Correlation Between Albumin-to-Gamma-Glutamyl Transferase Ratio and Type 2 Diabetes Mellitus with Comorbid Metabolic Dysfunction-Associated Fatty Liver Disease: A Postprint

Authors: Yan Ziwei, Nie Jiahua, Shi Yan, Wei Limin, Wei Limin

Date: 2025-06-17T00:00:00+00:00

Abstract

Background: In recent years, the incidence and prevalence of metabolic-associated fatty liver disease (MAFLD) have been increasing annually, with over a quarter of the global population afflicted by MAFLD. Type 2 diabetes mellitus (T2DM) is closely associated with MAFLD; however, there are currently few simple and accurate predictive indicators for T2DM patients with concurrent MAFLD. Objective: To investigate the correlation between the albumin/γ-glutamyl transferase ratio (AGTR) and T2DM with MAFLD, and to construct a nomogram prediction model for the risk of developing T2DM with MAFLD. Methods: A total of 1,050 adult patients with T2DM hospitalized in the Department of Endocrinology at Hebei Provincial People' s Hospital from 2018 to 2023 were selected as study subjects. After multiple rounds of rigorous screening, 723 patients ultimately met the study criteria and were enrolled, including 430 in the T2DM with MAFLD group and 293 in the T2DM alone group. Baseline patient data were collected and analyzed, and MAFLD was diagnosed by ultrasound. Spearman correlation analysis was employed to evaluate the correlation between AGTR and MAFLD risk factors. Multivariate logistic regression analysis was utilized to explore risk factors for T2DM with MAFLD, and an individualized nomogram model for predicting the risk of T2DM with MAFLD was constructed and validated accordingly. Results: Compared with the T2DM alone group, the T2DM with MAFLD group exhibited significantly higher levels of BMI, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), bile acid (BA), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (ApoB), and uric acid (UA), whereas age, diabetes duration, ALB, and HDL-C levels were significantly lower

(P<0.05). Patients were stratified into T1-T3 groups based on AGTR tertiles. Comparison of baseline characteristics among the three groups revealed that the T3 group had lower BMI, ALT, GGT, FBG, TC, TG, LDL-C, VLDL-C, ApoB, and UA, lower AST than the T1 group, and higher age and diabetes duration than the T2 and T1 groups (P<0.05). The T2 group had lower BMI, ALT, AST, GGT, TG, VLDL-C, and UA than the T1 group (P<0.05). Spearman correlation analysis demonstrated that AGTR was positively correlated with age, diabetes duration, ALB, and HDL-C (P<0.05), and negatively correlated with VLDL-C, BMI, ALT, AST, GGT, BA, FBG, TC, TG, LDL-C, ApoB, and UA (P<0.05). Multivariate logistic regression analysis revealed that elevated BMI and TG [OR (95%CI) = 1.256 (1.187-1.330), 1.272 (1.043-1.551)] and decreased AGTR [OR (95%CI) = 0.707 (0.562-0.890)] were influencing factors for T2DM with MAFLD. ROC curve analysis demonstrated that the AUC of the three-factor combined model for predicting MAFLD in T2DM was 0.827 (95%CI=0.790-0.864). The calibration curve indicated that predicted values were close to the ideal curve, suggesting good consistency. Clinical decision curve analysis demonstrated that the model had good clinical predictive efficacy for T2DM with MAFLD. Conclusion: Decreased AGTR is a protective factor for T2DM with MAFLD. The individualized nomogram model constructed based on BMI, TG, and AGTR can effectively predict the risk of T2DM with MAFLD.

Full Text

Correlation between the Albumin/Gamma-glutamyl Transferase Ratio and Metabolic-associated Fatty Liver Disease in Type 2 Diabetes Mellitus

YAN Ziwei[1],[2], NIE Jiahua[1], SHI Yan[3], WEI Limin[2]*

[1]Graduate School, Hebei Medical University, Shijiazhuang 050000, China
[2]Department of Endocrinology, Hebei General Hospital, Shijiazhuang 050000, China
[3]Graduate School, Hebei North University, Zhangjiakou 075000, China

Corresponding author: WEI Limin, Chief Physician; E-mail: 15133130672@163.com

---

Abstract

Background The incidence and prevalence of metabolic-associated fatty liver disease (MAFLD) have increased annually in recent years, affecting more than one-quarter of the global population. Type 2 diabetes mellitus (T2DM) is closely associated with MAFLD, yet simple and accurate predictive indicators for MAFLD in T2DM patients remain scarce. **Objective** To investigate the correlation between the albumin/gamma-glutamyl transferase ratio (AGTR) and

T2DM with MAFLD, and to construct a nomogram model for predicting the risk of T2DM combined with MAFLD. **Methods** A total of 1,050 adult patients with T2DM hospitalized in the Department of Endocrinology at Hebei General Hospital between 2018 and 2023 were enrolled. After multiple rounds of rigorous screening, 723 patients met the inclusion criteria and were included in the study, comprising 430 cases in the T2DM with MAFLD group and 293 cases in the T2DM without MAFLD group. Patient baseline data were collected and analyzed, and MAFLD was diagnosed by ultrasound. Spearman correlation analysis was used to examine the relationship between AGTR and MAFLD risk factors. Multivariate logistic regression analysis was employed to identify risk factors for T2DM with MAFLD, and an individualized nomogram model for predicting the risk of T2DM with MAFLD was constructed and validated. **Results** Compared with the T2DM without MAFLD group, the T2DM with MAFLD group exhibited significantly higher levels of body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bile acids (BA), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (ApoB), and uric acid (UA), while age, diabetes duration, albumin (ALB), and high-density lipoprotein cholesterol (HDL-C) were significantly lower ($P<0.05$). When patients were divided into T1–T3 groups according to AGTR tertiles, the T3 group showed lower BMI, ALT, GGT, FBG, TC, TG, LDL-C, VLDL-C, ApoB, and UA compared with the T1 and T2 groups, while HDL-C and AST were lower than in the T1 group; age and diabetes duration were higher than in the T1 and T2 groups ($P<0.05$). The T2 group exhibited lower BMI, ALT, AST, GGT, TG, VLDL-C, and UA compared with the T1 group ($P<0.05$). Spearman correlation analysis revealed that AGTR was positively correlated with age, diabetes duration, ALB, and HDL-C ($P<0.05$), and negatively correlated with VLDL-C, BMI, ALT, AST, GGT, BA, FBG, TC, TG, LDL-C, ApoB, and UA ($P<0.05$). Multivariate logistic regression analysis showed that increased BMI [OR (95%CI) = 1.256 (1.187-1.330)], increased TG [OR (95%CI) = 1.272 (1.043-1.551)], and decreased AGTR [OR (95%CI) = 0.707 (0.562-0.890)] were influencing factors for T2DM with MAFLD. ROC curve analysis demonstrated that the combined model of the three factors predicted MAFLD in T2DM patients with an AUC of 0.827 (95%CI = 0.790-0.864). The calibration curve showed that predicted values were close to the ideal curve, indicating good consistency, and clinical decision curve analysis revealed that the model had good clinical predictive utility for T2DM with MAFLD. **Conclusion** Decreased AGTR is a protective factor for T2DM with MAFLD. The individualized nomogram model constructed based on BMI, TG, and AGTR can effectively predict the risk of T2DM with MAFLD.

Keywords: Metabolic-associated fatty liver disease; Diabetes mellitus, type 2; Albumin; Gamma-glutamyl transferase; Albumin/gamma-glutamyl transferase ratio; Root cause analysis

Introduction

With improving living standards, the incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) have gradually increased. In 2016, NAFLD patients accounted for 25% of the world population, and the global prevalence of NAFLD reached 38% in 2019. It is projected that 20 million patients will ultimately die from liver disease related to NAFLD, imposing a substantial economic burden on society. In 2020, NAFLD and non-alcoholic steatohepatitis were renamed and redefined as metabolic-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatohepatitis (MASH). Currently, pathological biopsy remains the gold standard for diagnosing fatty liver disease, but its invasive nature limits widespread clinical use. Therefore, investigating practical, straightforward, and reliable predictive factors for fatty liver disease holds significant clinical value.

Recent studies have demonstrated that type 2 diabetes mellitus (T2DM) is a crucial risk factor for MAFLD development. T2DM can drive the progression of MAFLD from simple hepatic steatosis to steatohepatitis and fibrosis, and the risk of MAFLD is significantly higher in patients with diabetes compared with non-diabetic individuals. Consequently, investigating predictive factors for T2DM with MAFLD carries substantial clinical importance. The albumin/gamma-glutamyl transferase ratio (AGTR) is a recently proposed inflammatory marker that has been confirmed as a protective factor for MAFLD. Furthermore, research has shown that T2DM induces free radical production, which leads to decreased serum albumin, while GGT is closely associated with T2DM and serves as an important predictor, with T2DM risk increasing as GGT levels rise. Therefore, AGTR is also closely related to T2DM, though its predictive value for T2DM with MAFLD remains unclear. This study retrospectively analyzed the relationship between T2DM with MAFLD and AGTR and established an individualized prediction model for the risk of T2DM with MAFLD.

Methods

1.1 Clinical Data We retrospectively selected 1,050 adult patients with T2DM hospitalized in the Department of Endocrinology at Hebei General Hospital from 2018 to 2023 as the study population. After multiple rounds of rigorous screening, 723 patients met the inclusion criteria and were enrolled, including 430 cases with T2DM and MAFLD and 293 cases without MAFLD [Figure 1: see original paper]. T2DM diagnosis followed the 1999 WHO criteria, and MAFLD was diagnosed based on hepatic steatosis accompanied by overweight or obesity, T2DM, or two or more metabolic risk abnormalities.

Exclusion criteria were: (1) type 1 diabetes, gestational diabetes, or pregnant women; (2) T2DM patients under 18 years of age; (3) acute diabetic complications such as ketoacidosis, hyperosmolar hyperglycemic syndrome, or hypoglycemic coma; (4) history of hepatitis B or C, liver cirrhosis, or liver surgery; and (5) recent severe systemic diseases (infectious diseases, kidney disease, severe cardiovascular or cerebrovascular disease, cancer, blood disorders). This study was approved by the Ethics Committee of Hebei General Hospital (Approval No. 2025-LM-0072).

1.2 Research Methods We collected basic patient information (age, diabetes duration) and measured height and weight to calculate BMI. After an 8-10 hour fast, elbow venous blood samples were collected by professional medical staff the following morning. Fasting blood glucose (FBG), uric acid (UA), serum creatinine (Cr), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bile acids (BA), and albumin (ALB) were measured using an automatic biochemical analyzer, and AGTR was calculated. Hepatic steatosis was diagnosed by abdominal ultrasound.

1.3 Grouping Based on ultrasound findings, patients were divided into a T2DM without MAFLD group (n=293) and a T2DM with MAFLD group (n=430).

1.4 Statistical Analysis Data analysis was performed using SPSS 25.0 and R software version 4.2.2 (with rms and caret packages). Continuous variables were expressed as mean ± standard deviation if normally distributed, and intergroup comparisons were made using independent t-tests. Non-normally distributed data were expressed as median (P25, P75), with comparisons between two groups using the Mann-Whitney U test and among multiple groups using the Kruskal-Wallis H test. Spearman rank correlation analysis was used to explore the relationship between AGTR and MAFLD-related indicators. Multivariate logistic regression analysis was employed to identify influencing factors for T2DM with MAFLD. Based on the regression results, a nomogram model was developed to predict individualized risk of T2DM with MAFLD. Bootstrap resampling was used for internal validation, and a calibration curve was plotted to assess clinical consistency. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value for T2DM patients with MAFLD, and decision curve analysis was performed to assess clinical applicability. $P<0.05$ was considered statistically significant.

Results

2.1 Baseline Characteristics of T2DM and T2DM with MAFLD Groups Compared with the T2DM without MAFLD group, the T2DM with

MAFLD group showed significantly higher levels of body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bile acids (BA), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (ApoB), and uric acid (UA), while age, diabetes duration, albumin (ALB), and high-density lipoprotein cholesterol (HDL-C) were significantly lower (P<0.05) .

2.2 Comparison of General Data Across AGTR Tertile Groups Patients were further divided into three groups according to AGTR tertiles: T1 group (AGTR 0.036-1.116), T2 group (AGTR 1.117-1.918), and T3 group (AGTR 1.919-5.458). Significant differences were observed among the three groups in age, diabetes duration, BMI, ALB, ALT, AST, GGT, FBG, TC, TG, HDL-C, LDL-C, VLDL-C, ApoB, and UA (P<0.05). The T3 group had lower BMI, ALT, GGT, FBG, TC, TG, LDL-C, VLDL-C, ApoB, and UA compared with the T1 and T2 groups, while HDL-C and AST were lower than in the T1 group; age and diabetes duration were higher than in the T1 and T2 groups (P<0.05). The T2 group showed lower BMI, ALT, AST, GGT, TG, VLDL-C, and UA compared with the T1 group (P<0.05). No significant differences were found in BA, ApoA1, or Cr among the three groups (P>0.05) .

2.3 Correlation Analysis Between AGTR and General Parameters Spearman rank correlation analysis revealed that AGTR was positively correlated with age, diabetes duration, ALB, and HDL-C (rs=0.267, 0.146, 0.258, 0.152, respectively, P<0.05), and negatively correlated with BMI, ALT, AST, GGT, BA, FBG, TC, TG, VLDL-C, LDL-C, ApoB, and UA (rs=-0.310, -0.266, -0.319, -0.390, -0.094, -0.216, -0.308, -0.169, -0.184, -0.143, -0.148, -0.222, respectively, P<0.05) .

2.4 Multivariate Logistic Regression Analysis of Factors Associated with T2DM and MAFLD Using the presence or absence of MAFLD as the dependent variable (assignment: yes=1, no=0) and the indicators with P<0.05 in Table 1 (age, BMI, diabetes duration, AST, ALT, BA, UA, FBG, TC, TG, HDL-C, LDL-C, VLDL-C, ApoB, AGTR) as independent variables (assignment: actual values), multivariate logistic regression analysis showed that BMI, TG, and AGTR were influencing factors for T2DM with MAFLD (P<0.05) .

2.5 Construction of a Nomogram Model for Predicting T2DM with MAFLD Risk Based on the multivariate logistic regression results, an individualized nomogram model for predicting the risk of T2DM with MAFLD was constructed, incorporating three predictors: BMI, TG, and AGTR [Figure 2: see original paper].

2.6 Validation of the Nomogram Risk Prediction Model Using bootstrap resampling for internal validation, the calibration curve was close to the Y=X line. Hosmer-Lemeshow goodness-of-fit test for the calibration curve yielded P=0.606 (P>0.05), indicating good model fit [Figure 3: see original paper]. The ROC curve showed an AUC of 0.827 (95%CI=0.790-0.864, P<0.001), with a sensitivity of 68.8% and specificity of 83.8%, suggesting that the nomogram model based on BMI, TG, and AGTR has good predictive value [Figure 4: see original paper]. Decision curve analysis indicated that when the threshold probability ranged from 20% to 83%, using this model to predict the risk of T2DM with MAFLD had ideal clinical utility [Figure 5: see original paper].

Discussion

As the prevalence and incidence of MAFLD continue to rise, it has become the most common cause of chronic liver disease. Data indicate that chronic liver disease caused by MAFLD imposes a substantial burden on society, and the progression of fibrosis in MAFLD patients is closely related to T2DM. Statistics show that more than half of patients with T2DM also have MAFLD; in this study, the detection rate of MAFLD in T2DM patients was 59%. Therefore, the early detection and treatment of T2DM with MAFLD have become a common concern. While imaging examinations such as ultrasound, computed tomography (CT), and magnetic resonance imaging are effective means for clinically diagnosing fatty liver disease and can detect hepatic fat accumulation, there are currently no specific laboratory diagnostic indicators. MAFLD is often asymptomatic in its early stages, and diagnostic methods are relatively expensive; moreover, equipment and technical expertise are lacking in relatively remote areas. Consequently, MAFLD is often discovered only when severe complications have already developed. Thus, identifying convenient and inexpensive markers to assess the risk of T2DM with MAFLD for early diagnosis and intervention is of great clinical significance.

Our study data demonstrated that AGTR was significantly lower in the T2DM with MAFLD group compared with the T2DM without MAFLD group. Further analysis by AGTR tertiles showed that lower AGTR was associated with a higher incidence of MAFLD, and AGTR was negatively correlated with T2DM with MAFLD. Multivariate logistic regression analysis identified AGTR as a protective factor for T2DM with MAFLD. AGTR is an index derived from ALB/GGT, and 1/AGTR has previously been used as an independent predictor of coronary artery disease. AGTR has been confirmed as a protective factor for MAFLD, but its protective role in T2DM with MAFLD had not been previously established. ALB is an important protein synthesized and metabolized by the liver. Accumulation of lipids in the liver promotes MAFLD development, impairs liver function, and reduces ALB synthesis. Conversely, decreased ALB levels promote oxidative stress, thereby participating in MAFLD progression. GGT is a major enzyme localized on the cell membrane; increased hepatic lipid deposition and decreased albumin levels can stimulate GGT synthesis and release. Higher GGT levels are associated with increased risks of cerebrovascular disease, diabetes, metabolic syndrome, and all-cause mortality, and can increase the risk of insulin resistance, which is well known to be closely related to MAFLD development and progression. Therefore, higher GGT levels can promote MAFLD occurrence and development. Additionally, GGT can be used to detect cell damage and stress responses, so elevated GGT levels further suggest aggravated oxidative stress, exacerbating MAFLD. Studies have shown that GGT is also an important indicator of intrahepatic cholestasis, and the state of intrahepatic microcholestasis is also related to MAFLD occurrence. In summary, AGTR is closely associated with T2DM with MAFLD.

This study also demonstrated that BMI and TG are independent risk factors for T2DM with MAFLD, consistent with previous research findings. Obesity can increase the prevalence of MAFLD, and both obesity and elevated TG are currently considered to cause insulin resistance, thereby promoting MAFLD development. Moreover, elevated TG is a characteristic manifestation of metabolic syndrome, and the presence of metabolic syndrome is the strongest risk factor for MAFLD. Therefore, elevated TG is an independent risk factor for T2DM with MAFLD.

Using multivariate logistic regression, this study identified risk factors for T2DM with MAFLD and, for the first time, constructed a risk prediction model for T2DM with MAFLD, which demonstrated good clinical predictive value through internal validation. Our results indicate that this nomogram model can effectively predict the risk of developing T2DM with MAFLD, enabling early detection and intervention.

This study has several limitations. First, it is a cross-sectional study, and thus causal relationships cannot be established. Second, the gold standard for diagnosing fatty liver disease is liver biopsy, whereas this study used ultrasound, which may underestimate the incidence of fatty liver disease. Finally, this study only collected data from Hebei General Hospital, and the limited sample size may have introduced result bias.

In conclusion, AGTR levels were significantly lower in patients with T2DM and MAFLD compared with those without MAFLD, indicating that AGTR is a protective factor for T2DM with MAFLD. Furthermore, the constructed risk prediction model can effectively predict the risk of T2DM with MAFLD.

Author Contributions: WEI Limin was responsible for feasibility analysis, conceptualization, and quality control of the manuscript. YAN Ziwei contributed to conceptualization, statistical analysis, interpretation of results, and writing the manuscript. NIE Jiahua and SHI Yan participated in data collection, collation, and entry. YAN Ziwei and WEI Limin take overall responsibility for the manuscript.

Conflict of Interest: The authors declare no conflicts of interest.

References

[1] YOUNOSSI Z M, GOLABI P, PAIK J M, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review[J]. Hepatology, 2023, 77(4): 1335-1347. DOI: 10.1097/HEP.0000000000000004.

[2] RINELLA M, CHARLTON M. The globalization of nonalcoholic fatty liver disease: Prevalence and impact on world health[J]. Hepatology, 2016, 64(1): 19-22. DOI: 10.1002/hep.28524.

[3] ESLAM M, SANYAL A J, GEORGE J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease[J]. Gastroenterology, 2020, 158(7): 1999-2014.e1. DOI: 10.1053/j.gastro.2019.11.312.

[4] DECRAECKER M, DUTARTRE D, HIRIART J B, et al. Long-term prognosis of patients with metabolic (dysfunction)-associated fatty liver disease by non-invasive methods[J]. Aliment Pharmacol Ther, 2022, 55(5): 580-592. DOI: 10.1111/apt.16760.

[5] MUTHIAH M D, HAN N C, SANYAL A J. A clinical overview of non-alcoholic fatty liver disease: a guide to diagnosis, the clinical features, and complications-What the non-specialist needs to know[J]. Diabetes Obes Metab, 2022, 24(Suppl 2): 3-14. DOI: 10.1111/dom.14521.

[6] BUTT A S, HAMID S, HAIDER Z, et al. Nonalcoholic fatty liver diseases among recently diagnosed patients with diabetes mellitus and risk factors[J]. Euroasian J Hepatogastroenterol, 2019, 9(1): 9-13. DOI: 10.5005/jp-journals-10018-1288.

[7] LI X M, LIU S L, HE Y J, et al. Using new indices to predict metabolism dysfunction-associated fatty liver disease (MAFLD): analysis of the national health and nutrition examination survey database[J]. BMC Gastroenterol, 2024, 24(1): 109. DOI: 10.1186/s12876-024-03190-2.

[8] YARIBEYGI H, ATKIN S L, SAHEBKAR A. A review of the molecular mechanisms of hyperglycemia-induced free radical generation leading to oxidative stress[J]. J Cell Physiol, 2019, 234(2): 1300-1312. DOI: 10.1002/jcp.27164.

[9] ZHAO W, TONG J J, LIU J, et al. The dose-response relationship between gamma-glutamyl transferase and risk of diabetes mellitus using publicly available data: a longitudinal study in Japan[J]. Int J Endocrinol, 2020, 2020: 5356498. DOI: 10.1155/2020/5356498.

[10] LEE Y S, CHO Y, BURGESS S, et al. Serum gamma-glutamyl transferase and risk of type 2 diabetes in the general Korean population: a Mendelian randomization study[J]. Hum Mol Genet, 2016, 25(17): 3877-3886. DOI: 10.1093/hmg/ddw226.

[11] GABIR M M, HANSON R L, DABELEA D, et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes[J]. Diabetes Care, 2000, 23(8): 1108-1112. DOI: 10.2337/diacare.23.8.1108.

[12] YOUNOSSI Z M, KOENIG A B, ABDELATIF D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes[J]. Hepatology, 2016, 64(1): 73-84. DOI: 10.1002/hep.28431.

[13] GOLABI P, PAIK J M, ALQAHTANI S, et al. Burden of non-alcoholic fatty liver disease in Asia, the Middle East and North Africa: Data from Global Burden of Disease 2009-2019[J]. J Hepatol, 2021, 75(4): 795-809. DOI: 10.1016/j.jhep.2021.05.022.

[14] YOUNOSSI Z M, STEPANOVA M, ONG J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States[J]. Clin Gastroenterol Hepatol, 2021, 19(3): 580-589.e5. DOI: 10.1016/j.cgh.2020.05.064.

[15] MCPHERSON S, HARDY T, HENDERSON E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management[J]. J Hepatol, 2015, 62(5): 1148-1155. DOI: 10.1016/j.jhep.2014.11.034.

[16] ARRESE M, BARRERA F, TRIANTAFILO N, et al. Concurrent nonalcoholic fatty liver disease and type 2 diabetes: diagnostic and therapeutic considerations[J]. Expert Rev Gastroenterol Hepatol, 2019, 13(9): 849-866. DOI: 10.1080/17474124.2019.1649981.

[17] BESSONE F, RAZORI M V, ROMA M G. Molecular pathways of nonalcoholic fatty liver disease development and progression[J]. Cell Mol Life Sci, 2019, 76(1): 99-128. DOI: 10.1007/s00018-018-2947-0.

[18] TOPAL S, KIZILTUNÇ E, SEZENÖZ B, et al. Gamma-glutamyl transferase to albumin ratio can predict severity of coronary artery disease detected by coronary computed tomography angiography[J]. Anatol J Cardiol, 2021, 25(9): 653-660. DOI: 10.5152/AnatolJCardiol.2021.36330.

[19] PEISELER M, SCHWABE R, HAMPE J, et al. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease - novel insights into cellular communication circuits[J]. J Hepatol, 2022, 77(4): 1136-1160. DOI: 10.1016/j.jhep.2022.06.012.

[20] NEGRE-SALVAYRE A, SALVAYRE R, AUGÉ N, et al. Hyperglycemia and glycation in diabetic complications[J]. Antioxid Redox Signal, 2009, 11(12): 3071-3109. DOI: 10.1089/ars.2009.2484.

[21] ORTEGA E, KOSKA J, SALBE A D, et al. Serum gamma-glutamyl transpeptidase is a determinant of insulin resistance independently of adiposity

in Pima Indian children[J]. J Clin Endocrinol Metab, 2006, 91(4): 1419-1422. DOI: 10.1210/jc.2005-1783.

[22] FIGUEIRA T R, VERCESI A E, OLIVEIRA H C F. Lack of plasma albumin impairs intravascular lipolysis and explains the associated free fatty acids deficiency and hypertriglyceridemia[J]. Lipids Health Dis, 2010, 9: 146. DOI: 10.1186/1476-511X-9-146.

[23] NDREPEPA G, COLLERAN R, KASTRATI A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease[J]. Clin Chim Acta, 2018, 476: 130-138. DOI: 10.1016/j.cca.2017.11.026.

[24] YI S W, LEE S H, HWANG H J, et al. Gamma-glutamyltransferase and cardiovascular mortality in Korean adults: a cohort study[J]. Atherosclerosis, 2017, 265: 102-109. DOI: 10.1016/j.atherosclerosis.2017.08.028.

[25] HOSSAIN I A, RAHMAN SHAH M M, RAHMAN M K, et al. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: Association of GGT and HOMA-IR with NAFLD[J]. Diabetes Metab Syndr, 2016, 10(1 Suppl 1): S25-S29. DOI: 10.1016/j.dsx.2015.09.005.

[26] LIU D, ZHOU L, YANG M, et al. Oxidative stress mediates the association between dietary fat intake and cognition in US older adults[J]. Am J Geriatr Psychiatry, 2022, 30(7): 761-773. DOI: 10.1016/j.jagp.2022.01.001.

[27] SHI Z J, CHEN G, CAO Z, et al. Gut microbiota and its metabolite deoxycholic acid contribute to sucralose consumption-induced nonalcoholic fatty liver disease[J]. J Agric Food Chem, 2021, 69(13): 3982-3991. DOI: 10.1021/acs.jafc.0c07467.

[28] LIU J Y, AYADA I, ZHANG X F, et al. Estimating global prevalence of metabolic dysfunction-associated fatty liver disease in overweight or obese adults[J]. Clin Gastroenterol Hepatol, 2022, 20(3): e573-e582. DOI: 10.1016/j.cgh.2021.02.030.

[29] MISHRA S R, WALLER M, CHUNG H F, et al. Epidemiological studies of the association between reproductive lifespan characteristics and risk of Type 2 diabetes and hypertension: a systematic review[J]. Maturitas, 2022, 155: 14-23. DOI: 10.1016/j.maturitas.2021.09.009.

[30] GASEVIC D, FROHLICH J, JOHN MANCINI G B, et al. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort[J]. Metabolism, 2012, 61(4): 583-589. DOI: 10.1016/j.metabol.2011.09.009.

[31] HUANG P L. A comprehensive definition for metabolic syndrome[J]. Dis Model Mech, 2009, 2(5/6): 231-237. DOI: 10.1242/dmm.001180.

[32] FRIEDMAN S L, NEUSCHWANDER-TETRI B A, RINELLA M, et al. Mechanisms of NAFLD development and therapeutic strategies[J]. Nat Med,

2018, 24(7): 908-922. DOI: 10.1038/s41591-018-0104-9.

Received: January 10, 2025; Revised: May 15, 2025
Edited by: ZHAO Yuecui

Note: Figure translations are in progress. See original paper for figures.