Advances in Clinical Medicine 临床医学进展, 2025, 15(2), 1996-2004
Published Online February 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.152562

Hans汉斯

代谢相关脂肪性肝病与结直肠肿瘤相关性的研究进展

包　杨，晁冠群*

浙江大学医学院附属邵逸夫医院全科医学科，浙江　杭州

收稿日期：2025年1月28日；录用日期：2025年2月21日；发布日期：2025年2月28日

摘　要

代谢相关脂肪性肝病(metabolic-associated fatty liver disease, MAFLD)原名非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)，被认为是代谢综合征的肝脏表现，已成为发达国家和发展中国家最常见的慢性肝病，预计患病率在未来几年仍会有所上升，是终末期肝脏疾病、肝癌和肝移植的主要原因，影响着全球人口的1/3。结直肠癌(colorectal cancer, CRC)通过腺瘤－癌序列发展，是全球发病率第三、死亡率第二的恶性肿瘤。研究表明，MAFLD与总体癌症发病率增加相关，肿瘤是MAFLD患者第二大常见死因。既往已有多项研究发现NAFLD与结直肠肿瘤(colorectal neoplasia, CRN)存在相关性，但鉴于MAFLD与NAFLD诊断标准存在差异，MAFLD与CRN的相关性应得到进一步探索，本文旨在对MAFLD与CRN相关性进行综述，进而为CRN的预防与治疗提供新思路。

关键词

代谢相关脂肪性肝病，非酒精性脂肪肝，结直肠癌，结直肠腺瘤

Research Progress of the Relationship between Metabolic-Associated Fatty Liver Disease and Colorectal Neoplasia

Yang Bao, Guanqun Chao*

Department of General Practice, Sir Run Run Shaw Hospital, Affiliated with the Zhejiang University School of Medicine, Hangzhou Zhejiang

Received: Jan. 28th, 2025; accepted: Feb. 21st, 2025; published: Feb. 28th, 2025

Abstract

Metabolic-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver

*通讯作者。

文章引用: 包杨, 晁冠群. 代谢相关脂肪性肝病与结直肠肿瘤相关性的研究进展[J]. 临床医学进展, 2025, 15(2): 1996-2004. DOI: 10.12677/acm.2025.152562

disease (NAFLD), is considered as the liver manifestation of metabolic syndrome. It has become the most common chronic liver disease in both developed and developing countries, with prevalence expected to increase in the coming years, and is the leading cause of end-stage liver disease, liver cancer, and liver transplantation, affecting one-third of the global population. Colorectal cancer (CRC) develops through the adenomato-cancer sequence, and is the third most common malignant tumor in the world with the second highest mortality rate. Studies have shown that MAFLD is associated with an increased incidence of cancer overall, and tumors are the second most common cause of death in people with MAFLD. Many studies have found a correlation between NAFLD and colorectal neoplasia (CRN). However, due to differences in diagnostic criteria between MAFLD and NAFLD, the correlation between MAFLD and CRN should be further explored. This article aims to review the correlation between MAFLD and CRN, so as to provide new ideas for the prevention and treatment of CRN.

Keywords

Metabolic-Associated Fatty Liver Disease, Non-Alcoholic Fatty Liver Disease, Colorectal Cancer, Colorectal Adenoma

1. 引言

非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)最初于 1986 年由 Shaffner 和 Thalerin 提出，后逐步明确其定义为超过 5%的肝细胞存在脂肪变性，与肥胖等代谢风险因素相关、且排除过量饮酒(男性 ≥30 g/天，女性 ≥20 g/天)或其他慢性肝病的一种肝脏疾病[1] [2]。随着 NAFLD 患病率的上升及对其发病机制的深入了解，NAFLD 诊断标准为临床诊疗带来的不便逐渐显现。为便于疾病诊断及管理，2020 年国际脂肪肝专家组建议将 NAFLD 更名 MAFLD (metabolic-associated fatty liver disease, MAFLD)，定义其诊断标准为存在肝脏脂肪变性，且满足以下三个标准之一，包括超重/肥胖、存在 2 型糖尿病及代谢失调[3] [4]。随后亚太肝脏协会也制定了适用于亚洲人群的 MAFLD 的诊断和治疗指南[5]。既往研究报道 NAFLD 全球患病率约 25% [6]，更名后有研究发现，全球约有超过 1/3 的人口受 MAFLD 影响[7]。MAFLD 包括一系列肝脏病理表现，从单纯的肝脏脂肪变性到伴有不同程度纤维化的脂肪性肝炎，后者可进一步进展为肝硬化，甚至肝功能衰竭、肝细胞癌[2] [8]。同时，MAFLD 在识别脂肪肝进展高风险人群、判断患者全因死亡率方面较 NAFLD 有更好的表现[9]-[11]。其不仅与肝脏相关并发症的发生风险增加有关，还与多种肝外疾病如心血管疾病、2 型糖尿病和一些肝外癌症尤其是胃肠癌恶性肿瘤的发生风险增加有关[11]-[14]。

根据最新发布的 2022 年全球癌症统计数据，作为全球发病率第三、死亡率第二的恶性肿瘤，结直肠癌(colorectal cancer, CRC)患病率仍在逐年增加[15]。现学界公认大多结直肠癌通过腺瘤－癌序列发展[16]，从高危腺瘤到 CRC 的年转化率预估为 2%~6%，早期发现并切除结直肠腺瘤(colorectal adenoma, CRA)可以显著降低结直肠癌死亡风险。结肠镜检查是结直肠肿瘤(colorectal neoplasia, CRN)筛查的主要手段，病理活检是诊断金标准，但由于其成本相对高昂且为侵入性检查，一定程度上影响患者依从性。

既往有研究发现，NAFLD 是 CRN 的独立危险因素[17] [18]。自重新命名以来，已有多位学者对 MAFLD 与 CRN 的相关性进行了初步探索，但尚无一致结论，具体机制也有待进一步研究[14] [19]-[27]。

本文意在对近期 MAFLD 与 CRN 的相关性及其机制研究作一综述。

2. MAFLD 与 CRN 的相关性

2.1. MAFLD 与 CRA 的相关性

国内外已有多名学者发现 MAFLD 与 CRA 存在相关性。韩国学者进行的一项纳入 184,792 名成年人的横断面研究结果显示，MAFLD 与 CRA 患病风险增加相关，且该相关性与性别、超重或肥胖、糖尿病、存在的代谢综合征组分数目及 CRC 家族史无关[19]。我国 Gong、Yan 等研究人员在一项纳入 4463 名健康体检者的研究中发现，MAFLD 患者的 CRA 风险是非 MAFLD 患者的 1.303 倍(95%CI: 1.076~1.578, p = 0.007)，年龄增加、男性、较高的 BMI 和吸烟与 CRA 风险增加相关，但仅在女性群体中，MAFLD 是晚期结直肠腺瘤的独立危险因素[22]。同样地，我国另一项纳入 1395 名受试者的横断面研究发现，MAFLD 是 CRA 的独立危险因素，且与无脂肪肝的患者相比，瘦型、伴肥胖、伴中心性肥胖、伴糖尿病这四种 MAFLD 亚型患者的 CRA 患病风险均显著增加。其中，伴糖尿病的 MAFLD 患者 CRA 风险是非脂肪肝患者的 7.3 倍(95%CI 4.2, 12.6, p < 0.01)，伴中心性肥胖的 MAFLD 患者 CRA 风险是无脂肪肝患者的 7.0 倍(95%CI 4.3~11.4, p < 0.01)。同时，伴中心性肥胖的 MAFLD 患者高危腺瘤风险增加[25]。一项纳入 124 名健康查体人群的多中心回顾性研究同样发现 MAFLD 增加 CRA 患病风险，但进一步亚组分析显示，在三种 MAFLD 亚型，即非肥胖型 MAFLD、肥胖型 MAFLD 和 2 型糖尿病型 MAFLD 中，仅非肥胖型 MAFLD 是 CRA 的独立危险因素，其 CRA 患病风险是非 MAFLD 的 3.351 倍(95% CI 1.589~7.262, p ≤ 0.001) [21]。

然而，有研究人员得出了截然相反的结论。来自韩国的一项纳入 3044 例受试者的横断面研究发现，在单因素分析中，MAFLD 增加了 CRA 的风险，但校正年龄、性别、吸烟、内脏脂肪面积等变量后，MAFLD 与 CRA 无显著相关性。按性别进行进一步亚组分析后显示，MAFLD 仅为女性 CRA 的独立危险因素，女性 MAFLD 患者 CRA 风险增加 1.55 倍(95% CI 1.13~1.96, p = 0.004)。同时，在依据 BMI、糖尿病进一步分亚组进行多因素分析时发现，CRA 的患病风险在各亚组中无明显差异[24]。此外，Zhai、Dong 等研究者进行的孟德尔随机化分析同样发现 MAFLD 与 CRN 不存在因果关系[27]。

2.2. MAFLD 与 CRC 的相关性

Chung、Goh Eun 等学者在一项纳入 970 万韩国人的队列研究中发现，MAFLD 患者的癌症发生率及癌症相关死亡率均增加，其中混合病因 MAFLD (即伴随肝脏疾病和/或大量饮酒的 MAFLD)高于单一病因 MAFLD，调整协变量、进行敏感性分析后相关性仍显著。具体而言，MAFLD 组 CRC 发病率及死亡率均高于非 MAFLD 组，混合病因 MAFLD 组 CRC 发病风险较非 MAFLD 组增加 1.33 倍(95% CI 1.29~1.36, p < 0.001)，死亡风险增加约 1.25 倍(95% CI 1.16~1.34, p < 0.001) [20]。此外，一项利用英国生物库数据进行的研究显示，MAFLD 与包括 CRC 在内的 24 种癌症具有显著相关性，在男性中，MAFLD 与 CRC 的相关性进一步增强[28]。同样地，韩国一项纳入 8,933,017 名参与者的队列研究发现，与非脂肪肝个体相比，MAFLD 个体 CRC 的患病风险增加 1.32 倍(95%CI 1.28~1.35)，且随着肝纤维化程度增加，CRC 风险进一步上升，此外，非超重 MAFLD 组 CRC 风险高于超重组[23]。Zeng Yunqing 等人进行的一项纳入 14 项研究、37,824 例 MAFLD 患者的 meta 分析显示，CRC 的患病率随着 MAFLD 的进展而增加(OR = 1.93; 95% CI = 1.42~2.62)，其中，重度 MAFLD 更易引起左侧结肠肿瘤[26]。

上述，多数研究认为 MAFLD 的存在增加了 CRN 的风险，然而根据是否存在糖尿病、肥胖或超重等代谢特征进行亚组分析后，上述代谢因素在其中的作用存在争议。部分研究未发现 MAFLD 与 CRN 的相关性，这可能与不同研究所纳入的受试人群的样本量不同、代谢相关性疾病以及 CRN 等患病率基线特征

不同有关。同时，关于两者相关性的探索多为横断面研究，无法判断其因果关系。此外，研究对象多为自发体检的无症状人群，研究获得的结论代表性有限。未来有待更多大型前瞻性队列研究进一步探究、证实 MAFLD 的存在是否与 CRN 风险增加有关。

3. MAFLD 严重程度与 CRN 的相关性

NAFLD/MAFLD 严重程度与 CRN 的相关性

既往研究发现，经活检证实为非酒精性脂肪性肝炎(Nonalcoholic Steatohepatitis, NASH)的研究参与者 CRA 患病风险高于单纯脂肪变性的 NAFLD [18] [29]。随着 FLI、FIB-4 等无创化参数的开发与推广，已有许多研究者证实了上述无创指标在 NAFLD 中的诊断效能，并利用其分析了 NAFLD 严重程度与 CRA 的相关性。Eun Young Ze 等人发现 NAFLD 患者 CRA 患病率随 FLI 四分位数上升而增加[30]。韩国一项纳入 26,540 例无症状成年人的研究利用 APRI、FIB-4 评分和 NFS 对 NAFLD 患者进行进一步分层时发现，严重肝病患者的 CRN 患病率高于轻度肝病患者[31]。Min Cheol Kim 等人同样利用 FIB-4 指数和 NFS 评估肝纤维化严重程度，分析发现存在肝晚期纤维化的 NAFLD 患者发生 CRA 的风险显著升高，然而，当使用 APRI 和 BARD 评分分层时，没有发现类似相关性[32]。

NAFLD 更名为 MAFLD 后，由于诊断标准的差异，学界重新评估了上述无创化指标在 MAFLD 中的诊断效能，并通过他们评估了 MAFLD 肝脏脂肪化活纤维化程度与 CRN 的相关性。

我国一项利用肝活检评估 MFALD 肝脏纤维化程度的研究发现，FIB-4 和 NFS 预测肝晚期纤维化的曲线下面积分别为 0.736、0.724，优于 APRI 和 BARD，即 FIB-4 和 NFS 在评估 MAFLD 患者肝纤维化中表现较好，但提出了诊断肝晚期纤维化的新阈值[33]。随后韩国一项利用磁共振评估 MAFLD 严重程度的横断面研究证实了这一结论[34]。此外，多项研究肯定了 FLI 在 MAFLD 诊断中的优异表现[35] [36]。近年来，中国香港地区研究人员利用机器学习和向后逐步回归法，构建出了 MAFLD 纤维化评分(MAFLD fibrosis score, MFS)。在该研究的训练队列和验证队列中，MFS 评估 MAFLD 患者肝纤维化的 ROC 曲线下面积分别为 0.848 和 0.823，表明其可用于识别 MAFLD 患者中的晚期纤维化(≥ F3)，且优于传统的非侵入性评分[37]。

我国张莉敏等学者通过研究得出，FIB-4 是 MAFLD 合并 CRA 的独立危险因素，利用 ROC 曲线进一步分析发现 FIB-4 诊断目标疾病的 AUC 为 0.868，灵敏度和特异度分别为 67.6%、90.9% [38]。Chang J 等研究者进行的一项横断面研究发现，用 NFS 和 FIB-4 评估肝纤维化程度时，CRA 风险在年龄 ＜50 岁的 MAFLD 受试者中随肝纤维化程度的增加而升高[19]。无独有偶，在韩国一项纳入 3441 名健康体检人群的研究中，以 FIB-4 评估的 MAFLD 肝晚期纤维化个体 CRA 患病风险较无肝晚期纤维化的 MAFLD 个体增加了 45% (95%CI 1.13~1.96) [24]。然而，我国一项以 FIB-4 指数 ≥1.3 为截止值评估 MAFLD 与 CRA 相关性的横断面研究却发现，MAFLD 肝纤维化与 CRA 无明显相关性，这可能是由于以 FIB-4 指数 ≥1.3 为标准纳入的肝纤维化组样本量较少所致[22]。

此外，也有研究人员对 MAFLD 与 CRC 的相关性进行了研究。Lee 等人利用 BARD 评分对 MAFLD 纤维化程度进行评估，分析其与 CRC 的相关性，发现存在肝晚期纤维化患者 CRC 风险升高[23]。Chung Goh Eun 等人同样利用 BARD 评分评估肝纤维化程度，发现伴有晚期纤维化的 MAFLD 受试者包括 CRC 在内的所有癌症的发病率及癌症相关死亡风险均高于不伴晚期纤维化的 MAFLD 受试者[20]。

以上，目前诊断 MAFLD 脂肪变性及纤维化的主流手段仍为超声检查，但越来越多非侵入性指标被开发利用，总结见表 1。更名后多数研究认为 FIB-4 及 NFS 在 MAFLD 纤维化评估中具有良好的表现，但或许需要寻找更恰当的诊断界值。此外，关于 MAFLD 严重程度与 CRN 的相关性讨论多限于针对健康体检人群的横断面研究，存在选择偏倚，缺乏大规模队列研究，且 MAFLD 严重程度评判的金标准为肝

脏活组织检查，但由于其有创性，在临床研究中难以广泛应用以验证非侵入性指标诊断的准确性，未来有待更多前瞻性研究进一步讨论分析二者的关系。

Table 1. Summary of non-invasive indicators for the assessment of steatosis and fibrosis in MAFLD
表 1. MAFLD 脂肪变性及纤维化评估的无创指标总结

Formula	Equation	Lower cutoff	Higher cutoff
FLI	$FLI = (e^{0.953 \times \log e (\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log e (GGT) + 0.053 \times WC - 15.745})/(1 + e^{0.953 \times \log e (\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log e (GGT) + 0.053 \times WC - 15.745}) \times 100$	< 30	≥ 60 [61]
FIB-4	[Age (yr) × AST (IU/L)]/[platelet count (10^9) × ALT (IU/L)$^{1/2}$]	< 1.3	≥ 2.67 [62]
APRI	[(AST/ULN)/platelet count (10^9)] × 100	< 0.5	≥ 1.5 [63]
NFS	−1.675 + 0.037 × age (yr) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT − 0.013 × platelet count (×10^9/L) − 0.66x × albumin (g/dL)	< −1.455	> 0.676 [64]
BARD	Scale 0~4; BMI ≥28 kg/m^2 = 1 point; AST/ALT ≥ 0.8 = 2 points; Diabetes = 1 point	≥ 2 [65]	
MFS	0.078 × 年龄(岁) − 0.007363 × 血小板计数(10^9/L) + 0.0146 × AST (U/L) + 0.007618 × GGT (U/L) + 6.673 × INR + 0.09833 × BMI (kg/m^2) + 1.425 × 2 型糖尿病(yes = 1, no = 0)	≤ 14 [37]	

4. MAFLD 与 CRN 相关性的机制研究

关于 MAFLD 与 CRN 相关性的机制研究，目前主要集中于胰岛素抵抗、脂联素水平下降、肠道菌群失调、炎症状态等。

4.1. 胰岛素抵抗(Insulin Resistance, IR)

作为 MAFLD 的重要致病因素，IR 可升高血糖并抑制脂肪酶介导的脂解，导致游离脂肪酸(FFA)过量产生并促进肝脏中的脂质再分布和蓄积、促进 MAFLD 的发生和进展[39]。此外，肝脏脂肪蓄积也可以诱导肝脏 IR，从而可能形成一个恶性循环[40]。与此同时，美国一项荟萃分析显示，在调整肥胖因素后，高胰岛素血症和 IR 与 CRA 风险增加显著相关，HOMA-IR 每增加 1 U，CRA 风险显著增加 20% [41]。作为胰岛素抵抗的标志物，胰岛素水平上升与正常结直肠粘膜细胞的凋亡减少、CRA 发生风险增加呈正相关，表明 IR 可能通过高胰岛素血症促进 CRA 的发生发展[42]。此外，有研究表明，IR 及高胰岛素血症可能通过上调胰岛素样生长因子-1 (IGF-1)合成、减少胰高血糖素样肽-1 (GLP-1)的分泌，从而促进 CRC 的起病及发展[43] [44]。

4.2. 脂联素水平下降

脂联素是一种胰岛素增敏剂，主要由脂肪细胞分泌[45]。既往研究发现，肝脏中脂联素及其信号通路参与了肝脏中葡萄糖和脂质代谢的调节，此外，其通过促进抗炎细胞因子(如 IL-10)的分泌、阻碍 NF-$\kappa\beta$ 的活化、抑制 TNF-α 和 IL-6 的释放，在 MAFLD 中发挥抗炎和抗纤维化的作用[46]。脂联素在 CRN 中也发挥重要作用。有研究发现脂联素可以抑制参与细胞增殖和存活的瘦素和 TNF-α 诱导的信号级联[47] [48]。同时，还有研究人员发现，其可能通过作用于正常结肠上皮及结肠癌组织中表达的脂联素受体 1、2，调节涉及 CRC 发生的信号传导途径[49]。而 MAFLD 患者体内脂联素水平下降，这可能与 MAFLD 患者 CRN 风险增加相关[50] [51]。

4.3. 肠道菌群失调

近期有研究人员发现，儿童 MAFLD 患者肠道菌群丰度显著低于非 MAFLD 患儿[52]。在针对成年人

开展的研究中，MAFLD 与非 MAFLD 患者肠道菌群组分也表现出明显差异，但具体改变的微生物种类及丰度差异仍存在争议[53]-[55]。研究发现，肠道微生物通过肠道－肝脏轴在 MAFLD 中发挥重要作用，可能是由于紊乱的肠道菌群通过破坏肠道上皮细胞之间的紧密连接从而影响肠道屏障的完整性，同时释放多种微生物代谢产物和内毒素，后者通过通透性增加的肠道屏障进入体循环，从而诱导肝脏及全身炎症反应，促成 MAFLD 的发生发展[56] [57]。同时，肠道生态失调被认为是 CRN 发生的早期事件，失调的肠道菌群可通过产生遗传毒素诱导基因突变、与结肠上皮细胞表面受体相互作用从而参与 β-连环蛋白等致癌相关信号通路、诱导炎症等途径导致 CRN 的发生[58]。

4.4. 炎症状态

全身炎症在 MAFLD 的发生发展中存在重要作用。我国一项研究发现，脂肪肝患者全身炎症相关指标高于非脂肪肝患者，而 MAFLD 组患者全身炎症状态较 NAFLD 组患者更为严重，这或许是前述 IR、脂联素水平下降、肠道菌群紊乱综合作用的结果，表明 MAFLD 或是一种慢性全身炎症性疾病[59]。同时，炎症与 CRC 亦密切相关，其可能机制为通过氧化应激致 DNA 损伤、增加肠道屏障通透性导致具有促癌特征的病原微生物入侵、触发起始肿瘤细胞的增殖与克隆、影响肿瘤相关信号传导通路以及通过表观遗传机制沉默抑癌基因等从而诱导 CRC 的发生[60]。

5. 讨论

CRA 是结直肠息肉中最常见的病理类型，也是 CRC 的癌前病变。早期筛查对 CRC 的预防与控制、减轻个人及全球的疾病及经济负担具有重要意义，但其筛查及诊断主要通过价格高昂且具有侵入性的结肠镜检查，给患者带来了一定的经济及心理压力。NAFLD 是我国最常见的慢性肝病，可进一步进展为肝硬化甚至肝癌，目前主要诊断主要依靠价格相对低廉且无创的超声检查。NAFLD 与 CRN 共享多种危险因素，既往多项研究发现 NAFLD 患者 CRN 风险增加。同时，若相关性确切，NAFLD 较高的患病率及简便的检出手段使得将其纳入行 CRN 筛查的判断标准存在可行性。

2020 年 NAFLD 更名为 MAFLD 后，疾病由排除性诊断转变为肯定性诊断，不受饮酒量的限制，更注重于患者的代谢功能紊乱特征，能够更全面地反映代谢功能障碍在脂肪性肝病与结直肠肿瘤关系中的作用，有利于探索两者相关性中的潜在机制。目前学界已有多位学者对 MAFLD 与 CRN 的相关性进行了探索，其中多数研究表明 MAFLD 是 CRN 的危险因素，但也有部分研究得出了完全相反的结论，可能与研究对象基线特征差异有关。同时，MAFLD 与 CRN 相关性的机制有待进一步探索，MAFLD 严重程度与 CRN 的关系也尚不明确。此外，目前相关领域的探索多属于横断面研究，缺乏证据级别更高的前瞻性研究成果。

总之，MAFLD 及其与 CRN 的相关性应得到临床医生的关注与重视，以便在遏制 MAFLD 进一步进展的同时，做到 CRN 的早发现、早诊断、早治疗，最终降低两种疾病给个人和国家带来的负担。

参考文献

[1] Beygi, M., Ahi, S., Zolghadri, S. and Stanek, A. (2024) Management of Metabolic-Associated Fatty Liver Disease/Metabolic Dysfunction-Associated Steatotic Liver Disease: From Medication Therapy to Nutritional Interventions. *Nutrients*, **16**, Article 2220. https://doi.org/10.3390/nu16142220

[2] European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity. (2016) EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease. *Journal of Hepatology*, **64**, 1388-1402.

[3] Eslam, M., Newsome, P.N., Sarin, S.K., Anstee, Q.M., Targher, G., Romero-Gomez, M., *et al*. (2020) A New Definition for Metabolic Dysfunction-Associated Fatty Liver Disease: An International Expert Consensus Statement. *Journal of Hepatology*, **73**, 202-209. https://doi.org/10.1016/j.jhep.2020.03.039

[4] Eslam, M., Sanyal, A.J., George, J., Sanyal, A., Neuschwander-Tetri, B., Tiribelli, C., *et al*. (2020) MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*, **158**, 1999-2014.e1. https://doi.org/10.1053/j.gastro.2019.11.312

[5] Eslam, M., Sarin, S.K., Wong, V.W., Fan, J., Kawaguchi, T., Ahn, S.H., *et al*. (2020) The Asian Pacific Association for the Study of the Liver Clinical Practice Guidelines for the Diagnosis and Management of Metabolic Associated Fatty Liver Disease. *Hepatology International*, **14**, 889-919. https://doi.org/10.1007/s12072-020-10094-2

[6] Younossi, Z.M., Koenig, A.B., Abdelatif, D., Fazel, Y., Henry, L. and Wymer, M. (2016) Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes. *Hepatology*, **64**, 73-84. https://doi.org/10.1002/hep.28431

[7] Chan, K.E., Koh, T.J.L., Tang, A.S.P., Quek, J., Yong, J.N., Tay, P., *et al*. (2022) Global Prevalence and Clinical Characteristics of Metabolic-Associated Fatty Liver Disease: A Meta-Analysis and Systematic Review of 10 739 607 Individuals. *The Journal of Clinical Endocrinology & Metabolism*, **107**, 2691-2700. https://doi.org/10.1210/clinem/dgac321

[8] Subramanian, P., Hampe, J., Tacke, F. and Chavakis, T. (2022) Fibrogenic Pathways in Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD). *International Journal of Molecular Sciences*, **23**, Article 6996. https://doi.org/10.3390/ijms23136996

[9] Kang, S.H., Cho, Y., Jeong, S.W., Kim, S.U. and Lee, J. (2021) From Nonalcoholic Fatty Liver Disease to Metabolic-Associated Fatty Liver Disease: Big Wave or Ripple? *Clinical and Molecular Hepatology*, **27**, 257-269. https://doi.org/10.3350/cmh.2021.0067

[10] Lin, S., Huang, J., Wang, M., Kumar, R., Liu, Y., Liu, S., *et al*. (2020) Comparison of MAFLD and NAFLD Diagnostic Criteria in Real World. *Liver International*, **40**, 2082-2089. https://doi.org/10.1111/liv.14548

[11] Kim, K., Hong, S., Ahn, H. and Park, C. (2023) Metabolic Dysfunction-Associated Fatty Liver Disease and Mortality: A Population-Based Cohort Study. *Diabetes & Metabolism Journal*, **47**, 220-231. https://doi.org/10.4093/dmj.2021.0327

[12] Zhao, J., Liu, L., Cao, Y., Gao, X., Targher, G., Byrne, C.D., *et al*. (2024) MAFLD as Part of Systemic Metabolic Dysregulation. *Hepatology International*, **18**, 834-847. https://doi.org/10.1007/s12072-024-10660-y

[13] Zhou, X., Cai, J., Targher, G., Byrne, C.D., Shapiro, M.D., Sung, K., *et al*. (2022) Metabolic Dysfunction-Associated Fatty Liver Disease and Implications for Cardiovascular Risk and Disease Prevention. *Cardiovascular Diabetology*, **21**, Article No. 270. https://doi.org/10.1186/s12933-022-01697-0

[14] Kaya, E. and Yilmaz, Y. (2021) Metabolic-Associated Fatty Liver Disease (MAFLD): A Multi-Systemic Disease beyond the Liver. *Journal of Clinical and Translational Hepatology*, **10**, 329-338. https://doi.org/10.14218/jcth.2021.00178

[15] Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I., *et al*. (2024) Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **74**, 229-263. https://doi.org/10.3322/caac.21834

[16] Hill, M.J., Morson, B.C. and Bussey, H.J.R. (1978) ÆTIOLOGY of Adenoma—Carcinoma Sequence in Large Bowel. *The Lancet*, **311**, 245-247. https://doi.org/10.1016/s0140-6736(78)90487-7

[17] Stadlmayr, A., Aigner, E., Steger, B., Scharinger, L., Lederer, D., Mayr, A., *et al*. (2011) Nonalcoholic Fatty Liver Disease: An Independent Risk Factor for Colorectal Neoplasia. *Journal of Internal Medicine*, **270**, 41-49. https://doi.org/10.1111/j.1365-2796.2011.02377.x

[18] Cho, Y., Lim, S., Joo, S.K., Jeong, D., Kim, J.H., Bae, J.M., *et al*. (2019) Nonalcoholic Steatohepatitis Is Associated with a Higher Risk of Advanced Colorectal Neoplasm. *Liver International*, **39**, 1722-1731. https://doi.org/10.1111/liv.14163

[19] Chang, J., Chang, Y., Cho, Y., Jung, H., Park, D., Park, S., *et al*. (2023) Metabolic-Associated Fatty Liver Disease Is Associated with Colorectal Adenomas in Young and Older Korean Adults. *Liver International*, **43**, 2548-2559. https://doi.org/10.1111/liv.15738

[20] Chung, G.E., Yu, S.J., Yoo, J., Cho, Y., Lee, K., Shin, D.W., *et al*. (2023) Differential Risk of 23 Site-Specific Incident Cancers and Cancer-Related Mortality among Patients with Metabolic Dysfunction-Associated Fatty Liver Disease: A Population-Based Cohort Study with 9.7 Million Korean Subjects. *Cancer Communications*, **43**, 863-876. https://doi.org/10.1002/cac2.12454

[21] Fukunaga, S., Nakano, D., Kawaguchi, T., Eslam, M., Ouchi, A., Nagata, T., *et al*. (2021) Non-Obese MAFLD Is Associated with Colorectal Adenoma in Health Check Examinees: A Multicenter Retrospective Study. *International Journal of Molecular Sciences*, **22**, Article 5462. https://doi.org/10.3390/ijms22115462

[22] Gong, Y., Kang, J., Wang, X., Zheng, Y., Sui, Y. and Lu, W. (2023) Increased Detection Rates of Advanced Colorectal Adenoma in Women with Metabolic Dysfunction-Associated Fatty Liver Disease. *Heliyon*, **9**, e22391. https://doi.org/10.1016/j.heliyon.2023.e22391

[23] Lee, H., Lee, H.W., Kim, S.U. and Chang Kim, H. (2022) Metabolic Dysfunction-Associated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study. *Clinical and Translational Gastroenterology*, **13**, e00435. https://doi.org/10.14309/ctg.0000000000000435

[24] Seo, J., Bae, J., Kwak, M., Yang, J., Chung, S., Yim, J., *et al*. (2021) The Risk of Colorectal Adenoma in Nonalcoholic or Metabolic-Associated Fatty Liver Disease. *Biomedicines*, **9**, Article 1401. https://doi.org/10.3390/biomedicines9101401

[25] Xiong, J., Wu, Y., Chen, D., Zhang, Z., Liu, Y., Luo, J., *et al*. (2024) MAFLD with Central Obesity Is Associated with Increased Risk of Colorectal Adenoma and High-Risk Adenoma. *BMC Gastroenterology*, **24**, Article No. 138. https://doi.org/10.1186/s12876-024-03220-z

[26] Zeng, Y., Cao, R., Tao, Z. and Gao, Y. (2022) Association between the Severity of Metabolic Dysfunction-Associated Fatty Liver Disease and the Risk of Colorectal Neoplasm: A Systematic Review and Meta-Analysis. *Lipids in Health and Disease*, **21**, Article No. 52. https://doi.org/10.1186/s12944-022-01659-1

[27] Zhai, D., Xu, S., Liu, H. and Tong, X. (2024) Nonalcoholic or Metabolic-Associated Fatty Liver Disease and Colorectal Polyps: Evidence from Meta-Analysis and Two-Sample Mendelian Randomization. *Frontiers in Genetics*, **15**, Article 1422827. https://doi.org/10.3389/fgene.2024.1422827

[28] Liu, Z., Lin, C., Suo, C., Zhao, R., Jin, L., Zhang, T., *et al*. (2022) Metabolic Dysfunction-Associated Fatty Liver Disease and the Risk of 24 Specific Cancers. *Metabolism*, **127**, Article 154955. https://doi.org/10.1016/j.metabol.2021.154955

[29] Wong, V.W.-., Wong, G.L, Tsang, S.W., Fan, T., Chu, W.C., Woo, J., *et al*. (2011) High Prevalence of Colorectal Neoplasm in Patients with Non-Alcoholic Steatohepatitis. *Gut*, **60**, 829-836. https://doi.org/10.1136/gut.2011.237974

[30] Ze, E.Y., Kim, B.J., Jun, D.H., Kim, J.G., Kang, H. and Lee, D.Y. (2018) The Fatty Liver Index: A Simple and Accurate Predictor of Colorectal Adenoma in an Average-Risk Population. *Diseases of the Colon & Rectum*, **61**, 36-42. https://doi.org/10.1097/dcr.0000000000000973

[31] Ahn, J.S., Sinn, D.H., Min, Y.W., Hong, S.N., Kim, H.S., *et al*. (2016) Non-Alcoholic Fatty Liver Diseases and Risk of Colorectal Neoplasia. *Alimentary Pharmacology & Therapeutics*, **45**, 345-353. https://doi.org/10.1111/apt.13866

[32] Kim, M.C., Park, J.G., Jang, B.I., Lee, H.J. and Lee, W.K. (2019) Liver Fibrosis Is Associated with Risk for Colorectal Adenoma in Patients with Nonalcoholic Fatty Liver Disease. *Medicine*, **98**, e14139. https://doi.org/10.1097/md.0000000000014139

[33] Wu, Y., Kumar, R., Wang, M., Singh, M., Huang, J., Zhu, Y., *et al*. (2021) Validation of Conventional Non-Invasive Fibrosis Scoring Systems in Patients with Metabolic Associated Fatty Liver Disease. *World Journal of Gastroenterology*, **27**, 5753-5763. https://doi.org/10.3748/wjg.v27.i34.5753

[34] Park, H., Yoon, E.L., Kim, M., Lee, J., Kim, J., Cho, S., *et al*. (2021) Comparison of Diagnostic Performance between FIB-4 and NFS in Metabolic-Associated Fatty Liver Disease Era. *Hepatology Research*, **52**, 247-254. https://doi.org/10.1111/hepr.13737

[35] Theofilis, P., Vordoni, A. and Kalaitzidis, R.G. (2022) Metabolic Dysfunction-Associated Fatty Liver Disease in the National Health and Nutrition Examination Survey 2017-2020: Epidemiology, Clinical Correlates, and the Role of Diagnostic Scores. *Metabolites*, **12**, Article 1070. https://doi.org/10.3390/metabo12111070

[36] Han, A.L. (2022) Validation of Fatty Liver Index as a Marker for Metabolic Dysfunction-Associated Fatty Liver Disease. *Diabetology & Metabolic Syndrome*, **14**, Article No. 44. https://doi.org/10.1186/s13098-022-00811-2

[37] Cheung, J.T.K., Zhang, X., Wong, G.L., Yip, T.C., Lin, H., Li, G., *et al*. (2023) MAFLD Fibrosis Score: Using Routine Measures to Identify Advanced Fibrosis in Metabolic-Associated Fatty Liver Disease. *Alimentary Pharmacology & Therapeutics*, **58**, 1194-1204. https://doi.org/10.1111/apt.17722

[38] 张莉敏, 孙军. FIB-4 在代谢相关脂肪性肝病合并结直肠腺瘤性息肉患者的预测价值[J]. 临床荟萃, 2022, 37(4): 334-338.

[39] Khan, R.S., Bril, F., Cusi, K. and Newsome, P.N. (2019) Modulation of Insulin Resistance in Nonalcoholic Fatty Liver Disease. *Hepatology*, **70**, 711-724. https://doi.org/10.1002/hep.30429

[40] Lim, S., Kim, J. and Targher, G. (2021) Links between Metabolic Syndro me and Metabolic Dysfunction-Associated Fatty Liver Disease. *Trends in Endocrinology & Metabolism*, **32**, 500-514. https://doi.org/10.1016/j.tem.2021.04.008

[41] Yoon, Y.S., Keum, N., Zhang, X., Cho, E. and Giovannucci, E.L. (2015) Hyperinsulinemia, Insulin Resistance and Colorectal Adenomas: A Meta-Analysis. *Metabolism*, **64**, 1324-1333. https://doi.org/10.1016/j.metabol.2015.06.013

[42] Giovannucci, E. (2007) Metabolic Syndrome, Hyperinsulinemia, and Colon Cancer: A Review. *The American Journal of Clinical Nutrition*, **86**, 836S-842S. https://doi.org/10.1093/ajcn/86.3.836s

[43] Kasprzak, A. (2021) Insulin-Like Growth Factor 1 (IGF-1) Signaling in Glucose Metabolism in Colorectal Cancer. *International Journal of Molecular Sciences*, **22**, Article 6434. https://doi.org/10.3390/ijms22126434

[44] Jin, T. (2008) Why Diabetes Patients Are More Prone to the Development of Colon Cancer? *Medical Hypotheses*, **71**, 241-244. https://doi.org/10.1016/j.mehy.2008.03.025

[45] Barb, D., Williams, C.J., Neuwirth, A.K. and Mantzoros, C.S. (2007) Adiponectin in Relation to Malignancies: A Review of Existing Basic Research and Clinical Evidence. *The American Journal of Clinical Nutrition*, **86**, 858S-866S. https://doi.org/10.1093/ajcn/86.3.858s

[46] Barbalho, S.M., Méndez-Sánchez, N. and Fornari Laurindo, L. (2023) Adiporon and ADP355, Adiponectin Receptor Agonists, in Metabolic-Associated Fatty Liver Disease (MAFLD) and Nonalcoholic Steatohepatitis (NASH): A Systematic Review. *Biochemical Pharmacology*, **218**, Article 115871. https://doi.org/10.1016/j.bcp.2023.115871

[47] Fenton, J.I., Birmingham, J.M., Hursting, S.D. and Hord, N.G. (2008) Adiponectin Blocks Multiple Signaling Cascades Associated with Leptin-Induced Cell Proliferation in Apcmin/+ Colon Epithelial Cells. *International Journal of Cancer*, **122**, 2437-2445. https://doi.org/10.1002/ijc.23436

[48] Kobashi, C., Urakaze, M., Kishida, M., Kibayashi, E., Kobayashi, H., Kihara, S., *et al*. (2005) Adiponectin Inhibits Endothelial Synthesis of Interleukin-8. *Circulation Research*, **97**, 1245-1252. https://doi.org/10.1161/01.res.0000194328.57164.36

[49] Yoneda, K., Tomimoto, A., Endo, H., *et al*. (2008) Expression of Adiponectin Receptors, AdipoR1 and AdipoR2, in Normal Colon Epithelium and Colon Cancer Tissue. *Oncology Reports*, **20**, 479-483.

[50] Valenzuela-Vallejo, L., Chrysafi, P., Kouvari, M., Guatibonza-Garcia, V., Mylonakis, S.C., Katsarou, A., *et al*. (2023) Circulating Hormones in Biopsy-Proven Steatotic Liver Disease and Steatohepatitis: A Multicenter Observational Study. *Metabolism*, **148**, Article 155694. https://doi.org/10.1016/j.metabol.2023.155694

[51] Yamaji, T., Iwasaki, M., Sasazuki, S. and Tsugane, S. (2010) Interaction between Adiponectin and Leptin Influences the Risk of Colorectal Adenoma. *Cancer Research*, **70**, 5430-5437. https://doi.org/10.1158/0008-5472.can-10-0178

[52] Ji, J., Sun, J., Li, J., Xie, J., Xi, B. and Zhao, M. (2024) Altered Gut Microbiome Associated with Metabolic-Associated Fatty Liver Disease in Chinese Children. *Clinical Nutrition*, **43**, 187-196. https://doi.org/10.1016/j.clnu.2023.11.001

[53] Yang, Q., Zhang, L., Li, Q., Gu, M., Qu, Q., Yang, X., *et al*. (2022) Characterization of Microbiome and Metabolite Analyses in Patients with Metabolic Associated Fatty Liver Disease and Type II Diabetes Mellitus. *BMC Microbiology*, **22**, Article No. 105. https://doi.org/10.1186/s12866-022-02526-w

[54] Yang, C., Xu, J., Xu, X., Xu, W., Tong, B., Wang, S., *et al*. (2023) Characteristics of Gut Microbiota in Patients with Metabolic Associated Fatty Liver Disease. *Scientific Reports*, **13**, Article No. 9988. https://doi.org/10.1038/s41598-023-37163-4

[55] Oh, J.H., Lee, J.H., Cho, M.S., Kim, H., Chun, J., Lee, J.H., *et al*. (2021) Characterization of Gut Microbiome in Korean Patients with Metabolic Associated Fatty Liver Disease. *Nutrients*, **13**, Article 1013. https://doi.org/10.3390/nu13031013

[56] Adolph, T.E., Grander, C., Moschen, A.R. and Tilg, H. (2018) Liver-Microbiome Axis in Health and Disease. *Trends in Immunology*, **39**, 712-723. https://doi.org/10.1016/j.it.2018.05.002

[57] Alisi, A., McCaughan, G. and Grønbæk, H. (2024) Role of Gut Microbiota and Immune Cells in Metabolic-Associated Fatty Liver Disease: Clinical Impact. *Hepatology International*, **18**, 861-872. https://doi.org/10.1007/s12072-024-10674-6

[58] Wong, C.C. and Yu, J. (2023) Gut Microbiota in Colorectal Cancer Development and Therapy. *Nature Reviews Clinical Oncology*, **20**, 429-452. https://doi.org/10.1038/s41571-023-00766-x

[59] Liu, Q., Han, M., Li, M., Huang, X., Feng, R., Li, W., *et al*. (2023) Shift in Prevalence and Systemic Inflammation Levels from NAFLD to MAFLD: A Population-Based Cross-Sectional Study. *Lipids in Health and Disease*, **22**, Article No. 185. https://doi.org/10.1186/s12944-023-01947-4

[60] Schmitt, M. and Greten, F.R. (2021) The Inflammatory Pathogenesis of Colorectal Cancer. *Nature Reviews Immunology*, **21**, 653-667. https://doi.org/10.1038/s41577-021-00534-x

[61] Bedogni, G., Bellentani, S., Miglioli, L., Masutti, F., Passalacqua, M., Castiglione, A., *et al*. (2006) The Fatty Liver Index: A Simple and Accurate Predictor of Hepatic Steatosis in the General Population. *BMC Gastroenterology*, **6**, Article No. 33. https://doi.org/10.1186/1471-230x-6-33

[62] Shah, A.G., Lydecker, A., Murray, K., Tetri, B.N., Contos, M.J. and Sanyal, A.J. (2009) Comparison of Noninvasive Markers of Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. *Clinical Gastroenterology and Hepatology*, **7**, 1104-1112. https://doi.org/10.1016/j.cgh.2009.05.033

[63] Wai, C., Greenson, J.K., Fontana, R.J., Kalbfleisch, J.D., Marrero, J.A., Conjeevaram, H.S., *et al*. (2003) A Simple Noninvasive Index Can Predict Both Significant Fibrosis and Cirrhosis in Patients with Chronic Hepatitis C. *Hepatology*, **38**, 518-526. https://doi.org/10.1053/jhep.2003.50346

[64] Angulo, P., Hui, J.M., Marchesini, G., Bugianesi, E., George, J., Farrell, G.C., *et al*. (2007) The NAFLD Fibrosis Score. *Hepatology*, **45**, 846-854. https://doi.org/10.1002/hep.21496

[65] Harrison, S.A., Oliver, D., Arnold, H.L., Gogia, S. and Neuschwander-Tetri, B.A. (2008) Development and Validation of a Simple NAFLD Clinical Scoring System for Identifying Patients without Advanced Disease. *Gut*, **57**, 1441-1447. https://doi.org/10.1136/gut.2007.146019