The different characteristic of chronic liver damage in patients with metabolic-(dysfunction) associated fatty liver disease in different subtypes

Yu Wang
The Affiliated Hospital of Xuzhou Medical University
Zi-yu Liu
The Affiliated Hospital of Xuzhou Medical University
Fang Ji
The Affiliated Hospital of Xuzhou Medical University
Ming-jia Dai
The Affiliated Hospital of Xuzhou Medical University
Jian-zhong Li
The Affiliated Hospital of Xuzhou Medical University
Rui Huang
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School
Chao Wu
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School
Xue-bing Yan (yxbxuzhou@126.com)
The Affiliated Hospital of Xuzhou Medical University

Research Article

Keywords: metabolic-(dysregulation) associated fatty liver disease, subtypes, metabolic syndrome, liver damage

Posted Date: May 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1652130/v1

Abstract

BACKGROUND and AIMS: This study aimed to compare the difference on liver damage among MAFLD subgroup classification in MAFLD.

METHODS: A cross-sectional study of 882 Chinese patients who underwent ultrasonography or biopsy with metabolic-(dysfunction)-associated fatty liver disease (MAFLD) involved a cohort from a health screening program during the years 2018-2020. The liver damage characteristics of different MAFLD subtypes were compared. Liver damage was assessed based on the inflammation indicators and non-invasive diagnostic model.

RESULTS: The median age was 43 years, and 490 (55.56%) patients were male. There was significant difference among three MAFLD subgroups (Group1, 2, and 3) in age, BMI, GGT, TG, CHO, LDL, HDL, FPG, NFS, and FIB-4 ($p < 0.05$). The FIB-4 and NFS were higher in the Group 2 and the abnormal FPG-level Group than in the other groups to which they were compared ($p < 0.05$). The age, BMI, and GGT were lower in the only overweight/obese Group than the Concomitant metabolic dysregulation Group ($p < 0.05$).

CONCLUSION: There was statistically difference in liver inflammation and liver fibrosis among different subtypes in MAFLD. It's urgent to improve substantially in health care for patients and advance disease awareness, public health policy for MAFLD. [197 words]

Introduction

Nonalcoholic associated fatty liver disease (NAFLD), as the most prevalent chronic liver disease in the world, with a prevalence of about 25%, has renamed as metabolic-(dysfunction) associated fatty liver disease (MAFLD) considering to the close relation between the metabolic dysfunction and the fatty liver disease[1]. According to the new definition, MAFLD diagnosed by metabolic syndrome (Mets) regardless of concomitant the chronic liver disease or excessive alcoholic consumption. In western countries, MAFLD has become one of the leading causes of liver cirrhosis, end-stage liver disease and hepatocellular carcinoma [2]. In China there are an increasing number of patients with NAFLD, and especially because of the epidemics of obesity and diabetes, the disease burden is expected to increase[3], even in the obese pediatric patients, there is a high prevalence of MAFLD[4]. At the same time, the preventive diagnosis and treatment of MAFLD including its subgroups is not yet perfect, and both the relevant policies of the government and the awareness of the public are far less than other chronic liver diseases[5]. Owing to the high prevalence and the non-standard treatment of MAFLD, it's necessary to focus much on the liver damage of MAFLD so that a timely and precise treatment can be given to the MAFLD.

At present, previous studies have confirmed that type 2 diabetes mellitus (T2DM) is an independent risk factor for liver fibrosis in MAFLD[6, 7], and the close relationship between insulin resistant (IR) and fatty liver disease[8], yet there are few studies and insufficient understanding of the differences in liver injury between MAFLD subtypes[9, 10]. Liver damage has a greater impact on the health and requires early detection and diagnosis and treatment. We hypothesized that the risk and degree of liver damage may vary depending on the MAFLD subtypes, and can be treated precisely depending on the severity of the liver damage. Therefore, it is very important to evaluate the differences in liver injury of different MAFLD phenotypes and provide a theoretical basis for the precise treatment of MAFLD.

This study started from the differences in liver damage of different MAFLD phenotypes, and tried to infer the factors that different phenotypes have a relatively heavy impact on liver damage, so as to provide new ideas for the management and treatment of MAFLD disease.

Patients And Methods

Study Population

A total of 1909 subjects in the Affiliated Hospital of Xuzhou Medical University and Nanjing Drum Tower Hospital, Jiangsu province were collected, who were diagnosed with hepatic steatosis more than 5 % by percutaneous ultrasound-guided liver random biopsies and pathological diagnosis or fatty liver disease by ultrasonography. Of these subjects, a total of 1027 subjects were excluded, that is 680 patients were a lack of data for a diagnosis of MAFLD, 64 patients were diagnosed with hematonosis or active malignancy, 283 patients had antiviral or hepatoprotective medication history. Besides, there were 490 males and 392 females enrolled for comparison, including 882 patients diagnosed with MAFLD. This study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by prior approval from the institutional review board of the Affiliated Hospital of Xuzhou Medical University (ID XYFY2022-KL050).

Clinical parameters

We recorded anthropometric parameters, included age, sex, body weight and body height. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We use the Asian definition of overweight (BMI 23 - 24.9 kg/m2) and obesity (BMI ≥ 25 kg/m2) to select the records. We collected the clinical and laboratory data, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), albumin (ALB), triglyceride (TG), total cholesterol (CHO), low density lipoprotein (LDL), high density lipoprotein (HDL), platelet count (PLT), fasting plasma glucose (FPG). We also analyzed the AST-to-ALT ratio, AST to platelet ratio index (APRI), Fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) to estimate hepatic inflammation and liver fibrosis.

Definitions of MAFLD and NAFLD

The definition of MAFLD according to the international expert consensus statement[1] includes an intrahepatic triglyceride content (IHTG) of more than 5% plus one of the following three criteria, namely overweight or obesity (BMI ≥ 23 kg/m2 in Asians), presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation (MD) (≥ 2 metabolic risk abnormalities as follows: waist circumference (WC) ≥ 90/80 cm in Asian men and women, blood pressure ≥ 130/85 mmHg or specific drug treatment, plasma triglycerides ≥ 1.7 mmol/l or specific drug treatment, plasma high-density lipoprotein-cholesterol < 1.0 mmol/l for men and < 1.3 mmol/l for women or specific drug treatment, prediabetes (fasting plasma glucose 5.6-6.9 mmol/l or hemoglobin A1c 5.7 - 6.4%), homeostasis model assessment of insulin resistance score ≥ 2.5, and plasma high-sensitivity creactive protein level > 2 mg/L). And an important change is that a patients diagnosed with MAFLD regardless of whether it has excessive alcohol consumption or concomitant liver diseases.

Comparison of the patients with different metabolic dysregulation

Firstly, the patients were divided into four groups, Group1 (overweight/obese), Group2 (T2DM), and Group3 (lean/normal BMI with MD). Of these three groups, the patients in each group met each diagnostic criterion whether they satisfied other diagnostic criteria. Besides, based on the FPG level, there were 6 samples excluded for a lack of the FPG level, and the remained patients were divided into three groups, normal FPG-level group, IGT group, and T2DM group, in which the patients in the IGT group and T2DM group are also called abnormal FPG-level group. The patients in Group1 were also divided into two groups, “BMI ≥ 23 kg/m² alone” and “concomitant MD”, in which 66 samples were excluded for concomitant T2DM. The flow chart was shown in the **Figure1**.

Statistical analysis

Continuous and categorical variables are presented as median with percentiles or numbers with percentages, respectively. Categorical variables were analyzed using the chi-square test, whereas continuous variables between two groups were analyzed using either the Student's Independent t-test or Mann-Whitney U test as well as among three groups continuous variables were analyzed using Kruskal-Wallis H test. Kruskal-Wallis H test was also used for pairwise comparison. A two-tailed p□0.05 was considered to indicate statistical significance. The statistical analyses were conducted by PASW Statistics for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA)

Results

Patient characteristic

This study included 882 patients with MAFLD, 490 (55.56%) of whom were male, the median age of this study cohort was 43 (34 ~ 53)-years-old. The median BMI was 26.12 (24.43 ~ 28.05) kg/m². The median ALT, AST and GGT levels were 28 (18 ~ 53) U/L, 24 (19 ~ 33) U/L, and 29 (19.4 ~ 51) U/L, respectively. The median NFS, FIB-4 and APRI was -1.97 (-2.87 ~ -0.96), 0.36 (0.22 ~ 0.59), and 0.31 (0.23 ~ 0.44), respectively. There were 846 (95.92%) cases in Group1, 75 (8.5%) cases in Group2, 36 (4.08%) cases in Group3. The baseline characteristics of 882 patients with MAFLD are shown in **Table1**.

The comparison and pairwise comparison among three groups based on different subtypes

There was significant difference among three MAFLD subgroups in age, BMI, GGT, TG, CHO, LDL, FPG, NFS and FIB-4. The median GGT level in Group1, 2, and 3 were 28.8 (19 ~ 50), 38.25 (25 ~ 71.63), and 37 (21 ~ 90), respectively (p = 0.001). The median FIB-4 in Group1, 2, and 3 were 0.34 (0.21 ~ 0.58), 0.42 (0.30 ~ 0.79), and 0.49 (0.33 ~ 0.66), respectively (p = 0.007). The median NFS in Group1, 2, and 3 were -2.07 (-2.99 ~ -1.08), -0.96 (-1.68 ~ 0.14), and -1.66 (-2.72 ~ -0.50), respectively (p□0.001). The results of pairwise comparison among three groups in MAFLD are shown in **Figure 1**. In this study, the GGT level (27 (18 ~ 48) vs. 36 (24 ~ 72) vs. 38 (17.88 ~ 85.5)) and the NFS (-2.07 (-3.00 ~ -1.08) vs. -0.90 (-1.67 ~ 0.14) vs. -2.23 (-3.07 ~ -1.04)) in Group1 was significantly lower than the Group2 (P□0.05). Although there was significant difference in FIB-4 in the comparison of three groups (P = 0.029), the FIB-4 (0.36 (0.22 ~ 0.57) vs. 0.43 (0.28 ~ 0.69) vs. 0.48 (0.26 ~ 0.58)) in Group2 was no significant different from others based on the adjusted significance in the pairwise comparison.

The comparison and pairwise comparison among three groups based on different FPG level

The results of the comparison are shown in the **Table 2**. There was significant difference in some indicators among three groups including age (39 (32 ~ 49) vs. 49.5 (42.25 ~ 60) vs. 53.5 (41.25 ~ 61)), GGT (28 (18 ~ 50) vs. 28.3 (20 ~ 48) vs. 38.25 (25 ~ 71.63)), TG (1.43 (0.97 ~ 2.11) vs. 1.41 (1.04 ~ 2.03) vs. 1.70 (1.17 ~ 2.54)), CHO (4.89 (4.3 ~ 5.55) vs. 5.04 (4.40 ~ 5.62) vs. 5.16 (4.57 ~ 5.98)), LDL (2.94 (2.52 ~ 3.42) vs. 3.02 (2.60 ~ 3.51) vs. 3.24 (2.64 ~ 3.79)), FPG (5.08 (4.75 ~ 5.33) vs. 5.92 (5.72 ~ 6.18) vs. 8.02 (7.6 ~ 9.84)), NFS (-2.54 (-3.2 ~ -1.67) vs. -1.04 (-1.76 ~ -0.19) vs. -0.96 (-1.68 ~ 0.14)) and FIB-4 (0.31 (0.17 ~ 0.53) vs. 0.46 (0.27 ~ 0.69) vs. 0.42 (0.3 ~ 0.79)) (P□0.05), in which there was striking difference in some indicators between the subjects in normal FPG-level group and abnormal FPG-level group (no statistically difference between IGT and Diabetes) through the pairwise comparison including age, NFS, and FIB-4 (P□0.05) as well as these indicators were all lower in the normal FPG-level group. The GGT level was the highest in the T2DM group of the three groups (P□0.05). The results of pairwise comparison are shown in the **Figure3**.

The comparison of parameters between the group (BMI ≥ 23 kg/m² alone) and the group (concomitant MD)

The results of the comparison are shown in the **Table 3**. There was statistically difference in age (41 (33 ~ 50) vs. 43 (34 ~ 54)), BMI (25.97 (24.51 ~ 27.76) vs. 26.78 (25.24 ~ 28.89)), GGT (26 (18 ~ 45.68) vs. 31.75 (22 ~ 55.75)), TG

(1.25 (0.89 ~ 1.63) vs. 2.28 (1.85~3.07)), HDL (1.24 (1.08 ~ 1.42) vs. 0.97 (0.87 ~ 1.15)), FPG (5.21 (4.83 ~ 5.48) vs. 5.51 (4.97 ~ 5.81)), and NFS (-2.23(-3.10 ~ -1.31) vs. -1.93 (-2.81 ~ -0.88)). Of these indicators, only HDL level was lower in the concomitant MD group, the others indicators were all higher in the concomitant MD group (P<0.05).

Discussion

Our study main discussed the significant characteristic of the two subgroups of MAFLD, including Group1 (overweight/obese) and Group2 (T2DM), and focused on the difference of the degree of liver damage among the MAFLD subtypes. Since the close relationship between the metabolic abnormalities including abnormal glucose metabolism and fatty liver disease, it is imperative to compare alone the degree of the chronic liver damage including the inflammation and liver fibrosis of subjects diagnosed with T2DM and other subtypes in MAFLD. Our study suggests that the NFS and FIB-4 are higher in the patients with T2DM than other subgroups (Group 1 and Group 3) in MAFLD (P<0.05). It elucidated that the patients with T2DM in MAFLD may have higher risk of early liver fibrosis. In addition, the present results concerning the MAFLD patients with obesity alone may have the lowest risk in liver inflammation and liver fibrosis, and metabolic risk abnormalities may cause the adiposity and liver inflammation.

The conception of MAFLD is mainly focused on the metabolic risk abnormalities regardless of the patients with chronic liver disease and alcoholism[1]. Previous studies have found that T2DM is a risk factor for significant fibrosis in MAFLD patients[10] as well as patients diagnosed with metabolic fatty liver concomitant the excessive alcohol consumption and HBV infection may increase the risk of incident T2DM in MAFLD[11]. Moreover, BMI was also the risk indicators of liver fibrosis, but the effect of MD on liver fibrosis are still in debate[6, 10, 12] which may have relationship with the MD or not. Further, our study shows that the degree of liver fibrosis may deeper in T2DM through the non-invasive diagnostic model, FIB-4 and NFS concordance with a previous study[10]. Although in the pairwise comparison, there was no statistically difference on FIB-4 among three groups (Group1, Group2, and Group3) after adjustment which may well be owing to the less data of Group3, it's undeniable the statistically difference in the comparison among three groups and the significance of the indicative meaning of FIB-4 on liver fibrosis[13, 14]. We also find the patients in MD concomitant BMI ≥ 23 kg/m² may have deeper degree of obese and liver inflammation than those BMI ≥ 23 kg/m² alone (P<0.05) yet the degree of fibrosis is not significant difference. It may suggest that MD may contribute to the development of liver inflammation, and may have no effect on the liver fibrosis, which isn’t consistent with the study of Huang, J., et al[10]. It is possible that MD leads to high GGT level which is associated with high body fat percentage leading to Mets and increased cardiovascular risk and MD is also associated with the chronic kidney disease in MAFLD[15, 16], which can be inferred that the impact of BMI on liver damage and liver fibrosis was much lower than other risks in MAFLD, including T2DM and MD. Besides, stemming from the aforementioned results, three groups of parameters grouped by FPG level were compared in our study to verify the relationship between FPG level and the liver damage. Although there was significance in NFS in three groups, the FIB-4 was higher in IGT group than normal FPG group (P<0.05). It is similar to the previous research which verified the high glucose may induced the liver fibrosis, which may be associated with the IR[8, 17, 18]. However, the indicator of FPG-level is more commonly used than homeostasis model assessment-insulin resistance score (HOMA-IR) in routine physical examinations as well as the risk of liver fibrosis may higher in the abnormal FPG-level group than normal FPG-level group, which should draw more attention to the crowds with abnormal FPG level but not T2DM in MAFLD.

Moreover, there are some limitations in our study. The non-invasive diagnosed models including FIB-4 and NFS were used to evaluate the grade of fibrosis in our study, which is not the golden standard on the liver fibrosis, since it is difficult to enroll a number of patients diagnosed by liver biopsy and pathology due to the expensive fee and invasive diagnosis. Previous researches have verified the traditional non-invasive diagnostic models, suggesting that the two models have significance to diagnosing fibrosis, where FIB-4 is better than NFS, it’s urgently-needed that the non-

invasive diagnosed model should be re-evaluated[13, 14, 19]. Tang, L. J etc. have elucidated that ADAPT score may have good diagnostic performance in subgroup analyses[20], Wu, X. X etc. have proposed a new diagnostic model, acNASH index, which may have promising utility as a simple non-invasive biomarker for diagnosing NASH[21]. Besides, since some data in our study were missing, such as WC, hs-CRP and HOMA-IR, which mainly reduces the number of lean subjects with MD enrolled, the characteristic of subjects diagnosed as lean with MD in MAFLD may be not cross-sectional. It is imperative to enlarge the number of the lean cases with MD in MAFLD and focus on the MD influence on patients with MAFLD. Despite these limitations, this study still validated MAFLD subgroup characteristic in Asian patients with MAFLD due to a statistically difference in liver damage and liver fibrosis.

In MAFLD, the patients with T2DM even including the fasting hyperglycemia may have deeper liver fibrosis than others. Metabolic dysfunction may lead to obese and liver inflammation. Simple overweight or obese patients has the lowest risk of liver damage. Thus, it may be contributed to the prevention and diagnosis of MAFLD and substantially provide a theoretical basis for the precise treatment of MAFLD. Although the current guidelines recommendation for fatty liver disease mainly emphasizes revisions of lifestyle[22], the different subtypes should have different way of treatment, for instance, the patients with T2DM in MAFLD ought to focus much on the diabetes treatment supplemented with drugs to treat fatty liver, such as pioglitazone, liraglutide and so on[23].Thus, it's urgent to improve substantially in health care for patients and advance disease awareness, public health policy for MAFLD, especially the patients with T2DM.

Abbreviations

NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic-(dysfunction) associated fatty liver disease; Mets, metabolic syndrome; T2DM, type 2 diabetes mellitus; IR, insulin resistant; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALB, albumin; TG, triglycerides; CHO, total cholesterol; LDL, low density lipoprotein; HDL, high-density lipoprotein; PLT, platelet count; FPG, fasting plasma glucose; APRI, AST to Platelet Ratio Index; FIB-4, Fibrosis-4 index; NFS, low density lipoprotein; IHTG, intrahepatic triglyceride content; MD, metabolic dysfunction; WC, waist circumference; IGT, impaired glucose tolerance; HOMA-IR, homeostasis model assessment-insulin resistance score

Declarations

Ethics approval and consent to participate

This study was conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by prior approval from the institutional review board of the Affiliated Hospital of Xuzhou Medical University (ID XYFY2022-KL050).

Consent for publication

All presentations of our study have consent for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding statement

No funding

Authors' Contributions

Study concept and design: Yu Wang and Fang Ji

Acquisition, clearning of data: Jian-zhong Li, Rui Huang, and Chao Wu

Drafting of the manuscript: Yu Wang, Ming-jia Dai and Xue-bing Yan

Statistical analysis: Yu Wang and Zi-yu Liu

Study supervision: Fang Ji and Xue-bing Yan

Acknowledgements

The authors thank Da-ang Hao for his support in the writing process of this paper.

References

1. Eslam, M., P.N. Newsome, S.K. Sarin, et al., A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol, 2020; 73: 202–209.
2. Lin, H., X. Zhang, G. Li, G.L. Wong, and V.W. Wong, Epidemiology and Clinical Outcomes of Metabolic (Dysfunction)-associated Fatty Liver Disease. J Clin Transl Hepatol, 2021; 9: 972–982.
3. Estes, C., Q.M. Anstee, M.T. Arias-Loste, et al., Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol, 2018; 69: 896–904.
4. Liu, J., C. Mu, K. Li, et al., Estimating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or Obese Children and Adolescents: Systematic Review and Meta-Analysis. Int J Public Health, 2021; 66: 1604371.
5. Nan, Y., J. An, J. Bao, et al., The Chinese Society of Hepatology position statement on the redefinition of fatty liver disease. J Hepatol, 2021; 75: 454–461.
6. Sohn, W., H.J. Kwon, Y. Chang, S. Ryu, and Y.K. Cho, Liver Fibrosis in Asians With Metabolic Dysfunction-Associated Fatty Liver Disease. Clin Gastroenterol Hepatol, 2021.
7. Jarvis, H., D. Craig, R. Barker, et al., Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Med, 2020; 17: e1003100.
8. Tanase, D.M., E.M. Gosav, C.F. Costea, et al., The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD). J Diabetes Res, 2020; 2020: 3920196.
9. Ciardullo, S., T. Monti and G. Perseghin, Lack of awareness of liver organ damage in patients with type 2 diabetes. Acta Diabetol, 2021; 58: 651–655.
10. Huang, J., W. Ou, M. Wang, et al., MAFLD Criteria Guide the Subtyping of Patients with Fatty Liver Disease. Risk Manag Healthc Policy, 2021; 14: 491–501.
11. Liang, Y., H. Chen, Y. Liu, et al., Association of MAFLD With Diabetes, Chronic Kidney Disease, and Cardiovascular Disease: A 4.6-Year Cohort Study in China. J Clin Endocrinol Metab, 2022; 107: 88–97.
12. Kani, H.T., C.O. Demirtas, C. Keklikkiran, et al., Evaluation of the Impact of Metabolic Syndrome on Fibrosis in Metabolic Dysfunction-Associated Fatty Liver Disease. Turk J Gastroenterol, 2021; 32: 661–666.

13. Wu, Y.L., R. Kumar, M.F. Wang, et al., Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease. World J Gastroenterol, 2021; 27: 5753–5763.
14. Park, H., E.L. Yoon, M. Kim, et al., Comparison of diagnostic performance between FIB-4 and NFS in metabolic-associated fatty liver disease era. Hepatol Res, 2021.
15. Lee, H., Y.H. Lee, S.U. Kim, and H.C. Kim, Metabolic Dysfunction-Associated Fatty Liver Disease and Incident Cardiovascular Disease Risk: A Nationwide Cohort Study. Clin Gastroenterol Hepatol, 2020.
16. Deng, Y., Q. Zhao and R. Gong, Association Between Metabolic Associated Fatty Liver Disease and Chronic Kidney Disease: A Cross-Sectional Study from NHANES 2017–2018. Diabetes Metab Syndr Obes, 2021; 14: 1751–1761.
17. Dai, Y., P. Hao, Z. Sun, et al., Liver knockout YAP gene improved insulin resistance-induced hepatic fibrosis. J Endocrinol, 2021; 249: 149–161.
18. Yang, R.X., Z.S. Zou, B.H. Zhong, et al., The pathologic relevance of metabolic criteria in patients with biopsy-proven nonalcoholic fatty liver disease and metabolic dysfunction associated fatty liver disease: A multicenter cross-sectional study in China. Hepatobiliary Pancreat Dis Int, 2021; 20: 426–432.
19. Wu, Y., R. Kumar, J. Huang, et al., FIB-4 cut-off should be re-evaluated in patients with metabolic associated fatty liver disease (MAFLD). J Hepatol, 2021; 74: 247–248.
20. Tang, L.J., H.L. Ma, M. Eslam, et al., Among simple non-invasive scores, Pro-C3 and ADAPT best exclude advanced fibrosis in Asian patients with MAFLD. Metabolism, 2022; 128: 154958.
21. Wu, X.X., K.I. Zheng, J. Boursier, et al., acNASH index to diagnose nonalcoholic steatohepatitis: a prospective derivation and global validation study. EClinicalMedicine, 2021; 41: 101145.
22. Dibba, P., A.A. Li, B.J. Perumpail, et al., Emerging Therapeutic Targets and Experimental Drugs for the Treatment of NAFLD. Diseases, 2018; 6.
23. Iogna Prat, L. and E.A. Tsochatzis, The effect of antidiabetic medications on non-alcoholic fatty liver disease (NAFLD). Hormones (Athens), 2018; 17: 219–229.

Tables

Table 1. Comparison of the Characteristics Between MAFLD with Different Metabolic Conditions

Variable	MAFLD total (n=882)	Group 1 (n=846)	Group 2 (n=75)	Group 3 (n=36)	p*
Age (year)	43(33~54)	43 (33 ~ 53)	53.5 (41.25 ~ 61)	49 (41 ~ 60)	0
Male Sex, n (%)	490(55.56)	474(56.03)	45(60)	16(44)	0.296
BMI (kg/m²)	26.12(24.39~28.08)	26.23(24.62~28.09)	26.19(24.32~29.35)	21.78(20.52~22.64)	0
ALT (U/L)	28(18~53.1)	28(18~53)	27(21~69.88)	26(18~55.5)	0.65
AST (U/L)	24(19~33)	24(19.1~33)	23.5(18.25~43)	25(18.1~36)	0.855
GGT (U/L)	30(19.4~51.4)	28.8(19~50)	38.25(25~71.63)	37(21~90)	0.001
ALB (g/L)	44.8(42.9~46.8)	44.8(42.9~46.8)	44.65(43.2~46.48)	44.4(41.7~46.7)	0.528
TG (mmol/l)	1.48(1.03~2.19)	1.44(1.01~2.11)	1.71(1.16~2.57)	2.15(1.63~2.82)	0
CHO (mmol/l)	4.98(4.35~5.69)	4.96(4.34~5.67)	5.16(4.57~5.98)	4.94(4.29~5.4)	0.018
LDL (mmol/l)	2.99(2.55~3.5)	2.98(2.54~3.48)	3.24(2.64~3.79)	2.84(2.31~3.28)	0.016
HDL (mmol/l)	1.16(1.03~1.36)	1.18(1.04~1.36)	1.16(1.01~1.43)	1.1(0.94~1.26)	0.082
PLT (10^9/L)	206(171~244)	208(172~246)	195.5(147.25~243.75)	191(140~223)	0.096
FPG (mmol/l)	5.37(4.94~5.99)	5.3(4.89~5.7)	8.02(7.59~9.84)	5.79(4.96~7.38)	0
AST/ALT	0.85(0.62~1.11)	0.84(0.62~1.11)	0.85(0.70~1.05)	0.94(0.63~1.2)	0.572
NFS	-1.97(-2.87~-0.96)	-2.07(-2.99~-1.08)	-0.96(-1.68~0.14)	-1.66(-2.72~-0.50)	0
FIB-4	0.36(0.22~0.59)	0.34(0.21~0.58)	0.42(0.30~0.79)	0.49(0.33~0.66)	0.007
APRI	0.31(0.23~0.44)	0.30(0.23~0.43)	0.34(0.24~0.64)	0.32(0.24~0.66)	0.181

Data are presented as number (%) or median (25th–75th percentiles).

MAFLD: metabolic dysfunction-associated fatty liver disease; BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, ALB: albumin, TG: triglyceride, CHO: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, PLT: platelet count, FPG: fasting plasma glucose, NFS: NAFLD fibrosis score, FIB-4: fibrosis-4, APRI: AST to platelet ratio index.

*The statistical analysis and comparison were conducted among three groups(Group1, 2, and 3), p□0.05 was considered statistically significant.

Table 2. Comparison of the Characteristics Between MAFLD with Different FPG level

Variable	Normal-FPG group (n=599)	IGT (n=202)	Diabetes (n=75)	p*
Age (year)	39(32~49)	49.5(42.25~60)	53.5(41.25~61)	0
Male Sex, n (%)	340(56.76)	103(50.99)	45(60)	0.266
BMI (kg/m²)	26.06(24.31~28.03)	25.98(24.58~27.70)	26.19(24.32~29.35)	0.082
ALT (U/L)	30(18~55)	27(17~45.5)	27(21~69.88)	0.324
AST (U/L)	24(19.7~33)	24(20~30)	23.5(18.25~43)	0.95
GGT (U/L)	28(18~50	28.3(20~48)	38.25(25~71.63)	0
ALB (g/L)	44.7(42.6~46.9)	45.2(43.6~46.7)	44.65(43.2~46.48)	0.228
TG (mmol/l)	1.46(0.99~2.13)	1.41(1.04~2.04)	1.71(1.16~2.57)	0.032
CHO (mmol/l)	4.89(4.3~5.55)	5.04(4.40~5.62)	5.16(4.57~5.98)	0.012
LDL (mmol/l)	2.94(2.52~3.42)	3.02(2.60~3.51)	3.24(2.64~3.79)	0.007
HDL (mmol/l)	1.17(1.03~1.35)	1.19(1.05~1.36)	1.16(1.01~1.43)	0.992
PLT (10^9/L)	208(173~246)	205.5(172.5~238)	195.5(147.25~243.75)	0.435
FPG (mmol/l)	5.08(4.75~5.33)	5.92(5.72~6.18	8.02(7.6~9.84)	0
AST/ALT	0.81(0.58~1.11)	0.9(0.68~1.17)	0.85(0.7~1.05)	0.111
NFS	-2.54(-3.2~-1.67)	-1.04(-1.76~-0.19)	-0.96(-1.68~0.14)	0
FIB-4	0.31(0.17~0.53)	0.46(0.27~0.69)	0.42(0.3~0.79)	0
APRI	0.30(0.23~0.42)	0.30(0.23~0.42)	0.34(0.24~0.64)	0.193

Data are presented as number (%), or median (25th–75th percentiles).

FPG: fasting plasma glucose, IGT: impaired glucose tolerance, BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, ALB: albumin, TG: triglyceride, CHO: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, PLT: platelet count, NFS: NAFLD fibrosis score, FIB-4: fibrosis-4, APRI: AST to platelet ratio index.

*The statistical analysis and comparison were conducted among three groups, p0.05 was considered statistically significant.

Table 3. Comparison of the Characteristics Between MAFLD with Different Metabolic Conditions

Variable	BMI ≥ 23 kg/m² alone (n=588)	Concomitant MD (n=192)	p*
Age (year)	41 (33 ~ 50)	43 (34 ~ 54)	0.047
Male Sex, n (%)	335 (57)	99 (51.56)	0.19
BMI (kg/m²)	25.97 (24.51 ~ 27.76)	26.78 (25.24 ~ 28.89)	0
ALT (U/L)	28 (18 ~ 49.3)	30.15 (18.25 ~ 56)	0.122
AST (U/L)	24 (20 ~ 31.85)	24.1 (19 ~ 33.75)	0.429
GGT (U/L)	26 (18 ~ 45.68)	31.75 (22 ~ 55.75)	0.002
ALB (g/L)	44.7 (42.73 ~ 46.7)	45.3 (43.7 ~ 46.98)	0.096
TG (mmol/l)	1.25 (0.89 ~ 1.63)	2.28 (1.85~3.07)	0
CHO (mmol/l)	4.92 (4.28 ~ 5.68)	4.93 (4.44 ~ 5.46)	0.729
LDL (mmol/l)	2.94 (2.48 ~ 3.46)	2.99 (2.62 ~ 3.43)	0.291
HDL (mmol/l)	1.24 (1.08 ~ 1.42)	0.97 (0.87 ~ 1.15)	0
PLT (10^9/L)	206.5 (172 ~ 245.5)	216.5 (178 ~ 246)	0.373
FPG (mmol/l)	5.21 (4.83 ~ 5.48)	5.51 (4.97 ~ 5.81)	0
AST/ALT	0.85 (0.62 ~ 1.13)	0.79 (0.59 ~ 1.05)	0.074
NFS	-2.23(-3.10 ~ -1.31)	-1.93 (-2.81 ~ -0.88)	0.007
FIB-4	0.35 (0.20 ~ 0.58)	0.32 (0.20 ~ 0.51)	0.603
APRI	0.31 (0.23 ~ 0.42)	0.29 (0.23 ~ 0.42)	0.874

Data are presented as number (%) or median (25th–75th percentiles).

BMI: body mass index, MD: metabolic dysfunction; ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, ALB: albumin, TG: triglyceride, CHO: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, PLT: platelet count, FPG: fasting plasma glucose, NFS: NAFLD fibrosis score, FIB-4: fibrosis-4, APRI: AST to platelet ratio index.

*The statistical analysis and comparison were conducted between the two groups, p□0.05 was considered statistically significance

Figures

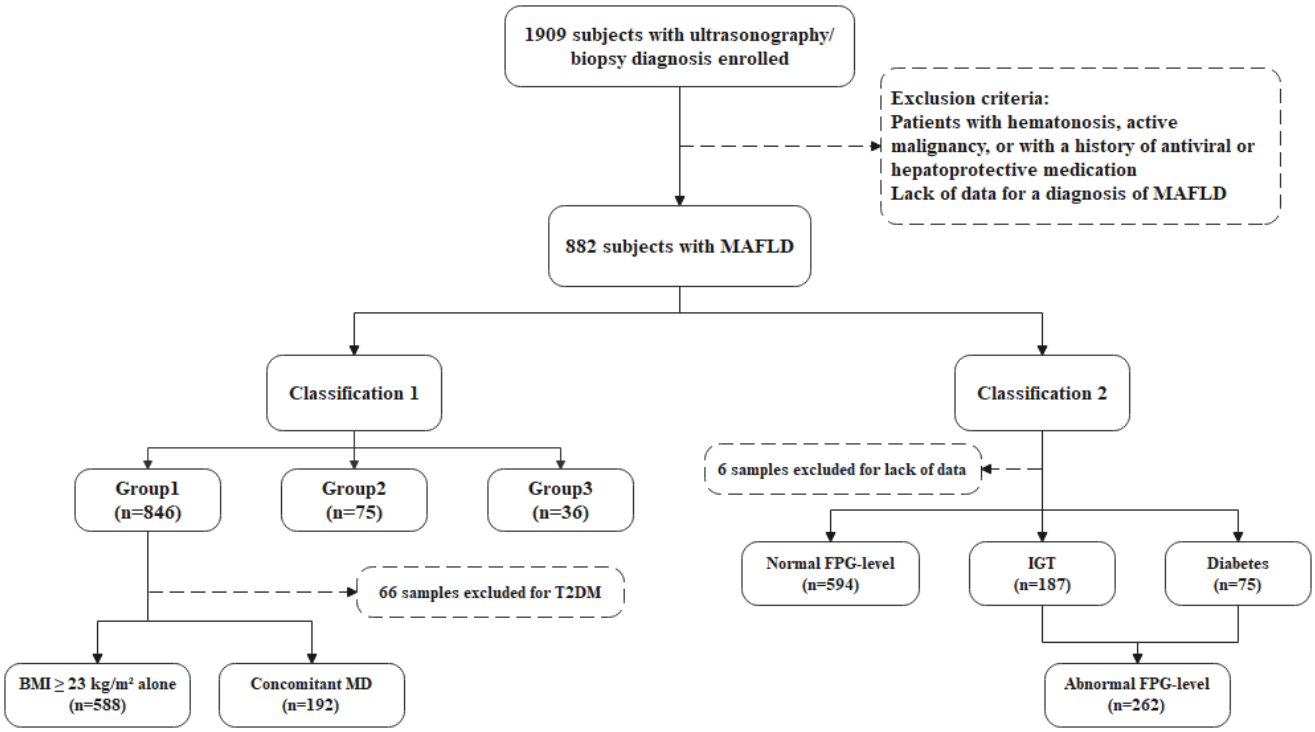

Figure 1

Flowchart of patient selection, the diagnostic criteria for metabolic dysfunction-associated fatty liver disease (MAFLD) and the grouping of our study.

Abbreviations: MAFLD, metabolic-(dysfunction) associated fatty liver disease; MD, metabolic dysfunction; FPG, fast plasma glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

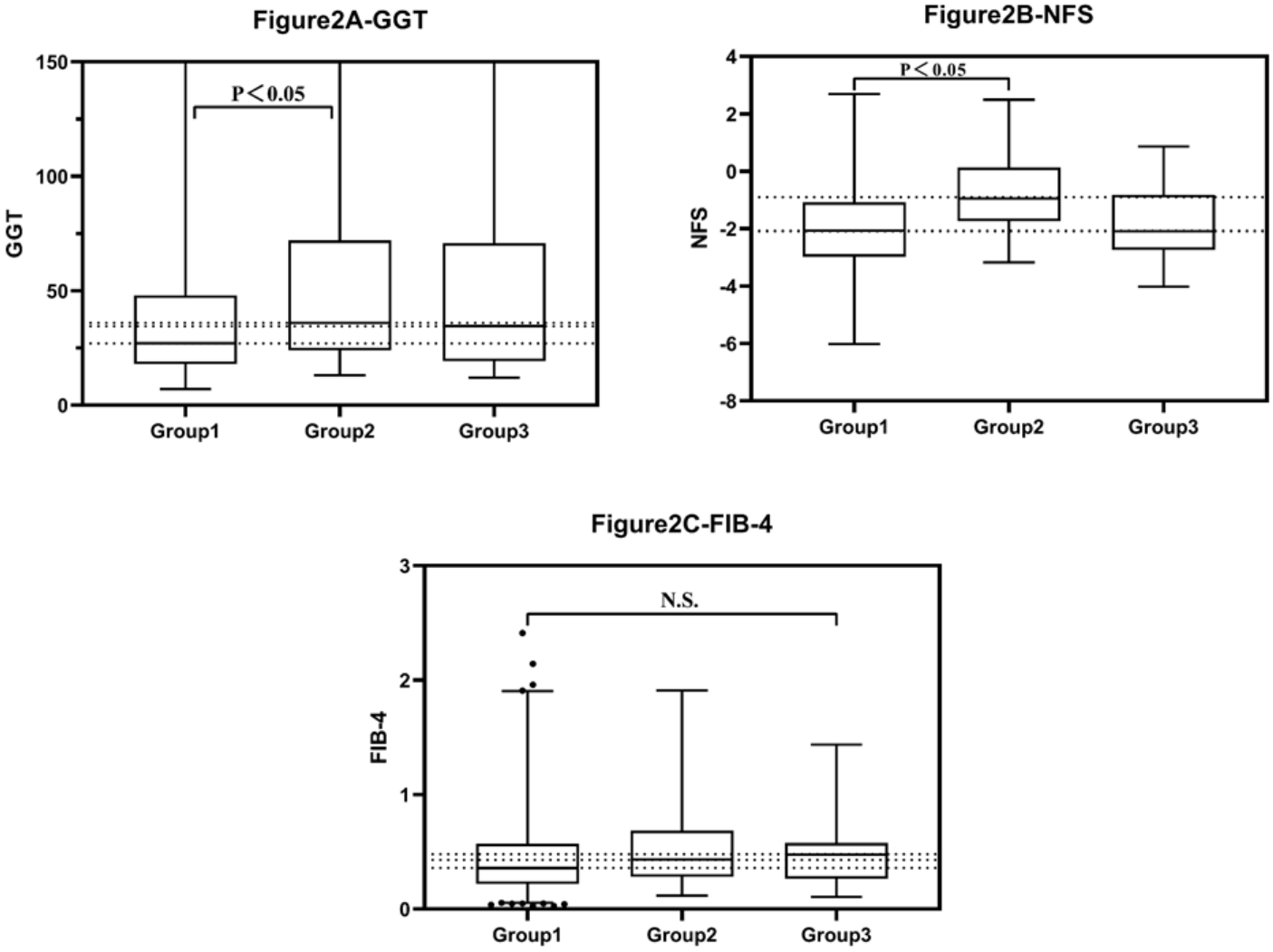

Figure 2

Pairwise comparison for the indicators of liver damage in all patients diagnosed with metabolic dysfunction-associated fatty liver disease (MAFLD). (A) GGT, (B) NAFLD fibrosis score, (C) FIB-4 index.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; GGT, gamma glutamyl transferase; FIB-4, fibrosis-4; N.S. not significant.

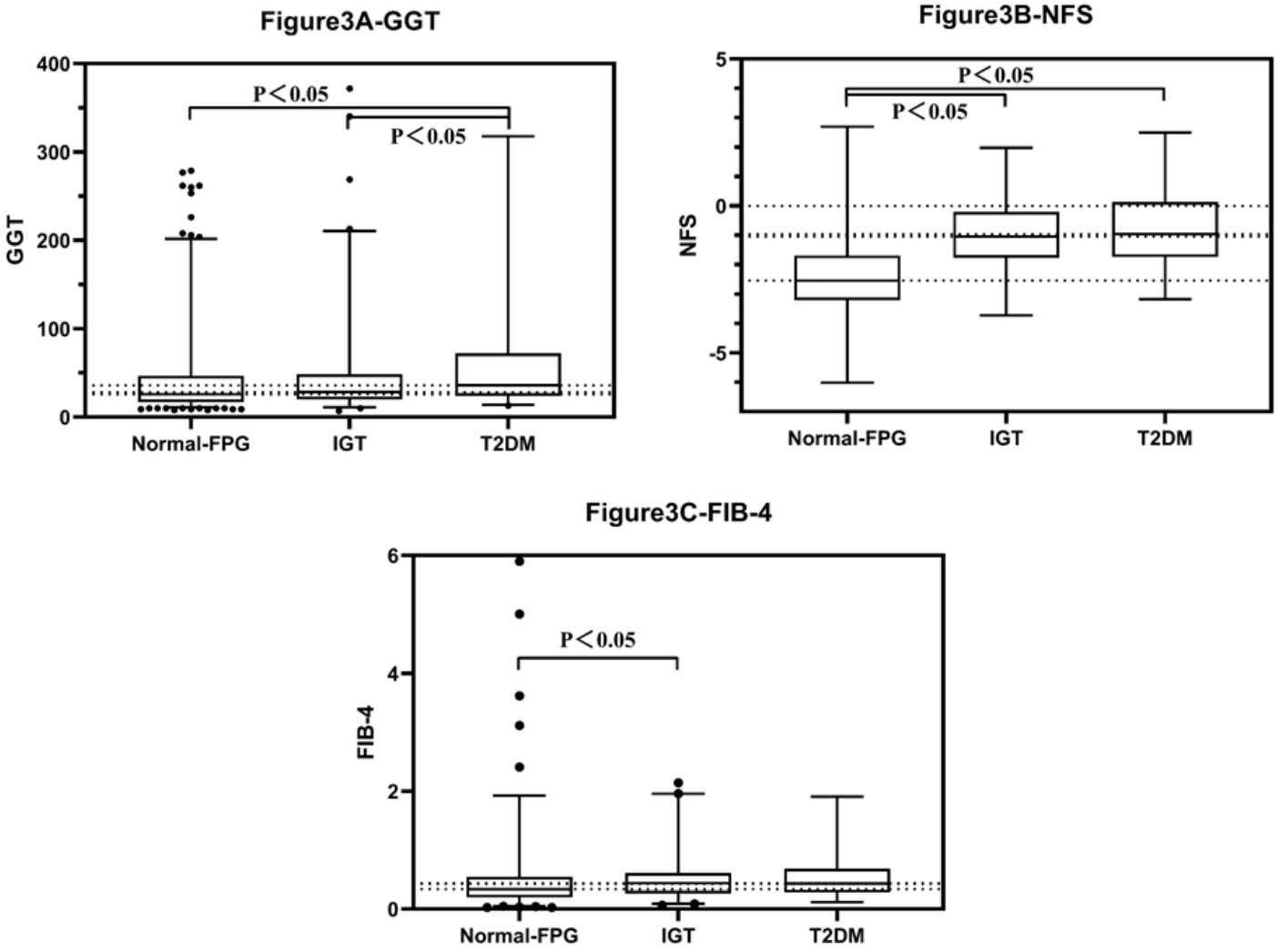

Figure 3

Pairwise comparison for the indicators of liver damage based on the FPG-level. (A) GGT, (B) NAFLD fibrosis score, (C) FIB-4 index.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; GGT, gamma glutamyl transferase; FIB-4, fibrosis-4.