

· 脂肪性肝病 ·

DOI: 10.12449/JCH260312

代谢相关脂肪性肝病患者肝纤维化标志物、炎症标志物与胆结石患病风险的关联性分析

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摘要: **目的** 阐明代谢相关脂肪性肝病(MAFLD)患者肝纤维化评分、炎症标志物与胆结石之间的关联,探索肝纤维化评分在炎症标志物与胆结石关系中的中介作用。**方法** 回顾性纳入2014年1月—2023年6月在苏北人民医院接受体检并确诊MAFLD的患者,根据腹部彩超检查结果分为胆结石组($n=1\,724$)和非胆结石组($n=12\,843$)。收集患者临床数据,包括人口统计学信息、相关病史和家族史,以及体格检查、彩色多普勒超声检查和实验室生化指标。与代谢紊乱和胰岛素抵抗相关的生物标志物包括甘油三酯-葡萄糖指数(TyG)、TyG-体重指数(TyG-BMI)、血浆致动脉粥样硬化指数(AIP)及非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(NHHR);与炎症和营养状况相关的生物标志物包括中性粒细胞与淋巴细胞比值(NLR)、中性粒细胞百分比与白蛋白比值(NPAR)及单核细胞与淋巴细胞比值(MLR);评估肝纤维化程度和肝功能的生物标志物包括白蛋白-胆红素(ALBI)评分、非酒精性脂肪性肝病纤维化评分(NFS)、纤维化-4(FIB-4)指数和天冬氨酸氨基转移酶与血小板比值指数(APRI)。符合正态分布的计量资料2组间比较采用成组 t 检验;非正态分布的计量资料2组间比较采用Mann-Whitney U 检验;计数资料2组间比较采用 χ^2 检验。采用多因素Logistic回归分析、限制性立方样条分析和中介效应分析研究肝纤维化标志物、炎症标志物与胆结石患病风险之间的关联。**结果** MAFLD患者的胆结石患病率为11.8%。胆结石组与非胆结石组在性别、年龄、吸烟史、糖尿病、高血压、淋巴细胞、血小板、葡萄糖、白蛋白、血清尿酸、丙氨酸氨基转移酶、天冬氨酸氨基转移酶、红细胞、NLR、NPAR、MLR、NFS、FIB-4指数和ALBI评分方面均存在显著差异(P 值均 <0.05)。多因素Logistic回归分析结果显示,在完全调整后的模型中,NLR[比值比(odds, ratio, OR)=1.091, 95%置信区间(95% confidence interval, 95%CI): 1.028~1.160]、NPAR (OR=1.073, 95%CI: 1.042~1.105)、MLR (OR=1.142, 95%CI: 1.057~1.232)、NFS (OR=1.239, 95%CI: 1.190~1.291)和FIB-4指数 (OR=1.326, 95%CI: 1.241~1.417)是胆结石患病风险的独立影响因素(P 值均 <0.05)。限制性立方样条分析显示,NFS和FIB-4指数与胆结石发生风险之间存在显著的非线性关联(非线性 P 值均 <0.05)。中介分析进一步表明,NLR、MLR和NPAR与胆结石的关联部分可通过NFS或FIB-4指数介导,NFS和FIB-4指数的中介占比分别为36.79%、28.09%、29.67%和18.31%、17.70%、11.57%。**结论** MAFLD患者中,NFS和FIB-4指数与胆结石的患病率呈非线性关联,且介导炎症标志物NLR、NPAR和MLR与胆结石风险之间的关联。

关键词: 代谢相关脂肪性肝病; 生物标记; 胆石**基金项目:** 江苏省基础研究计划(自然科学基金)青年基金项目(BK20240498); 国家自然科学基金青年项目(82400623)

Association of liver fibrosis markers and inflammation markers with the risk of gallstones in patients with metabolic dysfunction-associated fatty liver disease

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Abstract: Objective To investigate the association of liver fibrosis scores and inflammation markers with gallstones in patients with metabolic dysfunction-associated fatty liver disease (MAFLD), as well as the mediating role of liver fibrosis scores in the relationship between inflammation markers and gallstones. **Methods** A total of 14 567 patients who received physical examination and were diagnosed with MAFLD in Subei People's Hospital from January 2014 to June 2023 were enrolled in this study, and according to the results of abdominal color Doppler ultrasound, they were divided into gallstone group with 1 724 patients and non-gallstone group with 12 843 patients. Related clinical data were collected from all patients, including demographic data, medical history, family history, physical examination, Color Doppler ultrasound, and biochemical parameters. The biomarkers associated with metabolic disorders and insulin resistance included triglyceride-glucose index (TyG), TyG-body mass index (BMI) index, atherogenic index of plasma (AIP), and non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio (NHHR); the biomarkers associated with inflammation and nutritional status included neutrophil-to-lymphocyte ratio (NLR), neutrophil percentage-to-albumin ratio (NPAR), and monocyte-to-lymphocyte ratio (MLR); the biomarkers for assessing liver fibrosis degree and liver function included albumin-bilirubin (ALBI) score, NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, and aspartate aminotransferase-to-platelet ratio index (APRI). The independent-samples *t* test was used for comparison of normally distributed continuous data between two groups, while the Mann-Whitney *U* test was used for comparison of non-normally distributed continuous data between two groups; the chi-square test was used for comparison of categorical data between two groups. Multivariate Logistic regression analysis, restricted cubic spline analysis, and mediating effect analysis were used to assess the association of liver fibrosis markers and inflammation markers with the risk of gallstones. **Results** The prevalence rate of gallstones was 11.8% among the MAFLD patients. There were significant differences between the gallstone group and the non-gallstone group in sex, age, smoking history, diabetes, hypertension, lymphocytes, platelets, glucose, albumin, serum uric acid, alanine aminotransferase, aspartate aminotransferase, red blood cell, NLR, NPAR, MLR, NFS, FIB-4 index, and ALBI score (all $P<0.05$). The multivariate Logistic regression analysis showed that NLR (odds ratio [OR]=1.091, 95% confidence interval [CI]: 1.028—1.160, $P<0.05$), NPAR (OR=1.073, 95%CI: 1.042—1.105, $P<0.05$), MLR (OR=1.142, 95%CI: 1.057—1.232, $P<0.05$), NFS (OR=1.239, 95%CI: 1.190—1.291, $P<0.05$), and FIB-4 index (OR=1.326, 95%CI: 1.241—1.417, $P<0.05$) were influencing factors for the prevalence rate of gallstones. The restricted cubic spline analysis showed a significant non-linear association between NFS/FIB-4 index and the risk of gallstone (non-linear $P<0.05$). The mediating effect analysis further showed that the association of NLR, MLR, and NPAR with gallstones was partially mediated by NFS or FIB-4 index, with a mediating effect accounting for 36.79%、28.09%、29.67% and 18.31%、17.70%、11.57%, respectively. **Conclusion** NFS and FIB-4 index have a non-linear association with the prevalence rate of gallstones in MAFLD patients, and they also mediate the association of NLR, NPAR, and MLR with the risk of gallstone.

Key words: Metabolic Dysfunction-Associated Fatty Liver Disease; Biomarkers; Gallstones

Research funding: Jiangsu Provincial Basic Research Program (Natural Science Foundation) Youth Fund Project (BK20240498); National Natural Science Foundation of China Youth Project (82400623)

2023年,德尔菲共识采用代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)取代了非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD),标志着肝脏疾病命名法的重大转变^[1]。这一新术语强调了全身代谢功能障碍在肝脏疾病中的关键作用。肝脂肪变性会导致肝细胞损伤和炎症,激活免疫细胞,进而刺激肝星状细胞,最终促进肝纤维化的进展^[2]。MAFLD患者往往伴有更高水平的炎症

标志物及营养代谢指标,且与肝纤维化程度密切相关^[3-5]。

胆结石临床常表现为呕吐、恶心和厌食等症状,且其与肝癌和胰腺癌的风险升高显著相关^[6]。多项观察性研究表明,血糖、胆固醇水平和炎症指标与胆结石发生呈正相关^[7-8],且胆结石在MAFLD患者中通常具有较高的患病率^[9]。此外,美国的一项回顾性研究显示,与胆结石疾病相关死亡的危险因素包括糖尿病前期或糖

尿病、肝脏硬度和质子泵抑制剂等^[10]。作为MAFLD的两个不良结果,肝纤维化与胆结石之间的相关性值得进一步探讨。

1 资料与方法

1.1 研究对象 回顾性纳入2014年1月1日—2023年6月30日在苏北人民医院健康体检中心被诊断为MAFLD且年龄 ≥ 18 岁的患者。MAFLD定义为超声检查诊断存在肝脂肪变性以及合并 ≥ 1 项心脏代谢风险因素,如超重或血糖、血压、血脂水平或高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)异常,排除肝脂肪变性的继发性原因^[11]。肝脂肪变性和胆石症的诊断均基于腹部超声检查结果。排除标准:(1)超声检查中胆囊显影不清晰;(2)孕妇;(3)有肿瘤病史;(4)患有病毒性、药物性、自身免疫性或其他慢性肝病;(5)过度饮酒(定义为女性每周乙醇摄入 >70 g,男性每周乙醇摄入 >140 g)。通过腹部彩超检查分为胆结石组和非胆结石组。

1.2 资料收集 通过电子病历系统收集受检者的基本临床数据,包括人口统计学信息、相关病史和家族史。体检内容包括体格检查、彩色多普勒超声检查以及实验室生化指标。甘油三酯-葡萄糖指数(triglyceride-glucose index, TyG)、TyG-体重指数(TyG-body mass index, TyG-BMI)、血浆致动脉粥样硬化指数(atherogenic index of plasma, AIP)和非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值(non-high-density lipoprotein cholesterol to HDL-C ratio, NHHR)是与代谢紊乱和胰岛素抵抗相关的生物标志物^[12];中性粒细胞与淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、中性粒细胞百分比与白蛋白比值(neutrophil percentage-to-albumin ratio, NPAR)和单核细胞与淋巴细胞比值(monocyte-to-lymphocyte ratio, MLR)是与炎症和营养状况相关的生物标志物^[13];白蛋白-胆红素(albumin-bilirubin, ALBI)评分、NAFLD纤维化评分(NAFLD fibrosis score, NFS)、纤维化-4(fibrosis-4, FIB-4)指数和天冬氨酸氨基转移酶与血小板比值指数(aspartate aminotransferase-to-platelet ratio index, APRI)是用于评估肝纤维化程度和肝功能的生物标志物^[14-16]。

1.3 统计学方法 本研究使用R 4.4.1软件进行绘图与数据分析。符合正态分布的计量数据以 $\bar{x} \pm s$ 表示,2组间比较采用成组 t 检验;不符合正态分布的计量数据以 $M(P_{25} \sim P_{75})$ 表示,2组间比较采用Mann-Whitney U 检

验。计数资料2组间比较采用 χ^2 检验。为探讨特征变量与MAFLD患者发生胆结石之间的关联,本研究采用3种模型进行多因素Logistic回归分析。模型1:未调整任何混杂因素;模型2:以年龄、性别、BMI和吸烟史作为混杂变量进行调整;模型3:在模型2的基础上,进一步调整高血压、糖尿病、总蛋白(total protein, TP)、血清肌酐(serum creatinine, Scr)、红细胞(red blood cell, RBC)、白细胞(white blood cell, WBC)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、HDL-C、总胆红素(total bilirubin, TBil)、总胆固醇(total cholesterol, TC)、葡萄糖(glucose, Glu)和血清尿酸(serum uric acid, SUA)。使用限制性立方样条图可视化特征变量与胆结石之间的剂量反应关系。为探究肝纤维化指标是否在炎症指标与胆结石之间的关联中发挥中介作用,本研究进行了中介效应分析,将总效应分解为2个部分:平均直接效应,代表直接影响;平均因果中介效应,阐明通过这些指标的间接途径。中介占比定义为平均因果中介效应/总效应,并通过1 000次重复抽样的Bootstrap方法来评估其显著性。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料 共纳入14 567例MAFLD患者,其中1 724例被诊断为胆结石(11.8%)。胆结石组与非胆结石组性别、年龄、吸烟史、糖尿病、高血压、淋巴细胞、血小板、Glu、白蛋白、SUA、丙氨酸氨基转移酶、天冬氨酸氨基转移酶、RBC、NLR、NPAR、MLR、NFS、FIB-4指数和ALBI比较,差异均有统计学意义(P 值均 < 0.05)(表1)。

2.2 MAFLD患者中与胆结石相关变量的多因素分析 在完全调整后的模型(模型3)中,NFS、FIB-4指数、NLR、MLR和NPAR为影响胆结石患病的独立危险因素(P 值均 < 0.05)(表2)。在调整了与模型3相同的混杂变量后,限制性立方样条图显示,NFS(图1a)和FIB-4指数(图1b)与胆结石均呈先上升后趋于平坦的非线性关联(P 值均 < 0.05)。

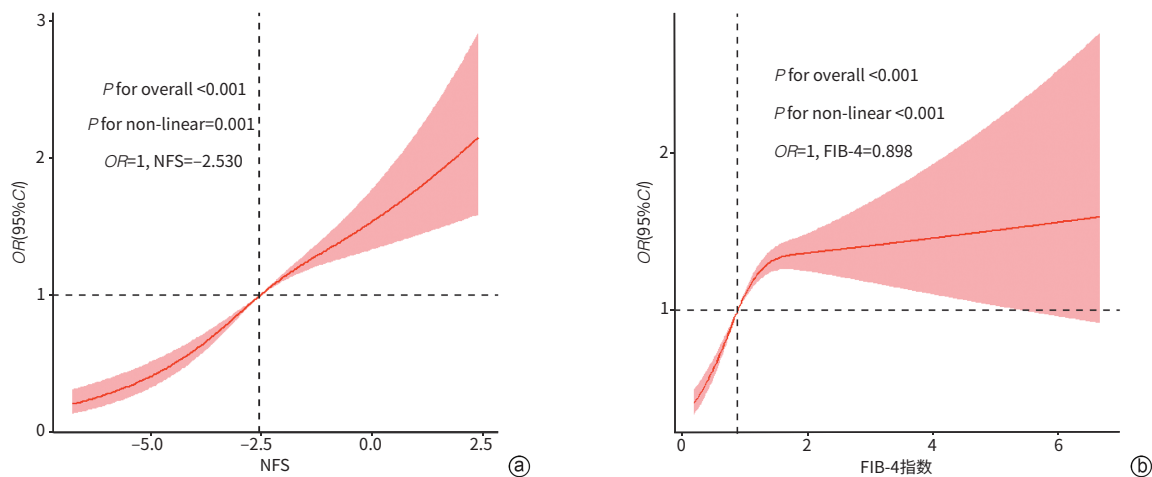
2.3 中介效应分析 中介效应分析结果显示,NFS和FIB-4指数在炎症指标与胆结石的关联中均发挥部分中介作用(P 值均 < 0.001)。具体而言,对于NPAR、NLR和MLR,NFS的中介效应占比分别为28.09%、29.67%和36.79%,而FIB-4指数的中介效应占比分别为11.57%、17.70%和18.31%(表3)。

表1 MAFLD患者胆结石组与非胆结石组基线资料

Table 1 Comparison of baseline characteristics between gallstone group and non-gallstone group in MAFLD patients

项目	胆结石组(<i>n</i> =1 724)	非胆结石组(<i>n</i> =12 843)	统计值	<i>P</i> 值
性别[例(%)]			$\chi^2=27.371$	<0.001
男	1 213(70.4)	9 778(76.1)		
女	511(29.6)	3 065(23.9)		
年龄(岁)	53.48±12.88	47.55±13.14	<i>t</i> =17.877	<0.001
BMI(kg/m ²)	26.62±2.91	26.61±3.04	<i>t</i> =0.159	0.872
吸烟史[例(%)]	381(22.1)	2 238(17.4)	$\chi^2=22.517$	<0.001
糖尿病[例(%)]	518(30.0)	2 926(22.8)	$\chi^2=44.421$	<0.001
高血压[例(%)]	474(27.5)	3 010(23.4)	$\chi^2=13.751$	<0.001
WBC(×10 ⁹ /L)	6.61±1.58	6.65±1.61	<i>t</i> =-0.873	0.382
NE(×10 ⁹ /L)	3.97±1.17	3.91±1.20	<i>t</i> =1.955	0.051
L(×10 ⁹ /L)	2.06±0.61	2.15±0.62	<i>t</i> =-5.758	<0.001
M(×10 ⁹ /L)	0.39±0.12	0.39±0.11	<i>t</i> =0.816	0.414
PLT(×10 ⁹ /L)	225.30±61.09	232.46±59.80	<i>t</i> =-4.581	<0.001
TC(mmol/L)	4.84±0.99	4.84±0.95	<i>t</i> =0.179	0.858
LDL-C(mmol/L)	3.03±0.82	3.02±0.81	<i>t</i> =0.435	0.663
HDL-C(mmol/L)	1.12±0.25	1.11±0.26	<i>t</i> =1.488	0.137
TG(mmol/L)	1.86(1.39~2.63)	1.90(1.38~2.78)	<i>Z</i> =-1.574	0.116
Glu(mmol/L)	6.01±1.83	5.73±1.65	<i>t</i> =5.981	<0.001
Alb(g/L)	46.54±2.36	46.95±2.39	<i>t</i> =-6.816	<0.001
TP(g/L)	73.89±3.88	73.87±3.81	<i>t</i> =0.166	0.867
SUA(μmol/L)	372.28±84.43	365.69±85.14	<i>t</i> =3.039	0.002
Ser(μmol/L)	83.15±17.13	82.77±14.61	<i>t</i> =0.891	0.372
ALT(U/L)	24.00(17.00~35.00)	26.00(18.00~40.00)	<i>Z</i> =-6.354	<0.001
AST(U/L)	21.00(17.00~26.00)	22.00(18.00~28.00)	<i>Z</i> =-5.705	<0.001
TBil(μmol/L)	11.10(8.60~14.40)	11.00(8.40~14.40)	<i>Z</i> =1.912	0.056
DBil(μmol/L)	4.00(3.20~5.00)	3.90(3.10~5.00)	<i>Z</i> =0.458	0.647
RBC(×10 ¹² /L)	4.99±0.48	5.06±0.47	<i>t</i> =-5.396	<0.001
TyG	9.82±0.63	9.79±0.64	<i>t</i> =1.301	0.193
TyG-BMI	261.48±34.19	260.83±35.54	<i>t</i> =0.736	0.462
AIP	0.52(0.14~0.97)	0.56(0.14~1.04)	<i>Z</i> =1.919	0.055
NHHR	3.38(2.70~4.16)	3.35(2.70~4.05)	<i>Z</i> =1.275	0.202
NLR	2.05±0.78	1.93±0.81	<i>t</i> =5.994	<0.001
NPAR	12.85±1.73	12.46±1.74	<i>t</i> =8.644	<0.001
MLR	0.198±0.065	0.188±0.063	<i>t</i> =5.936	<0.001
NFS	-2.15(-2.98~-1.21)	-2.58(-3.41~-1.67)	<i>Z</i> =12.939	<0.001
FIB-4指数	1.03(0.74~1.47)	0.88(0.61~1.27)	<i>Z</i> =11.681	<0.001
APRI	0.24(0.18~0.32)	0.24(0.19~0.33)	<i>Z</i> =1.597	0.124
ALBI评分	-3.26±0.21	-3.30±0.22	<i>t</i> =6.893	<0.001

注:MAFLD,代谢相关脂肪性肝病;BMI,体重指数;SUA,血清尿酸;L,淋巴细胞;M,单核细胞;NE,中性粒细胞;PLT,血小板;RBC,红细胞;Alb,白蛋白;Ser,血清肌酐;TG,甘油三酯;Glu,葡萄糖;LDL-C,低密度脂蛋白胆固醇;HDL-C,高密度脂蛋白胆固醇;TBil,总胆红素;AST,天冬氨酸氨基转移酶;ALT,丙氨酸氨基转移酶;ALBI,白蛋白-胆红素;FIB-4,纤维化-4;NFS,非酒精性脂肪性肝病纤维化评分;APRI,天冬氨酸氨基转移酶与血小板比值指数;NLR,中性粒细胞与淋巴细胞比值;NPAR,中性粒细胞百分比与白蛋白比值;AIP,血浆致动脉粥样硬化指数;TyG,甘油三酯-葡萄糖指数;NHHR,非高密度脂蛋白胆固醇与高密度脂蛋白胆固醇比值;MLR,单核细胞与淋巴细胞比值;TP,总蛋白;WBC,白细胞;TC,总胆固醇;DBil,直接胆红素。



注:a,NFS;b,FIB-4 指数。OR,比值比;95%CI,95%置信区间;NFS,非酒精性脂肪性肝病纤维化评分;FIB-4,纤维化-4。

图1 NFS和FIB-4指数与胆结石关联的限制性立方样条曲线

Figure 1 Restricted cubic spline curves of NFS and FIB-4 associated with gallstones

表2 多因素 Logistic 回归分析结果

Table 2 Multivariate Logistic regression analysis results

变量	模型 1		模型 2		模型 3	
	OR(95%CI)	P 值	OR(95%CI)	P 值	OR(95%CI)	P 值
NLR	1.168(1.104 ~ 1.237)	<0.001	1.097(1.037 ~ 1.161)	0.001	1.091(1.028 ~ 1.160)	0.002
NPAR	1.134(1.102 ~ 1.167)	<0.001	1.079(1.046 ~ 1.114)	<0.001	1.073(1.042 ~ 1.105)	<0.001
MLR	1.251(1.162 ~ 1.345)	<0.001	1.152(1.065 ~ 1.244)	<0.001	1.142(1.057 ~ 1.232)	<0.001
ALBI 评分	1.084(1.059 ~ 1.110)	<0.001	1.022(0.992 ~ 1.053)	0.157	1.011(0.986 ~ 1.037)	0.375
NFS	1.279(1.227 ~ 1.334)	<0.001	1.260(1.213 ~ 1.308)	<0.001	1.239(1.190 ~ 1.291)	<0.001
FIB-4 指数	1.367(1.281 ~ 1.459)	<0.001	1.346(1.252 ~ 1.447)	<0.001	1.326(1.241 ~ 1.417)	<0.001

注:FIB-4,纤维化-4;NFS,非酒精性脂肪性肝病纤维化评分;ALBI,白蛋白-胆红素;NLR,中性粒细胞与淋巴细胞比值;NPAR,中性粒细胞百分比与白蛋白比值;MLR,单核细胞与淋巴细胞比值;OR,比值比;95%CI,95%置信区间。

表3 NFS与FIB-4指数在炎症指标与胆结石关联中的中介效应

Table 3 Mediating effects of NFS and FIB-4 indices on the association between inflammatory markers and gallstones

中介变量	平均因果中介效应量(95%CI)	平均直接效应量(95%CI)	总效应量(95%CI)	中介占比 ¹⁾ (95%CI)	P 值
NPAR					
NFS	0.001(0.001 ~ 0.002)	0.002(0.002 ~ 0.003)	0.003(0.003 ~ 0.005)	29.67(21.42 ~ 41.06)	<0.001
FIB-4 指数	0.000(0.000 ~ 0.001)	0.003(0.003 ~ 0.004)	0.003(0.003 ~ 0.005)	11.57(7.76 ~ 17.23)	<0.001
NLR					
NFS	0.005(0.004 ~ 0.007)	0.008(0.003 ~ 0.014)	0.013(0.009 ~ 0.021)	36.79(24.91 ~ 66.22)	<0.001
FIB-4 指数	0.003(0.002 ~ 0.004)	0.011(0.007 ~ 0.020)	0.013(0.009 ~ 0.021)	18.31(11.92 ~ 30.03)	<0.001
MLR					
NFS	0.110(0.087 ~ 0.141)	0.285(0.139 ~ 0.442)	0.395(0.237 ~ 0.556)	28.09(18.76 ~ 43.42)	<0.001
FIB-4 指数	0.069(0.050 ~ 0.091)	0.322(0.173 ~ 0.482)	0.391(0.240 ~ 0.551)	17.70(10.44 ~ 29.12)	<0.001

注:NPAR,中性粒细胞百分比与白蛋白比值;NFS,非酒精性脂肪性肝病纤维化评分;FIB-4,纤维化-4;NLR,中性粒细胞与淋巴细胞比值;MLR,单核细胞与淋巴细胞比值;95%CI,95%置信区间。1)中介占比=平均因果中介效应/总效应×100%。

3 讨论

肝硬化患者的胆结石发病率是其他患者的2倍^[17]。在肝硬化患者中,胆固醇和磷脂的分泌减少,导致胆汁中胆红素和胆固醇的溶解度降低,胆固醇过饱和,破坏胆汁

稳定性,最终促进结石形成^[18]。同时,肝硬化患者还可能自主神经病变,导致Oddi括约肌功能障碍和胆囊排空受损,从而加重胆汁淤积^[19]。鉴于MAFLD通常被视为肝硬化的主要病因^[20-21],在MAFLD患者中使用肝纤维化指标评估胆结石的患病风险具有重要临床价值。

近年来,炎症与胆结石之间的关联是研究热点。多项临床研究表明,来自全血细胞计数的炎症标志物(如NPAR、NLR和MLR),与成年人胆结石的形成显著相关^[22-23]。炎症期间产生的细胞因子,如白细胞介素1、白细胞介素6和肿瘤坏死因子 α ,会干扰协调胆囊收缩和胆汁释放的神经肌肉信号传导,从而加剧胆汁淤积^[24-25]。此外,氧化应激诱导产生的活性氧可以直接与胆汁中的脂质和胆固醇发生反应,形成氧化胆固醇衍生物。此类氧化产物在胆汁中的溶解度较差,更易促进胆固醇晶体的形成和聚集^[26]。

MAFLD患者中的代谢紊乱和炎症反应通常被认为与胆结石的患病率增加有关^[27]。因此,本研究纳入TyG、TyG-BMI、AIP和NHHR等与代谢相关的指标进行分析,发现其与MAFLD患者中的胆结石疾病并无显著关联,不能用于预测胆结石患病风险。既往几项横断面研究也显示^[8,28-29],TyG仅与非糖尿病个体中的胆结石相关,与糖尿病患者无显著关联。这可能是因为,在MAFLD患者中,甘油三酯、LDL-C和HDL-C等血脂指标已经处于高水平,在患胆结石和未患胆结石的个体之间无显著差异。

本研究结果显示肝纤维化可以介导炎症标志物与胆结石之间的关联,其中NFS的作用尤为突出。在MAFLD患者中,脂蛋白代谢失调可以激活循环免疫细胞,引发肝脏炎症级联反应,加重肝纤维化^[30]。同时,氧化应激在肝纤维化中也发挥重要作用。肝细胞脂肪堆积导致线粒体功能障碍和活性氧产生增加,而MAFLD患者的体内抗氧化酶活性降低,进而促进肝纤维化^[31]。此外,炎症细胞因子可以招募免疫细胞浸润肝脏,释放更多的炎症介质和活性氧,从而加重肝脏炎症和纤维化^[32]。

本研究也存在一定的局限性。首先,横断面研究无法探索因果关系。其次,缺乏长期用药史、饮食和运动、职业和收入水平的数据。最后,单次健康体检的数据仅能检测白蛋白、淋巴细胞、丙氨酸氨基转移酶和血小板在单个时间点的水平,这些血液指标会随着时间的推移而变化,因此无法确定其与胆结石动力学之间的关系。

伦理学声明:本研究于2024年2月6日经由扬州大学附属苏北人民医院伦理审查委员会审批通过,批号:2024ky024。

利益冲突声明:本文不存在任何利益冲突。

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参考文献:

- [1] RINELLA ME, LAZARUS JV, RATZIU V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature[J]. J Hepatol, 2023, 79(6): 1542-1556. DOI: 10.1016/j.jhep.2023.06.003.
- [2] KOYAMA Y, BRENNER DA. Liver inflammation and fibrosis in the US population: A nationally representative cross-sectional study using NHANES data from 2017 to 2020[J]. BMC Gastroenterol, 2024, 24(1): 300. DOI: 10.1186/s12876-024-03394-6.
- [3] LU YN, XU XL, WU JL, et al. Association between neutrophil-to-high-density lipoprotein cholesterol ratio and metabolic dysfunction-associated steatotic liver disease and liver fibrosis in the US population: A nationally representative cross-sectional study using NHANES data from 2017 to 2020[J]. BMC Gastroenterol, 2024, 24(1): 300. DOI: 10.1186/s12876-024-03394-6.
- [4] LIU ZY, ZHUANG YJ, DONG X, et al. Construction of a non-invasive diagnostic model for liver fibrosis in non-alcoholic fatty liver disease [J]. Chin J Med Offic, 2024, 52(7): 688-691. DOI: 10.16680/j.1671-3826.2024.07.07.
刘正一, 庄颖洁, 董旭, 等. 非酒精性脂肪性肝病肝纤维化无创诊断模型构建[J]. 临床军医杂志, 2024, 52(7): 688-691. DOI: 10.16680/j.1671-3826.2024.07.07.
- [5] PAN L, WANG LX, MA HJ, et al. Relevance of combined influence of nutritional and inflammatory status on non-alcoholic fatty liver disease and advanced fibrosis: A mediation analysis of lipid biomarkers[J]. J Gastroenterol Hepatol, 2024, 39(12): 2853-2862. DOI: 10.1111/jgh.16760.
- [6] ZHAO XY, WANG N, SUN YY, et al. Screen-detected gallstone disease and risk of liver and pancreatic cancer: The Kailuan Cohort Study[J]. Liver Int, 2020, 40(7): 1744-1755. DOI: 10.1111/liv.14456.
- [7] WANG YK, SHANG XC, ZHANG YC, et al. The association between neutrophil to high-density lipoprotein cholesterol ratio and gallstones: A cross-sectional study[J]. BMC Public Health, 2025, 25(1): 157. DOI: 10.1186/s12889-025-21392-5.
- [8] GONG L, FAN SJ, PENG ZF, et al. The association between triglyceride-glucose index and gallstones: NHANES 2017-2020[J]. Front Endocrinol, 2024, 15: 1437711. DOI: 10.3389/fendo.2024.1437711.
- [9] ZHANG YY, ZHANG JJ, YU D, et al. Association between metabolic dysfunction associated steatotic liver disease and gallstones in the US population using propensity score matching[J]. Sci Rep, 2025, 15(1): 910. DOI: 10.1038/s41598-025-85218-5.
- [10] DAWOD S, BROWN K. Non-invasive testing in metabolic dysfunction-associated steatotic liver disease[J]. Front Med, 2024, 11: 1499013. DOI: 10.3389/fmed.2024.1499013.
- [11] CHAN WK, CHUAH KH, RAJARAM RB, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD): A state-of-the-art review[J]. J Obes Metab Syndr, 2023, 32(3): 197-213. DOI: 10.7570/jomes23052.
- [12] ZENG YL, LIN L, CHEN JL, et al. Prognostic value of glycolipid metabolism index on complications and mechanical ventilation in intensive care unit patients with intracerebral hemorrhage: A retrospective cohort study using the MIMIC-IV database[J]. Front Neurol, 2025, 16: 1516627. DOI: 10.3389/fneur.2025.1516627.
- [13] ZAWIAH M, KHAN AH, ABU FARHA R, et al. Predictors of stroke-associated pneumonia and the predictive value of neutrophil percentage-to-albumin ratio[J]. Postgrad Med, 2023, 135(7): 681-689. DOI: 10.1080/00325481.2023.2261354.
- [14] HYDES TJ, KENNEDY OJ, GLYN-OWEN K, et al. Liver fibrosis assessed via noninvasive tests is associated with incident heart failure in a general population cohort[J]. Clin Gastroenterol Hepatol, 2024,

- 22(8): 1657-1667. DOI: 10.1016/j.cgh.2024.03.045.
- [15] TOYODA H, JOHNSON PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function[J]. JHEP Rep, 2022, 4(10): 100557. DOI: 10.1016/j.jhepr.2022.100557.
- [16] LUO S, WENG XL, XU J, et al. Correlation between ZJU index and hepatic steatosis and liver fibrosis in American adults with NAFLD[J]. Front Med, 2024, 11: 1443811. DOI: 10.3389/fmed.2024.1443811.
- [17] ACALOVSKI M. Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects[J]. World J Gastroenterol, 2014, 20(23): 7277-7285. DOI: 10.3748/wjg.v20.i23.7277.
- [18] MALLICK B, ANAND AC. Gallstone disease in cirrhosis: Pathogenesis and management[J]. J Clin Exp Hepatol, 2022, 12(2): 551-559. DOI: 10.1016/j.jceh.2021.09.011.
- [19] KUL K, SERIN E, YAKAR T, et al. Autonomic neuropathy and gallbladder motility in patients with liver cirrhosis[J]. Turk J Gastroenterol, 2015, 26(3): 254-258. DOI: 10.5152/tjg.2015.4469.
- [20] KANWAL F, KRAMER JR, LI L, et al. GLP-1 receptor agonists and risk for cirrhosis and related complications in patients with metabolic dysfunction-associated steatotic liver disease[J]. JAMA Intern Med, 2024, 184(11): 1314-1323. DOI: 10.1001/jamainternmed.2024.4661.
- [21] JIANG TT, DENG W, WANG SY, et al. Diagnosis and evaluation of fatty liver disease[J/OL]. Chin J Liver Dis (Electronic Version), 2024, 16(2): 22-28. DOI: 10.3969/j.issn.1674-7380.2024.02.005. 蒋婷婷, 邓雯, 王诗雨, 等. 脂肪性肝病的诊断和评估[J/OL]. 中国肝脏病杂志(电子版), 2024, 16(2): 22-28. DOI: 10.3969/j.issn.1674-7380.2024.02.005.
- [22] FU C, CHEN JH, WANG YX, et al. Association between complete blood cell count-derived inflammatory biomarkers and gallstones prevalence in American adults under 60 years of age[J]. Front Immunol, 2024, 15: 1497068. DOI: 10.3389/fimmu.2024.1497068.
- [23] WANG JJ, SHEN ZW, LIANG YW, et al. Association of neutrophil percentage to albumin ratio with gallstones: A cross-sectional study from the United States NHANES[J]. BMC Public Health, 2024, 24(1): 3503. DOI: 10.1186/s12889-024-21071-x.
- [24] WANG HH, PORTINCASA P, MENDEZ-SANCHEZ N, et al. Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones[J]. Gastroenterology, 2008, 134(7): 2101-2110. DOI: 10.1053/j.gastro.2008.03.011.
- [25] MAURER KJ, CAREY MC, FOX JG. Roles of infection, inflammation, and the immune system in cholesterol gallstone formation[J]. Gastroenterology, 2009, 136(2): 425-440. DOI: 10.1053/j.gastro.2008.12.031.
- [26] KÄRKKÄINEN J, ASPINEN S, HARJU J, et al. Plasma glutathione peroxidase (GPX1) levels and oxidative stress in gallstone patients operated with two different cholecystectomy techniques: A randomized study with special reference to cancer patients[J]. Anticancer Res, 2017, 37(12): 6921-6927. DOI: 10.21873/anticancer.12156.
- [27] JIANG GH, LI S, LI HY, et al. Bidirectional associations among gallstone disease, non-alcoholic fatty liver disease, kidney stone disease[J]. World J Gastroenterol, 2024, 30(46): 4914-4928. DOI: 10.3748/wjg.v30.i46.4914.
- [28] ZHANG S, LIU J, SHI XJ, et al. Association between triglyceride-glucose index and gallstones in women: A cross-sectional study[J]. J Clin Hepatol, 2025, 41(7): 1407-1413. DOI: 10.12449/JCH250727. 章帅, 刘军, 史茜菁, 等. 甘油三酯-葡萄糖(TyG)指数与女性胆囊结石的相关性分析[J]. 临床肝胆病杂志, 2025, 41(7): 1407-1413. DOI: 10.12449/JCH250727.
- [29] WANG JJ, LI H, HU JC, et al. Relationship of triglyceride-glucose index to gallstone prevalence and age at first gallstone surgery in American adults[J]. Sci Rep, 2024, 14(1): 16749. DOI: 10.1038/s41598-024-67883-0.
- [30] LAM SM, WANG ZH, SONG JW, et al. Non-invasive lipid panel of MASLD fibrosis transition underscores the role of lipoprotein sulfatides in hepatic immunomodulation[J]. Cell Metab, 2025, 37(1): 69-86.e7. DOI: 10.1016/j.cmet.2024.09.009.
- [31] JUAN CA, PÉREZ DE LA LASTRA JM, PLOU FJ, et al. The chemistry of reactive oxygen species (ROS) revisited: Outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies[J]. Int J Mol Sci, 2021, 22(9): 4642. DOI: 10.3390/ijms22094642.
- [32] MA M, JIANG W, ZHOU RB. DAMPs and DAMP-sensing receptors in inflammation and diseases[J]. Immunity, 2024, 57(4): 752-771. DOI: 10.1016/j.immuni.2024.03.002.

收稿日期: 2025-09-08;录用日期: 2025-12-02

本文编辑: 林姣

引证本文: ZHANG S, JIN SL, LI WQ, et al. Association of liver fibrosis markers and inflammation markers with the risk of gallstones in patients with metabolic dysfunction-associated fatty liver disease[J]. J Clin Hepatol, 2026, 42(3): 579-585. 章帅, 靳寿璐, 李晚情, 等. 代谢相关脂肪性肝病患者肝纤维化标志物、炎症标志物与胆结石患病风险的关联性分析[J]. 临床肝胆病杂志, 2026, 42(3): 579-585.