; Glomerular Filtration Rate; Mendelian Randomization Analysis

CLC number: R735.9

胰腺癌 (pancreatic cancer, PC) 是全球致死率最高的消化道恶性肿瘤之一, 发病与死亡曲线近年来在多国呈上升趋势, 其 5 年相对生存率仅为 13%^[1-2]。由于其起病隐匿, 且缺乏有效的普筛策略, 美国预防服务工作组 (USPSTF) 目前仍不推荐对无症状一般人群进行 PC 筛查^[3]。现有血清肿瘤标志物以 CA19-9 最为常用, 但其在早期诊断中的敏感度与特异度不足, 难以胜任人群筛查或单独用于早期发现^[4-5]。因此, 如何从可规模化、可重复测量的体液指标中挖掘与 PC 发生相关的可干预线索, 依旧是早诊早治研究的关键方向^[6-7]。

与传统肿瘤标志物不同, 常规血液/尿液生化指标可同时反映炎症、糖脂代谢、肝胆胰功能、肾功能与内分泌等多条病理生理轴线, 为 PC 风险刻画提供系统健康状态的补充视角。近年来的前瞻性研究逐步揭示了若干与 PC 风险及预后密切相关的生物标志物, 代谢相关指标如 γ -谷氨酰转氨酶^[8]、糖化血红蛋白^[9]以及低水平的高密度脂蛋白胆固醇^[10]均被证实与 PC 风险相关, 其中新发糖尿病或 HbA1c 升高更是短期风险的重要提示^[11]; 此

外, 肾功能不全 [表现为估算肾小球滤过率 (estimated glomerular filtration rate, eGFR) 降低]^[12]与高尿酸血症^[13]也被报道与肝胆胰肿瘤的风险存在剂量-反应关系。

然而, 这些观察性研究提供的关联证据常存在不一致性。以胰岛素样生长因子 (insulin-like growth factor, IGF) 通路为例, Qian 等^[14]和 Knuppel 等^[15]对其与 PC 风险的关联结论存在差异, 且有研究提示同一通路内不同组分部位的风险信号都可能存在差异^[16]。无独有偶, 维生素 D 与 PC 风险的观察性研究亦长期面临相互矛盾的结果^[17-18]。上述不一致性很大程度上源于观察性研究难以规避的固有局限, 特别是无法完全控制的残余混杂, 以及由疾病亚临床阶段所导致的反向因果关系 (如 PC 可提前数年引发代谢表型改变)^[19]。

为克服上述局限并强化因果推断, 本研究采用孟德尔随机化 (Mendelian randomization, MR) 方法, 利用与暴露强相关的胚系遗传变异作为工具变量, 能够尽量规避环境混杂与反向因果的影响, 从而为观察性线索提供更接近因果层面的证

据^[20-22]。近年来,MR已广泛用于肿瘤流行病学以系统筛查可干预危险因素与潜在点^[23]。基于此,研究整合大规模GWAS汇总统计数据,对35项常规体液生化指标与PC风险之间的潜在因果关联进行系统评估,以逆方差加权法(inverse-variance weighted, IVW)-MR^[24]为主的分析方法,并结合多种稳健性与敏感性分析验证结果可靠性,旨在为PC的风险分层线索与机制研究提供更具可信度的遗传流行病学证据。

1 资料与方法

1.1 数据来源

本研究涉及的35项血液与尿液生化指标的遗传工具变量,源自基于英国生物样本库(UK Biobank)参与者的大规模全基因组关联研究(GWAS)汇总数据。该数据集共纳入363 228名欧洲个体,系统解析了涵盖血脂、肝肾功能、糖代谢、炎症等多类临床常规检测指标的遗传基础。本研究使用了从GWAS Catalog获取的对应汇总统计数据(GCST90019492-GCST90019526)。

PC的GWAS汇总数据来自芬兰FinnGen联盟的第12轮数据发布,编号为finngen_R12_C3_PANCREAS_EXALLC,共纳入381 888名欧洲个体。数据公开获取自FinnGen研究平台。

1.2 工具变量筛选

本研究在MR的三项基本前提(工具与暴露显著相关、与潜在混杂独立、仅经暴露作用于结局)下构建工具变量。具体做法为:首先从各暴露性状的GWAS汇总统计中选取达到全基因组学显著性的变异位点($P < 5 \times 10^{-8}$)作为候选集合;随后基于欧洲人群连锁不平衡参考实施clumping,设置 $r^2 < 0.001$ 、窗口10 000 kb,以确保候选位点之间相互独立。对进入集合的每个位点计算 F 统计量并剔除 $F \leq 10$ 的弱工具^[25],以降低弱工具偏倚的风险;在分析前,对暴露与结局数据的等位基因进行统一与效应方向校准,同时删除中间等位基因频率的回文位点以避免链向歧义。对在结局数据中缺失的候选位点,若能在相同基因座找到与之高度连锁的代理变异($r^2 > 0.80$)则以代理替代,否则予以丢弃。经上述步骤得到的、相互独立且强度充足的SNP集合作为工具进入分析。

1.3 敏感度分析

为检验主结果的稳健性,在以IVW^[24]作为主测量方法的同时,平行实施MR-Egger^[26]、加权中位数法(weighted median)^[27]及加权模式(weighted mode)^[28]替代估计;当不同方法在效应方向与量级上保持一致且IVW显著时,认为证据更为可靠。异质性通过Cochran's Q统计量^[29]评估;水平多效性则以MR-Egger截距项检验^[26]。为进一步识别并处置异常工具位点,使用MR-PRESSO^[30]进行全局检验与离群定位,同时调用RadialMR^[31]修正SNP离群值,并在清除后再次复算。因果方向性通过Steiger检验^[32]验证,对方向不一致的工具予以剔除。为最大程度降低残余混杂,借助FastTraitR系统检索GWAS Catalog,将与潜在混杂因素达到全基因组显著关联的候选位点标记并按预设规则排除,同时实施逐一剔除(leave-one-out)分析以判断是否由单一变异驱动。全部统计过程在R(4.5.1)环境完成。

2 结果

2.1 常规血液与尿液生化标志物与PC风险的因果关联

对35项常规血/尿生化指标进行了双样本MR分析,并在四种估计方法下汇总结果(图1A)。基于IVW识别出两项与PC风险存在稳定因果关联的指标(图1B):血肌酐与eGFR。其中,遗传预测的血肌酐每升高1个标准差,PC风险增加18%($OR=1.18$, $95\% CI=1.03\sim 1.36$, $P=0.019$);而eGFR与风险呈负相关,每升高1个标准差,PC风险降低17%($OR=0.83$, $95\% CI=0.72\sim 0.97$, $P=0.016$)。其余33项指标未发现显著因果关联。

2.2 敏感度分析验证

为评估主要因果关联的稳健性,本研究进行了全面的敏感度分析。结果显示,多种MR估计方法(MR-Egger、加权中位数、加权模式)得出的效应估计值与IVW主分析方向一致。未在结果中检测到显著的异质性(Cochran's Q检验 $P > 0.05$)或水平多效性(MR-Egger截距项检验 $P > 0.05$)(表1)。此外,漏斗图(图2A-B)与散点图(图2C-D)均显示效应分布对称,且不同方法的回归线高度重合。通过MR-PRESSO、Radial MR及留一法分析,进一

步证实了结果不受离群 SNP 或单个强效工具变量的驱动。综上，确认肌酐与 eGFR 同 PC 风险的因果关联具备良好的稳健性。

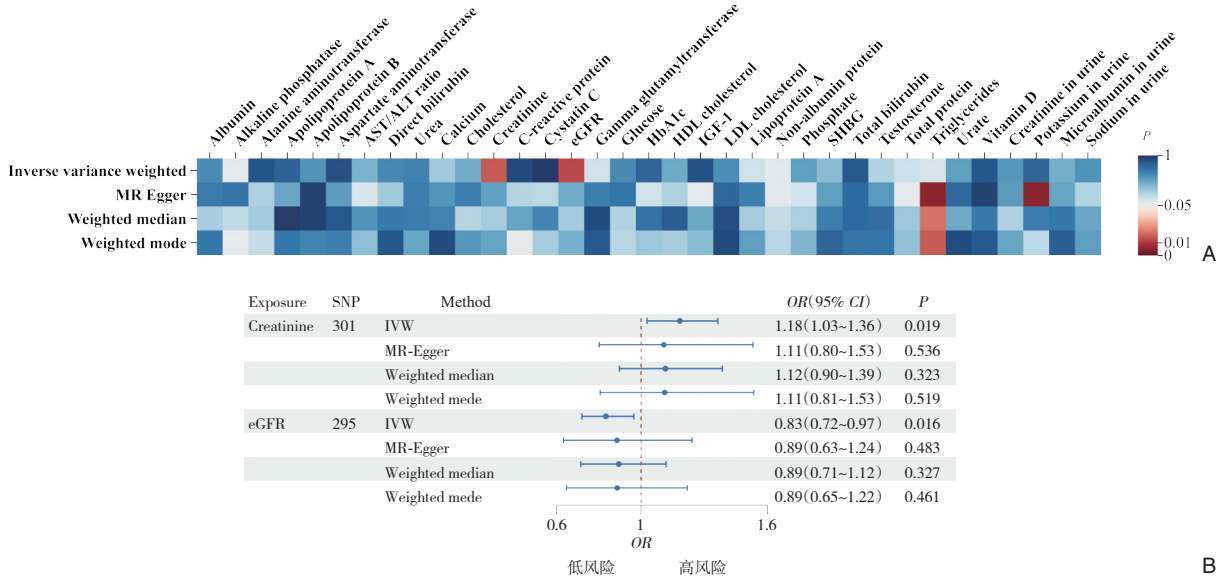


图 1 常规血/尿生化标志物与 PC 的 MR 分析结果 A: 35 项生物标志物在四种 MR 估计方法 (IVW、MR-Egger、加权中位数、加权模式) 下的结果热图; B: 肌酐与 eGFR 与 PC 风险因果关联的森林图 (结果以 IVW 为准, 并标了工具变量数量与统计学显著性)

Figure 1 Mendelian randomization results of routine blood and urine biochemical biomarkers and pancreatic cancer risk A: Heatmap of MR estimates for 35 biomarkers across four methods (IVW, MR-Egger, weighted median, weighted mode); B: Forest plot showing causal associations of creatinine and eGFR with pancreatic cancer risk (based on IVW estimates, with number of instrumental variables and statistical significance indicated)

表 1 敏感性分析结果

Table 1 Results of sensitivity analysis

暴露	方法	异质性检验			水平多效性检验		
		Q	自由度	P	截距	S.E.	P
肌酐	MR-Egger	248.739	265	0.756	0.002	0.004	0.654
	IVW	249.952	266	0.752			
eGFR	MR-Egger	265.119	233	0.073	-0.002	0.004	0.693
	IVW	266.523	234	0.071			

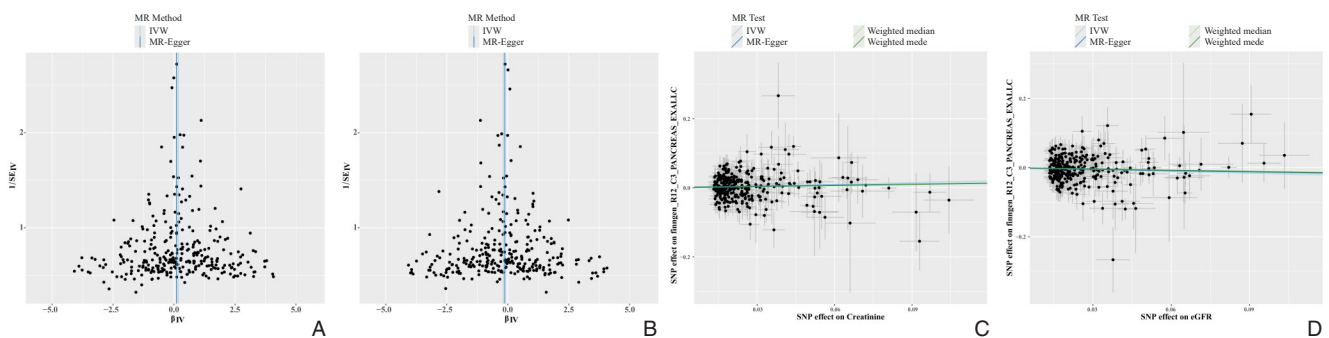


图 2 肌酐与估算 eGFR 因果关联的稳健性验证 A-B: 肌酐与 eGFR 的漏斗图均呈现大致对称分布, 提示无明显水平多效性; C-D: 肌酐与 eGFR 的散点图显示, 不同 MR 方法的回归线斜率相近且均指向同一方向, 印证了主分析结果的稳健性

Figure 2 Robustness assessment of causal associations for creatinine and eGFR A-B: Funnel plots showing symmetric distribution, suggesting no substantial horizontal pleiotropy; C-D: Scatter plots demonstrating consistent slopes across different MR methods, supporting robustness of the main findings

3 讨论

本研究的核心发现是首次从遗传学层面支持“肾功能轴-PC风险”的潜在因果联系。尽管近年来诊疗不断进步,PC的发病与死亡仍居高不下,早期识别依然是关键瓶颈;现有肿瘤标志物(如CA19-9)在普筛与早检中的性能有限。基于此,本研究以两样本MR系统评估35项临床常规、可规模化检测的血液/尿液生化指标与PC风险的潜在因果关系。在多种分析方法一致性基础上,识别出两条稳定的遗传证据:遗传预测的肌酐水平升高与PC风险增加相关,而eGFR升高与风险降低相关。这两项指标从不同侧面共同指向“肾功能轴”的长期状态可能是影响PC发生的一个重要因素,是除代谢与炎症之外值得重视的一条通路。

本研究的发现与既往观察性流行病学证据相互印证。来自韩国的大型前瞻性队列研究^[12]显示,eGFR降低会增加PC的风险,这为上述因果关联提供了直接的人群证据。其次,UK Biobank的大样本研究进一步提示:当肾功能采用更敏感的Cystatin C估算(eGFR_{cys})时,即使在轻度肾功能下降阶段也能更清晰地捕捉到总体癌症发生与癌症死亡风险上升的信号^[33]。此外,慢性肾脏病预后联盟(Chronic Kidney Disease Prognosis Consortium)基于超过百万人的个体参与者数据Meta分析^[34-35]提示,慢性肾脏病人群的总体肿瘤发生率更高。这些研究总体提示,肾功能受损相关表型(尤其是eGFR_{cys}、白蛋白尿等敏感指标)可能反映个体整体健康与代谢炎症状态的长期异常,从而为笔者在MR分析中观察到的肾功能相关信号提供了更有力的外部证据支持。

从生物学机制层面看,肾功能减退常伴慢性低度炎症、氧化应激、胰岛素抵抗与尿毒素负荷等全身稳态异常^[36-38],这些病理生理状态与PC相关的促炎微环境、纤维化、免疫重塑和代谢重编程存在交叉^[39]。系统性炎症与氧化应激不仅是慢性肾脏病进展的重要驱动,也可能通过促进DNA损伤、影响免疫监视与细胞因子网络等途径,提高肿瘤发生发展的易感性^[40],如Xie等^[36]发现,蓄积的尿毒素可通过激活AhR等信号通路,可参与纤维化、免疫反应与代谢调控,塑造出有利于肿瘤发生发展的微环境。因此,肌酐与eGFR作为肾功能与整体代谢状态的核心临床指标,其与PC风

险之间的因果关联具备合理的生物学基础。但要强调的是,eGFR与肌酐在测量学上高度相关(eGFR多由肌酐等参数推算),两者方向相反的信号更可能提示肾功能轴的不同观测维度而非完全独立的两条通路;这一点在解读时应保持谨慎。

在临床与转化启示方面,研究结果提示肾功能轴可能为PC风险分层与早期识别提供一个值得进一步验证的新维度。在传统高危因素(如糖代谢异常、慢性炎症)的基础上^[41],未来可探索将肌酐、eGFR、Cystatin C等肾功能指标纳入风险评估模型,并前瞻性验证其增量预测价值。与此同时,已有研究提示肌酐/胱抑素C比值等指标与PC患者术后预后及肌少症相关,提示肾功能/肌肉代谢相关表型可能还与肿瘤进程与宿主状态有关^[42];这也为肾-代谢-肿瘤交叉轴提供了补充的临床线索。鉴于CA19-9在早期检测中的局限性,若在未来构建以肾功能轴、代谢/炎症轴和肿瘤特异性标志物为核心的多标志物组合策略,有望在高危队列中提升早期识别效能。从机制研究的角度,未来或应优先围绕关键通路节点(如肌酸合成的限速酶GATM、肾小管分泌转运体等)^[43]展开深入功能研究,以明确最有效的干预靶点。

同时,本研究也存在若干局限性。首先,暴露与结局数据主要源于欧洲人群,结论的外推性需在其他祖源人群中验证^[20]。其次,eGFR与肌酐在生理与测量学上高度相关,二者共同反映肾功能这一潜在性状,不宜过度解读为完全独立的证据,而更像是肾功能潜在性状的两个方面。第三,MR估计反映的是生命早期遗传倾向的终身平均效应,不能等同于短期临床干预的效果^[20]。此外,本研究的风险分层意义仍需前瞻性 with 真实世界研究进一步确认,尤其应评估肾功能指标在不同高危亚群中的表现及其与现有指标体系的互补价值。

总之,在多指标系统筛查的基础上,本研究提供了肌酐水平升高导致PC风险增加,eGFR升高导致PC风险下降的因果证据,指向肾功能相关通路在PC发生中的潜在作用。这一发现不仅为理解PC的病因提供了新的视角,也为未来构建更精准的风险预测模型与机制驱动的干预研究奠定了科学基础。

作者贡献声明:贺逸嘉参与课题设计、文献调研及论文初稿撰写;刘雍容负责数据收集与孟德尔随机

化分析工作；张欣参与结果分析、论文修改与图表整理；吴可柯统筹课题设计与研究实施，指导数据分析，定稿论文并负责学术沟通。

利益冲突：所有作者均声明不存在利益冲突。

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(本文编辑 宋涛)

本文引用格式:贺逸嘉,刘雍容,张欣,等.常规血/尿生化指标与胰腺癌风险因果关联的孟德尔随机化分析[J].中国普通外科杂志,2026,35(2):343–349. doi:10.7659/j.issn.1005-6947.250598

Cite this article as: He YJ, Liu YR, Zhang X, et al. Routine blood and urine biochemical biomarkers in relation to pancreatic cancer risk: a Mendelian randomization analysis[J]. *Chin J Gen Surg*, 2026, 35(2): 343–349. doi:10.7659/j.issn.1005-6947.250598