Original Article

# Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China

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**Background:** To evaluate the associations between a new definition of metabolic dysfunction-associated fatty liver disease (MAFLD) and extrahepatic cancers and compare with nonalcoholic fatty liver disease (NAFLD).

**Methods:** We enrolled 151,391 Chinese participants in the Kailuan cohort. Hepatic steatosis was detected by abdominal ultrasound. Fine and Gray competing risk regression models were used to estimate hazard ratios (HRs) and 95% confidence interval (CI) between MAFLD and extrahepatic cancers.

**Results:** MAFLD was associated with increased risk of prostate (HR =1.49, 95% CI: 1.07–2.08) and obesity-related cancers, including thyroid (HR =1.47, 95% CI: 1.01–2.12), kidney (HR =1.54, 95% CI: 1.18–2.00), colorectal (HR =1.15, 95% CI: 0.98–1.34) and breast cancer (HR =1.31, 95% CI: 1.04–1.66). The results were consistent in NAFLD *vs.* non-NAFLD and MAFLD-NAFLD *vs.* neither FLD. Compared with the neither FLD group, the NAFLD-only group had a higher risk of extrahepatic cancers (HR =1.57, 95% CI: 1.18–2.09), esophageal (HR =5.11, 95% CI: 2.25–11.62), and bladder cancer (HR =3.36, 95% CI: 1.23–9.17). The additional risk of extrahepatic cancers (HR =1.42, 95% CI: 1.17–1.73), esophageal (HR =4.37, 95% CI: 2.55–7.49), and breast cancer (HR =1.99, 95% CI: 1.01–3.92) was observed in MAFLD with metabolic dysregulation, and kidney (HR =1.83, 95% CI: 1.38–2.43), prostate (HR =1.46, 95% CI: 1.00–2.14) and breast cancer (HR =1.33, 95% CI: 1.02–1.74) was observed in MAFLD with overweight and metabolic dysregulation, as well as colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21) in MAFLD with three risk factors. Additionally, MAFLD with excessive alcohol consumption would increase extrahepatic cancers (HR =1.14, 95% CI: 1.01–1.29) and breast cancer (HR =7.27, 95% CI: 2.33–22.69) risk.

**Conclusions:** MAFLD and NAFLD shared similar excessive risks of obesity-related cancers, suggesting a driving role of FLD in these cancers. Metabolic dysregulation beyond obesity may play additional kidney, colorectal, and prostate cancer risks in MAFLD patients. It may be helpful in the clinic to relieve symptoms by treating metabolic disorders and preventing adverse outcomes of extrahepatic cancers.

**Keywords:** Metabolic dysfunction-associated fatty liver disease (MAFLD); nonalcoholic fatty liver disease (NAFLD); extrahepatic cancers; metabolic risk; dual etiology

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## Introduction

Nonalcoholic fatty liver disease (NAFLD), characterized by hepatic steatosis after excluding competing liver disease etiologies, is a rapidly increasing common chronic liver disease affecting 25.2% of the global adult population (1) and 20.1% of the adults in China (2). NAFLD has been reported as a risk factor for some extrahepatic cancers, i.e., colorectal, cholangiocarcinoma, breast, gastric, pancreatic, prostate, and esophageal cancer (3,4).

However, NAFLD's heterogeneous pathogenesis and inaccuracies terminology has posed significant challenges to accurate diagnosis and treatment regimens development. Therefore, a panel of international experts from 22 countries proposed a new definition that is both comprehensive yet simple for the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD) (5,6). Several studies have reported that this new definition could replace NAFLD, representing the real relationship with adverse outcomes, such as cardiovascular disease (7-9), chronic kidney disease (9-11), and death (9,12). Also, some studies demonstrated a positive association between MAFLD and hepatocellular cancer and extrahepatic cancers (9,13,14). Although some studies showed that the MAFLD definition might better identify significant fibrosis (15) and cardiovascular disease (CVD) risk (16,17) compared to NAFLD, it remains unclear the difference of the association between MAFLD, NAFLD, and extrahepatic cancers.

Therefore, this study aimed to examine the association between MAFLD and extrahepatic cancers in the general population and compare with NAFLD's findings based on the same cohort. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-546/rc).

## Methods

### *Study design and participants*

The Kailuan cohort was established in the Kailuan community in 2006 in Tangshan, Hebei Province, China, where each participant underwent a comprehensive check-up every 2 years (18). In our study, 159,018 participants aged 12–109 years who underwent a check-up between June 2006 and April 2014 were recruited. After excluding those who lack abdominal "real-time" ultrasonography (n=6,864), with self-reported or diagnosed cancer (n=504) or liver cirrhosis (n=250) at baseline, and those younger than 18 years old (n=9), 151,391 participants were finally included (Figure S1).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committees of the Kailuan General Hospital approved this study. All participants provided informed consent forms.

### *Ascertainment of MAFLD and NAFLD*

According to the criteria for the diagnosis of MAFLD proposed in 2020 (5), MAFLD was diagnosed as evidence of hepatic steatosis, with one of the following three criteria, (I) overweight/obesity [body mass index (BMI) ≥23.00 kg/m$^2$ for Asians], (II) type 2 diabetes mellitus, or (III) metabolic dysregulation. In this study, experienced clinicians defined hepatic steatosis by abdominal ultrasound according to Asia-Pacific region definition (19). Type 2 diabetes mellitus was defined according to fasting blood glucose (FBG) level ≥7.0 mmol/L, oral hypoglycemic agent or insulin use, or a self-reported physician diagnosis. Metabolic dysregulation was determined by the presence of at least two metabolic risk abnormalities of the followings: (I) waist circumference ≥90/80 cm in men and women, (II) blood pressure ≥130/85 mmHg or specific drug treatment, (III) plasma triglycerides (TG) ≥1.70 mmol/L or specific drug treatment, (IV) plasma high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women or specific drug treatment, (V) prediabetes as FBG levels 5.6 to 6.9 mmol/L, (VI) plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L (5). Non-MAFLD was defined as the subjects who did not meet the diagnosis criteria of MAFLD, which included those without fatty liver disease or those with fatty liver disease but did not meet one of the three criteria described above.

We further divided MAFLD patients into seven subgroups according to their metabolic conditions: (I) overweight (BMI ≥23 kg/m$^2$) only; (II) diabetes only (DB-only); (III) metabolic dysregulation only (MD-only, only with at least two metabolic risk abnormalities); (IV) overweight and DB; (V) overweight and MD; (VI) DB and MD; (VII) overweight, DB, and MD.

NAFLD was diagnosed as having fatty liver in the participants without excessive alcohol intake (≥30 g/day for men and ≥20 g/day for women) or positive hepatitis B surface antigen (HBsAg) (19,20).

### *Cancer assessment and follow-up*

Incident cancer cases were collected by self-report, linked with the local vital statistics data, the Tangshan

medical insurance system, and the Kailuan Social Security Information System. Then, all the cases were validated by checking medical and discharge records by clinical experts as in the previous study (21). Extrahepaitc cancers were selected, and 12 of the most common extrahepatic cancers were identified. The follow-up started from the baseline and ended at the date of cancer diagnosis, death, or study termination (12-31-2019).

### *Covariates at baseline*

Demographic characteristics (age, sex, education level), lifestyle factors (smoking status, alcohol intake, and physical activity), medical history, related medication, and laboratory tests were collected as in the previous study (21). Excessive alcohol consumption was defined as alcohol intake ≥30 g/day for men or ≥20 g/day for women. Physical activity level was categorized as inactive, moderately active, and active according to the frequency of physical activity (≥20 min/time) during leisure time. Weight, height, and blood pressure were measured, and BMI was calculated as weight in kilograms divided by height in square meters. In addition, the total cholesterol (TC), TG, HDL-C, alanine aminotransferase (ALT), hs-CRP, FBG, and HBsAg were tested in the central laboratory of the Kailuan General Hospital.

### *Statistical analyses*

The covariates between MAFLD status were compared using *t*-test, analysis of variance test, or Wilcoxon signed-rank test for continuous variables and chi-square test for categorical variables. Cumulative incidence was estimated using the Kaplan-Meier methods. The incidence between MAFLD and non-MAFLD was compared by log-rank test. Considering the competing risk of death, we used three Fine and Gray competing risk regression models (22) to analyze the associations between MAFLD and extrahepatic cancers: unadjusted, age-, sex-adjusted, and multivariable-adjusted model (adjusting sex, age, education level, smoking, alcohol consumption, physical activity, and family history of cancer). Stratified analyses were conducted by sex and age (<50 *vs.* ≥50 years, the median age of our cohort).

Due to the partial overlap between MAFLD and NAFLD, we used the generalized estimating equation (GEE) model to compare the direct incidence difference between MAFLD and NAFLD as the previous studies described (16). Then we separated all participants into four mutually exclusive groups (neither-FLD, NAFLD-only, MAFLD-only, and MAFLD-NAFLD) to compare the different associations of NAFLD and MAFLD on cancer (12). We also investigated the association of subgroup of MAFLD by dividing MAFLD into different subgroups according to BMI, diabetes and metabolic dysregulation, or HBsAg and drinking status. Finally, we conducted sensitivity analyses by excluding the participants who developed incident cancers within the three years of follow-up and with the original dataset without imputation to test the robustness of our results.

All analyses were performed with Statistical Analysis System (SAS) (version 9.4, SAS Institute Inc. Cary, NC, USA). Missing data were imputed using Multivariate Imputation by Chained Equations (MICE) by R (version 3.5.2., https://www.rproject.org/) (23). Details of missing data were presented in Table S1. All tests were two-sided, with statistical significance set at P<0.05.

## Results

### *Population characteristics*

Among 151,391 participants, the prevalence of MAFLD was 31.4% (32.6% in men and 26.5% in women). Participants with MAFLD showed higher levels of age, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, TG, TC, low-density lipoprotein-cholesterol (LDL-C), hs-CRP, and ALT, as well as a lower level of HDL-C. In addition, higher proportions of males, lower education level, unhealthy lifestyle factors like smoking, excessive alcohol consumption, and lower prevalence of positive HBsAg than those without MAFLD were also seen (*Table 1*).

### *MAFLD and extrahepatic cancers*

After a median follow-up of 12.64 years, 5,405 incident extrahepatic cancers were identified. After adjusting the competing risk of death, the cumulative incidence of extrahepatic cancers and site-specific cancers with and without MAFLD was presented in *Figure 1* and Figures S2,S3. Log-rank tests showed that extrahepatic cancers (P=0.003), colorectal (P=0.037), kidney (P<0.001), breast cancers (P<0.001) were significantly different.

*Table 2* showed the associations between MAFLD and extrahepatic cancers under different models. The significantly increased risk of all extrahepatic cancers was only observed in the unadjusted model [hazard ratio (HR) =1.09, 95% confidence interval (CI): 1.03–1.15]. For the

**Table 1** Baseline characteristics in the participants with and without MAFLD

| Characteristics | Non-MAFLD | MAFLD | P |
|---|---|---|---|
| n | 103,854 | 47,537 | |
| Age, years | 48.8±14.5 | 51.0±12.6 | <0.001 |
| Male | 82,808 (79.7) | 39,957 (84.1) | <0.001 |
| Education level | | | <0.001 |
| Junior high school or below | 76,700 (73.9) | 36,422 (76.6) | |
| Senior high school or higher | 27,154 (26.1) | 11,115 (23.4) | |
| Past/current smoking | 41,288 (39.8) | 20,591 (43.3) | <0.001 |
| Excessive alcohol consumption | 13,752 (13.2) | 8,373 (17.6) | <0.001 |
| Physical activity | | | 0.384 |
| Inactive | 15,050 (14.5) | 6,879 (14.5) | |
| Moderately active | 73,350 (70.6) | 33,455 (70.4) | |
| Active | 15,454 (14.9) | 7,203 (15.2) | |
| Family history of cancers | | | <0.001 |
| Yes | 4,369 (4.2) | 2,508 (5.3) | |
| No | 64,348 (62.0) | 28,618 (60.2) | |
| Unknown | 35,137 (33.8) | 16,411 (34.5) | |
| BMI, kg/m$^2$ | 23.8±3.1 | 27.4±3.2 | <0.001 |
| WC, cm | 84.0±9.5 | 92.5±9.2 | <0.001 |
| SBP, mmHg | 126.6±20.1 | 135.8±20.5 | <0.001 |
| DBP, mmHg | 81.4±11.2 | 87.2±11.6 | <0.001 |
| FBG, mmol/L | 5.3±1.4 | 5.9±2.0 | <0.001 |
| TG, mmol/L | 1.4±1.0 | 2.2±1.5 | <0.001 |
| TC, mmol/L | 4.8±1.1 | 5.1±1.2 | <0.001 |
| LDL-C, mmol/L | 2.4±0.9 | 2.5±0.9 | <0.001 |
| HDL-C, mmol/L | 1.5±0.3 | 1.4±0.4 | <0.001 |
| hs-CRP, mg/dL | 0.8 (0.3, 2.0) | 1.4 (0.6, 3.2) | <0.001 |
| ALT, U/L | 17.0 (12.0, 23.0) | 22.7 (16.1, 32.0) | <0.001 |
| HBsAg positive | 2,986 (2.9) | 1,061 (2.2) | <0.001 |

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. MAFLD, metabolic associated fatty liver disease; BMI, body mass index; WC, waist circumstance; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

site-specific cancers, MAFLD was associated with kidney and breast cancer in the unadjusted, age-, sex-adjusted, and multivariable-adjusted model. The HRs (95% CI) in multivariate model were 1.54 (1.18–2.00) and 1.31 (1.04–1.66), respectively. For thyroid and prostate cancer, an increased risk was observed in age-, sex-adjusted and multivariate-adjusted models, with HRs (95% CI) of 1.47 (1.01–2.12) and 1.49 (1.07–2.08) in the multivariate-adjusted model, respectively. For colorectal cancer, an increased risk was observed in unadjusted and marginally significant in age-, sex-adjusted, and multivariate model, with HRs (95% CI) of 1.15 (0.98–1.34) in the multivariate-adjusted model.

There was no interaction between age, sex, and MAFLD in cancer occurrence after stratified by sex and age (details in Tables S2,S3).

### *Comparison between MAFLD, NAFLD, and extrahepatic cancers*

The proportion of NAFLD was lower than that of MAFLD in our population (26.0% *vs.* 31.4%). Table S4 showed the characteristics of the participants with NAFLD and non-NAFLD. Compared with non-NAFLD, the HR (95% CI) of NAFLD was 1.58 (1.09–2.30), 1.21 (1.02–1.43), 1.55 (1.17–2.05), 1.44 (1.01–2.06) and 1.28 (1.01–1.62) for developing thyroid, colorectal, kidney, prostate, and breast cancer in the multivariate-adjusted model (Table S5).

Considering the overlap between MAFLD and NAFLD, we used the GEE model to compare the incidence of extrahepatic cancers (Table S6). We only observed a significantly lower risk of esophageal [adjusted odds ratio (OR) =0.19, 95% CI: 0.08–0.45] and bladder cancer (adjusted OR =0.33, 95% CI: 0.12–0.95) in patients with MAFLD than in patients with NAFLD.

When considering the combination of MAFLD and NAFLD, the neither FLD, NAFLD-only, MAFLD-only, and MAFLD-NAFLD group accounted for 67.9%, 0.6%, 6.2%, and 25.3%, respectively. MAFLD-only group had the highest proportion of past/current smokers, excessive alcohol consumption, positive HBsAg, and ALT levels. In comparison, the NAFLD-only group had the lowest BMI, WC, FBG, SBP, and DBP (Table S7). *Table 3* showed the extrahepatic cancers risks by the combination of MAFLD and NAFLD status. Compared with the neither FLD group, MAFLD-NAFLD participants showed higher risks of the thyroid (HR =1.62, 95% CI: 1.11–2.35), colorectal (HR =1.19, 95% CI: 1.00–1.41), kidney (HR =1.58, 95% CI: 1.19–2.09), prostate (HR =1.48, 95% CI: 1.04–2.11), and

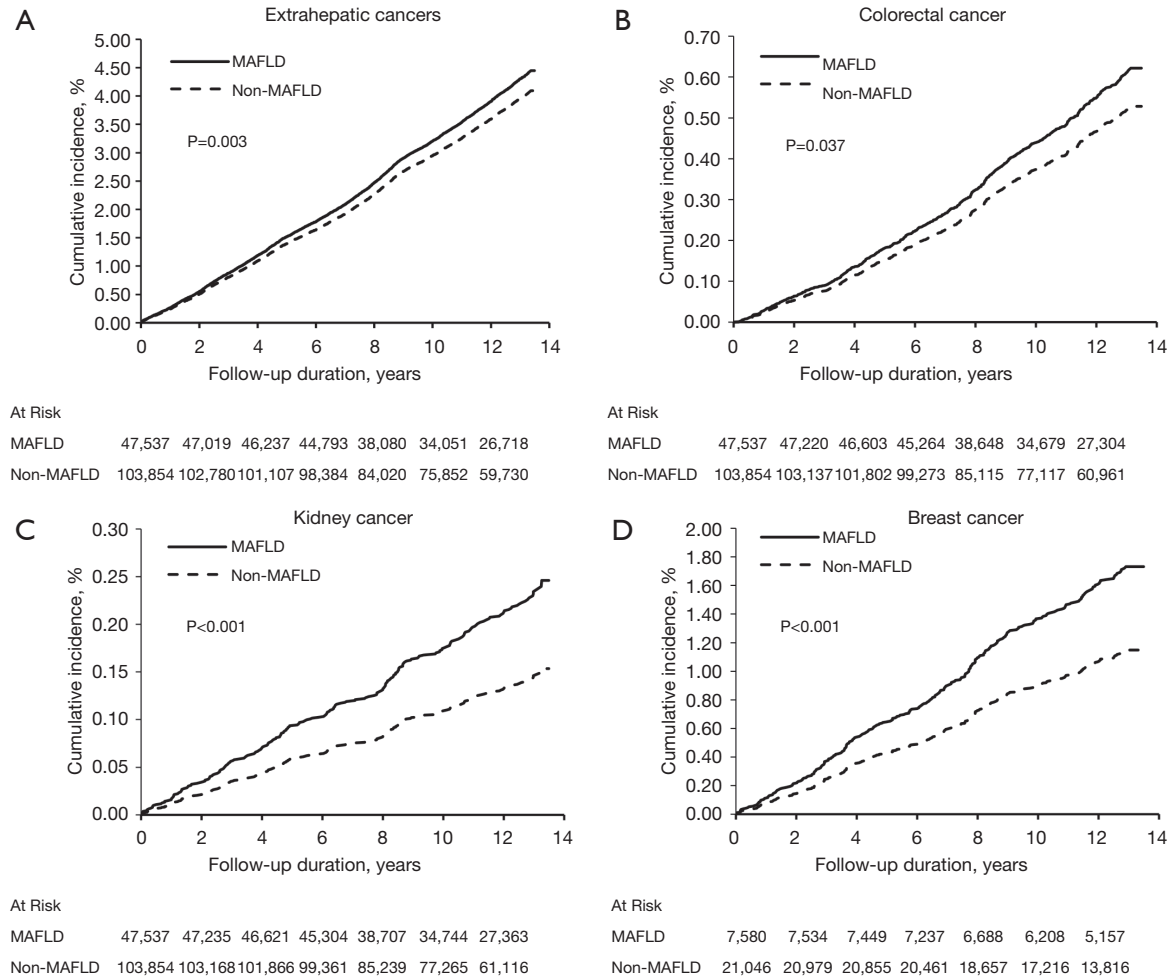


**Figure 1** Cumulative incidence of extrahepatic (A), colorectal (B), kidney (C) and breast cancer (D) after adjusting competing risk of death. MAFLD, metabolic associated fatty liver disease.

breast cancer (HR =1.29, 95% CI: 1.02–1.64). In addition, a significantly higher risk of extrahepatic cancers (HR =1.57, 95% CI: 1.18–2.09), esophageal (HR =5.11, 95% CI: 2.25–11.62), and bladder cancer (HR =3.36, 95% CI: 1.23–9.17) was observed in the NAFLD-only group (*Table 3*).

### *Associations between subgroup of MAFLD and extrahepatic cancers*

MAFLD individuals were divided into seven subgroups according to BMI, diabetes, and metabolic dysregulation. The baseline characteristics of subgroups were presented in Table S8, and the association results were observed in *Table 4*. Compared with non-MAFLD, MAFLD with MD-only group showed an increased risk of extrahepatic cancers (HR =1.42, 95% CI: 1.17–1.73), esophageal (adjusted HR =4.37, 95% CI: 2.55–7.49), and breast cancer (HR =1.99, 95% CI: 1.01–3.92) after adjusting covariates. Also, increased risk of the kidney (HR =1.83, 95% CI: 1.38–2.43), prostate (HR =1.46, 95% CI: 1.00–2.14), and breast cancer (HR =1.33, 95% CI: 1.02–1.74) were found in MAFLD with both overweight/obesity and MD. In addition, MAFLD with three metabolic disorders had an increased risk of colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21).

### *Associations between MAFLD with other risk factors and extrahepatic cancers*

Table S9 and *Table 5* showed the baseline characteristics

**Table 2** Associations between MAFLD and extrahepatic cancers in all participants

| Cancer types | MAFLD | | Non-MAFLD | | Unadjusted | | Age-, sex-adjusted | | Multivariate adjusted[†] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of events | Incidence rate (/$10^5$ PYs) | No. of events | Incidence rate (/$10^5$ PYs) | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Extrahepatic | 1,790 | 344.90 | 3,615 | 316.31 | 1.09 (1.03–1.15) | 0.003 | 1.05 (0.99–1.11) | 0.123 | 1.05 (0.99–1.11) | 0.114 |
| Thyroid | 46 | 8.75 | 85 | 7.36 | 1.19 (0.83–1.70) | 0.343 | 1.44 (1.00–2.08) | 0.049 | 1.47 (1.01–2.12) | 0.042 |
| Lung | 495 | 94.39 | 1138 | 98.71 | 0.95 (0.85–1.05) | 0.330 | 0.92 (0.83–1.02) | 0.126 | 0.92 (0.83–1.02) | 0.130 |
| Esophageal | 68 | 12.94 | 158 | 13.67 | 0.95 (0.71–1.26) | 0.698 | 0.91 (0.69–1.21) | 0.522 | 0.89 (0.67–1.15) | 0.421 |
| Gastric | 132 | 25.13 | 278 | 24.07 | 1.04 (0.85–1.28) | 0.699 | 1.01 (0.82–1.24) | 0.924 | 1.02 (0.83–1.25) | 0.863 |
| Biliary | 29 | 5.52 | 72 | 6.23 | 0.88 (0.57–1.36) | 0.575 | 0.87 (0.57–1.34) | 0.530 | 0.89 (0.58–1.37) | 0.595 |
| Pancreatic | 44 | 8.37 | 100 | 8.65 | 0.97 (0.68–1.38) | 0.845 | 0.94 (0.66–1.34) | 0.729 | 0.97 (0.68–1.38) | 0.849 |
| Small intestine | 16 | 3.04 | 23 | 1.99 | 1.53 (0.81–2.89) | 0.193 | 1.47 (0.78–2.78) | 0.236 | 1.52 (0.80–2.87) | 0.199 |
| Colorectal | 250 | 47.65 | 466 | 40.38 | 1.18 (1.01–1.38) | 0.035 | 1.14 (0.98–1.33) | 0.090 | 1.15 (0.98–1.34) | 0.078 |
| Kidney | 98 | 18.66 | 134 | 11.60 | 1.59 (1.22–2.06) | 0.001 | 1.53 (1.18–1.99) | 0.002 | 1.54 (1.18–2.00) | 0.001 |
| Bladder | 66 | 12.56 | 147 | 12.72 | 0.99 (0.74–1.32) | 0.921 | 0.99 (0.74–1.32) | 0.941 | 0.98 (0.73–1.32) | 0.903 |
| Prostate[§] | 59 | 3.28 | 94 | 10.28 | 1.29 (0.93–1.80) | 0.122 | 1.44 (1.04–2.01) | 0.030 | 1.49 (1.07–2.08) | 0.018 |
| Breast[¶] | 120 | 136.63 | 217 | 89.42 | 1.51 (1.21–1.89) | <0.001 | 1.30 (1.03–1.65) | 0.028 | 1.31 (1.04–1.66) | 0.024 |

[†], adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers; [§], only for men; [¶], only for women. MAFLD, metabolic associated fatty liver disease; PYs, person-years; HR, hazard ratio; CI, confidence interval.

**Table 3** Extrahepatic cancers risks in participants by the combination of MAFLD and NAFLD status

| Cancer types | Incidence rate (/$10^5$ PYs) | | | | HR (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | Neither FLD[†] | NAFLD-only | MAFLD-only | MAFLD-NAFLD[‡] | Neither FLD | NAFLD-only | MAFLD-only | MAFLD-NAFLD |
| Extrahepatic | 315.01 | 451.24 | 350.07 | 343.70 | 1 | 1.57 (1.18–2.09) | 1.01 (0.89–1.15) | 1.06 (0.99–1.13) |
| Thyroid | 7.43 | 0.00 | 2.01 | 10.33 | 1 | – | 0.41 (0.09–1.82) | 1.62 (1.11–2.35) |
| Lung | 98.70 | 99.73 | 114.02 | 89.82 | 1 | 1.10 (0.61–2.00) | 0.90 (0.72–1.13) | 0.93 (0.83–1.05) |
| Esophageal | 13.28 | 54.27 | 24.17 | 10.32 | 1 | 5.11 (2.25–11.62) | 0.86 (0.53–1.41) | 0.95 (0.67–1.35) |
| Gastric | 23.95 | 36.18 | 34.26 | 23.00 | 1 | 1.60 (0.59–4.30) | 1.51 (0.96–2.36) | 0.93 (0.73–1.17) |
| Biliary | 6.20 | 9.04 | 4.03 | 5.86 | 1 | 1.60 (0.22–11.56) | 0.79 (0.27–2.38) | 0.91 (0.57–1.45) |
| Pancreatic | 8.65 | 9.04 | 6.04 | 8.92 | 1 | 1.13 (0.16–8.08) | 0.70 (0.29–1.72) | 1.02 (0.70–1.50) |
| Small intestine | 2.01 | 0.00 | 3.02 | 3.05 | 1 | – | 2.85 (0.85–9.55) | 1.36 (0.69–2.72) |
| Colorectal | 39.98 | 81.78 | 50.44 | 47.00 | 1 | 2.32 (1.19–4.49) | 1.06 (0.74–1.50) | 1.19 (1.00–1.41) |
| Kidney | 11.62 | 9.05 | 16.12 | 19.25 | 1 | 0.76 (0.11–5.45) | 1.42 (0.74–2.72) | 1.58 (1.19–2.09) |
| Bladder | 12.50 | 36.23 | 14.10 | 12.20 | 1 | 3.36 (1.23–9.17) | 0.79 (0.43–1.46) | 1.07 (0.77–1.49) |
| Prostate[§] | 10.42 | 0.00 | 8.23 | 14.72 | 1 | – | 1.45 (0.59–3.54) | 1.48 (1.04–2.11) |
| Breast[¶] | 89.27 | 109.60 | 241.97 | 134.09 | 1 | 1.19 (0.30–4.79) | 2.01 (0.90–4.48) | 1.29 (1.02–1.64) |

The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [†], neither FLD: participants without MAFLD or NAFLD; [‡], MAFLD-NAFLD: participants with MAFLD and NAFLD; [§], only for men; [¶], only for women; –, no cancer was observed in this group. MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; PYs, person-years; FLD, fatty liver disease; HR, hazard ratio; CI, confidence interval.

**Table 4** HRs of extrahepatic cancers in participants by MAFLD risk factors

| Cancer types | One | | | Two | | | Three |
|---|---|---|---|---|---|---|---|
| | Overweight-only | DB-only | MD-only | Overweight and DB | Overweight and MD | DB and MD | |
| Extrahepatic | 0.91 (0.78–1.07) | 0.52 (0.17–1.60) | 1.42 (1.17–1.73) | 1.23 (0.89–1.71) | 1.04 (0.97–1.11) | 1.36 (0.89–2.07) | 1.05 (0.93–1.19) |
| Thyroid | 1.97 (0.95–4.06) | – | 0.78 (0.11–5.62) | 2.26 (0.31–16.42) | 1.45 (0.95–2.20) | – | 1.25 (0.50–3.11) |
| Lung | 0.92 (0.70–1.20) | 1.00 (0.25–4.04) | 1.26 (0.87–1.82) | 1.45 (0.85–2.45) | 0.93 (0.82–1.05) | 0.59 (0.19–1.84) | 0.78 (0.60–1.01) |
| Esophageal | 0.53 (0.22–1.30) | – | 4.37 (2.55–7.49) | – | 0.75 (0.53–1.07) | 1.46 (0.20–10.50) | 0.86 (0.44–1.68) |
| Gastric | 0.89 (0.51–1.55) | – | 1.28 (0.60–2.70) | 0.84 (0.21–3.38) | 1.05 (0.83–1.33) | 0.84 (0.12–6.05) | 0.95 (0.59–1.53) |
| Biliary | 1.51 (0.61–3.74) | – | 0.70 (0.10–5.00) | 1.72 (0.24–12.38) | 0.69 (0.40–1.21) | – | 1.37 (0.63–2.97) |
| Pancreatic | 1.19 (0.52–2.73) | – | 2.11 (0.78–5.73) | – | 0.89 (0.58–1.36) | – | 1.02 (0.48–2.21) |
| Small intestine | 0.81 (0.11–5.91) | – | – | – | 1.71 (0.85–3.43) | – | 1.95 (0.58–6.51) |
| Colorectal | 0.91 (0.59–1.40) | – | 1.60 (0.96–2.68) | 1.80 (0.85–3.80) | 1.07 (0.89–1.29) | 1.44 (0.46–4.46) | 1.45 (1.07–1.96) |
| Kidney | 1.16 (0.59–2.28) | – | 0.79 (0.20–3.20) | 0.87 (0.12–6.19) | 1.83 (1.38–2.43) | – | 1.02 (0.52–2.00) |
| Bladder | 0.98 (0.46–2.09) | – | 0.64 (0.16–2.61) | 2.39 (0.76–7.51) | 0.90 (0.63–1.28) | 1.45 (0.20–10.40) | 1.27 (0.72–2.23) |
| Prostate[§] | 0.51 (0.13–2.09) | – | 1.22 (0.30–4.98) | 1.37 (0.19–9.86) | 1.46 (1.00–2.14) | – | 2.44 (1.42–4.21) |
| Breast[¶] | 0.83 (0.37–1.87) | – | 1.99 (1.01–3.92) | 1.46 (0.20–10.58) | 1.33 (1.02–1.74) | 2.65 (0.84–8.33) | 1.17 (0.71–1.93) |

Data were presented as HR (95% confidence interval). The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women; –, no cancer was observed in this group. HR, hazards ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; DB, diabetes; MD, metabolic dysregulation.

**Table 5** HRs of extrahepatic cancers in participants stratified by dual etiology of MAFLD

| Cancer types | MAFLD without positive HBsAg and excessive alcohol consumption | MAFLD with positive HBsAg only | MAFLD with excessive alcohol consumption only | MAFLD with excessive alcohol consumption and positive HBsAg |
|---|---|---|---|---|
| Extrahepatic | 1.03 (0.97–1.10) | 1.17 (0.83–1.65) | 1.14 (1.01–1.29) | 1.48 (0.74–2.95) |
| Thyroid | 1.57 (1.08–2.27) | – | 0.74 (0.18–3.05) | – |
| Lung | 0.90 (0.80–1.01) | 1.31 (0.73–2.37) | 1.00 (0.81–1.24) | 2.03 (0.76–5.42) |
| Esophageal | 0.76 (0.55–1.07) | 1.66 (0.41–6.71) | 1.41 (0.88–2.25) | 3.29 (0.46–23.38) |
| Gastric | 0.93 (0.74–1.17) | 1.90 (0.71–5.11) | 1.36 (0.92–2.02) | 2.35 (0.33–16.84) |
| Biliary | 0.91 (0.58–1.43) | – | 0.87 (0.32–2.40) | – |
| Pancreatic | 1.02 (0.70–1.49) | – | 0.78 (0.34–1.78) | – |
| Small intestine | 1.47 (0.74–2.89) | – | 1.95 (0.51–7.41) | – |
| Colorectal | 1.12 (0.95–1.33) | 1.71 (0.76–3.83) | 1.29 (0.93–1.78) | – |
| Kidney | 1.60 (1.22–2.11) | 1.84 (0.46–7.43) | 1.28 (0.72–2.26) | – |
| Bladder | 0.97 (0.70–1.34) | – | 1.20 (0.69–2.11) | – |
| Prostate[§] | 1.54 (1.09–2.18) | 1.81 (0.25–12.91) | 1.17 (0.53–2.55) | – |
| Breast[¶] | 1.29 (1.02–1.64) | 1.23 (0.30–5.00) | 7.27 (2.33–22.69) | * |

Data were presented as HR (95% confidence interval). The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women; *, no participants in this group; –, no cancer was observed in this group. HR, hazards ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; HBsAg, hepatitis B surface antigen.

and associations between the MAFLD with or without positive HBsAg, excessive alcohol consumption, and the risk of extrahepatic cancers among MAFLD individuals. MAFLD without positive HBsAg and excessive alcohol consumption accounted for 93.9% of all MAFLD patients. Compared with non-MAFLD, MAFLD without positive HBsAg and excessive alcohol consumption had a higher chance of thyroid (HR =1.57, 95% CI: 1.08–2.27), kidney (HR =1.60, 95% CI: 1.22–2.11), prostate (HR =1.54, 95% CI: 1.09–2.18), and breast cancer (HR =1.29, 95% CI: 1.02–1.64). In addition, an increased risk of extrahepatic cancers (HR =1.14, 95% CI: 1.01–1.29) and breast cancer (HR =7.27, 95% CI: 2.33–22.69) was observed in MAFLD with excessive alcohol consumption only, which accounted for 5.4% of the MAFLD patients. However, MAFLD with HBsAg (+) (with or without excessive alcohol consumption) only made up 0.12% and 0.58% of the MAFLD patients. We did not observe any significant difference in extrahepatic cancers between them and non-MAFLD.

### *Sensitivity analysis*

After excluding the participants who had developed incident cancers within the first 3 years of follow-up (Table S10), and the original dataset without imputation (Table S11), the association between MAFLD and thyroid, kidney, prostate, and breast cancer remained constant.

## Discussion

This prospective cohort study provides vital results to the knowledge of MAFLD, NAFLD, and their associations with extrahepatic cancers. Firstly, MAFLD was observed to have a higher risk of developing overweight & obesity-related cancers (thyroid, kidney, breast, and colorectal cancer) and prostate cancer. Similar associations were observed in NAFLD *vs.* non-NAFLD, MAFLD-NAFLD *vs.* neither FLD. However, a higher probability of extrahepatic, esophageal, and bladder cancer was only observed in NAFLD-only *vs.* neither FLD group. Secondly, our results showed different site-specific cancer risks in populations with various metabolic components. A higher probability of extrahepatic, esophageal, and breast cancer was demonstrated in MAFLD with MD; kidney, prostate, and breast cancer in MAFLD with overweight and MD; and colorectal and prostate cancer in MAFLD with three risk factors. Lastly, when considering other etiological factors, we observed that MAFLD with excessive alcohol consumption showed the highest risk of extrahepatic and breast cancer than the other groups.

In our population, increased risk with similar HRs of overweight & obesity-related cancers, including thyroid, kidney, breast, and colorectal cancer, were observed in MAFLD *vs.* non-MAFLD, NAFLD *vs.* non-NAFLD, and MAFLD-NAFLD *vs.* neither FLD. Our results are consistent with a meta-analysis and a Danish cohort study, which showed a positive association between NAFLD and colorectal, prostate, breast, and kidney cancer (3,24). The association between obesity and cancers could be explained by insulin-like growth factor-1, adipokines, chronic inflammation, and sex steroid hormones (25). However, no significant association of overweight & obesity-related cancers was observed in MAFLD with overweight-only *vs.* non-MAFLD, suggesting a driver role of FLD in the occurrence of overweight & obesity-related cancers. Our hypothesis could be demonstrated by a cohort study in a US population that reported a higher risk of extrahepatic cancers in NAFLD than obesity-only (26).

Our study also observed an increased risk of the kidney (HR =1.83, 95% CI: 1.38–2.43) in MAFLD with overweight and metabolic dysregulation, as well as colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21) in MAFLD with three risk factors but not in MAFLD with overweight. A close relationship between insulin resistance and prostate (27), kidney (28), and colorectal cancers (29) could partially explain it. Furthermore, our results were consistent with a study from Fukunaga *et al.* (30), which also observed that MAFLD, particularly non-obese MAFLD, could better predict the presence of colorectal adenoma rather than NAFLD. All above results indicate roles of metabolic dysregulation beyond obesity in these three cancers development in MAFLD participants.

Also, our study found a consistent relationship between NAFLD, MAFLD, and prostate cancer. Although meta-analysis reported an inverse association between DB and prostate cancer (31), MAFLD with overweight-MD, MAFLD with overweight-MD-DB groups displayed elevated prostate cancer risk in our cohort. This phenomenon highlights the importance of MD as a comprehensive indicator involved in central obesity, elevated blood pressure, abnormal blood lipids, and systemic inflammatory response, with or without overweight/obesity, in developing prostate cancer (32).

Compared with the neither FLD group, the NAFLD-only group had a higher risk of esophageal (HR =5.11,

95% CI: 2.25–11.62) and bladder cancer (HR =3.36, 95% CI: 1.23–9.17). This relationship may be false-positive because only six esophageal and four bladder cancer cases occurred in the NAFLD-only group. However, another two studies reported a positive relationship between NAFLD and esophageal cancer (a pooled HR =1.77, 95% CI: 1.19–2.62) (3) and one study of NAFLD and bladder cancer (OR =2.61, 95% CI: 1.30–5.22) (33). So, we called for further research with larger populations to validate the results. Once confirmed, it would suggest a unique mechanism between NAFLD and these two cancers.

Clinically meaningful interactions between MAFLD and hepatitis B virus (HBV)/hepatitis C virus (HCV) infection on hepatocellular carcinoma and all cancers were reported by other studies (34). However, the increased risk of all extrahepatic cancers did not reach statistically significant in MAFLD patients with HBsAg (+) (with or without excessive alcohol consumption) in our study. False negativity by the small sample size of the MAFLD-only group in our study population may partially explain it because of only 877 MAFLD with HBsAg (+) only and 184 MAFLD with HBsAg (+) and excessive alcohol consumption. A Finland reported that 30–49 g/day alcohol intake could increase the risk of all cancers in patients with FLD (35). And a Japan cohort reported that ≥40 g/day was associated with increased risk for Hepatocarcinogenesis in FLD (36). Our study also found that the risk of breast cancer significantly increased with excessive alcohol consumption, with HR reaching 7.27 (95% CI: 2.33–22.69). Alcohol intake is closely related to breast cancer risk in a positive dose-response relationship (37). Thus result underlines the importance of decreasing alcohol consumption to prevent breast cancer in MAFLD patients.

Several studies have shown better identification of clinical outcomes of MAFLD than NAFLD (38), especially for the Asia-Pacific region where fatty liver disease is frequently observed in lean/normal-weight individuals and patients with concomitant viral hepatitis (34). The consistent relationship between NAFLD, MAFLD, and most cancers in our study also suggests that this definition may be proper in a clinic where more patients in need of treatment can be easily diagnosed. In addition, treatment of metabolic disorders and dual etiology may reduce the incidence of cancers in these high-risk populations.

Before making any recommendations, it is essential to discuss the limitations involved. Firstly, we used abdominal ultrasound to identify fatty liver, which could not detect hepatic steatosis when fat content is <20% (39). Therefore, misclassification of MAFLD with mild steatosis would underestimate the relationships of MAFLD with cancers. Secondly, 2-hour-post-load glucose, HbA1c, and serum insulin for homeostasis model assessment-insulin resistance scores were unavailable in our cohort, which might misclassify MAFLD to be non-MAFLD and cause underestimating the association between MAFLD and cancers. Thirdly, we did not have data on other potential confounders to be further adjusted for each site-specific cancer. For instance, we were not considering menopause status when estimating the association between MAFLD and breast cancer which would bring about residual confounding. Thus, more comprehensive and detailed studies are needed to verify the results.

## Conclusions

This study demonstrated increased risks with similar HRs of prostate cancer and obesity-related cancers, including thyroid, kidney, breast, and colorectal cancer in MAFLD and NAFLD. MAFLD with more metabolic disorders beyond obesity, especially MD, leads to other risks of kidney, colorectal, and prostate cancer. Additionally, MAFLD with excessive alcohol consumption would dramatically increase extrahepatic and breast cancer risk. Though the MAFLD definition still leaves a great deal of ambiguity, it may be helpful in the clinic to relieve symptoms by treating metabolic disorders and preventing adverse outcomes like extrahepatic cancers.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was based on The Kailuan Study (trial identification: ChiCTR-TNC-11001489), approved by ethics committee of Kailuan General Hospital, and Institute of Basic Medical Sciences Chinese Academy of Medical Sciences Informed consent was taken from all individual participants.



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