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TG/HDL-C联合肝功指标预测代谢相关脂肪性肝病的价值*

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【摘要】 **目的**　研究三酰甘油与高密度脂蛋白胆固醇比值（triglycerides to high-density lipoprotein cholesterol ratio, TG/HDL-C）联合肝功指标预测代谢相关脂肪性肝病（metabolic-associated fatty liver disease, MAFLD）的价值。**方法**　纳入明确诊断为MAFLD的门诊患者2 971例，健康对照人群2 794例，并收集相关数据。采用两样本Mann-Whitney *U*检验和二元logistic回归分析，研究TG/HDL-C与MAFLD的关系及构建MAFLD联合诊断模型，使用受试者工作特征（ROC）曲线筛选最优模型。**结果**　MAFLD患者的TG/HDL-C明显高于健康人群。在多因素分析中，调整体质量指数、收缩压、舒张压、空腹血糖、三酰甘油、高密度脂蛋白胆固醇、尿酸和肌酐后，TG/HDL-C的*OR*值为2.356（95%置信区间：1.028～5.400），TG/HDL-C是MAFLD的独立危险因素。进行ROC曲线分析，TG/HDL-C预测MAFLD的曲线下面积（area under the curve, *AUC*）为0.795（95%置信区间：0.784～0.807），cut-off值为1.09时，敏感性为0.679，特异性为0.755。由TG/HDL-C联合丙氨酸氨基转移酶、天门冬氨酸氨基转移酶和白蛋白建立的诊断模型的*AUC*为0.890（95%置信区间：0.882～0.898），cut-off值为0.47时，敏感性为0.792，特异性为0.839。**结论**　TG/HDL-C是MAFLD的独立危险因素，当其联合丙氨酸氨基转移酶、天门冬氨酸氨基转移酶、白蛋白时，可较好地预测MAFLD。

【关键词】 代谢相关脂肪性肝病　TG/HDL-C　诊断模型

Application of TG/HDL-C Combined with Liver Function Indexes to Predict Metabolic-Associated Fatty Liver Disease

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【**Abstract**】 **Objective**　To study the application of triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C) combined with liver function indexes to predict metabolic-associated fatty liver disease (MAFLD). **Methods**　A total of 2971 outpatients diagnosed with MAFLD and 2794 healthy controls were enrolled, and their relevant data were collected. Two-sample Mann-Whitney *U* test and binary logistic regression analysis were conducted to study the relationship between TG/HDL-C and MAFLD and to construct combined diagnosis models of MAFLD. The area under the curve (*AUC*) of receiver operating characteristic (ROC) was used to pick out the optimal model. **Results**　The TG/HDL-C of MAFLD patients was significantly higher than that of healthy controls. In multivariate analysis, after adjusting for body mass index, systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglycerides, high-density lipoprotein cholesterol, uric acid and creatinine, the odds ratio of TG/HDL-C was 2.356 (95% confidence interval [*CI*]: 1.028-5.400). Therefore, TG/HDL-C was an independent risk factor for MAFLD. ROC curve analysis showed that the *AUC* of using TG/HDL-C to predict MAFLD was 0.795 (95% *CI*: 0.784-0.807), and when the cut-off value was 1.09, the sensitivity was 0.679 and the specificity was 0.755. The *AUC* of the diagnosis model established by a combined use of TG/HDL-C, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin (ALB) was 0.890 (95% *CI*: 0.882-0.898), and when the cut-off value was 0.47, the sensitivity and specificity were 0.792 and 0.839, respectively. **Conclusion**　TG/HDL-C is an independent risk factor for MAFLD. TG/HDL-C can well predict MAFLD when it is used in combination with ALT, AST, and ALB.

【**Key words**】 Metabolic-associated fatty liver disease　TG/HDL-C　Diagnosis model

代谢相关脂肪性肝病（metabolic-associated fatty liver disease, MAFLD）是一种以肝脂肪变性为特征的临床综合征，是全球最常见的慢性肝病[1-2]，估计全球患病率为25.24%[3]。随着MAFLD全球流行率的急剧上升，它经常与其他疾病共存[4]。MAFLD患者不仅有肝脏相关并发症（肝硬化和/或肝癌）的风险，而且还与不良心血管事件相关，这是其死亡的主要原因[3]。MAFLD以前被称为非酒精性脂肪性肝病（nonalcoholic fatty liver disease, NAFLD），ESLAM、GEORGE等专家国际小组在2020年将其更名为MAFLD。MAFLD可从简单的脂肪变性发展为脂肪性肝炎，并最终发展为终末期肝病，MAFLD患者存在发生肝纤维化的高风险[5]。因此提高MAFLD的早期诊断，及早进行干预，对改善患者的预后具有重要的意义。

目前，MAFLD的肝脂肪变性需影像学检查或肝活检来确定。尽管B超、CT及MRI可用于MAFLD的定性诊断，但敏感性欠佳。磁共振波谱分析能检测5%以上的脂

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肪变，但费用高，难以普及。肝活检作为一种侵入性方法，不仅因取样量小，对疾病的诊断及严重程度评估造成偏差，而且有很多潜在并发症，如出血、腹部不适、疼痛等，常不被患者接受[6]。虽然新的专家共识肯定了血液生物标志物在诊断MAFLD中的价值，但是目前临床上仍缺乏有效的生物标志物。因此，挖掘MAFLD生物标记物已成为临床迫切的需求。

近年来，三酰甘油与高密度脂蛋白胆固醇比值（triglycerides to high-density lipoprotein cholesterol ratio, TG/HDL-C）受到越来越多的关注。研究表明TG/HDL-C是高血压[7]、心血管疾病[8]、糖尿病[9]、代谢综合征[10]、高尿酸血症[11]和慢性肾病[12]的预测指标。对TG/HDL-C进行严格的监测和控制，有助于预防肾功能障碍，特别是对于超重或处于糖尿病或高血压边缘的人群[13]。已有研究表明，TG/HDL-C在不同的人群中均与胰岛素抵抗（insulin resistance, IR）密切相关，并且建议使用TG/HDL-C作为IR的替代指标[14]，且IR是MAFLD的重要预测因素[15]。值得注意的是，一些研究表明TG/HDL-C与MAFLD有关，TG/HDL-C的升高与脂肪肝发生和MAFLD风险增加密切相关，TG/HDL-C是发生脂肪肝的独立预测因素[16]，TG/HDL-C可用作MAFLD的一个辅助诊断指标[17]。但TG/HDL-C与MAFLD的研究目前尚不多，需要进一步研究TG/HDL-C和MAFLD之间的关系。本研究旨在分析我国西南地区人群TG/HDL-C与MAFLD的关系及其联合肝功指标建立诊断模型，以期为MAFLD的临床预测提供帮助。

1　资料与方法

1.1　研究人群

收集2016年5月–2020年5月于四川大学华西医院就诊且被诊断为MAFLD的门诊患者作为病例组。MAFLD的纳入标准按照更名前的指南制定：①具有完整人体测量参数、实验室测试结果和肝腹部超声检查结果的患者；②按照《中国非酒精性脂肪性肝病诊疗指南（2010年修订版）》被确诊为NAFLD的患者。MAFLD的排除标准：①人体测量参数或实验室检查结果不全的患者；②近两周内正在接受口服降血脂药物治疗的患者；③接受已知促进肝脂肪变性药物（例如：他莫昔芬、胺碘酮、雌激素或皮质类固醇）治疗的患者；④恶性肿瘤或其他严重器官功能障碍疾病的患者；⑤妊娠期、哺乳期女性；⑥其他慢性肝病患者（包括过量饮酒造成的肝脏疾病、病毒性肝病、自身免疫性肝病等）；⑦心血管疾病患者；⑧人类免疫缺陷病毒患者；⑨移植患者。收集同期与病例组性别相匹配的表观健康体检人群为对照组。本研究已获四川大学华西医院生物医学伦理审查委员会批准（2020年审1096号），所有数据均采用匿名分析。

1.2　数据收集

收集身高、体质量、腰臀比（waist-to-hip ratio, WHR）、收缩压（systolic blood pressure, SBP）、舒张压（diastolic blood pressure, DBP）、体质量指数（body mass index, BMI）等人体测量参数。同时收集实验室检查数据，包括总胆固醇（total cholesterol, TC）、三酰甘油（triglycerides, TG）、高密度脂蛋白胆固醇（high-density lipoprotein cholesterol, HDL-C）、低密度脂蛋白胆固醇（low-density lipoprotein cholesterol, LDL-C）、总蛋白（total protein, TP）、白蛋白（albumin, ALB）、球蛋白（globulin, GLB）、总胆红素（total bilirubin, TBIL）、直接胆红素（direct bilirubin, DBIL）、间接胆红素（indirect bilirubin, IBIL）、丙氨酸氨基转移酶（alanine aminotransferase, ALT）、天门冬氨酸氨基转移酶（aspartate aminotransferase, AST）、碱性磷酸酶（alkaline phosphatase, ALP）、γ-谷氨酰转肽酶（γ-glutamyl transpeptidase, GGT）、肌酸激酶（creatine kinase, CK）、乳酸脱氢酶（lactate dehydrogenase, LDH）、α-羟丁酸脱氢酶（alpha-hydroxybutyrate dehydrogenase, HBDH）、空腹血糖（fasting blood glucose, FPG）、尿素（urea, UREA）、尿酸（uric acid, URIC）、肌酐（creatinine, CREA）、胱抑素c（cystatin c, CYs-C）。

残余胆固醇（residual cholesterol, RC）等于TC减去HDL-C与LDL-C之和；非高密度脂蛋白胆固醇（non-high density lipoprotein cholesterol, Non-HDL-C）等于TC减去HDL-C。

1.3　统计学方法

连续变量用中位数（四分位间距）表示，分类变量采用百分率表示。用两样本Mann-Whitney *U*检验对非正态分布变量进行非参数比较，用二元logistic回归分析对TG/HDL-C和MAFLD的关系进行评估并探索对MAFLD诊断的最佳模型，用受试者工作特征（receiver operator characteristic, ROC）曲线分析TC、TG、ALT、AST、RC、Non-HDL-C、TG/HDL-C及联合诊断模型对MAFLD诊断的能力，并计算ROC曲线下面积（area under the curve, *AUC*）。$P<0.05$为差异有统计学意义。

2　结果

2.1　研究人群的基本特征

本研究共收集MAFLD患者22 927例，排除19 956例，最终纳入2 971例。纳入研究的病例组中男性1 546例（52.0%），女性1 425例（48.0%），年龄47（38 ~ 55）岁。对照

组共2 794例,男性1 425例(51.0%),女性1 369例(49.0%),年龄47(42 ~ 53)岁。病例组和对照组年龄、性别、WHR、TP、TC、LDL-C比较,差异无统计学意义。两组BMI、SBP、DBP、TBIL、DBIL、IBIL、ALB、GLB、TG、HDL-C、ALT、AST、ALP、GGT、CK、LDH、HBDH、FPG、UREA、CREA、URIC、CYs-C、Non-HDL-C、RC、TG/HDL-C比较,差异均有统计学意义(P< 0.05)。与对照组相比,病例组BMI、TBIL、DBIL、IBIL、GLB、TG、ALT、AST、ALP、GGT、CK、LDH、HBDH、FPG、UREA、URIC、CYs-C、Non-HDL-C、RC、TG/HDL-C水平增高,SBP、DBP、ALB、HDL-C、CREA水平降低。见表1。

2.2 TG/HDL-C与MAFLD的关系

用二元logistic回归分析TG/HDL-C与MAFLD的关系。在未经调整的单变量分析中,TG/HDL-C的OR值为4.476(95%置信区间:4.036 ~ 4.963);经调整BMI、SBP、DBP后,TG/HDL-C的OR值为3.297(95%置信区间:

表 1 代谢相关脂肪性肝病组与健康对照组基本特征的比较

Table 1 Comparison of basic characteristics of the metabolic-associated fatty liver disease group and the healthy control group

Variable	MAFLD group (n=2971)	Normal group (n=2794)	P
Age/yr., median (P_{25}-P_{75})	47 (38-55)	47 (42-53)	0.720
Male/case (%)	1 546 (52.0)	1 425 (51.0)	0.432
BMI/(kg/m^2), median (P_{25}-P_{75})	24.1 (21.5-26.6)	22.5 (20.8-24.3)	<0.001
WHR (median [P_{25}-P_{75}])	0.82 (0.77-0.87)	0.83 (0.78-0.88)	0.650
SBP/mmHg, median (P_{25}-P_{75})	109 (102-121)	116 (108-123)	<0.001
DBP/mmHg, median (P_{25}-P_{75})	69 (64-75)	71 (65-77)	0.047
TBIL/(μmol/L), median (P_{25}-P_{75})	12.7 (9.6-16.8)	11.7 (9.4-14.8)	<0.001
DBIL/(μmol/L), median (P_{25}-P_{75})	3.6 (2.7-4.9)	3.5 (2.8-4.4)	<0.001
IBIL/(μmol/L), median (P_{25}-P_{75})	8.9 (6.6-11.9)	8.2 (6.5-10.5)	<0.001
TP/(g/L), median (P_{25}-P_{75})	75.3 (72.0-78.4)	75.3 (72.8-78.0)	0.222
ALB/(g/L), median (P_{25}-P_{75})	47.3 (44.7-49.4)	48.0 (46.3-49.7)	<0.001
GLB/(g/L), median (P_{25}-P_{75})	27.8 (25.2-30.7)	27.3 (25.0-29.4)	<0.001
TC/(mmol/L), median (P_{25}-P_{75})	4.69 (4.06-5.39)	4.67 (4.22-5.17)	0.106
TG/(mmol/L), median (P_{25}-P_{75})	1.73 (1.23-2.52)	1.03 (0.77-1.35)	<0.001
HDL-C/(mmol/L), median (P_{25}-P_{75})	1.14 (0.95-1.37)	1.39 (1.18-1.66)	<0.001
LDL-C/(mmol/L), median (P_{25}-P_{75})	2.75 (2.18-3.30)	2.78 (2.36-3.21)	0.053
ALT/(IU/L), median (P_{25}-P_{75})	34 (22-55)	18 (13-24)	<0.001
AST/(IU/L), median (P_{25}-P_{75})	28 (22-39)	20 (18-24)	<0.001
ALP/(IU/L), median (P_{25}-P_{75})	81 (67-99)	70 (58-83)	<0.001
GGT/(IU/L), median (P_{25}-P_{75})	35 (21-67)	17 (12-27)	<0.001
CK/(IU/L), median (P_{25}-P_{75})	95 (70-130)	90 (70-119)	<0.001
LDH/(IU/L), median (P_{25}-P_{75})	196 (169-230)	170 (154-189)	<0.001
HBDH/(IU/L), median (P_{25}-P_{75})	149 (129-175)	132 (120-147)	<0.001
FPG/(mmol/L), median (P_{25}-P_{75})	5.35 (4.90-6.02)	4.87 (4.59-5.17)	<0.001
UREA/(mmol/L), median (P_{25}-P_{75})	4.8 (3.9-5.7)	4.5 (3.9-5.3)	<0.001
CREA/(μmol/L), median (P_{25}-P_{75})	67 (56-79)	71 (62-78)	<0.001
URIC/(μmol/L), median (P_{25}-P_{75})	353 (294-417)	301 (255-351)	<0.001
CYs-C/(mg/L), median (P_{25}-P_{75})	0.85 (0.77-0.95)	0.76 (0.70-0.83)	<0.001
Non-HDL-C/(mmol/L), median (P_{25}-P_{75})	3.52 (2.90-4.18)	3.24 (2.75-3.72)	<0.001
RC/(mmol/L), median (P_{25}-P_{75})	0.67 (0.46-0.96)	0.43 (0.32-0.55)	<0.001
TG/HDL-C (median [P_{25}-P_{75}])	1.50 (0.95-2.51)	0.73 (0.49-1.08)	<0.001

BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; TP: Total protein; ALB: Albumin; GLB: Globulin; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; CK: Creatine kinase; LDH: Lactate dehydrogenase; HBDH: Alpha-hydroxybutyrate dehydrogenase; FPG: Fasting blood glucose; UREA: Urea; CREA: Creatinine; URIC: Uric acid; CYs-C: Cystatin c; Non-HDL-C: Non-high density lipoprotein cholesterol; RC: Residual cholesterol; TG/HDL-C: Triglycerides to high-density lipoprotein ratio.

2.739 ~ 3.968)；经调整BMI、SBP、DBP、FPG、TG、HDL-C、URIC和CREA后，TG/HDL-C的*OR*值为2.356(95%置信区间：1.028 ~ 5.400)。由此可见，TG/HDL-C是MAFLD的独立风险因子。

2.3　联合诊断模型构建及其对MAFLD的诊断效能分析

采用二元logistic回归将表1中差异有统计学有意义的指标进行多个指标联合构建MAFLD诊断模型，最终得到TG/HDL-C联合ALT、AST、ALB的最优模型(*AUC*最大，且敏感性和特异性最高)。为了评估该联合诊断模型对MAFLD的预测能力，本研究对TG/HDL-C、TC、TG、ALT、AST、RC、Non-HDL-C及联合诊断模型进行ROC曲线分析。如表2所示，TG/HDL-C的*AUC*为0.795(95%置信区间：0.784 ~ 0.807)，高于TG、RC、Non-HDL-C、AST的诊断能力($P<0.05$)，与ALT的效果等同($P>0.05$)。TG/HDL-C的cut-off值为1.09时，诊断敏感性为0.679，特异性为0.755。纳入TG/HDL-C、ALT、AST、ALB建立的联合诊断模型的*AUC*为0.890(95%置信区间：0.882 ~ 0.898)，均大于TG、ALT、AST、RC、Non-HDL-C、TG/HDL-C的*AUC*($P<0.05$)，联合诊断模型的cut-off值为0.47时，诊断敏感性为0.792，特异性为0.839(图1)。故与单个指标相比，TG/HDL-C联合ALT、AST、ALB时能更好地预测MAFLD。

表 2　生物指标与联合诊断模型在MAFLD中的*AUC*

Table 2　*AUC* of biological indicators and combined diagnosis model for MAFLD

Variable	*AUC*	95% *CI*	Cut-off value	Sensitivity	Specificity	*P*
TC	0.512	0.497-0.527	5.79 mmol/L	0.161	0.957	0.106
TG	0.793	0.782-0.805	1.48 mmol/L	0.621	0.816	<0.001
ALT	0.801	0.790-0.812	27 IU/L	0.637	0.817	<0.001
AST	0.778	0.766-0.790	26 IU/L	0.593	0.839	<0.001
RC	0.746	0.734-0.759	0.61 mmol/L	0.577	0.830	<0.001
Non-HDL-C	0.599	0.584-0.613	3.83 mmol/L	0.378	0.804	<0.001
TG/HDL-C	0.795	0.784-0.807	1.09	0.679	0.755	<0.001
Combined diagnosis model	0.890	0.882-0.898	0.47	0.792	0.839	<0.001

TC, TG, ALT, AST, RC, Non-HDL-C, and TG/HDL-C: The denotaions are the the same as those in table 1; *AUC*: Area under the curve; *CI*: Confidence interval.

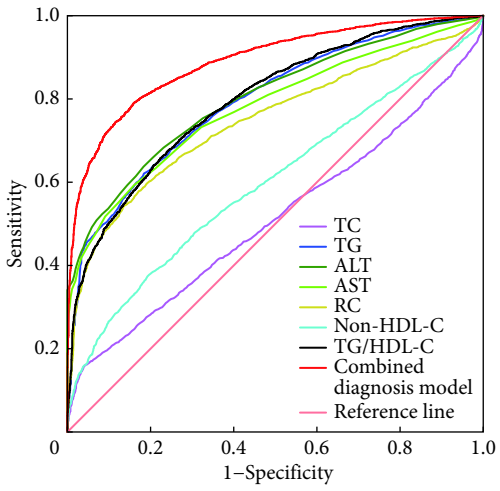

图 1　各生化指标及联合诊断模型的ROC曲线

Fig 1　ROC curve of each biochemical index and the combined diagnosis model

TC, TG, ALT, AST, RC, Non-HDL-C, and TG/HDL-C: The denotaions are the the same as those in table 1.

3　讨论

MAFLD被认为是全球最常见的慢性肝病，随着新的诊断标准的制定，它不需要排除饮酒或其他伴随的肝病[1-2]，新的定义明确提出MAFLD的诊断标准是通过影像学、血液生物标志物或肝组织学检查明确肝脂肪变性，并有超重/肥胖、2型糖尿病或代谢失调三者之一[1]。MAFLD发病机制很复杂，受多种因素的影响。研究表明，肠道微生物失调、种族差异、环境因素(酗酒、不健康的饮食习惯)和遗传倾向，都可能会引起MAFLD代谢异常[18]。此外，脂肪酸转运酶、CD36促进了肝脏对游离脂肪酸的摄取，增加单糖摄入，均会导致MAFLD的发展[19]。虽然TG/HDL-C和MAFLD之间的联系机制尚未被完全阐明，但IR与MAFLD密切相关，IR是MAFLD发展和进展的关键[20-22]。TG/HDL-C已被证明是IR的替代指标[14-15]，它在MAFLD发病机制中起着核心作用。TG/HDL-C和MAFLD之间的关系受IR和脂联素的影响。IR可以促进分泌较大且TG过度富集的极低密度脂蛋白颗粒，降低HDL-C的浓度，从而导致TG/HDL-C增加[23]。脂联素可增加血清HDL-C浓度，相反地降低血清TG浓度[24]。有研究表明，在血脂水平正常的非肥胖患者中，TG/HDL-C升高的受试者MAFLD风险增高[25]。WU等[26]研究也发现，TG/HDL-

C值越高，患MAFLD的风险越大，尤其是在MAFLD进展期。虽然已有TG/HDL-C与MAFLD相关的研究，但研究数据并不多，需要更多的研究来验证。

本研究中，MAFLD患者肝功指标ALT、AST、ALP、GGT、LDH等，肾功指标UREA、URIC、CYs-C，以及血脂指标TG、Non-HDL-C、RC、TG/HDL-C明显高于对照组，而HDL-C、ALB低于对照组。该结果与FAN等[17]的研究结果一致。本研究二元logistic回归分析中，未经调整的单变量分析发现TG/HDL-C是MAFLD的危险因素。在对BMI、SBP、DBP、FPG、TG、HDL-C、URIC和CREA进行调整后，TG/HDL-C仍然与MAFLD相关，说明TG/HDL-C是MAFLD的独立危险因素。在一项涉及儿童和青少年样本的大样本横断面研究也证实TG/HDL-C与NAFLD独立相关[27]。

为了进一步探究TG/HDL-C对MAFLD的诊断价值，本研究用ROC曲线分析TG/HDL-C诊断MAFLD的*AUC*值。与其他血脂参数和肝功能的标记物相比，TG/HDL-C有较高的*AUC*值，诊断价值等同于ALT，其诊断敏感性和特异性分别为0.679和0.755。一项研究显示，与其他脂质指标相比，TG/HDL-C可以更好地预测非肥胖人群中的MAFLD[25]。同时，本研究将TG/HDL-C与其他脂质指标及肝功标志物进行诊断模型探索，最后得到TG/HDL-C和ALT、AST、ALB构建的联合诊断模型，该模型*AUC*为0.890（95%置信区间：0.882～0.898），比TG、ALT、AST、RC、Non-HDL-C、TG/HDL-C的*AUC*均显著增大，诊断敏感性和特异性分别为0.792、0.839，该联合诊断模型对MAFLD的诊断价值比单个上述指标更好。李楠等[28]研究发现，TG和HDL-C分别是MAFLD的危险因素和保护因素。由此可见，TG、HDL-C以及其比值在MAFLD诊断中具有重要价值。

本研究也存在一定的局限性。首先，没有对MAFLD的严重程度进行分组分析。其次，本研究未评估饮食习惯的影响。最后，本研究属于横断面研究，不能对TG/HDL-C和MAFLD的关系进行因果判断。因此，需要更大样本和多中心的研究来进一步证实。

综上，TG/HDL-C是MAFLD的独立危险因素，当TG/HDL-C联合ALT、AST、ALB时，可较好的预测MAFLD。

* * *

利益冲突 所有作者均声明不存在利益冲突

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