

• 脂肪性肝病 •

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代谢相关脂肪性肝病与动脉粥样硬化性心血管疾病发病风险的相互影响

赵亚男¹, 齐 祺², 吴欣雨², 韩全乐², 杨 静², 张伯亨², 李旭阳², 李 雷¹, 张 云³, 吴寿岭⁴, 李康博⁵

1 唐山市工人医院导管室, 河北 唐山 063000

2 唐山市工人医院心内科, 河北 唐山 063000

3 唐山市工人医院老年病科, 河北 唐山 063000

4 开滦总医院心内科, 河北 唐山 063000

5 华北理工大学临床医学院, 河北 唐山 063000

通信作者: 韩全乐, hanquanle@126.com (ORCID: 0000-0002-3200-9224)

摘要: **目的** 探讨代谢相关脂肪性肝病(MAFLD)与动脉粥样硬化性心血管疾病(ASCVD)发病风险之间的关联,为临床此类代谢相关疾病防治提供数据支持。**方法** 以2006年6月—2007年10月参加首次健康体检,且肝脏评估资料完整、既往无恶性肿瘤病史以及无MAFLD病史或ASCVD病史的开滦职工为观察队列。根据是否患有MAFLD将患者分为非MAFLD组($n=67\,565$)和MAFLD组($n=29\,004$);根据是否患有ASCVD将患者分为非ASCVD组($n=69\,141$)和ASCVD组($n=481$)。计量资料两组间比较采用成组 t 检验或Wilcoxon秩和检验。计数资料两组间比较采用 χ^2 检验。采用寿命表法计算ASCVD及MAFLD的累积发病率,通过Kaplan-Meier法绘制MAFLD组与非MAFLD组ASCVD累积发病率的生存曲线及ASCVD组与非ASCVD组MAFLD累积发病率的生存曲线,并使用Log-rank检验比较两组患者累积发病率的差异。采用多因素Cox比例风险回归模型分析MAFLD对ASCVD发病风险的影响及ASCVD对MAFLD发病风险的影响。**结果** MAFLD组体重指数(BMI)、腰围、收缩压(SBP)、舒张压(DBP)、静息心率、丙氨酸氨基转移酶(ALT)、尿酸(UA)、空腹血糖(FBG)、甘油三酯(TG)、总胆固醇(TC)、低密度脂蛋白胆固醇(LDL-C)和超敏C反应蛋白(hs-CRP)等均高于非MAFLD组,估算肾小球滤过率(eGFR)、高密度脂蛋白胆固醇等均低于非MAFLD组,差异均有统计学意义(P 值均 <0.05);ASCVD组BMI、腰围、SBP、DBP、UA、FBG、TG、hs-CRP等均显著高于非ASCVD组,eGFR显著低于非ASCVD组(P 值均 <0.05)。随着时间的增长,MAFLD组与非MAFLD组ASCVD的累积发病率持续上升;而ASCVD组与非ASCVD组MAFLD的累积发病率先随时间增长,随后趋于平稳。MAFLD组新发ASCVD为4 263例(14.70%),发病密度为12.90/千人年;非MAFLD组新发ASCVD为6 529例(9.66%),发病密度为8.24/千人年,两组ASCVD的发病密度和累积发病率比较,差异均有统计学意义(χ^2 值分别为519.09、531.80, P 值均 <0.05)。ASCVD组新发MAFLD为148例(30.77%),发病密度为40.10/千人年;非ASCVD组新发MAFLD为32 194例(46.56%),发病密度为57.59/千人年,两组MAFLD的发病密度和累积发病率比较,差异均有统计学意义(χ^2 值分别为19.29、30.78, P 值均 <0.05)。校正后的多因素Cox比例风险回归模型分析结果显示,MAFLD是新发ASCVD的危险因素(风险比=1.11,95%置信区间:1.06~1.16, $P<0.001$),而ASCVD是新发MAFLD的保护因素(风险比=0.72,95%置信区间:0.61~0.85, $P<0.001$)。**结论** MAFLD与ASCVD发病风险存在显著关联,MAFLD人群的ASCVD发病风险升高,而ASCVD人群的MAFLD发病风险降低。

关键词: 代谢相关脂肪性肝病;动脉粥样硬化;影响因素分析**基金项目:** 河北省医学课题重点研究计划项目(20231775)

Bidirectional association between metabolic associated fatty liver disease and the risk of atherosclerotic cardiovascular disease

ZHAO Yanan¹, QI Qi², WU Xinyu², HAN Quanle², YANG Jing², ZHANG Boheng², LI Xuyang², LI Lei¹, ZHANG Yun³, WU Shouling⁴, LI Kangbo⁵

1. Department of Catheter Room, Tangshan Workers' Hospital, Tangshan, Hebei 063000, China; 2. Department of Cardiology, Tangshan Workers' Hospital, Tangshan, Hebei 063000, China; 3. Department of Geriatrics, Tangshan Workers' Hospital, Tangshan, Hebei 063000, China; 4. Department of Cardiology, Kailuan General Hospital, Tangshan, Hebei 063000, China; 5. School of Clinical Medicine, North China University of Science and Technology, Tangshan, Hebei 063000, China

Corresponding author: HAN Quanle, hanquanle@126.com (ORCID: 0000-0002-3200-9224)

Abstract: Objective To investigate the association between metabolic associated fatty liver disease (MAFLD) and the risk of atherosclerotic cardiovascular disease (ASCVD), and to provide data support for the prevention and treatment of such metabolic-associated diseases in clinical practice. **Methods** An observation cohort was established for the workers of Kailuan who underwent physical examination for the first time from June 2006 to October 2007 and had complete liver assessment data, without the history of malignant tumor, MAFLD or ASCVD. According to the presence or absence of MAFLD, the patients were divided into non-MAFLD group with 67 565 patients and MAFLD group with 29 004 patients, and according to the presence or absence of ASCVD, the patients were divided into non-ASCVD group with 69 141 patients and ASCVD group with 481 patients. The group *t*-test or the Wilcoxon rank-sum test was used for comparison of continuous data between the two groups. The χ^2 test was used for comparison of categorical data between the two groups. The life-table method was used to calculate the cumulative incidence rates of new-onset ASCVD and MAFLD; the Kaplan-Meier method was used to plot the survival curves of the cumulative incidence rates of ASCVD in the MAFLD group and the non-MAFLD group and the cumulative incidence rates of MAFLD in the ASCVD group and the non-ASCVD group, and the log-rank test was used for comparison of cumulative incidence rates between two groups. A multivariate Cox proportional-hazards regression model analysis was used to investigate the impact of MAFLD on the risk of ASCVD and the impact of ASCVD on the risk of MAFLD. **Results** Compared with the non-MAFLD group, the MAFLD group had significantly higher levels of body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate, alanine aminotransferase, uric acid (UA), fasting blood glucose (FBG), triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol, and high sensitivity C-reactive protein (hs-CRP), as well as significantly lower levels of estimated glomerular filtration rate (eGFR) and high-density lipoprotein cholesterol (all $P < 0.05$). Compared with the non-ASCVD group, the ASCVD group had significantly higher levels of BMI, waist circumference, SBP, DBP, UA, FBG, TG, and hs-CRP and a significantly lower level of eGFR (all $P < 0.05$). The incidence rate of new-onset ASCVD continued to increase over time in the MAFLD group and the non-MAFLD group, while the incidence rate of new-onset MAFLD firstly increased and then remained stable over time in the ASCVD group and the non-ASCVD group. There were 4 263 cases (14.70%) of new-onset ASCVD in the MAFLD group, with an incidence density of 12.90 per 1 000 person-years, while there were 6 529 cases (9.66%) of new-onset ASCVD in the non-MAFLD group, with an incidence density of 8.24 per 1 000 person-years, and there were significant differences in the incidence density and cumulative incidence rate of ASCVD between the two groups ($\chi^2=519.09$ and 531.80 , both $P < 0.05$). There were 148 cases (30.77%) of new-onset MAFLD in the ASCVD group, with an incidence density of 40.10 per 1 000 person-years, while there were 32 194 cases (46.56%) of new-onset MAFLD in the non-ASCVD group, with an incidence density of 57.59 per 1 000 person-years, and there were significant differences in the incidence density and cumulative incidence rate of MAFLD between the two groups ($\chi^2=19.29$ and 30.78 , both $P < 0.05$). The corrected multivariate Cox proportional-hazards regression model analysis showed that MAFLD was a risk factor for new-onset ASCVD (hazard ratio [HR]=1.11, 95% confidence interval [CI]: 1.06—1.16, $P < 0.001$), while ASCVD was a protective factor against new-onset MAFLD (HR=0.72, 95%CI: 0.61—0.85, $P < 0.001$). **Conclusion** There is a significant association between MAFLD and ASCVD, with an increase in the risk of ASCVD in the MAFLD population and a reduction in the risk of MAFLD in the ASCVD population.

Key words: Metabolic Associated Fatty Liver Disease; Atherosclerosis; Root Cause Analysis

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据统计,代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD)全球累积发病率为39.22%,其

中东南亚地区为高发区域^[1-2]。研究表明,MAFLD与较高的体重指数(body mass index, BMI)、高血压、糖尿病和血

脂异常等代谢相关因素呈显著正相关,而上述因素同时也增加了动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)的发病风险^[3-5]。近年来,MAFLD与ASCVD发病风险之间的关联受到越来越多的关注。韩国学者研究结果显示,从非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)到MAFLD诊断标准的变化,可能会筛查出更多的MAFLD和ASCVD风险增加的个体^[6]。日本学者研究结果显示,MAFLD较NAFLD更能有效地识别ASCVD风险加重的患者^[7]。新加坡学者研究发现,中度至重度脂肪变性 with 临床ASCVD相关联,该结果强调了在NAFLD中开展ASCVD的早期筛查和及时干预的重要性^[8]。目前,尚缺乏针对中国人群MAFLD与ASCVD发病风险相互影响的研究报道。鉴于MAFLD不仅直接引发肝脏病变^[9-10],还会增加罹患ASCVD、糖尿病、慢性肾病和死亡的风险^[6-7,11-13],且ASCVD本身具有高致残率和致死率,二者相互叠加,严重威胁个体健康,并显著加重家庭和社会的医疗负担^[3-5,14]。

本研究旨在利用开滦研究队列,进一步明确我国人群中MAFLD与ASCVD发病风险的相互影响,以期为二者的临床风险筛查与早期干预提供数据支持。

1 资料与方法

1.1 研究对象 本研究选取2006年6月—2007年10月首次在开滦总医院及其下属10家医院完成体检的开滦研究队列人群为研究对象。纳入标准:(1)开滦集团在职及离退休职工;(2)同意参与本研究并能完成问卷调查,且签署知情同意书。排除标准:(1)肝脏评估资料不完整者;(2)既往有恶性肿瘤病史者;(3)既往有MAFLD或ASCVD病史者。

1.2 研究方法

1.2.1 基线资料 流行病学调查内容、人体测量学指标、相关生化指标检测参见本课题组既往研究^[15]。通过调查问卷获取受试者的人口学资料、生活方式、病史及服药史等资料。受试者需在体检前禁食8~12 h,于体检当天7:00—9:00采集5 mL空腹静脉血。所有血液样本均送至开滦总医院检验科,使用日立7600全自动分析仪(日立,日本)对所有空腹静脉血样本进行生化分析。

1.2.2 诊断标准及定义 MAFLD的诊断依据《2023年国际多学科专家共识:代谢相关脂肪性肝病和心血管疾病风险》^[9],经空腹腹部彩超证实肝脂肪变性,同时至少满足以下一项条件。(1)超重/肥胖: BMI ≥ 23 kg/m²; (2)已确诊为2型糖尿病; (3)至少符合以下两种代谢异常:

①腰围 ≥ 90 cm(男性)或 ≥ 80 cm(女性); ②血压升高:收缩压(systolic blood pressure, SBP) ≥ 130 mmHg或舒张压(diastolic blood pressure, DBP) ≥ 85 mmHg,或正在接受降压药物治疗; ③甘油三酯(triglyceride, TG)水平升高:空腹TG ≥ 1.7 mmol/L,或正在接受降脂治疗; ④高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)降低:男性 < 1.0 mmol/L,女性 < 1.3 mmol/L,或正在接受相关治疗; ⑤糖尿病前期状态:空腹血糖(fasting blood glucose, FBG)为5.6~6.9 mmol/L,或糖化血红蛋白为5.7%~6.4%; ⑥胰岛素抵抗:胰岛素抵抗评分 ≥ 2.5 分; ⑦炎症标志物升高:超敏C反应蛋白(high-sensitivity C reactive protein, hs-CRP) > 2 mg/L。

本研究纳入的ASCVD患者包括心肌梗死、冠状动脉血运重建、缺血性脑卒中。(1)心肌梗死,需同时满足心肌酶学标志物(以心肌肌钙蛋白为最佳指标)高于第99百分位上限参考值,以及以下任意一项^[16]: ①胸痛持续时间 ≥ 30 min等心肌缺血症状; ②心电图出现缺血性改变,新发的ST段、T波改变或左束支传导阻滞; ③心电图动态变化出现病理性Q波; ④存活心肌出现局部运动异常的影像学证据; ⑤通过血管造影证实冠状动脉血栓形成。(2)冠状动脉血运重建:冠状动脉介入治疗或冠状动脉旁路移植术^[17]。(3)缺血性脑卒中:基于临床症状、计算机断层成像或磁共振成像获得的图像以及其他诊断报告进行判定^[18]。

糖尿病、高血压及血脂异常的诊断标准参考相关指南^[19-21]。吸烟史、饮酒史、体育锻炼、收入水平以及教育程度的定义详见文献^[22]。

1.2.3 随访 以观察对象完成健康体检时间为随访起点,以新发ASCVD(或MAFLD)事件、死亡或至随访结束(2021年12月31日)为随访终点。

1.3 分组 根据是否患有MAFLD,将研究对象分为非MAFLD组和MAFLD组,并根据是否患有ASCVD将研究对象分为非ASCVD组和ASCVD组。

1.4 统计学方法 体检数据均由各医院相关工作人员录入,经网络上传至开滦总医院计算机系统组成Oracle 10.2数据库。应用SAS 9.4统计软件进行数据分析。符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用成组 t 检验;非正态分布的计量资料以 $M(P_{25} \sim P_{75})$ 表示,两组间比较采用Wilcoxon秩和检验。计数资料两组间比较采用 χ^2 检验。采用寿命表法计算ASCVD或MAFLD的累积发病率,通过Kaplan-Meier法绘制MAFLD组与非MAFLD组ASCVD累积发病率的生存曲线及ASCVD组与非ASCVD

组 MAFLD 累积发病率的生存曲线,并采用 Log-rank 检验比较组间差异。多因素 Cox 比例风险回归模型分析 MAFLD 对新发 ASCVD 事件的影响以及 ASCVD 对新发 MAFLD 事件的影响,计算风险比(hazard ratio, *HR*)和 95% 置信区间(95% confidence interval, 95%*CI*)。为进一步证实结果的可靠性,排除随访 2 年内新发事件的参与者后重复 Cox 比例风险回归模型,进行敏感性分析。考虑到全因死亡与结局事件存在竞争关系,进行死亡竞争风险分析。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 基线资料

2.1.1 MAFLD 组与非 MAFLD 组研究对象临床基本特征 参加体检者共 101 510 例,排除肝脏评估资料不完

整者 1 219 例、既往有恶性肿瘤病史者 376 例以及既往有 ASCVD 病史者 3 346 例,最终纳入统计分析 96 569 例,其中 MAFLD 组 29 004 例,非 MAFLD 组 67 565 例。两组临床基线资料比较结果显示,MAFLD 组年龄、BMI、腰围、SBP、DBP、静息心率、丙氨酸氨基转移酶(alanine amino-transferase, ALT)、尿酸(uric acid, UA)、FBG、TG、总胆固醇(total cholesterol, TC)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、hs-CRP 水平,以及男性、月人均收入 ≥ 800 元、体育锻炼、饮酒史、糖尿病史、高血压史、血脂异常史、服用降糖药、服用降压药、服用降脂药占比均高于非 MAFLD 组,估算肾小球滤过率(estimated glomerular filtration rate, eGFR)、HDL-C 水平、高中及以上教育程度占比均低于非 MAFLD 组,差异均有统计学意义(P 值均 <0.05)(表 1)。

表 1 MAFLD 组与非 MAFLD 组临床基本特征比较

Table 1 Comparison of basic clinical characteristics between MAFLD and non-MAFLD groups

项目	总人群($n=96\ 569$)	MAFLD 组($n=29\ 004$)	非 MAFLD 组($n=67\ 565$)	统计值	P 值
年龄(岁)	51.48 ± 12.57	52.32 ± 11.42	51.11 ± 13.02	$t=-13.73$	<0.001
BMI(kg/m^2)	25.02 ± 3.49	27.61 ± 3.06	23.91 ± 3.05	$t=-172.26$	<0.001
腰围(cm)	86.96 ± 10.04	92.75 ± 8.74	84.47 ± 9.52	$t=-126.90$	<0.001
SBP(mmHg)	130.68 ± 20.90	137.06 ± 20.83	127.94 ± 20.32	$t=-63.43$	<0.001
DBP(mmHg)	83.40 ± 11.77	87.31 ± 11.80	81.73 ± 11.35	$t=-69.30$	<0.001
静息心率(次/min)	73.80 ± 10.17	74.56 ± 10.28	73.47 ± 10.11	$t=-15.26$	<0.001
ALT(U/L)	18.00(13.00 ~ 25.00)	22.00(16.00 ~ 30.00)	17.00(12.00 ~ 23.00)	$Z=80.48$	<0.001
UA($\mu\text{mol}/\text{L}$)	288.95 ± 83.65	311.67 ± 90.03	279.20 ± 78.77	$t=-56.19$	<0.001
eGFR($\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)	82.30 ± 25.79	80.65 ± 25.10	83.01 ± 26.05	$t=13.02$	<0.001
FBG(mmol/L)	5.47 ± 1.67	5.91 ± 2.04	5.28 ± 1.44	$t=-54.26$	<0.001
TG(mmol/L)	1.27(0.89 ~ 1.93)	1.76(1.22 ~ 2.65)	1.13(0.81 ~ 1.62)	$Z=105.79$	<0.001
TC(mmol/L)	4.95 ± 1.15	5.10 ± 1.24	4.88 ± 1.10	$t=-28.22$	<0.001
HDL-C(mmol/L)	1.55 ± 0.40	1.53 ± 0.41	1.56 ± 0.40	$t=9.71$	<0.001
LDL-C(mmol/L)	2.34 ± 0.91	2.38 ± 0.92	2.33 ± 0.91	$t=-9.05$	<0.001
hs-CRP(mg/L)	0.83(0.30 ~ 2.34)	1.21(0.50 ~ 3.12)	0.70(0.26 ~ 2.00)	$Z=51.98$	<0.001
男性[例(%)]	76 835(79.56)	23 773(81.96)	53 062(78.53)	$\chi^2=146.82$	<0.001
高中及以上教育程度[例(%)]	19 336(20.02)	5 544(19.11)	13 792(20.41)	$\chi^2=21.36$	<0.001
月人均收入 ≥ 800 元[例(%)]	69 073(71.53)	21 082(72.69)	47 991(71.03)	$\chi^2=27.36$	<0.001
体育锻炼[例(%)]	88 264(91.40)	26 649(91.88)	61 615(91.19)	$\chi^2=12.18$	0.023
吸烟史[例(%)]	32 902(34.07)	10 016(34.53)	22 886(33.87)	$\chi^2=3.94$	0.139
饮酒史[[例(%)]	35 946(37.22)	11 318(39.02)	24 628(36.45)	$\chi^2=57.42$	<0.001
糖尿病史[例(%)]	9 312(9.64)	5 012(17.28)	4 300(6.36)	$\chi^2=2\ 775.31$	<0.001
高血压史[例(%)]	42 007(43.50)	16 968(58.50)	25 039(37.06)	$\chi^2=379.50$	<0.001
血脂异常[例(%)]	57 444(59.48)	21 642(74.62)	35 802(52.99)	$\chi^2=3\ 938.80$	<0.001
服降糖药[例(%)]	2 557(2.65)	1 585(5.46)	972(1.44)	$\chi^2=1\ 276.10$	<0.001
服降压药[例(%)]	8 338(8.63)	4 038(13.92)	4 300(6.36)	$\chi^2=1\ 469.42$	<0.001
服降脂药[例(%)]	7 162(7.42)	3 412(11.76)	3 750(5.55)	$\chi^2=1\ 141.06$	<0.001

注: BMI, 体重指数; SBP, 收缩压; DBP, 舒张压; ALT, 丙氨酸氨基转移酶; UA, 尿酸; eGFR, 估算肾小球滤过率; FBG, 空腹血糖; TG, 甘油三酯; TC, 总胆固醇; HDL-C, 高密度脂蛋白胆固醇; LDL-C, 低密度脂蛋白胆固醇; hs-CRP, 超敏 C 反应蛋白; MAFLD, 代谢相关脂肪性肝病。

2.1.2 ASCVD组与非ASCVD组研究对象临床基本特征 101 510例体检者中,排除肝脏评估资料不完整者1 219例、既往有恶性肿瘤病史者376例以及既往有MAFLD病史者30 293例,最终纳入统计分析者69 622例,其中ASCVD组481例,非ASCVD组69 141例。两组临床基线资料比较结果显示,ASCVD组年龄、BMI、腰围、SBP、DBP、UA、FBG、TG、hs-CRP水平,以及男性、体育锻炼、糖尿病史、高血压史、服用降压药、服用降脂药占比均显著高于非ASCVD组,饮酒史、eGFR、高中及以上教育程度占比均显著低于非ASCVD组(P 值均<0.05)(表2)。

2.2 MAFLD与新发ASCVD的关系 MAFLD组新发ASCVD为4 263例(14.70%),发病密度为12.90/千人年;非MAFLD组新发ASCVD为6 529例(9.66%),发病密度

为8.24/千人年,两组ASCVD的发病密度和累积发病率比较,差异均有统计学意义(χ^2 值分别为519.09、531.80, P 值均<0.05)(图1,表3)。不同年龄分层的ASCVD发病密度和累积发病率详见表3。

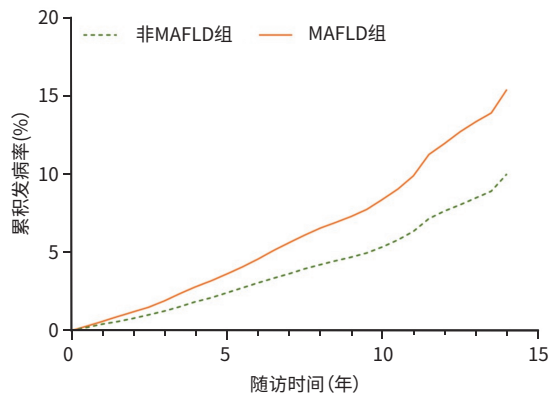
2.3 ASCVD与新发MAFLD的关系 ASCVD组新发MAFLD为148例(30.77%),发病密度为40.10/千人年;非ASCVD组新发MAFLD为32 194例(46.56%),发病密度为57.59/千人年,两组MAFLD的发病密度和累积发病率比较,差异均有统计学意义(χ^2 值分别为19.29、30.78, P 值均<0.05)(图2,表4)。不同年龄分层的MAFLD发病密度和累积发病率详见表4。

2.4 MAFLD与ASCVD相互影响的多因素Cox比例风险回归模型分析 以是否新发ASCVD(赋值:是=1,否=0)为因变量,以MAFLD(赋值:是=1,否=0)为自变量,进行

表2 ASCVD组与非ASCVD组临床基本特征比较
Table 2 Comparison of basic clinical characteristics between ASCVD and non-ASCVD groups

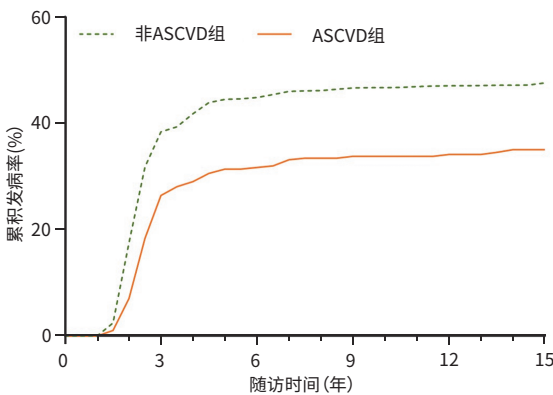
项目	总人群($n=69\ 622$)	ASCVD组($n=481$)	非ASCVD组($n=69\ 141$)	统计值	P 值
年龄(岁)	51.49±13.11	63.29±10.50	51.40±13.09	$t=-19.87$	<0.001
BMI(kg/m^2)	23.92±3.05	24.64±3.15	23.92±3.05	$t=-5.18$	<0.001
腰围(cm)	84.53±9.50	88.19±8.86	84.51±9.50	$t=-8.48$	<0.001
SBP(mmHg)	128.32±20.52	143.40±24.20	128.21±20.45	$t=-16.21$	<0.001
DBP(mmHg)	81.81±11.37	86.88±12.50	81.77±11.35	$t=-9.81$	<0.001
静息心率(次/min)	73.46±10.11	73.88±10.70	73.46±10.11	$t=-0.91$	0.664
ALT(U/L)	17.00(12.00~22.90)	17.00(12.00~22.20)	17.00(12.00~22.92)	$t=-1.39$	0.382
UA($\mu\text{mol}/\text{L}$)	280.39±76.38	320.87±93.34	280.10±79.20	$t=-11.24$	<0.001
eGFR($\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$)	82.69±25.91	74.82±30.18	82.75±25.87	$t=6.69$	<0.001
FBG(mmol/L)	5.29±1.46	5.90±2.38	5.28±1.45	$t=-9.23$	<0.001
TG(mmol/L)	1.13(0.81~1.62)	1.24(0.91~1.82)	1.13(0.81~1.62)	$Z=4.51$	<0.001
TC(mmol/L)	4.88±1.10	4.97±1.09	4.88±1.10	$t=-1.86$	0.178
HDL-C(mmol/L)	1.56±0.40	1.54±0.41	1.56±0.40	$t=0.67$	0.798
LDL-C(mmol/L)	2.33±0.91	2.37±1.10	2.33±0.91	$t=-1.01$	0.997
hs-CRP(mg/L)	0.70(0.27~2.00)	1.28(0.48~3.49)	0.70(0.26~2.00)	$Z=8.31$	<0.001
男性[例(%)]	54 930(78.90)	443(92.10)	54 487(78.81)	$\chi^2=50.71$	<0.001
高中及以上教育程度[例(%)]	14 107(20.26)	73(15.18)	14 034(20.30)	$\chi^2=7.75$	0.021
月人均收入≥800元[例(%)]	49 204(70.67)	351(72.97)	48 853(70.66)	$\chi^2=1.24$	0.539
体育锻炼[例(%)]	63 473(91.17)	457(95.01)	63 016(91.14)	$\chi^2=8.88$	0.012
吸烟史[例(%)]	23 756(34.12)	149(30.98)	23 607(34.14)	$\chi^2=2.13$	0.345
饮酒史[例(%)]	25 310(36.35)	132(27.44)	25 178(36.42)	$\chi^2=16.62$	<0.001
糖尿病史[例(%)]	4 718(6.78)	99(20.58)	4 619(6.68)	$\chi^2=146.13$	<0.001
高血压史[例(%)]	26 457(38.00)	325(67.57)	26 132(37.80)	$\chi^2=125.92$	<0.001
血脂异常[例(%)]	36 978(53.11)	273(56.76)	36 705(53.09)	$\chi^2=2.58$	0.275
服降糖药[例(%)]	1 028(1.48)	8(1.66)	1 020(1.48)	$\chi^2=0.12$	0.944
服降压药[例(%)]	4 733(6.80)	133(27.65)	4 600(6.65)	$\chi^2=332.40$	<0.001
服降脂药[例(%)]	4 119(5.92)	126(26.20)	3 993(5.78)	$\chi^2=357.85$	<0.001

注: BMI, 体重指数; SBP, 收缩压; DBP, 舒张压; ALT, 丙氨酸氨基转移酶; UA, 尿酸; eGFR, 估算肾小球滤过率; FBG, 空腹血糖; TG, 甘油三酯; TC, 总胆固醇; HDL-C, 高密度脂蛋白胆固醇; LDL-C, 低密度脂蛋白胆固醇; hs-CRP, 超敏C反应蛋白; ASCVD, 动脉粥样硬化性心血管疾病。



注:MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

图1 MAFLD组与非MAFLD组ASCVD累积发病率的生存曲线
Figure 1 Survival curves of cumulative incidence of new-onset ASCVD in MAFLD group and non-MAFLD group



注:MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

图2 ASCVD组与非ASCVD组MAFLD累积发病率的生存曲线
Figure 2 Survival curves of cumulative incidence of new-onset MAFLD in ASCVD group and non-ASCVD group

表3 MAFLD组与非MAFLD组ASCVD累积发病率与发病密度

Table 3 The cumulative incidence and incidence density of new ASCVD in the MAFLD group and the non-MAFLD group

项目	新发 ASCVD[例(%)]	发病密度(/千人年)	累积发病率(%)
非 MAFLD 组	6 529(9.66)	8.24	10.02
年龄			
18 ~ <45 岁	767(11.75)	2.65	3.26
45 ~ <60 岁	3 415(52.31)	8.94	10.82
≥60 岁	2 347(35.95)	19.25	22.13
MAFLD 组	4 263(14.70)	12.90	15.43
年龄			
18 ~ <45 岁	577(13.54)	5.88	6.99
45 ~ <60 岁	2 400(56.30)	13.25	15.97
≥60 岁	1 286(30.17)	25.08	28.01

注:MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

表4 ASCVD组与非ASCVD组ASCVD累积发病率与发病密度

Table 4 Cumulative incidence and incidence density of new ASCVD in the ASCVD group and the non-ASCVD group

项目	新发 MAFLD[例(%)]	发病密度(/千人年)	累积发病率(%)
非 ASCVD 组	32 194(46.56)	57.59	47.57
年龄			
18 ~ <45 岁	11 517(35.77)	70.73	56.01
45 ~ <60 岁	15 580(48.39)	60.65	50.35
≥60 岁	5 097(15.83)	36.58	33.15
ASCVD 组	148(30.77)	40.10	35.01
年龄			
18 ~ <45 岁	10(6.76)	85.24	54.39
45 ~ <60 岁	72(48.65)	52.23	45.16
≥60 岁	66(44.59)	30.07	26.56

注:MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

多因素 Cox 比例风险回归模型分析。模型 1 校正年龄、收入水平、吸烟史、饮酒史、病史(高血压、糖尿病、血脂性别;模型 2 在模型 1 基础上校正教育水平、体育锻炼、异常)以及服药史(降压药、降糖药、降脂药);模型 3 在模

型2基础上校正BMI、腰围、SBP、DBP、静息心率、ALT、UA、eGFR、FBG、TG、TC、HDL-C、LDL-C和hs-CRP。模型3结果显示,MAFLD是新发ASCVD的危险因素($HR=1.11, 95\%CI: 1.06 \sim 1.16, P<0.001$)(表5)。年龄分层分析结果显示,非MAFLD组各年龄组新发ASCVD风险高于MAFLD组各年龄组(表5)。

以是否新发MAFLD(赋值:是=1,否=0)为因变量,以ASCVD(赋值:是=1,否=0)为自变量,进行多因素Cox比例风险回归模型分析。模型3结果显示,ASCVD是新发MAFLD的保护因素($HR=0.72, 95\%CI: 0.61 \sim 0.85, P<0.001$)(表6)。年龄分层分析中,非ASCVD组各年龄组新发MAFLD风险高于ASCVD组各年龄组(表6)。

2.5 敏感性分析 排除随访2年内新发ASCVD或MAFLD事件患者后,敏感性分析结果与上述主要分析结果基本一致。考虑到全因死亡与结局事件存在竞争

关系,以模型3进行死亡竞争风险分析,发现风险分析结果与主要分析结果相似(表7)。

3 讨论

本研究结果发现,MAFLD与ASCVD发病风险存在显著关联,MAFLD是新发ASCVD的独立危险因素($HR=1.11, 95\%CI: 1.06 \sim 1.16$),罹患MAFLD的人群新发ASCVD事件呈高风险状态;进一步行年龄分层分析显示,随着年龄增长,代谢功能障碍相关危险因素累积暴露增加,从而导致ASCVD发病风险升高,进一步证实了本研究的结论。一项来自韩国2009—2010年全国性健康筛查数据库中年人群的队列研究,纳入8 962 813例年龄40~64岁的受试者,中位随访时间为10.1年,结果显示,MAFLD与ASCVD呈显著高风险相关($HR=1.43, 95\%CI: 1.41 \sim 1.45$)^[6],与本研究结果一致。该研究一方

表5 多因素Cox比例风险回归模型分析MAFLD对新发ASCVD风险的影响

Table 5 Multivariate Cox proportional risk regression model analysis of the effect of MAFLD on the risk of new-onset ASCVD

项目	模型1		模型2		模型3	
	HR(95%CI)	P值	HR(95%CI)	P值	HR(95%CI)	P值
非MAFLD组	1.00		1.00		1.00	
年龄						
18~<45岁	1.00		1.00		1.00	
45~<60岁	3.15(2.92~3.41)	<0.001	2.48(2.29~2.69)	<0.001	2.32(2.14~2.52)	<0.001
≥60岁	6.21(5.72~6.74)	<0.001	4.62(4.25~5.03)	<0.001	4.13(3.78~4.52)	<0.001
MAFLD组 ¹⁾	1.53(1.47~1.59)	<0.001	1.24(1.19~1.29)	<0.001	1.11(1.06~1.16)	<0.001
年龄						
18~<45岁	1.00		1.00		1.00	
45~<60岁	2.39(2.18~2.62)	<0.001	2.08(1.90~2.28)	<0.001	1.97(1.79~2.17)	<0.001
≥60岁	4.37(3.96~4.82)	<0.001	3.66(3.31~4.05)	<0.001	3.30(2.96~3.68)	<0.001

注:1),以非MAFLD组为参照。HR,风险比;95%CI,95%置信区间;MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

表6 多因素Cox比例风险回归模型分析ASCVD对新发MAFLD风险的影响

Table 6 Multivariate Cox proportional risk regression model analysis of the effect of ASCVD on the risk of new-onset MAFLD

项目	模型1		模型2		模型3	
	HR(95%CI)	P值	HR(95%CI)	P值	HR(95%CI)	P值
非ASCVD组	1.00		1.00		1.00	
年龄						
18~<45岁	1.00		1.00		1.00	
45~<60岁	0.80(0.78~0.82)	<0.001	0.74(0.72~0.76)	<0.001	0.70(0.69~0.72)	<0.001
≥60岁	0.45(0.43~0.46)	<0.001	0.40(0.39~0.42)	<0.001	0.39(0.37~0.40)	<0.001
ASCVD组 ¹⁾	0.80(0.68~0.94)	0.006	0.77(0.66~0.91)	0.002	0.72(0.61~0.85)	<0.001
年龄						
18~<45岁	1.00		1.00		1.00	
45~<60岁	0.58(0.30~1.11)	0.101	0.59(0.30~1.18)	0.141	0.40(0.20~0.83)	0.014
≥60岁	0.30(0.16~0.59)	<0.001	0.29(0.14~0.57)	<0.001	0.23(0.11~0.48)	<0.001

注:1),以非ASCVD组为参照。HR,风险比;95%CI,95%置信区间;MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

表7 MAFLD与ASCVD相互影响的敏感性分析
Table 7 Sensitivity analyses for bidirectional MAFLD and ASCVD study

项目	HR(95%CI)	P值
ASCVD		
排除2年内新发ASCVD事件的患者		
非MAFLD组	1.00	
MAFLD组	1.12(1.07~1.17)	<0.001
死亡竞争风险模型		
非MAFLD组	1.00	
MAFLD组	1.11(1.06~1.16)	<0.001
MAFLD		
排除2年内新发MAFLD事件的患者		
非ASCVD组	1.00	
ASCVD组	0.69(0.56~0.84)	<0.001
死亡竞争风险模型		
非ASCVD组	1.00	
ASCVD组	0.59(0.50~0.69)	<0.001

注:HR,风险比;95%CI,95%置信区间;MAFLD,代谢相关脂肪性肝病;ASCVD,动脉粥样硬化性心血管疾病。

面表明,MAFLD加重了患者的糖脂代谢紊乱,而异常的糖脂水平增加了ASCVD的发病风险;另一方面提示,MAFLD作为代谢性疾病,与同为代谢相关疾病的ASCVD具有相似的发病机制。实际上,MAFLD在ASCVD的早期阶段已表现出其作为危险因素的特征。Wang等^[23]研究显示,在中国成年人中,MAFLD与颈动脉内膜中层厚度、颈动脉斑块、冠状动脉钙化、视网膜动脉粥样硬化等亚临床动脉粥样硬化的发生相关,其比值比(95%CI)分别为1.41(1.18~1.68)、1.23(1.02~1.48)、1.60(1.24~2.08)和1.79(1.28~2.52),特别是与同时存在多部位动脉粥样硬化的相关性更强,甚至早于亚临床动脉粥样硬化阶段。基于血脂成分计算出的血浆致动脉粥样硬化指数(atherogenic index of plasma, AIP),可反映机体的糖脂代谢状况,与MAFLD发病风险亦存在明显线性量-效关系^[24]。同时,随着AIP的升高,MAFLD诊断中代表糖脂代谢异常的必备三要素,即超重/肥胖、2型糖尿病和代谢性疾病^[25-29]的发病风险亦随之增加。有研究显示,AIP对ASCVD发生风险的预测价值在中青年人群(年龄<65岁)中优势更明显^[25],且AIP对新发缺血性脑卒中风险的预测作用可能在疾病发生前数年已开始显现^[26]。

此外,胰岛素抵抗、氧化应激、脂肪组织代谢增加和脂肪细胞动力学改变等均可能是MAFLD患者发生ASCVD的相关机制^[25,27-31]。除MAFLD和ASCVD共有的危险因素外,MAFLD本身亦会增加ASCVD发病风险。肝脏在调节机体的脂质代谢中发挥核心作用,负责脂蛋

白的合成和清除,同时也是TG生成转化和TC代谢的主要场所。当肝内脂肪堆积达到一定程度后,即构成了MAFLD发展形成的先决条件,而MAFLD所伴随的肝脏脂质代谢异常会促进动脉粥样硬化的发生和发展^[32-35]。上述循证研究从不同维度均佐证了本研究有关MAFLD增加ASCVD发病风险的结论。

为了进一步明确MAFLD和ASCVD的相互作用,本研究同时探讨了ASCVD对MAFLD发病风险的影响,结果显示,ASCVD可降低MAFLD的发病风险($HR=0.72$, $95\%CI:0.61\sim0.85$)。分析其原因可能在于,ASCVD患者(包括急性冠脉综合征、稳定性冠心病、缺血性心肌病和缺血性卒中等),特别是急危重症及失能人群,受到医生与家属的更高关注^[36],除积极控制血压、血糖、血脂以及使用抗血小板药物等常规干预外,控制体重、低盐低脂饮食,增加水果、蔬菜、鱼类及谷物摄入等健康生活方式亦被积极推行^[5,37-39],这些综合性管理策略可能共同降低了MAFLD的发病风险^[40]。年龄分层分析表明,在积极控制代谢相关危险因素后,年龄增长可提升因危险因素控制所带来的临床获益,进一步印证了本研究的结论,即ASCVD人群的MAFLD发病风险降低。

本研究的优势在于样本量大、随访时间长,是有关MAFLD与ASCVD发病风险关联的大型队列研究,结果更具有普适性和可行性。但本研究也存在一定局限性,例如部分血脂成分可能受潜在的混杂因素影响,其结果可能存在偏倚。

综上所述,MAFLD和ASCVD同为代谢相关疾病,除

共有的危险因素外,本研究对二者的关联机制进行研究分析,其结果为人群健康保健及临床实践中MAFLD与ASCVD的共防共治提供了数据支持,对改善人群健康具有重要临床价值和社会意义。

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利益冲突声明: 本文不存在任何利益冲突。

作者贡献声明: 赵亚男、韩全乐负责文章的构思和设计,撰写论文;齐祺、吴欣雨、杨静负责统计学分析;张伯亨、李旭阳、张云、李雷负责查阅文献,撰写论文;吴寿岭、李康博负责论文修订;韩全乐对文章整体负责和监督。

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