The Risk of HCC in Patients with Chronic Hepatitis B is Increased by Concomitant Presence of MAFLD but not NAFLD

Jiaofeng Huang
Fujian Medical University
Mingfang Wang
Fujian Medical University
Yinlian Wu
Fujian Medical University
Jiaji Jiang
Fujian Medical University
Yueyong Zhu
Fujian Medical University
Rahul Kumar
Changi General Hospital
Su Lin (sumer5129@fjmu.edu.cn)
Fujian Medical University https://orcid.org/0000-0001-7517-9859

Research

Keywords: MAFLD, NAFLD, HCC, HBV, hepatic steatosis

Posted Date: October 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-961657/v1

Abstract

Background: Chronic Hepatitis B virus infection (CHB) and non-alcoholic fatty liver disease (NAFLD) are both independent risk factors for hepatocellular carcinoma (HCC). Current literature suggests the concomitance of CHB and NAFLD do not increase the risk of HCC. The risk of HCC in patients with concomitant CHB and metabolic associated fatty liver disease (MAFLD) is unclear.

Methods: CHB patients who underwent liver biopsy from 2005 to 2015 were retrospectively recruited and followed up till March 2020. Cox hazard ratio analysis was used to investigate the risk of HCC.

Results: A total of 529 patients were included. MAFLD was diagnosed in 184 (34.78%) and NAFLD in 250 (47.26%) patients. The median follow-up duration was 6.33 years. In the entire cohort, 9 (1.7%) patients developed HCC. The prevalence of MAFLD was significantly higher in HCC group than non-HCC group (77.8% vs. 34.04%, p=0.010), while of the prevalence of NAFLD was not statistically significant (46.73% vs. 77.78%, p=0.092). The presence of MAFLD (HR=6.434; 95%CI: 1.252-33.060) was an independent risk factor for HCC in CHB patients while NAFLD was not. Significantly higher rate of HCC was found in patients with metabolic conditions than those without (2.83% vs. 0.41%, P=0.043), but not in the comparison between steatosis and non-steatosis (2.77% vs. 0.72%, P=0.094).

Conclusion: Presence of MAFLD is independently associated with the risk of HCC development in patients with CHB. Between MAFLD and NAFLD, MAFLD will serve these patients better for risk stratification as far as development of HCC is concerned.

Lay Summary

The main finding of our study is that MAFLD (HR=6.434; 95%CI: 1.252-33.060) was an independent risk factor for HCC in HBV population while NAFLD was not.

The presence of steatosis alone was not associated with increased HCC incidence when compared to patients without steatosis (2.77% vs. 0.72%, P=0.092).

A significantly higher rate of HCC was found in patients with metabolic conditions than without (2.83% vs. 0.41%, P=0.043).

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is associated with substantial cancer-related mortality in the world[1]. The most important etiological risk factors for HCC development include chronic viral infections, i.e. chronic hepatitis B virus (CHB) and chronic hepatitis C virus (CHC), nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease[2]. Despite the recent great strides in the management of HCC with advent of chemotherapeutic agents, the 5-year transplant

free survival of these patients remains dismal[3–5]. Thus, control of etiological risk factor and periodic surveillance is of utmost clinical importance for the prevention and management of HCC[6, 7].

CHB is a major global public health problem which is worse in Asian countries. Although with the use of effective preventive vaccine and well-tolerated viral suppression regimens, the prevalence of CHB are on decline, currently there are still 248 million individuals with active CHB infection globally[8]. NAFLD is another common chronic liver disease affecting over 25% of the world's population[9]. Both CHB and NAFLD are reported to be independently associated with the development of HCC[10–13]. For this reason, it is reasonable to believe that the presence of hepatic steatosis which is central to the diagnosis of NAFLD will lead to accelerated development of HCC in CHB patients. However, studies focusing on the same question showed that presence of NAFLD did not increase the risk of HCC in patients with CHB[14, 15]. Further studies demonstrated that hepatic steatosis was actually associated with lower risk of cirrhosis and HCC and higher rate of HBsAg seroclearance in patients with CHB [16, 17]. On the other hand, metabolic risk factor specifically diabetes mellitus (DM) in patients with CHB is known to be associated with increased risk of HCC.

Metabolic dysfunction associated fatty liver disease (MAFLD) is a novel concept that looks at hepatic steatosis in the light of metabolic syndrome and derangements[18]. MAFLD does not require the exclusion of other liver diseases, but the presence of metabolic disorder is necessary for the diagnosis, which is different from NAFLD[19]. Several recently published studies have reported that this new definition of fatty liver disease identifies a greater number of patients at risk of adverse outcomes than the traditional NAFLD definition[20–22]. However, it is not yet known whether the presence of concomitant MAFLD plays any role in hepatocarcinogenesis in patients with CHB. With this question in mind, we designed this study to look at the influence of concomitant MAFLD or NAFLD on HCC development in patients with CHB. The specific aim of our study is to compare the HCC incidence rates between biopsy-proven NAFLD and MAFLD in patients with CHB.

2. Methods

2.1. Study population

The study cohort includes all patients with CHB who underwent liver biopsy at the First Affiliated Hospital of Fujian Medical University from May 2005 to July 2015 for diagnostic purposes. We excluded patients with diagnosis of HCC at the time of liver biopsy and patients with follow-up duration of less than 6 months. This study population did not include any excessive alcoholic user as those would have been advised to be abstinence from alcohol rather than to undergo biopsy for diagnosis.

This retrospective study protocol was approved by the ethics committee of the First Affiliated Hospital of Fujian Medical University and was conducted in accordance with the Declaration of Helsinki.

2.2. Diagnostic criteria and definition of groups

2.2.1. MAFLD

MAFLD was diagnosed based on a biopsy-proven hepatic steatosis in the presence of any one of the following three metabolic conditions: diabetes mellitus, overweight /obesity, or metabolic dysregulation[23].

2.2.2. NAFLD

NAFLD was defined by the presence and pattern of fat accumulation (steatosis) on liver biopsy, and by the exclusion significant alcohol consumption of ³30g/d for male and ³20g/d for female or other known cause of liver disease[24]. In this study, the HBV infection was considered as the concomitant liver disease but not the exclusion criterion for the diagnosis of NAFLD.

2.2.3. CHB

CHB was defined as seropositivity of HBsAg for more than 6 months.[25].

2.2.4. HCC

HCC was diagnosed based on compatible imaging characteristic on a dynamic imaging modality or by pathological evaluation according to the existing diagnostic definitions[26,27].

2.2.5. Cirrhosis

Cirrhosis was defined as fibrosis stage 4 on histology or clinical comprehensive assessment of portal hypertension, splenomegaly, thrombocytopenia, esophageal and gastric varix, and ascites[28].

2.3. Demographic variables

The following demographic variables were obtained from the original database: age, sex, body mass index (BMI), and the history of diabetes mellitus. BMI was calculated as weight (in kilograms) divided by the square of height (in meters).

2.4. Laboratory parameters

Laboratory measurement studied included alpha fetoprotein (AFP), total bilirubin (TBIL), aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT), total cholesterol (TC), total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), fasting plasma glucose (FPG), HBsAg, hepatitis e surface antigen (HBeAg), hepatitis B virus deoxyribonucleic acid (HBV-DNA). All biochemical assessments were performed by standard laboratory methods.

2.5. Histologic evaluation

All patients underwent ultrasonography guided percutaneous liver biopsy using a 16-gauge hepatic needle. The liver specimens were immediately immersed in formalin, embedded with paraffin, and stained with hematoxylin and eosin, as well as Masson's trichrome. A biopsy tissue with the minimum length of 15 mm and at least 6 portal areas was regard as a sufficient tissue[29]. The histopathological examination was carried by two experienced independent pathologists. Fatty liver was defined as the presence of steatosis in at least 5% hepatocytes. Mild steatosis (S1) was defined if 5%-33% of examined liver surface area was involved with steatosis, moderate steatosis (S2) if 34% - 66%, and severe steatosis (S3) if > 66% [30]. Moderate to severe steatosis was defined as steatosis grade ≥2. The stages of liver inflammation were graded from 0 to 4 points (0=no inflammation; 1=portal inflammation; 2=mild piecemeal necrosis; 3=moderate piecemeal necrosis; 4=severe piecemeal necrosis)[31,32]. Significant inflammation was classified inflammation grade ≥2[33]. Liver fibrosis was scored from 0 to 4 (0=no fibrosis; 1=perisinusoidal or portal/periportal only; 2=perisinusoidal and periportal; 3=bridging fibrosis; 4=cirrhosis)[31,32]. Liver cirrhosis was defined as fibrosis score ≥4 or with clear evidence of cirrhosis in images.

2.6. Statistical analysis

Continuous variables are expressed as means ± standard deviation or median (interquartile- range). Categorical variables are expressed as percentages. The Student t-test (for normally distributed variables), Mann-Whitney U-test (for non-normally distributed variables) and Chi-squared test or Fisher exact test (for categorical variables) were used to investigate the differences between the groups. Survival analysis was carried according to the Kaplan - Meier method with log-rank test to compare the HCC incidence in different groups. A univariate cox regression analysis was performed to evaluate the prognostic factors. The indicators with approaching statistical significance ($p < 0.10$) in univariate analysis were included into multivariate regression analysis. All tests were two-tailed and results with a p value less than 0.05 were considered statistically significant. All analysis was conducted using SPSS 16.0 or R 3.6.2 (https://www.r-project.org/).

3. Results

3.1. Baseline characteristics of the study population

A total of 529 patients who fulfilled the predefined study criteria were identified from the digital clinical history records (Figure 1). The baseline characteristics are listed in Table 1. The cohort was predominantly male; 427 (80.72%). The mean age was 37.99 ± 10.44 years, and mean BMI of 23.03 ± 3.17 Kg/m^2. A total of 51 (9.64%) patients had diabetes mellitus. Based on the standard diagnostic criteria, MAFLD was identified in 184 (34.78%), while NAFLD in 250 (47.26%) patients. The median follow-up duration was 6.33 years (interquartile range: 4.41- 8.17 years). Significant inflammation (METAVIR grade ≥2) was found in 433 (81.85%) patients, moderate to severe steatosis (grade ≥2) in 102 (19.28%) patients, and cirrhosis (fibrosis grade ≥4) in 144 (27.22%) patients. After biopsy, a total of 463 (87.52%) patients received oral nucleoside/nucleotide analogue (NA) treatment for CHB due to the

presence of significant inflammation (grade≥2) or advanced liver fibrosis (scores ≥2). The prevalent antiviral drug was entecavir during the study period as it was covered by the Chinese medical insurance, with 418 (90.3%) received entecavir and 45 (9.7%) receiving with others such as adefovir or telbivudine. Over the course of follow-up, 9 (1.7%) patients were detected to have developed HCC.

3.2. Comparison between MAFLD and NAFLD group

The comparison of variables in patients diagnosed with NAFLD and MAFLD are illustrated in Table 2. Patients with MAFLD had higher BMI (25.61 ± 2.61 Kg/m^2 vs. 24.36 ± 3.13 Kg/m^2, P<0.05), and lower HDL-C level (1.14 ± 0.34 mmol/L vs. 1.23 ± 0.37 mmol/L, P<0.05). There was no difference in other studied parameters including age, gender, quantitative HBsAg, HBVDNA, serum albumin, ALT, AST, ALP and GGT between the two groups (P> 0.05). The results of liver histopathological analysis showed no significant difference between the groups (P>0.05).

3.3. Comparison between HCC and Non-HCC group

Nine (1.7%) patients developed HCC during the follow-up. The incidence of HCC was 3.8% in MAFLD group and 2.8% in NAFLD group. The characteristics of HCC group and non-HCC patients are compared in Table 1. No significantly difference was found in age, gender, blood lipid profile (TG, TC, HDL-C, LDL-C, VLDL-C, etc.), blood glucose, blood pressure, diabetes, liver function and liver histology. The prevalence of MAFLD was 34.04% in non-HCC group and 77.78% in HCC group (p=0.010), while the NAFLD was found in nearly half of non-HCC cases (46.73%) and 77.78% in HCC group, this difference however did not reach statistical significance (p=0.092). The Kaplan-Meier analysis further demonstrated a significantly higher 10-year cumulative incidence of HCC in MAFLD group compared with the non-MAFLD group (10.90% vs. 0.60%, P=0.023, Figure 2A). In contrast, the 10-year cumulative incidence of HCC did not significantly differ between NAFLD and non-NAFLD groups (7.90% vs. 0.70%, P=0.191, Figure 2B).

3.4. Univariate and multivariate analysis for the risk of HCC in HBV infected population

A univariate Cox proportional hazards regression analysis for overall survival was performed, showing FPG, cirrhosis and MAFLD were associated with higher incidence of HCC (P<0.10 for all) and were finally included into multivariate regression analysis (Table 3). The results of multivariate analysis showed that cirrhosis (HR=4.688; 95%CI: 1.166-18.848, P=0.030) and co-existence of MAFLD (HR=6.434; 95%CI: 1.252-33.060, P=0.026) were independent risk factors for HCC whereas NAFLD was not.

3.5. Comparison of hepatic steatosis and metabolic conditions

As MAFLD definition requires the presence of metabolic conditions (MC), which differs from NAFLD, to further evaluate the impact hepatic steatosis or MC may have on the incidence of HCC in CHB patients, we classified patients by the presence of MC or steatosis. The results of this comparison between different groups thus created (with or without MC and with or without steatosis) are shown in Table 4. Compared with patients without MC or steatosis, patients with MC or steatosis tended to be older, more

likely to be male and had higher levels of metabolic related parameters including BMI, TG, LDL-C, HDL-C, VLDL-C, and glucose levels (P<0.05 for all). MC positive group or steatosis positive group had significantly lower level of the quantitative HBsAg and HBVDNA when compared to the MC negative or steatosis negative group. The liver histopathological examination showed that steatosis positive group had a lower grade of inflammation and lesser prevalence of cirrhosis (≥F4) than steatosis negative group. But the comparison between MC positive and MC negative groups did not find such difference. There was significantly higher incidence of HCC in MC positive group than MC negative group (2.83% vs. 0.41%, P=0.043), while no statistical difference was found between cases with and without steatosis (2.77% vs. 0.72%, P=0.094).

4. Discussion

In this long follow-up study of a biopsy proven cohort of patients with CHB, we report the incidence of HCC and the influence concomitant MAFLD or NAFLD could have on the development of HCC. The results of our study demonstrate that the 10-year accumulative incidence of HCC is significantly higher in CHB patients with concomitant MAFLD, but not NAFLD. Further analysis of the data showed that hepatic steatosis alone did not significantly increase the risk of development of HCC in the CHB patients. It may actually be the metabolic derangements rather than the hepatic steatosis that accelerates the progression of HCC. Compared to the old definition for fatty liver disease (NAFLD), the new one (MAFLD) that requires the presence of metabolic disorder helps to identify higher rate of patients at risk of future HCC development at least in CHB population.

This to our knowledge is the first study which compared the influence of MAFLD and NAFLD on HCC development in patients with CHB, however ours is not the only study focusing on the association between liver steatosis and HCC in CHB patients. Different from previous studies, we compared the two contrasting definitions for classifying patients with fatty liver disease. The results of our study are supported by some previous studies[14, 15], which did not find any higher risk of HCC in patients with concurrent NAFLD and CHB. However, our study found that the risk of HCC is increased by the presence of concomitant MAFLD. This interesting difference in the added risk of HCC between concomitant NAFLD and MAFLD is related to the higher proportion of metabolic disorder in MAFLD. As shown in previous studies which adjusted for both metabolic disorder and steatosis in multivariate analysis, the burden of metabolic risk factor is the major determinant for HCC development in CHB with fatty liver disease[14, 34]. The oncogenic potential of metabolic risk factors is well-accepted and is shown by many studies[35, 36]. The increased growth-promoting effect of insulin resistance and insulin-like growth factors[37, 38] as well as lipo-toxicity and pro-inflammatory adipokine secretion in obesity have been shown to be involved in this carcinogenic process[39]. Once the metabolic disorders were added into fatty liver, creating a new umbrella term and definition for MAFLD, the risk of future development of HCC in these patients are significantly increased.

Our study also shows that the presence of simple steatosis in absence of any metabolic risk factors is not an independent factor for future development of HCC in CHB patients. In-fact some of the previous

studies have similar observations that steatosis alone has no impact on the development of HCC in these patients[16, 40]. The likely explanation of this observation is the complex interplay among HBV DNA level, HBsAg levels and hepatic steatosis. While higher HBV DNA and HBsAg levels are known to increase the risk of HCC[41, 42], increasing steatosis is independently associated with lower serum HBV DNA [43] and quantitive HBsAg levels[40]. Recent scientific literature even suggested that liver steatosis could in fact reduce the burden of liver fibrosis in patients with CHB and that steatosis increased the chance of cure from hepatitis B virus[44, 45]. The hypothesis behind this positive impact of hepatic steatosis in patients with CHB is that, the presence of fat within the hepatocytes is associated with abnormal lipid metabolism and may alter HBsAg cytoplasmic distribution[40]. This may in turn induce hepatocyte apoptosis leading to inhibition of viral replication and eventual loss of HBsAg expression[46] and subsequent seroclearance[47, 48].

The strength of our study is that, liver biopsy is used for the diagnosis of steatosis as well as the inflammation and cirrhosis, which is considered the gold-standard for the evaluation of fibrosis and inflammation. The sample size of this study is large with a long follow-up duration. However, the results of our study must be interpreted in the light of some limitations. First, the study cohort is from a single center with high prevalence of HBV and low BMI. Although a common occurrence in Asian[49, 50], this may limit the generality of the conclusions of our study in the western cohorts. However, at the very least the results of our study are applicable to a subset of MAFLD namely “HBV-MAFLD”, which is the most important subtype of MAFLD in clinical practice in Asia. Second, compared with our previous population-based study[21], this study only included highly selected patients who underwent liver biopsy, which may have created inadvertent selection bias. Last, because of the wide-spread use of antiviral agents against HBV, the HCC risk is extremely low in our cohort which is what is expected in CHB patients on NA[51]. The incidence of HCC may be too low to investigate multiple factors predicting HCC and could potentially lead to reduced power of statistical analysis. Also, patients untreated for CHB may carry a different risk of HCC development in presence of concomitant MAFLD.

To conclude, in patients with CHB who have concomitant fatty liver disease the MAFLD definition helps to identify more patients at risk of developing HCC while NAFLD definition does not.

Abbreviations

CHB: Chronic Hepatitis B virus infection; MAFLD: Metabolic Associated Fatty Liver Disease; NAFLD: Nonalcoholic Fatty Liver Disease; MC, metabolic conditions; HCC: Hepatocellular Carcinoma; HBsAg: Hepatitis B Surface Antigen; HBeAg: Hepatitis B e Antigen; HBVDNA: Hepatitis B Virus Deoxyribonucleic Acid; AFP: Alpha Fetoprotein; TBIL: Total Bilirubin; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transpeptidase; TC: Total Cholesterol; TG: Triglyceride; HDL-C: Digh-density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; VLDL-C: Very Low Density Lipoprotein Cholesterol; FPG: Fasting Plasma Glucose.

Declarations

Ethics approval and informed consent

An informed consent was obtained from each participant on admission to use their medical data anonymously. The ethics approval was approved by the First Affiliated Hospital, Fujian Medical University Institution Review Board ([2015]084-1). This study conforms to the principles outlined in the Declaration of Helsinki.

Authors' Contributions

Study concept and design: Jiaofeng Huang, Su Lin and Rahul Kumar

Acquisition, cleaning of data: Mingfang Wang and Yinlian Wu

Drafting of the manuscript: Su Lin, Jiaofeng Huang and Rahul Kumar.

Critical revision: Rahul Kumar, Jiaji Jiang and Yueyong Zhu

Statistical analysis: Jiaofeng Huang and Yinlian Wu

Study supervision: Su Lin

Funding: This research is supported by Chinese Medical Science Research Fund (13071120497), Qingzhong Medical Science Research Fund (B17344) and Startup Fund for scientific research, Fujian Medical University (2018QH1047).

Competing interests

The authors declare that they have no competing interests in this work.

References

1. Zakharia K, Luther CA, Alsabbak H, Roberts LR. Hepatocellular carcinoma: Epidemiology, pathogenesis and surveillance - implications for sub-Saharan Africa. S Afr Med J. 2018;108(8b): 35-40.
2. Tateishi R, Koike K. Changing etiology of hepatocellular carcinoma. J Gastroenterol. 2020;55(1): 125-126.
3. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4): 271-289.
4. Brown ZJ, Greten TF, Heinrich B. Adjuvant Treatment of Hepatocellular Carcinoma: Prospect of Immunotherapy. Hepatology. 2019;70(4): 1437-1442.
5. Iñarrairaegui M, Melero I, Sangro B. Immunotherapy of Hepatocellular Carcinoma: Facts and Hopes. Clin Cancer Res. 2018;24(7): 1518-1524.

6. Kumar R, Goh BG, Kam JW, Chang PE, Tan CK. Comparisons between non-alcoholic steatohepatitis and alcohol-related hepatocellular carcinoma. Clin Mol Hepatol. 2020;26(2): 196-208.
7. Su F, Weiss NS, Beste LA, Moon AM, Jin GY, Green P, et al. Screening is associated with a lower risk of hepatocellular carcinoma-related mortality in patients with chronic hepatitis B. J Hepatol. 2020;74(4): 850-859.
8. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003): 1546-1555.
9. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1): 73-84.
10. Bengtsson B, Stål P, Wahlin S, Björkström NK, Hagström H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int. 2019;39(6): 1098-1108.
11. Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol. 2019;71(3): 523-533.
12. Piccinin E, Villani G, Moschetta A. Metabolic aspects in NAFLD, NASH and hepatocellular carcinoma: the role of PGC1 coactivators. Nat Rev Gastroenterol Hepatol. 2019;16(3): 160-174.
13. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology. 2015;62(6): 1723-1730.
14. Yu MW, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of Metabolic Risk Factors on Risk of Hepatocellular Carcinoma and Liver-Related Death in Men With Chronic Hepatitis B: A Large Cohort Study. Gastroenterology. 2017;153(4): 1006-1017.e1005.
15. Lim CT, Goh GBB, Li H, Lim TK, Leow WQ, Wan WK, et al. Presence of Hepatic Steatosis Does Not Increase the Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Over Long Follow-Up. Microbiol Insights. 2020;13: 1178636120918878.
16. Li J, Yang HI, Yeh ML, Le MH, Le AK, Yeo YH, et al. Association between fatty liver and cirrhosis, hepatocellular carcinoma, and HBsAg seroclearance in chronic hepatitis B. J Infect Dis. 2020.
17. Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology. 2008;135(1): 111-121.
18. Eslam M, Sanyal AJ, George J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158(7): 1999-2014.e1991.
19. Liver EAftSoT, Diabetes EAftSo. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Obesity facts. 2016;9(2): 65-90.
20. Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int. 2020 (Online ahead of print);40(12): 3018-3030.

21. Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int. 2020;40(9): 2082-2089.
22. Sun DQ, Jin Y, Wang TY, Zheng KI, Rios RS, Zhang HY, et al. MAFLD and risk of CKD. Metabolism. 2020;115: 154433.
23. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020;73(1): 202-209.
24. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6): 1388-1402.
25. Bell S, Lau A, Thompson A, Watson K, Demediuk B, Shaw G, et al. Chronic hepatitis B: recommendations for therapy based on the natural history of disease in Australian patients. J Clin Virol. 2005;32(2): 122-127.
26. Zhou J, Sun HC, Wang Z, Cong WM, Wang JH, Zeng MS, et al. Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition). Liver Cancer. 2018;7(3): 235-260.
27. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1): 182-236.
28. Barnett R. Liver cirrhosis. Lancet. 2018;392(10144): 275.
29. Crawford AR, Lin XZ, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. Hepatology. 1998;28(2): 323-331.
30. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6): 1313-1321.
31. Brunt EM. Grading and staging the histopathological lesions of chronic hepatitis: the Knodell histology activity index and beyond. Hepatology. 2000;31(1): 241-246.
32. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol. 1991;13(3): 372-374.
33. Hong M, Zhang R, Chen G, Huang W, Min F, Chen T, et al. Liver stiffness measurement-based scoring system for significant inflammation related to chronic hepatitis B. PloS one. 2014;9(10): e111641.
34. Tan Y, Zhang X, Zhang W, Tang L, Yang H, Yan K, et al. The Influence of Metabolic Syndrome on the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection in Mainland China. Cancer Epidemiol Biomarkers Prev. 2019;28(12): 2038-2046.
35. Taura N, Ichikawa T, Miyaaki H, Yatsuhashi H, Ishibashi H, Nakao K. Prevalence of type 2 diabetes mellitus in Japanese patients with hepatocellular carcinoma. Exp Ther Med. 2011;2(1): 81-84.
36. Cotrim HP, Oliveira CP, Coelho HS, Alvares-da-Silva MR, Nabuco L, Parise ER, et al. Nonalcoholic steatohepatitis and hepatocellular carcinoma: Brazilian survey. Clinics (Sao Paulo). 2016;71(5): 281-284.

37. Alexia C, Fallot G, Lasfer M, Schweizer-Groyer G, Groyer A. An evaluation of the role of insulin-like growth factors (IGF) and of type-I IGF receptor signalling in hepatocarcinogenesis and in the resistance of hepatocarcinoma cells against drug-induced apoptosis. Biochem Pharmacol. 2004;68(6): 1003-1015.
38. Weng CJ, Hsieh YH, Tsai CM, Chu YH, Ueng KC, Liu YF, et al. Relationship of insulin-like growth factors system gene polymorphisms with the susceptibility and pathological development of hepatocellular carcinoma. Ann Surg Oncol. 2010;17(7): 1808-1815.
39. Karagozian R, Derdák Z, Baffy G. Obesity-associated mechanisms of hepatocarcinogenesis. Metabolism. 2014;63(5): 607-617.
40. Chu CM, Lin DY, Liaw YF. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci. 2013;58(1): 275-281.
41. Yip TC, Wong GL, Chan HL, Tse YK, Lam KL, Lui GC, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. J Hepatol. 2019;70(3): 361-370.
42. Huang G, Li PP, Lau WY, Pan ZY, Zhao LH, Wang ZG, et al. Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels: A Randomized Controlled Trial. Ann Surg. 2018;268(6): 943-954.
43. Hui RWH, Seto WK, Cheung KS, Mak LY, Liu KSH, Fung J, et al. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. J Viral Hepat. 2018;25(1): 97-104.
44. Seto WK, Hui RWH, Mak LY, Fung J, Cheung KS, Liu KSH, et al. Association Between Hepatic Steatosis, Measured by Controlled Attenuation Parameter, and Fibrosis Burden in Chronic Hepatitis B. Clin Gastroenterol Hepatol. 2018;16(4): 575-583.e572.
45. Mak LY, Hui RW, Fung J, Liu F, Wong DK, Cheung KS, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. J Hepatol. 2020;73(4): 800-806.
46. Chu CM, Lin DY, Liaw YF. Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? Int J Obes (Lond). 2007;31(5): 871-875.
47. Fung J, Yuen MF, Lai CL. The role of steatosis in HBsAg seroclearance for patients with chronic hepatitis B infection: fact or fiction? Dig Dis Sci. 2013;58(1): 20-22.
48. Raimondo G, Saitta C, Lombardo D, Giraudi PJ, Rosso N, Ieni A, et al. Occult hepatitis B virus infection predicts non-alcoholic steatohepatitis in severely obese individuals from Italy. Liver Int. 2020;40(7): 1601-1609.
49. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet (London, England). 2004;363(9403): 157-163.

50. Huang J, Jing M, Wang C, Wang M, You S, Lin S, et al. The impact of hepatitis B virus infection status on the prevalence of nonalcoholic fatty liver disease: A population-based study. J Med Virol. 2020;92(8): 1191-1197.
51. Nishikawa H, Nishijima N, Arimoto A, Inuzuka T, Kita R, Kimura T, et al. Effect of nucleoside analog use in patients with hepatitis B virus-related hepatocellular carcinoma. Hepatol Res. 2014;44(6): 608-620.

Tables

Table 1 Comparison between HCC and Non-HCC

Variables	Total	Non-HCC	HCC	P
N	529	520	9	
Age (years)	37.99 ± 10.44	37.94 ± 10.43	41.11 ± 11.04	0.416
Male, n (%)	427 (80.72)	419 (80.58)	8 (88.89)	1.000
Follow-up period (years)	6.33 (4.41, 8.17)	6.33 (4.41, 8.17)	6.98 (2.16, 9.17)	0.611
BMI (Kg/m^2)	23.03 ± 3.17	23 ± 3.15	24.77 ± 3.85	0.206
Diabetes, n (%)	51 (9.64)	49 (9.42)	2 (22.22)	0.212
HBsAg (Log_{10} IU/ml)	3.37 ± 0.95	3.38 ± 0.95	2.96 ± 0.60	0.097
HBeAg positive, n (%)	281 (57.23)	277 (57.35)	4 (50.00)	0.729
HBVDNA (Log_{10} IU/ml)	5.44 ± 1.87	5.45 ± 1.88	4.95 ± 1.09	0.211
AFP (μg/L)	3.84 (2.46, 9.05)	3.82 (2.44, 8.39)	18.97 (8.37, 28.57)	0.005
TBIL (μmolL)	15.3 (11.05, 20.85)	15.25 (11.03, 20.7)	15.5 (13.4, 22.1)	0.788
ALT (U/L)	68 (41, 178.5)	69 (41.3, 182)	57 (31, 65)	0.147
AST (U/L)	49 (31.75, 104)	49 (32, 104)	33 (30, 72)	0.245
GGT (U/L)	48 (26, 92.5)	48 (26, 93)	53 (30, 91)	0.424
TC (mmol/L)	4.62 ± 1.17	4.62 ± 1.18	4.77 ± 0.92	0.646
TG (mmol/L)	1.22 ± 0.68	1.22 ± 0.68	1.31 ± 0.54	0.619
LDL-C (mmol/L)	2.69 ± 1.00	2.68 ± 1.01	3.06 ± 0.49	0.068
HDL-C (mmol/L)	1.29 ± 0.41	1.29 ± 0.41	1.32 ± 0.34	0.769
VLDL-C (mmol/L)	0.40 ± 0.29	0.4 ± 0.29	0.36 ± 0.21	0.559
FPG (mmol/L)	5.07 ± 1.13	5.05 ± 1.09	5.90 ± 2.42	0.323
Pathology				
Significant inflammation (G≥2, n (%))	433 (81.85)	425 (81.73)	8 (88.89)	1.000
Moderate to severe steatosis (S≥2, n (%))	102 (19.28)	100 (19.23)	2 (22.22)	0.687
Cirrhosis, n (%)	144 (27.22)	139 (26.73)	5 (55.56)	0.067
MAFLD, n (%)	184 (34.78)	177 (34.04)	7 (77.78)	0.010

NAFLD, n (%)	250 (47.26)	243 (46.73)	7 (77.78)	0.092

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range].

Abbreviations: MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis e surface antigen; HBVDNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 2 Comparison between MAFLD and NAFLD

Variables	MAFLD	NAFLD	P
N	184	250	
Age (years)	40.17 ± 9.49	39.48 ± 10.08	0.465
Male, n (%)	162 (88.04)	214 (85.60)	0.551
Follow-up period (years)	6.94 (4.96, 9.05)	6.97 (4.92, 9.10)	0.834
BMI (Kg/m^2)	25.61 ± 2.61	24.36 ± 3.13	< 0.001
Diabetes, n (%)	42 (22.83)	42 (16.80)	0.148
HBsAg (Log_{10} IU/ml)	3.17 ± 0.93	3.17 ± 0.95	0.982
HBeAg positive, n (%)	85 (53.12)	117 (53.92)	0.962
HBVDNA (Log_{10} IU/ml)	5.12 ± 2.03	5.21 ± 2.06	0.642
AFP (μg/L)	3.64 (2.5, 7.78)	3.64 (2.42, 7.62)	0.696
TBIL (μmolL)	14.2 (10.2, 18.9)	14.4 (10.3, 18.8)	0.977
ALT (U/L)	63 (43, 140.25)	65 (43, 133)	0.97
AST (U/L)	42 (30, 80.25)	43 (31, 79)	0.869
GGT (U/L)	72.85 ± 66.70	69.21 ± 62.67	0.566
TC (mmol/L)	4.8 ± 1.28	4.79 ± 1.17	0.956
TG (mmol/L)	1.57 ± 0.88	1.44 ± 0.82	0.102
LDL-C (mmol/L)	2.96 ± 1.10	2.9 ± 1.04	0.583
HDL-C (mmol/L)	1.14 ± 0.34	1.23 ± 0.37	0.010
VLDL-C (mmol/L)	0.5 ± 0.37	0.44 ± 0.33	0.154
FPG (mmol/L)	5.4 ± 1.51	5.23 ± 1.34	0.241
Pathology			
Significant inflammation (G≥2, n (%))	140 (76.09)	192 (76.80)	0.953
Moderate to severe steatosis (S≥2, n (%))	81 (44.02)	100 (40.00)	0.459
Cirrhosis, n (%)	36 (19.57)	57 (22.80)	0.488

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range].

Abbreviations: MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis e surface antigen;

HBVDNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 3 Univariate and multivariate Cox analysis of the factors associated with HCC development

Characteristics	HCC development			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)	1.024 (0.964–1.088)	0.440		
Male, n (%)	1.632 (0.203–13.116)	0.645		
BMI (Kg/m^2)	1.122 (0.939–1.340)	0.204		
Diabetes, n (%)	2.772 (0.575–13.365)	0.204		
HBsAg (Log_{10} IU/ml)	0.790 (0.383–1.629)	0.523		
HBeAg positive	0.782 (0.195–3.131)	0.728		
HBVDNA (Log_{10} IU/ml)	0.867 (0.609–1.234)	0.429		
AFP (μg/L)	1.001 (0.996–1.005)	0.808		
TBIL (μmolL)	0.995 (0.961–1.031)	0.782		
ALT (U/L)	0.991 (0.978–1.004)	0.173		
AST (U/L)	0.990 (0.974–1.007)	0.251		
GGT (U/L)	1.001 (0.993–1.01)	0.733		
TC (mmol/L)	1.140 (0.722–1.799)	0.574		
TG (mmol/L)	1.179 (0.5–2.785)	0.707		
LDL-C (mmol/L)	1.313 (0.838–2.056)	0.234		
HDL-C (mmol/L)	1.468 (0.277–7.793)	0.652		
VLDL-C (mmol/L)	1.345 (0.106–17.029)	0.819		
FPG (mmol/L)	1.355 (1.054–1.743)	0.018	1.158 (0.880–1.522)	0.295

Pathology				
Significant inflammation (G≥2, n (%))	1.603 (0.200–12.833)	0.657		
Moderate to severe steatosis (S≥2, n (%))	1.057 (0.219–5.099)	0.945		
Cirrhosis, n (%)	3.407 (0.914–12.707)	0.068	4.688 (1.166-18.848)	0.030
MAFLD, n (%)	5.223 (1.073–25.418)	0.041	6.434 (1.252–33.060)	0.026
NAFLD, n (%)	2.783 (0.565–13.707)	0.208		

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range].

Abbreviations: MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis e surface antigen; HBVDNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 4 Comparison of hepatic steatosis and metabolic conditions

Variables	MC negative	MC positive	P	Steatosis negative	Steatosis positive	P
N	246	283		276	253	
Age (years)	35.28 ± 10.59	40.35 ± 9.72	< 0.001	36.62 ± 10.57	39.48 ± 10.1	0.002
Male, n (%)	188 (76.42)	239 (84.45)	0.026	211 (76.45)	216 (85.38)	0.013
Follow-up period (years)	5.96 (4.24, 8.21)	6.57 (4.68, 8.12)	0.203	5.84 (4.23, 7.56)	6.97 (4.93, 9.08)	< 0.001
BMI (Kg/m^2)	20.53 ± 1.7	25.2 ± 2.48	< 0.001	21.8 ± 2.69	24.36 ± 3.12	< 0.001
Diabetes, n (%)	0 (0)	51 (18.02)	< 0.001	9 (3.26)	42 (16.6)	< 0.001
HBsAg (Log_{10} IU/ml)	3.51 ± 0.95	3.24 ± 0.93	0.002	3.53 ± 0.92	3.17 ± 0.94	< 0.001
HBeAg positive, n (%)	138 (58.72)	143 (55.86)	0.583	163 (59.93)	118 (53.88)	0.21
HBVDNA (Log_{10} IU/ml)	5.7 ± 1.77	5.23 ± 1.93	0.005	5.66 ± 1.66	5.21 ± 2.05	0.008
AFP (μg/L)	3.87 (2.4, 8.32)	3.84 (2.53, 9.49)	0.482	4.29 (2.46, 12.37)	3.66 (2.44, 7.46)	0.134
TBIL (μmolL)	15.7 (11.5, 21.5)	14.65 (10.22, 20.2)	0.196	16 (11.4, 22.05)	14.4 (10.28, 18.8)	0.011
ALT (U/L)	71 (42, 187)	65 (41, 149)	0.634	78 (37.75, 224.75)	65 (43, 133)	0.355
AST (U/L)	53 (34, 119)	45 (30, 92)	0.049	57 (34, 136.25)	43 (30.75, 79.25)	< 0.001
GGT (U/L)	46 (24, 82)	51 (27, 103)	0.07	79.82 ± 89.31	69.38 ± 62.45	0.118
TC (mmol/L)	4.55 ± 1.03	4.69 ± 1.28	0.162	4.47 ± 1.17	4.79 ± 1.16	0.002
TG (mmol/L)	0.97 ± 0.39	1.43 ± 0.8	< 0.001	1.02 ± 0.43	1.44 ± 0.82	< 0.001
LDL-C (mmol/L)	2.53 ± 0.83	2.82 ± 1.11	0.001	2.49 ± 0.93	2.89 ± 1.04	< 0.001
HDL-C (mmol/L)	1.43 ± 0.4	1.17 ± 0.37	< 0.001	1.35 ± 0.43	1.22 ± 0.37	< 0.001

VLDL-C (mmol/L)	0.31 ± 0.21	0.47 ± 0.33	< 0.001	0.36 ± 0.24	0.44 ± 0.33	0.003
FPG (mmol/L)	4.81 ± 0.69	5.29 ± 1.36	< 0.001	4.92 ± 0.88	5.23 ± 1.33	0.002
Pathology						
Significant inflammation (G≥2, n (%))	204 (82.93)	229 (80.92)	0.628	238 (86.23)	195 (77.08)	0.009
Moderate to severe steatosis (S≥2, n (%))	21 (8.54)	81 (28.62)	< 0.001	0 (0)	102 (40.32)	< 0.001
Cirrhosis, n (%)	69 (28.05)	75 (26.5)	0.764	87 (31.52)	57 (22.53)	0.026
MAFLD, n (%)	0 (0)	184 (65.02)	< 0.001	0 (0)	184 (72.73)	< 0.001
NAFLD, n (%)	68 (27.64)	182 (64.31)	< 0.001	0 (0)	250 (98.81)	< 0.001
HCC, n (%)	1 (0.41)	8 (2.83)	0.042	2 (0.72)	7 (2.77)	0.094

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range].

Abbreviations: MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; MC, metabolic conditions; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis e surface antigen; HBVDNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha fetoprotein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; FPG, fasting plasma glucose.

Figures

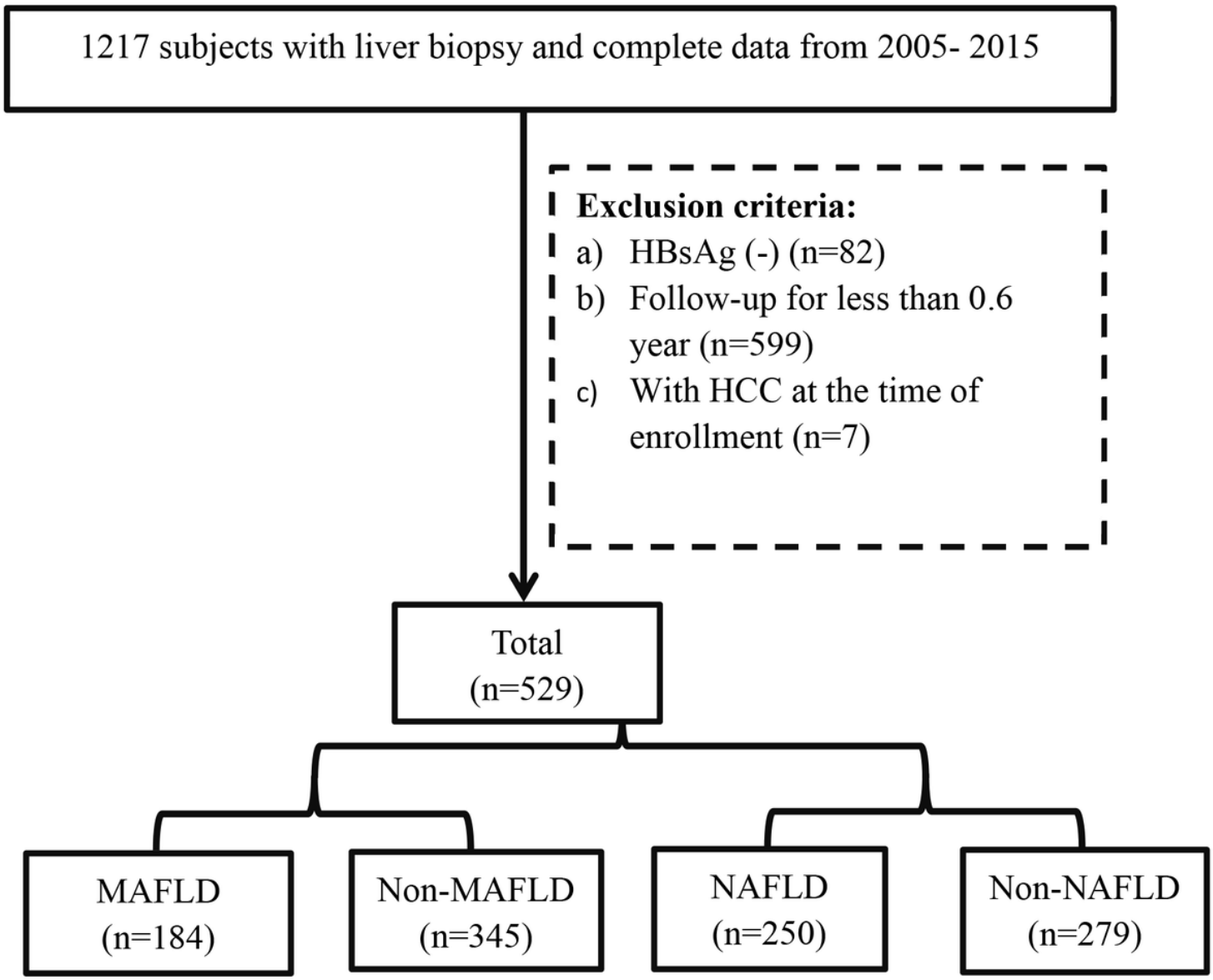

Figure 1

The flow chart.

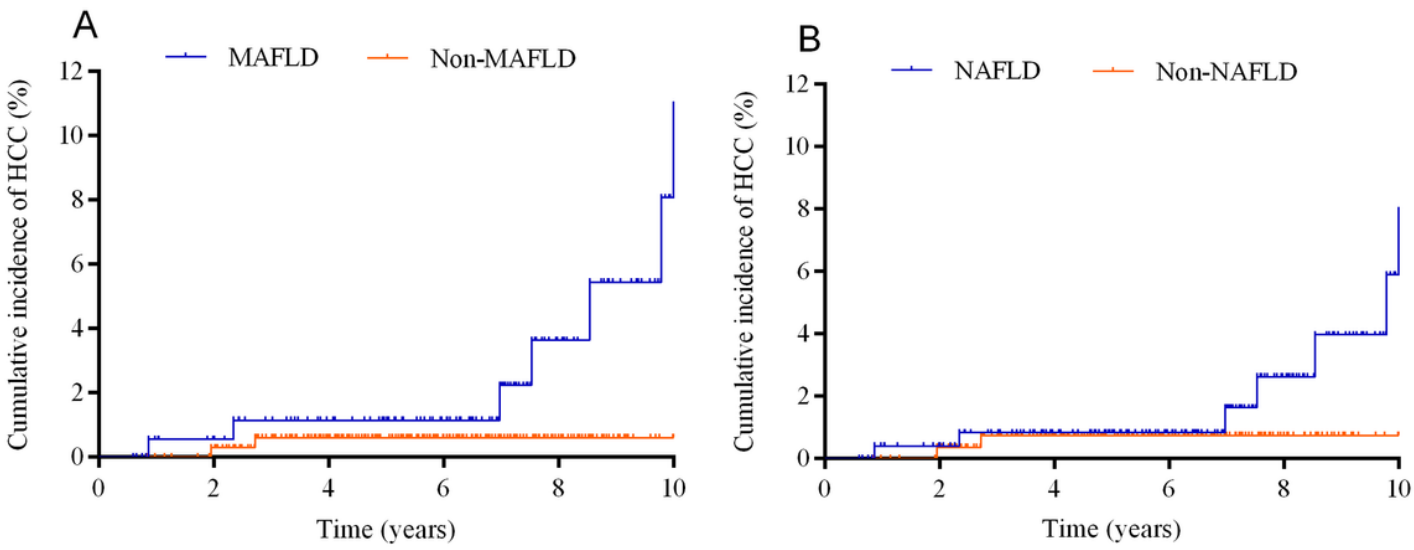

Figure 2

Cumulative incidence of HCC grouped by MAFLD and NAFLD according to the Kaplan-Meier method. Figure 2A: grouped by MAFLD; Figure 2B: grouped by NAFLD.