Correlation Analysis of Metabolic Characteristics and the Risk of Metabolic-Associated Fatty Liver Disease–Related Hepatocellular Carcinoma

Xuancheng Xie
Second Affiliated Hospital of Kunming Medical University
Jinhui Yang (yangjinhuikmmc@163.com)
Second Affiliated Hospital of Kunming Medical University
Mengyao Zheng
Second Affiliated Hospital of Kunming Medical University
Weibo Guo
Second Affiliated Hospital of Kunming Medical University
Ying Zhou
Second Affiliated Hospital of Kunming Medical University
Zhao Xiang
Second Affiliated Hospital of Kunming Medical University
Yuting Li
Second Affiliated Hospital of Kunming Medical University

Research Article

Keywords: MAFLD, hepatocellular carcinoma, metabolic syndrome, risk stratification, obesity

Posted Date: February 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1359185/v1

Abstract

Metabolic-associated fatty liver disease (MAFLD) is currently the most common chronic liver disease worldwide and the main cause of hepatocellular carcinoma (HCC). To explore the risk factors of MAFLD-HCC, we evaluated the independent and combined effects of metabolic characteristics on the risk of MAFLD-HCC. We retrospectively analyzed 135 MAFLD-HCC patients who were treated at the Second Affiliated Hospital of Kunming Medical University from January 2015 to December 2020 and 137 MAFLD patients as the control group. Independent and joint effects of metabolic traits on the risk of HCC were evaluated. Each metabolic feature was significantly correlated with the increased risk of MAFLD-HCC ($p < 0.05$); obesity had the strongest correlation (adjusted odds ratio [OR] = 3.1, 95% confidence interval [CI] = 1.66–5.70). In patients with superimposed features, HCC risk was higher with more metabolic features ($p < 0.05$). Patients with concurrent obesity, prediabetes, and hypertension had the highest risk of HCC (adjusted OR = 5.7, 95% CI = 1.47–21.78). The correlation between metabolic characteristics and risk of MAFLD-HCC in patients without cirrhosis was basically consistent with the overall analysis. Metabolic characteristics increase the risk of MAFLD-HCC, and the risk is positively correlated with the number of metabolic characteristics. Obesity has the strongest correlation with HCC.

Introduction

Metabolic-associated fatty liver disease (MAFLD), once known as non-alcoholic fatty liver disease, is a chronic fatty liver disease related to metabolic syndrome, and its incidence has rapidly increased in the past two decades. MAFLD, which now affects 25% of the world's population and has become the most common chronic liver disease, is considered to be the leading cause of hepatocellular carcinoma (HCC) in developed countries[1,2]. Currently, regional differences in the prevalence of MAFLD are no longer obvious. The prevalence of MAFLD in Asian countries is even higher than in Western Europe and North America, and the onset is gradually occurring at younger ages[3]. However, there is still a lack of specific drugs for the treatment of MAFLD here in China and abroad. Although lifestyle interventions can prevent and treat MAFLD and metabolic cardiovascular risk factors, they are difficult to implement.

HCC is the fifth most common tumor in the world and the third leading cause of cancer-related deaths. Unlike HCC resulting from other causes, the etiology of MAFLD-HCC is unclear, and HCC may also occur in MAFLD patients without cirrhosis[4]. The incidence of MAFLD-HCC is increasing continually, and treatment methods are scarce. Studying the etiology and risk factors of this disease is therefore helpful in the screening, monitoring, and prevention of early HCC. Due to the close relationship between MAFLD and metabolic syndrome, several recent studies have pointed out that in the Western populations, metabolic characteristics, especially risk factors for diseases such as obesity, hypertension, type 2 diabetes mellitus (T2 DM), and dyslipidemia, are closely related to MAFLD-HCC[5,6]. However, the strength and extent of this association have not been clarified. Due to the superposition and interaction of metabolic characteristics and the differences in metabolic characteristics and HCC risk factors among people of different races and geographic locations, the etiology and pathogenesis of MAFLD-HCC are complex[7]. To study the

etiology of MAFLD- HCC in Asians and its association with metabolic syndrome, we conducted a retrospective cohort study to evaluate the independent and combined effects of metabolic characteristics on the disease.

Materials And Methods

Study design and patient population

We retrospectively analyzed 18 to 80-year-old MAFLD-HCC patients who attended the Second Affiliated Hospital of Kunming Medical University from January 2015 to December 2021. The inclusion criteria were patients with MAFLD who were diagnosed with HCC for the first time, and HCC was diagnosed according to the 2010 American Association for the Study of Liver Diseases criteria[8]. The diagnosis of MAFLD was defined by international expert consensus as evidence of liver steatosis with histological biopsy, imaging or blood biomarkers, and included any one of the following three criteria: overweight/obesity, T2 DM, or metabolic syndrome[9]. The exclusion criteria were past history of HCC or other liver diseases that can lead to liver cancer, including viral hepatitis, alcoholic liver disease, and other rare causes (autoimmune liver disease, primary biliary cirrhosis, hemochromatosis, alpha-1 antitrypsin disease, etc.).

We selected patients who were diagnosed with simple MAFLD in 2015 and followed up until December 2021 as the control group. The inclusion criteria were the patient's visit records for at least 5 years after the diagnosis of MAFLD showed that the patient did not have any other liver diseases. We used random sampling without replacement to select a control cohort that matched the baseline data of the study cohort in terms of gender and age. Demographic data (age, sex) and biochemical indicators of all patients were recorded at the time of first diagnosis of MAFLD/MAFLD-HCC. Biochemical indicators included bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, plasma high-density lipoprotein (HDL), plasma triglycerides, and fasting blood glucose. The body mass index (BMI) was calculated by the formula: weight/height in meters squared (kg/m^2).

This study was approved by the Ethical Committee of Second Affiliated Hospital of Kunming Medical University (Approval No. Shen-PJ-2020-26). Subjects were entirely informed about the purpose and constraints of this study prior to data collection, and all participants provided their written informed consent. All methods were carried out in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki.

Variable specification

Liver cirrhosis was defined as histological or non-invasive elastography showing fibrosis stage 4, portal hypertension syndrome (unexplained splenomegaly or thrombocytopenia, ascites, hepatic encephalopathy, or imaging/endoscopic varicose veins). The main exposure metabolic disorders observed included obesity/overweight (BMI ≥23 kg/m^2 in Asians), type 2 diabetes, prediabetes, hypertension, and dyslipidemia. Dyslipidemia included hypertriglyceridemia (plasma triglycerides ≥1.70

mmol/L) and low HDL (plasma HDL <1.0 mmol/L). Prediabetes was defined as fasting blood glucose levels of 5.6-6.9 mmol/L or 2-h post-load blood glucose levels of 7.8-11.0 mmol/L. T2 DM and hypertension were defined as fasting blood glucose ≥7.0 mmol/L or 2-h postprandial blood glucose ≥11.1 mmol/L or oral hypoglycemic drugs, insulin, and blood pressure ≥130/85 mmHg or specific drug treatment, respectively[9]. Metabolic characteristics of all patients were assessed using data at the time of first diagnosis of MAFLD-HCC/MAFLD.

Statistical analysis

Descriptive statistics are reported as percentage for categorical variables and mean ± SD or median (interquartile range) for continuous variables. Continuous variables with a normal distribution were compared by *t* test, and continuous variables with a non-normal distribution were compared by the Wilcoxon rank sum statistic. Categorical variables were compared using the chi-square test. The chi-square test was also used to analyze the differences in different factors between the two groups of patients, and then single-factor and multivariate logistic regression analyses were used to determine whether the independent and combined effects of these factors were significantly different.

It is common to have multiple metabolic characteristics superimposed in one patient. To analyze the combined effects of different metabolic variables, in the subgroup analysis, we modeled the metabolic characteristic variables as additive indicators (as the number of traits) and analyzed the combined effects of different variables on the risk of MAFLD-HCC.

Sensitivity analyses

A substantial proportion of MAFLD-HCC occurs in patients without cirrhosis, and it is unclear whether metabolic characteristics have the same effect in this subset of patients. We screened all MAFLD-HCC patients without cirrhosis in this study and used the same model as the overall analysis to analyze the independent and combined effects of metabolic characteristics and HCC risk. We investigated whether the influence of metabolic characteristics among this portion of the patients and the overall cohort was different. In addition, when analyzing the association of dyslipidemia with MAFLD-HCC risk, we assessed the independent and combined effects of dyslipidemia as two variables, hypertriglyceridemia and low HDL, in order to analyze the potential independent effects of different types of dyslipidemia.

All statistical analyses were performed using SPSS, version 19.0.0.1 (IBM SPSS, 2010, Chicago, IL, USA). All *p* values were two-tailed, and results were considered statistically significant at $p<0.05$.

Results

Patient characteristics

A total of 135 patients with MAFLD HCC were included in this study, and 137 matched patients with only MAFLD were randomly selected as a control cohort. There was no significant difference in the average

age or sex ratio between the two groups of patients ($p > 0.05$). Among MAFLD-HCC patients, 26 had liver cirrhosis (19.3%), 31 had T2 DM (23%), 46 had prediabetes (34.1%), 110 had obesity (81.5%), and 74 had hypertension (54.8%). There were 91 patients (61.4%) with dyslipidemia, of which 62 (45.9%) had hypertriglyceridemia and 64 (47.4%) had low HDL. Compared with the control cohort, patients with MAFLD-HCC had a higher prevalence of prediabetes, obesity, hypertension, and dyslipidemia, and the difference was statistically significant ($p < 0.05$), However, there was no statistically significant difference in the prevalence of T2 DM ($p = 0.264$). The biochemical indicators of the two groups of patients revealed worse liver function in patients with MAFLD- HCC ($p < 0.05$) (Table 1).

Table 1
Baseline characteristics of patients with MAFLD and MAFLD-HCC. BMI, body mass index; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase (AST).

Characteristic	HCC (n = 135)	Non-HCC (n = 137)	χ^2, *t* or z	*p*
Age (y)	57.26 ± 12.59	54.54 ± 12.97	1.754	0.081
Sex	82 (60.7%)	82 (59.9%)	0.022	0.881
Male	53 (39.3%)	55 (40.1%)		
Female				
Cirrhosis	26 (19.3%)	0 (0%)	-	-
Prediabetes	46 (34.1%)	30 (21.9%)	5.007	0.025
Type II diabetes	31 (23%)	24 (17.5%)	1.249	0.264
BMI	25.62 ± 3.01	24.60 ± 3.19	−2.599	0.01
BMI ≥ 23 kg/m^2	110 (81.5%)	86 (63.7%)	10.723	0.001
Hypertension	74 (54.8%)	44 (32.4%)	13.905	0.000
Dyslipidemia	91 (61.4%)	56 (40.9%)	19.948	0.000
HDL < 1.0 mmol/L	64 (47.4%)	46 (33.6%)	5.400	0.020
Triglycerides	62 (45.9%)	42 (30.7%)	6.713	0.010
≥ 1.70 mmol/L				
Albumin (g/L)	39.4 ± 6.94	41.62 ± 3.64	−3.297	0.001
Bilirubin (μmol/L)	17.0 [10.7, 39.2]	13.2 [10.15, 16.35]	−2.626	0.009
ALT (U/L)	37.0 [24.5, 68.0]	26.0 [17.0, 40.5]	−3.845	0.000
AST (U/L)	35.0 [25.5, 60.0]	23.0 [19.0, 29.5]	−6.921	0.000

Independent Correlation Of Metabolic Characteristics

We conducted an independent correlation analysis for each significantly different metabolic characteristic, and the results showed that each characteristic was significantly related to the increased risk of MAFLD-HCC ($p < 0.05$). The risk of MAFLD-HCC in patients with prediabetes, obesity, hypertension, and dyslipidemia was 1.8 times (95% confidence interval [CI] = 1.08–3.16), 2.5 times (95% CI = 1.44–4.38), 2.5 times (95% CI = 1.55–4.16), and 3 times (95% CI = 1.82–4.91) greater than that of patients without the disease. In addition, both hypertriglyceridemia and low HDL had independent effects, and the risk of HCC was 1.2 times (95% CI = 1.03–1.45) and 1.8 times higher (95% CI = 1.09–2.91) than that of patients without the disease, respectively (Table 2).

Table 2
Association between metabolic traits and MAFLD-HCC on univariate and multivariate logistic regression analysis. BMI, body mass index; HDL, high-density lipoprotein.

Characteristic	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Prediabetes	1.843 (1.08–3.16)	0.026	2.14 (1.16–3.96)	0.015
BMI ≥ 23 kg/m^2	2.507 (1.44–4.38)	0.001	3.07 (1.66–5.70)	0.000
Hypertension	2.537 (1.55–4.16)	0.000	2.76 (1.60–4.77)	0.000
Dyslipidemia	2.991 (1.82–4.91)	0.000	2.78 (1.62–4.76)	0.000
Triglycerides ≥ 1.70 mmol/L	1.219 (1.03–1.45)	0.023	2.40 (1.36–4.22)	0.003
HDL < 1.0 mmol/L	1.783 (1.09–2.91)	0.021	-	-

In the multivariate model, the prediabetes, obesity, and hypertension patients had an adjusted increased risk of disease compared with those without disease: 2.1 times (95% CI = 1.16–3.96), 3.1 times (95% CI = 1.66–5.70), and 2.8 times (95% CI = 1.60–4.77) increased risk compared with that of patients without disease, respectively. The risk of patients with dyslipidemia after adjustment was 2.8 times (95% CI = 1.62–4.76) lower than that of patients without dyslipidemia. The increased risk of patients with hypertriglyceridemia was greater than that of non-hypertriglyceridemia patients by 2.4 times (95% CI = 1.36–4.22), and the correlation between low HDL and risk of disease was no longer different (Fig. 1).

Joint Correlation Of Metabolic Characteristics

A ubiquitous superposition of metabolic characteristics was observed in patients with MAFLD-related HCC. The proportions of patients with two metabolic characteristics were 56.3% (obesity and dyslipidemia), 41.5% (obesity and hypertension), 20.7% (prediabetes and hypertension), 29.6% (prediabetes and obesity), 36.3% (hypertension and dyslipidemia), and 25.2% (prediabetes and dyslipidemia). The proportions of patients with three metabolic characteristics at the same time were

29.6% (obesity, hypertension, and dyslipidemia), 14.1% (prediabetes, hypertension, and dyslipidemia), 17.8% (obesity, prediabetes, and hypertension), and 30% (obesity, prediabetes, and dyslipidemia). Patients with four characteristics at the same time accounted for 12.6% of the study group. Compared with the control cohort, all data differences were statistically significant ($p < 0.05$) (Table 3).

Table 3
Types of metabolic traits of patients with MAFLD and MAFLD-HCC.

Characteristics	HCC (n = 135)	Non-HCC (n = 137)	χ^2	*p*
Obesity and dyslipidemia	76 (56.3%)	33 (24.1%)	29.373	0.000
Obesity and hypertension	56 (41.5%)	28 (20.4%)	14.107	0.000
Prediabetes and hypertension	28 (20.7%)	7 (5.1%)	14.818	0.000
Prediabetes and obesity	40 (29.6%)	11 (8.0%)	21.568	0.000
Hypertension and dyslipidemia	49 (36.3%)	17 (12.4%)	21.113	0.000
Prediabetes and dyslipidemia	34 (25.2%)	11 (8.0%)	14.495	0.000
Obesity, hypertension, and dyslipidemia	40 (29.6%)	11 (8.0%)	22.131	0.000
Prediabetes, hypertension, dyslipidemia	19 (14.1%)	3 (2.2%)	12.918	0.000
Obesity, prediabetes, hypertension	24 (17.8%)	3 (2.2%)	18.479	0.000
Obesity, prediabetes, dyslipidemia	30 (22.2%)	3 (2.2%)	25.596	0.000
Prediabetes, obesity, hypertension, and dyslipidemia	17 (12.6%)	0 (0%)	18.402	0.000

In the univariate model, the correlation analysis between the superimposition of each metabolic feature and the risk of MAFLD-HCC showed that all patients with superimposed characteristics had higher risk than those without superimposition ($p < 0.05$). In the multivariate model, only four specific combinations of metabolic characteristics were significantly related to the risk of disease. Compared with patients without superimposed metabolic characteristics, the risk of patients with obesity and dyslipidemia was 2.3 times higher (adjusted OR = 2.25, 95% CI = 1.21–4.16), and the risk of patients with hypertension and dyslipidemia was also 2.3 times higher (adjusted OR = 2.25, 95% CI = 1.15–4.77). Patients with obesity, prediabetes, and hypertension had a 5.7 times higher risk of morbidity (adjusted OR = 5.7, 95% CI = 1.47–21.78), whereas patients with obesity, prediabetes, and dyslipidemia had a 4.6 times higher risk of morbidity (adjusted OR = 4.58, 95% CI = 1.19–17.58) ((Table 4, Fig. 2).

Table 4
Association between types of metabolic traits and MAFLD-HCC on univariate and multivariate logistic regression analysis.

Characteristics	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Obesity and dyslipidemia	4.060 (2.42–6.82)	0.001	2.25 (1.21–4.16)	0.01
Obesity and hypertension	2.759 (1.61–4.73)	0.000	-	-
Prediabetes and hypertension	4.860 (2.04–11.56)	0.000	-	-
Prediabetes and obesity	4.785(2.33–9.82)	0.000	-	-
Hypertension and dyslipidemia	2.991 (1.82–4.91)	0.000	2.34 (1.15–4.77)	0.019
Prediabetes and dyslipidemia	3.856 (1.86–7.99)	0.000	-	-
Obesity, hypertension, dyslipidemia	1.739 (0.95–3.19)	0.074	-	-
Prediabetes, hypertension, dyslipidemia	7.316 (2.11–25.35)	0.002	-	-
Obesity, prediabetes, hypertension	9.658 (2.83–32.92)	0.000	5.65 (1.47–21.78)	0.012
Obesity, prediabetes, dyslipidemia	12.762 (3.79–42.97)	0.000	4.58 (1.19–17.58)	0.027

Sensitivity Analyses

In this study, a total of 107 patients were diagnosed with HCC without cirrhosis, and only 19.3% of patients were diagnosed with liver cirrhosis and HCC. The analysis of the relationship between metabolic characteristics and risk of disease in patients with MAFLD- HCC without liver cirrhosis showed that patients with prediabetes, obesity, hypertension, dyslipidemia, and hypertriglyceridemia had 2.6 times (95% CI = 1.41–4.96), 3.1 times (95% CI = 1.62–6.08), 2.3 times (95% CI = 1.27–4.04), 2.7 times (95% CI = 1.51–4.74), and 2.2 times (95% CI = 1.19–3.96) higher risk than those without the disease; after adjustment, the differences were statistically significant ($p < 0.05$) (Table 5).

Table 5
Associations between metabolic traits and MAFLD-HCC in patients without cirrhosis on univariate and multivariate logistic regression analysis. BMI, body mass index.

Characteristics	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Prediabetes	2.32 (1.33–4.06)	0.003	2.64 (1.41–4.96)	0.002
BMI ≥ 23 kg/m^2	2.32 (1.47–4.95)	0.001	3.14 (1.62–6.08)	0.001
Hypertension	2.13 (1.27–3.58)	0.004	2.26 (1.27–4.04)	0.006
Dyslipidemia	2.93 (1.74–4.96)	0.000	2.68 (1.51–4.74)	0.001
Triglycerides ≥ 1.70 mmol/L	1.78 (1.06–3.01)	0.031	2.17 (1.19–3.96)	0.011

Discussion

The global prevalence of MAFLD has risen from 15–25% over the past 10 years, and this trend is expected to continue[10]. The risk of HCC, the most serious complication of MAFLD, is also increasing. At present, MAFLD is considered as the most common risk factor for liver cancer in the United States and Japan, and MAFLD-HCC is considered an emerging indication for liver transplantation[11,12]. However, data from large-scale studies of the incidence and risk of MAFLD-HCC in China are lacking. MAFLD is the manifestation of metabolic syndrome in the liver. Numerous studies have confirmed that metabolic characteristics are closely related to the development of HCC. Particularly patients without cirrhosis, obesity and T2 DM are considered independent risk factors for the development of HCC[13,14]. In this study, we found that prediabetes, obesity, hypertension, and hyperlipidemia are all individually or in combination associated with an increased risk of HCC, and this risk is positively correlated with the number of metabolic characteristics.

As there was no statistically significant difference in the prevalence of T2 DM in the two study cohorts in the independent and joint correlation analyses of metabolic characteristics, we selected prediabetes as an alternative metabolic characteristic based on the diagnostic criteria of MAFLD and confirmed that it has a strong correlation with HCC risk. In the multivariate model, obesity was the factor most strongly associated with risk of HCC progression; this risk was 3.1 times that of non-obese individuals. Several studies have noted that although obesity is associated with increased risk of many cancers, it has the strongest correlation with increased risk of HCC, which is consistent with our results[15,16]. Dyslipidemia is a key risk factor for MAFLD-related HCC[17]. Our study confirmed that dyslipidemia is associated with the risk of MAFLD-HCC, and we therefore analyzed the associations between hypertriglyceridemia and low HDL and HCC separately. Although both factors exhibited independent effects, in the multivariate model, only hypertriglyceridemia was associated with risk of HCC (adjusted OR = 2.40, 95% CI = 1.36–4.22).

In the joint correlation analysis of metabolic characteristics, patients with two metabolic characteristics only exhibited obesity and dyslipidemia or obesity and hypertension, which are related to the risk of HCC, which to some extent demonstrates that obesity has a strong impact. Patients with three metabolic characteristics had a significantly higher correlation with the risk of HCC, demonstrating that the number of metabolic characteristics is positively correlated with disease risk. Among these patients, obesity, prediabetes, and hypertension had the highest correlation with MAFLD-HCC risk (adjusted OR = 5.7, 95% CI = 1.47–21.78). Our results are basically consistent with those of previous studies in which obesity, T2 DM, and hypertension exhibited the highest combined correlation with HCC risk[18].

The results of the current study indicate that a considerable proportion of MAFLD-HCC appears in patients without cirrhosis[19,20]. In our study, this proportion was 80%, slightly higher than that reported from studies in other parts of the world. In the correlation analysis of metabolic characteristics in this group of patients, the correlation between obesity and prediabetes and HCC risk was slightly higher than that in the overall analysis, whereas the correlation between hypertension and dyslipidemia and HCC risk was slightly lower, with obesity remaining the most strongly correlated risk factor (adjusted OR = 3.14, 95% CI = 1.62–6.08).

Surveillance of MAFLD-HCC is very challenging. The current guidelines of European Association for the Study of the Liver only recommend monitoring patients with MAFLD-cirrhosis. It is recommended that abdominal ultrasound and serum alpha-fetoprotein examinations be performed every 6 months[21]. However, the guidelines ignore the occurrence of HCC in patients without cirrhosis, and there is no precise screening recommendation. Our research provides a basis for accurate screening and risk stratification of MAFLD-HCC. According to our research results, HCC surveillance is critical for patients with obesity, prediabetes, and hypertension. In addition, data regarding related metabolic factors such as obesity, prediabetes, dyslipidemia, and hypertension, as confirmed by our research, are objective and easy to obtain, which can provide a scientific basis for the establishment of a cost-effective accurate surveillance tool for HCC. Simultaneously, these metabolic factors could also be used as an important target of secondary prevention to delay the progress of MAFLD-HCC.

This study has several limitations. First, this was a retrospective analysis, and the retrospective, non-randomized design could introduce selection bias. Second, there may be problems with the selection of the patient metabolic factors. For example, we only selected biochemical indicators when a patient was first diagnosed with HCC, which could have introduced errors, and there are obesity markers that are more sensitive than BMI. Third, considering that patients in the control group also have risk factors of HCC, a long-term follow-up is needed to observe the prognosis and outcome of these patients. Finally, our research did not involve treatment methods or patient prognosis. Our proposed strategy for secondary prevention goals thus requires prospective risk reduction trials to demonstrate its effectiveness.

In summary, our study found that metabolic characteristics increase the risk of MAFLD-HCC, and this risk is positively correlated with the number of metabolic characteristics. Regardless of the presence or absence of cirrhosis, obesity has the strongest correlation with risk of HCC. Our results indicate that

monitoring of prediabetes, hypertension, dyslipidemia, and obesity can be used to comprehensively assess the risk of HCC, which can in turn facilitate the establishment of reasonable, cost-effective risk stratification and precise screening strategies.

Declarations

Data availability

The datasets used and analysed during the current study available from the corresponding author(Jinhui Yang, email: yangjinhuikmmc@163.com) on reasonable request.

None

Acknowledgments

None

Author Contributions

X.X. and J.Y. contributed to conception and design of the study. M.Z. and W.G. organized the database. Y.Z. and Z.X. performed the statistical analysis. X.X. wrote the first draft of the manuscript. Y.L. and J.Y. wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Additional information

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Eslam, M., Sanyal, A. J., George, J. & International Consensus, P. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* **158**, 1999–2014.e1991. https://doi.org/10.1053/j.gastro.2019.11.312 (2020).
2. Valery, P. C. *et al.*:Projections of primary liver cancer to 2030 in 30 countries worldwide. :Hepatology (Baltimore, Md.):**67**,:600–611. https://doi.org/10.1002/hep.29498 (2018).
3. Fan, J. G., Kim, S. U. & Wong, V. W.:New trends on obesity and NAFLD in Asia. :Journal of hepatology:**67**,:862–873. https://doi.org/10.1016/j.jhep.2017.06.003 (2017).
4. Singal, A. G., Lampertico, P. & Nahon, P.:Epidemiology and surveillance for hepatocellular carcinoma: New trends. :Journal of hepatology:**72**,:250–261. https://doi.org/10.1016/j.jhep.2019.08.025 (2020).
5. Chen, V. L. *et al.*:Effects of Cirrhosis and Diagnosis Scenario in Metabolic-Associated Fatty Liver Disease-Related Hepatocellular Carcinoma. :Hepatology communications:**5**,:122–132.

https://doi.org/10.1002/hep4.1606 (2021).

6. Kanwal, F. *et al.*:Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. :*Gastroenterology*:**155**,:1828–1837.e1822. https://doi.org/10.1053/j.gastro.2018.08.024 (2018).
7. White, D. L., Kanwal, F. & El-Serag, H. B. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association **10**, 1342–1359.e1342, doi:10.1016/j.cgh.2012.10.001. https://doi.org/10.1016/j.cgh.2012.10.001 (2012).
8. Bruix, J. & Sherman, M.:Management of hepatocellular carcinoma: an update. :Hepatology (Baltimore, Md.):**53**,:1020–1022. https://doi.org/10.1002/hep.24199 (2011).
9. Eslam, M. *et al.*:A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. :Journal of hepatology:**73**,:202–209. https://doi.org/10.1016/j.jhep.2020.03.039 (2020).
10. Younossi, Z. *et al.*:Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. :Nature reviews. Gastroenterology & hepatology:**15**,:11–20. https://doi.org/10.1038/nrgastro.2017.109 (2018).
11. Kawamura, Y. *et al.*:Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. :The American journal of gastroenterology:**107**,:253–261. https://doi.org/10.1038/ajg.2011.327 (2012).
12. Wong, R. J., Cheung, R. & Ahmed, A.:Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. :Hepatology (Baltimore, Md.):**59**,:2188–2195. https://doi.org/10.1002/hep.26986 (2014).
13. Margini, C. & Dufour, J. F.:The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. :Liver international: official journal of the International Association for the Study of the Liver:**36**,:317–324. https://doi.org/10.1111/liv.13031 (2016).
14. Reeves, H. L., Zaki, M. Y. & Day, C. P.:Hepatocellular Carcinoma in Obesity, Type 2 Diabetes, and NAFLD. :Digestive diseases and sciences:**61**,:1234–1245. https://doi.org/10.1007/s10620-016-4085-6 (2016).
15. Bhaskaran, K. *et al.*:Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. :Lancet (London, England):**384**,:755–765. https://doi.org/10.1016/s0140-6736(14)60892-8 (2014).
16. Chen, Y., Wang, X., Wang, J., Yan, Z. & Luo, J.:Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. :European journal of cancer (Oxford, England: 1990):**48**,:2137–2145. https://doi.org/10.1016/j.ejca.2012.02.063 (2012).
17. Kaur, J.:A comprehensive review on metabolic syndrome. :*Cardiology research and practice*:2014,:943162. https://doi.org/10.1242/dmm.001180 (2014).
18. Kanwal, F. *et al.*:Effect of Metabolic Traits on the Risk of Cirrhosis and Hepatocellular Cancer in Nonalcoholic Fatty Liver Disease. :Hepatology (Baltimore, Md.):**71**,:808–819. https://doi.org/10.1002/hep.31014 (2020).

19. Dyson, J. *et al.*:Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. :Journal of hepatology:**60**,:110–117. https://doi.org/10.1016/j.jhep.2013.08.011 (2014).
20. Piscaglia, F. *et al.*:Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. :Hepatology (Baltimore, Md.):**63**,:827–838. https://doi.org/10.1002/hep.28368 (2016).
21. European Association for the Study of the Liver.:EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. :Journal of hepatology:**69**,:182–236. https://doi.org/10.1016/j.jhep.2018.03.019 (2018).

Figures

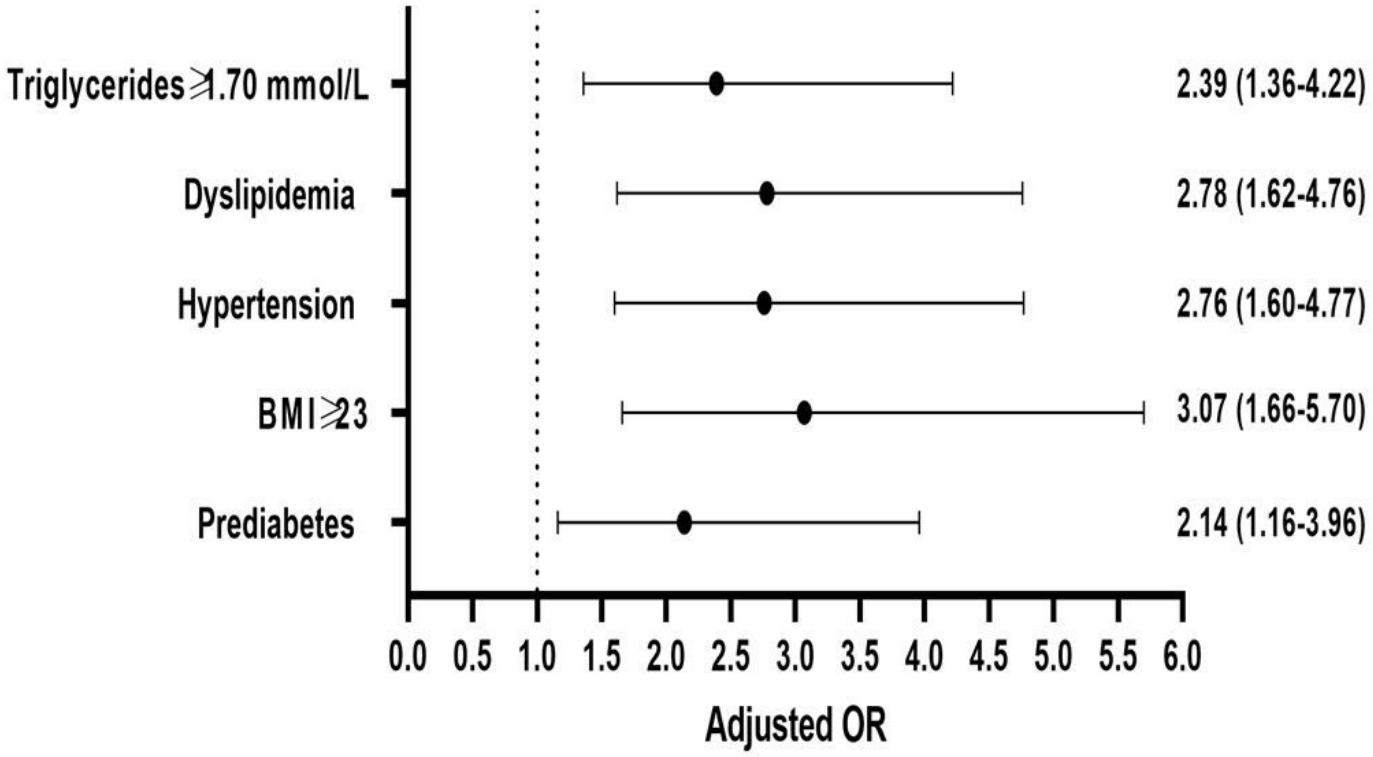

Figure 1

Adjusted associations between metabolic traits and MAFLD-HCC on multivariate logistic regression analysis.

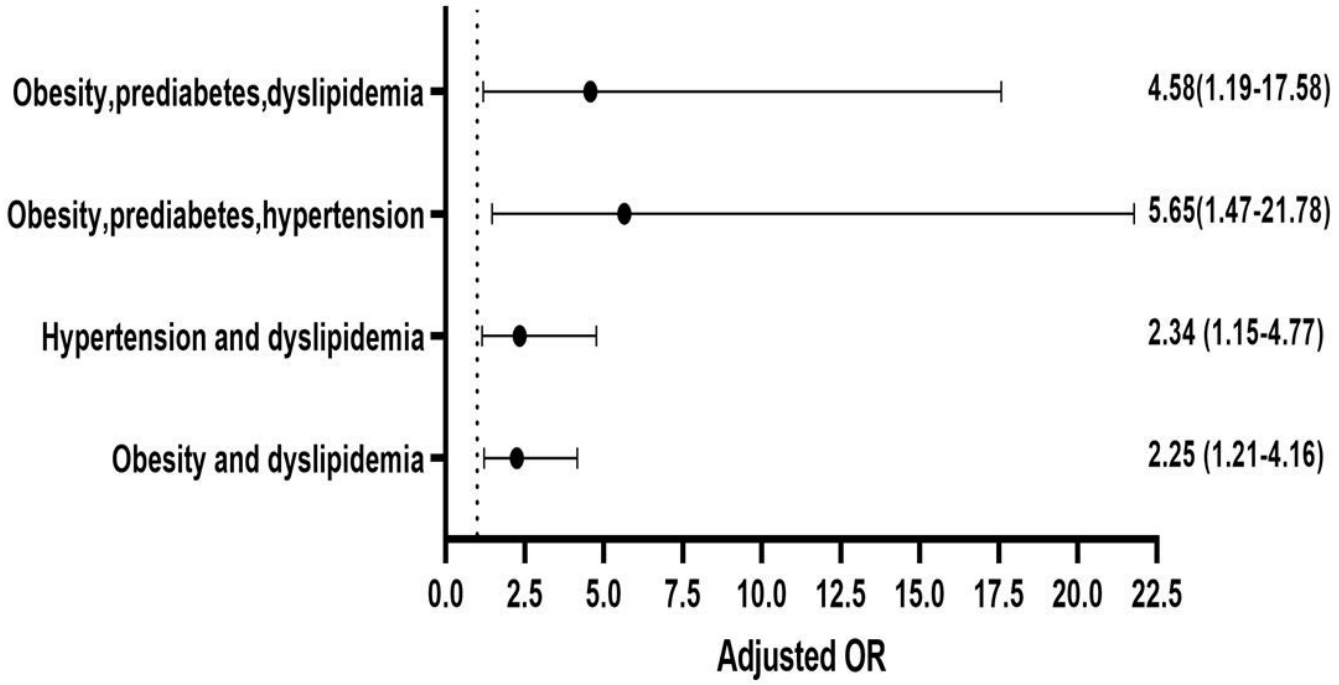

Figure 2

Adjusted associations between types of metabolic traits and MAFLD-HCC on multivariate logistic regression analysis.