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Original Article

Hypertension Associated with the Risk of Extrahepatic Cancers in the Metabolic Dysfunction-associated Steatotic Liver Disease Population: A Multicenter Cross-sectional Study in China

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Abstract

Background and Aims: Extrahepatic cancers have been recognized as a significant outcome of metabolic dysfunction–associated steatotic liver disease (MASLD), which involves five cardiometabolic risk factors, including hypertension, and is associated with the tumorigenesis of several cancers or with anti-cancer treatment. We aimed to investigate the association between hypertension, liver fibrosis, and extrahepatic cancers in the MASLD population. ***Methods:*** This multicenter cross-sectional study was based on a MASLD population from hospital-based databases across 11 centers nationwide in China, according to MASLD diagnostic criteria identified using keywords and ICD-10 codes. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between risk factors and extrahepatic cancers. ***Results:*** A total of 103,652 individuals with MASLD were identified, among whom 6,605 were diagnosed with extrahepatic cancers. The primary outcome revealed that hypertension was significantly associated with extrahepatic cancers (OR 1.14, 95% CI: 1.08–1.21), and its combination with hyperglycemia further increased this association (OR 1.36, 95% CI: 1.22–1.51). Risk factors for extrahepatic cancers included being over 40 years of age and female sex. Conversely, certain metabolism-based treatments were found to have potentially protective effects, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, fibrates, GLP-1 receptor agonists, and thiazolidinediones. After adjusting for confounding factors, the fibrosis-4 (FIB-4) score was associated with extrahepatic cancers. In the hypertension subgroup, FIB-4 scores of 1.30–2.66, 2.67–3.47, and ≥ 3.48 were associated with extrahepatic cancers in individuals aged 35–64 years, consistent with findings in those aged ≥ 65 years of age with FIB-4 ≥ 2. ***Conclusions:*** Hypertension combined with liver fibrosis is associated with extrahepatic cancers in patients with MASLD.

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Keywords: Metabolic dysfunction–associated steatotic liver disease; MASLD; Extrahepatic cancer/malignancy; Cardiometabolic risk factor; Hypertension; Liver fibrosis.

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Introduction

In 2023, three major liver associations redefined metabolic dysfunction–associated steatotic liver disease (MASLD), which was updated from non-alcoholic fatty liver disease (NAFLD), and renamed non-alcoholic steatohepatitis as metabolic dysfunction–associated steatohepatitis.[1] This new nomenclature included five cardiometabolic risk factors: overweight or increased waist circumference; prediabetes and type 2 diabetes mellitus (T2DM); hypertension; hypertriglyceridemia; and low high-density lipoprotein cholesterol (HDL-C). The population affected by MASLD has been estimated to be consistent with that of NAFLD.[2] The global burden of MASLD in 2021 was 15,018.1 cases (95% UI 13,756.5–16,361.4) per 100,000 population, along with the largest increase occurring in China from 2010 to 2021 (16.9%, 95% UI 14.7–18.9%).[3]

Previous studies demonstrated that cardiovascular diseases, as the primary extrahepatic fatal outcomes among chronic liver disease, were the leading cause-specific mortality in the NAFLD population.[4,5] However, extrahepatic cancers were identified as another cause-specific mortality in the NAFLD population and were even regarded as the first cause-specific mortality in some studies.[6] Meanwhile, obesity or overweight, along with T2DM, are acknowledged risk factors for extrahepatic cancers in NAFLD populations.[7] Interestingly, in the general cancer population, hypertension has been identified as a comorbidity during anti-cancer treatment or as a risk factor of cancers.[8]

Although emerging evidence has shown a strong association between MASLD and an increased risk of extrahepatic cancers,[7] the association between cardiometabolic risk factors—especially hypertension—and extrahepatic cancers in patients with MASLD remains unclear. Therefore, we hypothesize that hypertension is associated with the risk of extrahepatic cancers in the MASLD population. The combined effects of these factors, including widely acknowledged diabetes or dyslipidemia, metabolism-based treatments, and the severity of liver fibrosis, will also be illustrated in this study.

Methods

Population and study design

This multicenter cross-sectional retrospective study was based on a multicenter hospital-based database from 11 tertiary hospitals across six cities in China (Beijing, Shanghai, Xi'an, Chongqing, Shenyang, and Wuhan), which was compiled between 1/1/2020 and 12/31/2022.

Definition

Definition of MASLD: According to the criteria for the diagnosis of MASLD proposed in 2023,[9] MASLD was diagnosed in individuals aged ≥18 years as evidence of hepatic steatosis with one of the following five cardiometabolic criteria: (I) overweight/obesity [BMI ≥ 23.00 kg/m^2 for Asians] OR waist circumference ≥94 cm (male) or ≥80 cm (female); (II) fasting serum glucose ≥5.6 mmol/L [100 mg/dL] OR 2-h post-load glucose levels ≥7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/mol] OR type 2 diabetes OR treatment for T2DM; (III) blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment; (IV) plasma triglycerides ≥1.70 mmol/L [150 mg/dL] OR lipid-lowering treatment; (V) plasma HDL-C ≤ 1.0 mmol/L [40 mg/dL] (male) or ≤ 1.3 mmol/L [50 mg/dL] (female) OR lipid-lowering treatment.

Definition of hyperlipidemia: Hyperlipidemia was defined when ≥1 of the following fasting venous plasma test indicators was met: total cholesterol ≥5.2 mmol/L; low-density lipoprotein cholesterol ≥3.4 mmol/L; triglycerides ≥1.7 mmol/L; HDL-C < 1.0 mmol/L for males and <1.3 mmol/L for females, termed lower HDL-C in the following analyses.[10]

Ascertainment of MASLD population and extrahepatic cancers

The accuracy of diagnosis was evaluated by experienced clinicians. First, individuals diagnosed with "hepatic steatosis" were extracted from the database using ICD-10 codes with keywords (in Chinese), excluding other etiologies of hepatic steatosis. The ICD-10 codes and keywords (in Chinese) used to identify patients with MASLD are illustrated in Supplementary Table 1. Screening and appraisal to identify and extract individuals who met the MASLD diagnostic criteria were performed. According to real-world clinical practice, MASLD cardiometabolic criterion (IV) included the diagnosis of hyperlipidemia. The absence of BMI and waist circumference data (criterion I) in our database meant that these two criteria were not utilized. As primary or secondary tumors were uncertain, in subsequent logistic analyses, populations with extrahepatic cancers who were identified as having hepatic tumors were excluded, along with the non-cancer population as their counterparts.

Subgroups

In logistic regression analyses, metabolic dysfunctions were classified as follows: hypertension, including diagnosed hypertension and use of antihypertensive agents; abnormal lipid metabolism, including plasma triglycerides ≥ 1.70 mmol/L, diagnosed hyperlipidemia, lower HDL-C, and use of lipid-lowering treatment; hyperglycemia and pre-diabetes, defined as fasting blood glucose 5.6–6.9 mmol/L, HbA1c 5.7–6.4%, 2-h post-meal blood glucose 7.8–11.0 mmol/L; and T2DM and treatment for T2DM. In metabolic dysfunction subgroup analyses, groups included the hypertension group (diagnosed hypertension and use of antihypertensive agents), abnormal lipid metabolism group (plasma triglycerides ≥ 1.70 mmol/L, diagnosed hyperlipidemia, lower HDL-C, and lipid-lowering treatment), and T2DM group (diagnosed T2DM and treatment for T2DM). Ascertainment of pharmacological treatments for metabolic dysfunctions and comorbidities was shown in the supplementary materials (Supplementary Table 2).

Fibrosis assessment

The fibrosis-4 (FIB-4) score[11,12] was calculated using the established equation incorporating age, aspartate aminotransferase level, alanine aminotransferase level, and platelet count. In individuals aged 35 to 64 years,[13] a FIB-4 score <1.3 (F0–F1) was considered low risk for advanced fibrosis, while a score ranging from 1.3 to 2.67 (F2) indicated intermediate risk and required further evaluation through liver stiffness measurement via elastography, liver function tests, or other methods. A score exceeding 2.67 and 3.48[14] was classified as high risk for advanced fibrosis (F3–F4) and cirrhosis, which was linked to an increased risk of adverse liver outcomes. For those those aged ≥ 65 years old, the FIB-4 cutoff was raised to 2.[13] Stratified age analyses and adjusted odds ratios (aORs) were used to demonstrate the association between liver fibrosis assessed by FIB-4 score and extrahepatic cancers in the MASLD population.

Statistical analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, with $p < 0.05$ considered statistically significant. Continuous variables were expressed

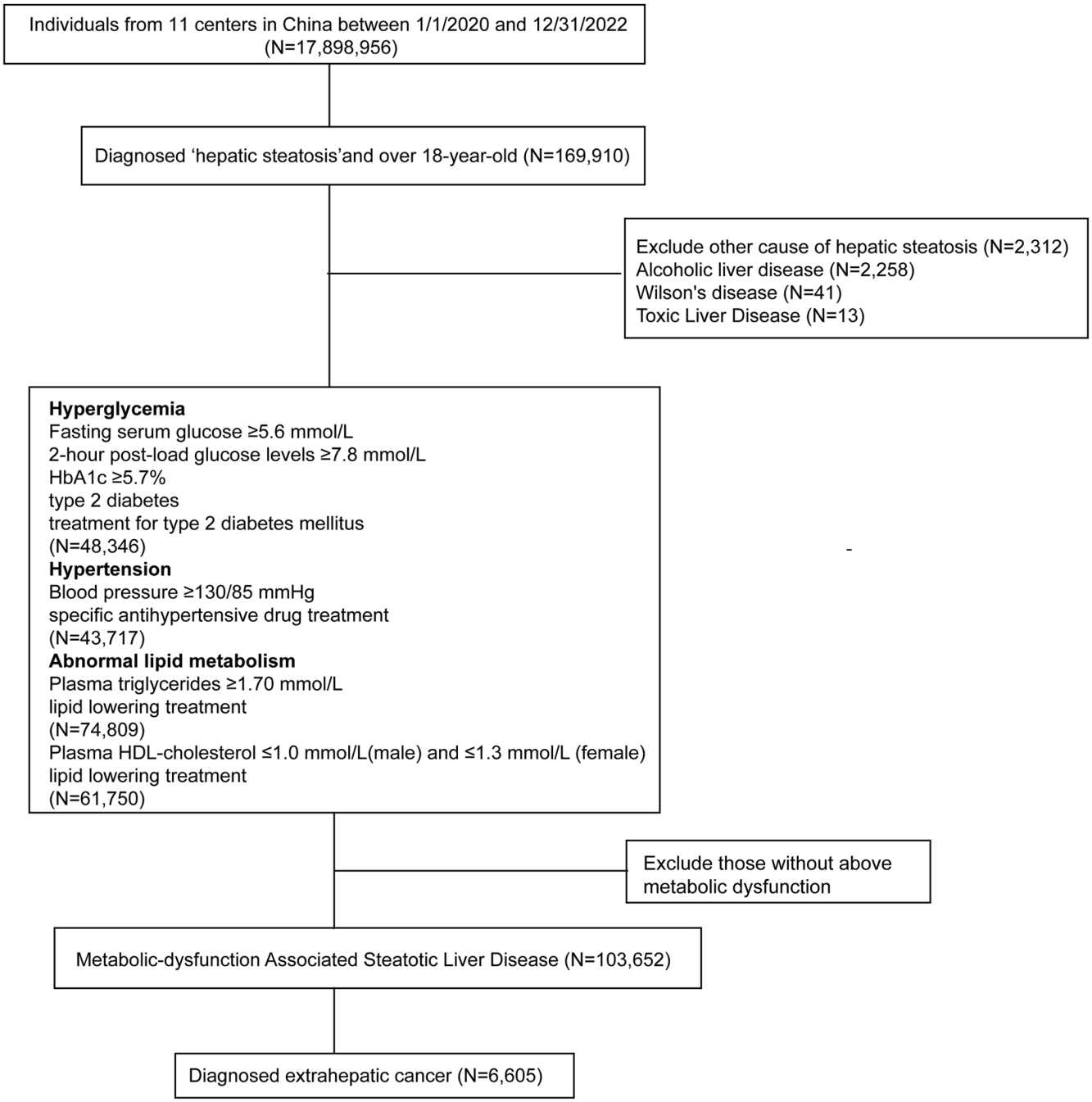

Fig. 1. The flow chart of the screening of extrahepatic cancer in the MASLD population. MASLD, metabolic dysfunction–associated steatotic liver disease.

as mean ± standard deviation; skewed distributions were presented as median and interquartile range (Q1, Q3) and analyzed using the Wilcoxon test or Kruskal–Wallis test. Univariate and multivariate logistic regression analyses were conducted to evaluate risk factors for extrahepatic cancers, with odds ratios (ORs), aORs, and 95% confidence intervals (95% CIs) calculated. Covariates were identified according to clinical importance and statistical significance. Considering clinical impact and statistical results from univariate logistic analyses, multivariate logistic regression analyses were performed. A product term (Hypertension*Hyperglycemia) was included in the model to explore their interaction effect on the risk of extrahepatic cancers. Forest plots were generated using R version 4.4.2.

Results

Demographic and baseline characteristics of patients with MASLD and extrahepatic cancers

A total of 103,652 patients with MASLD were included in this study (Fig. 1). Among them, 6,605 individuals with MASLD

and extrahepatic cancers were identified, including 3,243 females (49.10%). The mean age was 58.61 ± 12.49 years. Dyslipidemia was the most prevalent condition, observed in 4,275 patients (64.72%). The combination of cardiometabolic risk factors and other baseline clinical characteristics, including comorbidities and metabolism-based treatments, is presented in Table 1. Overall, lung cancer, thyroid cancer, and breast cancer were identified as the top three extrahepatic malignancies. Gender differences in site-specific extrahepatic cancers were also reported in detail. There was no difference in incidence between genders (Fig. 2, Supplementary Table 3).

Hypertension associated with extrahepatic cancers in the MASLD population

To exclude selection bias and metastatic hepatic tumors, patients with both extrahepatic cancers and hepatic tumors were excluded, and the non-cancer population was included as counterparts in the logistic analysis. Finally, 6,499 patients with extrahepatic cancers and 93,065 non-cancer MASLD individuals were included. Univariate logistic analysis indicated that aging, female gender, and cardiometabolic risk factors were significantly associated with extrahepatic cancers (Supplementary Table 4). Considering the interaction of risk factors, multivariate logistic regression analysis was performed.

Hypertension was significantly associated with the risk of extrahepatic cancers in the MASLD population (OR 1.15, 95% CI: 1.04–1.26, $p = 0.044$). As for age, compared with individuals under 30 years old, those aged 30–39 (OR 1.46, 95% CI: 1.17–1.82, $p < 0.001$), 40–49 (OR 2.75, 95% CI:2.23–3.39, $p < 0.001$), 50–59 (OR 4.58, 95% CI: 3.74–5.61, $p < 0.001$), 60–69 (OR 6.47, 95% CI: 5.27–7.95, $p < 0.001$), and over 70 years (OR 7.47, 95% CI: 6.05–9.22, $p < 0.001$) had a higher likelihood of comorbidity with extrahepatic cancers, as shown in Figure 3. In 10-year age stratifications, hypertension was associated with extrahepatic cancers in the 40–49 and 50–59 age groups without statistical significance, likely due to the low incidence of events in these subgroups. Subsequently, hypertension was significantly associated with extrahepatic cancers in patients aged ≥40 years (OR 1.19, 95% CI: 1.13–1.25, $p < 0.001$), as shown in Supplementary Figure 1. Additionally, female gender (OR 1.41, 95% CI: 1.33–1.48, $p < 0.001$), aspartate aminotransferase (OR 1.25, 95% CI: 1.14–1.38, $p < 0.001$), and alanine aminotransferase (OR 1.19, 95% CI: 1.09–1.29, $p < 0.001$) levels over 40 U/L were associated with a higher risk of extrahepatic cancers (Fig. 3). Furthermore, the combination of hypertension and hyperglycemia (OR 1.36, 95% CI: 1.22–1.51, $p < 0.001$) was significantly associated with the risk of extrahepatic cancers in patients with MASLD (Fig. 4). Potential effect modification was assessed by including an interaction term (Hypertension*Hyperglycemia) in the same regression model shown in Figure 3. This term was associated with extrahepatic cancers (OR 1.09, 95% CI: 0.98–1.22, $p = 0.116$) but did not reach statistical significance, indicating that the interaction effect was insignificant. Specifically, as shown in Supplementary Figure 2, diagnosed hypertension (OR 1.14, 95% CI: 1.08–1.21, $p < 0.001$) and T2DM (OR 1.19, 95% CI: 1.12–1.26, $p < 0.001$) were identified as risk factors for extrahepatic cancers.

Pharmacological treatments of hypertension showed a protective impact on extrahepatic cancers in the MASLD population

Pharmacological treatments were identified as protective factors, as shown in Supplementary Figures 2–4. To determine which categories of agents conferred protection against extrahepatic cancers, subgroup analyses were conducted among those with hypertension, abnormal lipid metabolism, and T2DM.

After adjustment for confounding factors (Supplementary Tables 5–7), all forms of agents acted as protective factors in univariate analyses. In multivariate analyses (Supplementary Table 8), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (hereinafter referred to as ACEIs/ARBs) (aOR 0.68, 95% CI: 0.61–0.77, $p < 0.001$) and beta-blockers (aOR 0.78, 95% CI: 0.68–0.91, $p = 0.001$) were protective factors. For lipid-modifying agents, fibrates demonstrated the strongest protective effect (aOR 0.47, 95% CI: 0.35–0.62, $p < 0.001$), while statins (aOR 0.65, 95% CI: 0.58–0.72, $p < 0.001$) and cholesterol absorption inhibitors (aOR 0.69, 95% CI: 0.49–0.96, $p = 0.026$) also exhibited protective effects. In the T2DM subgroup, glucagon-like peptide-1 receptor agonists (hereinafter referred to as GLP-1 RAs) (aOR 0.52, 95% CI: 0.35–0.76, $p < 0.001$) and thiazolidinediones (aOR 0.45, 95% CI: 0.26–0.79, $p = 0.005$) showed the strongest protective effects despite lower usage rates. Insulin, sodium–glucose cotransporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors exhibited similar protective patterns. Metformin, although the most commonly used agent, was only associated with a 16% reduction in risk ($p = 0.005$).

FIB-4 index associated with extrahepatic cancers in the MASLD population

After adjustment for confounding factors (Supplementary Tables 5–7), multivariate logistic regression analysis was conducted (Table 2). Among individuals aged 35 to 64 years, compared with those with FIB-4 < 1.3, those with FIB-4 ≥ 1.3 showed a higher likelihood of developing extrahepatic cancers. The risk increased across FIB-4 categories of 1.3–2.66 (aOR 1.37, 95% CI: 1.26–1.48, $p < 0.001$), 2.67–3.47 (aOR 1.50, 95% CI: 1.23–1.82, $p < 0.001$), and ≥3.48 (aOR 1.62, 95% CI: 1.40–1.87, $p < 0.001$), respectively. However, when compared with the FIB-4 1.3–2.66 category, only FIB-4 < 1.3 acted as a significant protective factor. Across all subgroups, patients with FIB-4 ≥ 1.3 were identified as having a higher likelihood of developing extrahepatic cancers. Specifically, in the hypertension subgroup, individuals aged 35–64 years with FIB-4 values of 1.3–2.66, 2.67–3.47, and ≥3.48 had 47%, 40%, and 73% higher likelihoods of developing extrahepatic cancers, respectively, compared with those with FIB-4 < 1.3; similar patterns were observed in the T2DM subgroup (50%, 46%, and 90%). In the abnormal lipid metabolism subgroup, individuals aged 35–64 years with FIB-4 values of 2.67–3.47 and ≥3.48 exhibited more than a two-fold increased likelihood. Among individuals older than 65 years, all those with FIB-4 ≥ 2 showed a higher likelihood of developing extrahepatic cancers.

Discussion

This multicenter cross-sectional study, encompassing a population of 103,652 Chinese individuals with MASLD, found that the incidence of all extrahepatic cancers was higher than that reported by the National Cancer Center of China.[15] In the current study, we found that hypertension was independently associated with a modest but significantly higher likelihood of extrahepatic cancers (OR 1.15, 95% CI: 1.04–1.26), with the risk further increased when hypertension coexisted with hyperglycemia (OR 1.36, 95% CI: 1.22–1.51). Meanwhile, several metabolism-targeted medications (ACEIs/ARBs, fibrates, GLP-1 RAs, and thiazo-

Table 1. Baseline characteristics of MASLD with extrahepatic cancers

	MASLD (%)	Non cancer (%)	Extrahepatic cancers (%)	*p*
Total	103,652	93,065	6,605	
Male	67,421 (65.05)	61,597 (66.19)	3,362 (50.90)	<0.001
Female	36,231 (34.95)	31,468 (33.81)	3,243 (49.10)	<0.001
Age, year				
<30	6,084 (5.87)	5,913 (6.35)	105 (1.59)	<0.001
30–39	16,491 (15.91)	15,808 (16.99)	380 (5.75)	<0.001
40–49	21,768 (21.00)	20,226 (21.73)	913 (13.82)	<0.001
50–59	29,683 (28.64)	26,342 (28.30)	2,147 (32.51)	<0.001
60–69	18,458 (17.81)	15,574 (16.73)	1,839 (27.84)	<0.001
≥70	11,168 (10.77)	9,202 (9.89)	1,221 (18.49)	<0.001
Cardiometabolic factors				
Hypertension	43,717 (42.18)	38,539 (41.41)	3,271 (49.52)	<0.001
Blood pressure ≥ 130/85 mmHg	41,254 (39.80)	36,411 (39.12)	3,034 (45.93)	<0.001
Utility of antihypertensive drug	24,219 (23.37)	21,970 (23.61)	1,183 (17.91)	<0.001
Dyslipidemia	84,488 (81.51)	77,299 (83.06)	4,275 (64.72)	<0.001
Diagnosis of hyperlipidemia	41,735 (40.26)	38,843 (41.74)	1,666 (25.22)	<0.001
Triglycerides ≥ 1.7 mmol/L	46,757 (45.11)	43,005 (46.21)	2,401 (36.35)	<0.001
Lower HDL-C	41,885 (40.41)	37,689 (40.50)	2,568 (38.88)	<0.001
LDL-C ≥ 3.4 mmol/L	22,451 (21.66)	20,687 (22.23)	1,143 (17.31)	<0.001
Total cholesterol ≥ 5.2 mmol/L	26,449 (25.52)	24,338 (26.15)	1,420 (21.50)	<0.001
Utility of lipid-lowering agent	24,417 (23.56)	22,577 (24.26)	738 (11.17)	<0.001
Hyperglycemia	48,346 (46.64)	42,962 (46.16)	3,237 (49.01)	<0.001
Type 2 diabetes mellitus	39,003 (37.63)	34,409 (36.97)	2,691 (40.74)	<0.001
Fasting blood-glucose 5.6–6.9 mmol/L	9,368 (9.04)	8,420 (9.05)	629 (9.52)	<0.001
HbA1c 5.7–6.4%	13,645 (13.16)	12,402 (13.33)	810 (12.26)	<0.001
2-h post-meal blood glucose 7.8–11.0 mmol/L	998 (0.96)	936 (1.01)	38 (0.58)	<0.001
Utility of hypoglycemic agent	20,134 (19.42)	18,511 (19.89)	903 (13.67)	<0.001
Other related indicators				<0.001
HOMA-IR ≥ 2.5	987 (0.95)	954 (1.03)	13 (0.20)	<0.001
hs-CRP over 2 mg/L	10,456 (10.09)	8,793 (9.45)	1,281 (19.39)	<0.001
Combination of cardiometabolic risk factors				
Hypertension and abnormal lipid metabolism	35,863 (34.60)	29,934 (32.16)	1,760 (26.65)	<0.001
Hypertension and hyperglycemia	23,617 (22.78)	20,948 (22.51)	1,570 (23.77)	<0.001
Abnormal lipid metabolism and hyperglycemia	35,863 (34.60)	32,621 (35.05)	1,857 (28.12)	<0.001
Hypertension, abnormal lipid metabolism, and hyperglycemia	15,152 (14.62)	13,683 (14.70)	1,009 (15.28)	<0.001
Liver function				
AST > 40 U/L	16,296 (15.72)	14,370 (15.44)	1,097 (16.61)	<0.001
AST > 80 U/L	4,830 (4.66)	4,096 (4.40)	333 (5.04)	<0.001

(continued)

Table 1. *(continued)*

	MASLD (%)	Non cancer (%)	Extrahepatic cancers (%)	*p*
ALT > 40 U/L	27,909 (26.93)	25,242 (27.12)	1,608 (24.35)	<0.001
ALT > 80 U/L	9,713 (9.37)	8,720 (9.37)	522 (7.90)	<0.001
Fibrosis-4 index				
Age 35–64				
FIB-4 < 1.3	30,071 (29.01)	27,454 (29.50)	1,789 (27.09)	<0.001
FIB-4 1.3–2.66	13,498 (13.02)	11,776 (12.65)	1,175 (17.79)	<0.001
FIB-4 2.67–3.47	1,289 (1.24)	1,074 (1.15)	130 (1.97)	<0.001
FIB-4 ≥ 3.48	2,483 (2.40)	1,941 (2.09)	267 (4.04)	<0.001
Age ≥ 65				
FIB-4 < 2	8,630 (8.33)	7,301 (7.85)	934 (14.14)	<0.001
FIB-4 ≥ 2	6,930 (6.69)	5,446 (5.85)	955 (14.46)	<0.001
Comorbidities				
Cardiovascular disease	48,261 (46.56)	42,649 (45.83)	3,445 (52.16)	<0.001
Abnormal liver function	10,849 (10.47)	9,986 (10.73)	509 (7.71)	<0.001
Viral hepatitis	9,759 (9.42)	8,948 (9.61)	233 (3.53)	<0.001
Cirrhosis	2,061 (1.99)	1,602 (1.72)	50 (0.76)	<0.001
Chronic kidney disease	7,646 (7.38)	7,132 (7.66)	258 (3.91)	<0.001
Osteoporosis	4,603 (4.44)	4,098 (4.40)	307 (4.65)	<0.001
Hypothyroidism	3,025 (2.92)	2,598 (2.79)	302 (4.57)	<0.001
Obstructive sleep apnea	1,557 (1.50)	1,480 (1.59)	41 (0.62)	<0.001
Polycystic ovarian syndrome	325 (0.31)	313 (0.34)	6 (0.09)	<0.001
Hp. Infection	1,888 (1.82)	1,695 (1.82)	83 (1.26)	<0.001
Autoimmune hepatitis	304 (0.29)	285 (0.31)	7 (0.11)	<0.001
Chronic obstructive pulmonary disease	1,008 (0.97)	771 (0.83)	134 (2.03)	<0.001
Metabolic-based treatments				
Hyperglycemia				
Insulin (aspart insulin and glargine insulin)	5,133 (4.95)	4,732 (5.08)	226 (3.42)	<0.001
Biguanides (metformin)	9,173 (8.85)	8,447 (9.08)	404 (6.12)	<0.001
SGLT-2 inhibitors	2,786 (2.69)	2,605 (2.80)	87 (1.32)	<0.001
GLP-1 receptor agonists	1,177 (1.14)	1,122 (1.21)	28 (0.42)	<0.001
DPP-4 inhibitors	2,433 (2.35)	2,224 (2.39)	101 (1.53)	<0.001
Thiazolidinediones	630 (0.61)	601 (0.65)	13 (0.20)	<0.001
Dyslipidemia				
Statins	12,980 (12.52)	11,905 (12.79)	442 (6.69)	<0.001
Fibrates	2,575 (2.48)	2,459 (2.64)	47 (0.71)	<0.001
Cholesterol absorption inhibitors (ezetimibe)	1,326 (1.28)	1,209 (1.30)	37 (0.56)	<0.001
Hypertension				
Calcium channel blockers	12,561 (12.12)	11,321 (12.16)	705 (10.67)	<0.001
ACEIs/ARBs	11,795 (11.38)	10,843 (11.65)	451 (6.83)	<0.001
Beta-blockers	7,635 (7.37)	6,974 (7.43)	282 (4.27)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, insulin resistance index; FIB-4, Fibrosis-4 index; hs-CRP, high-sensitivity C-reactive protein; SGLT-2, sodium–glucose cotransporter-2; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

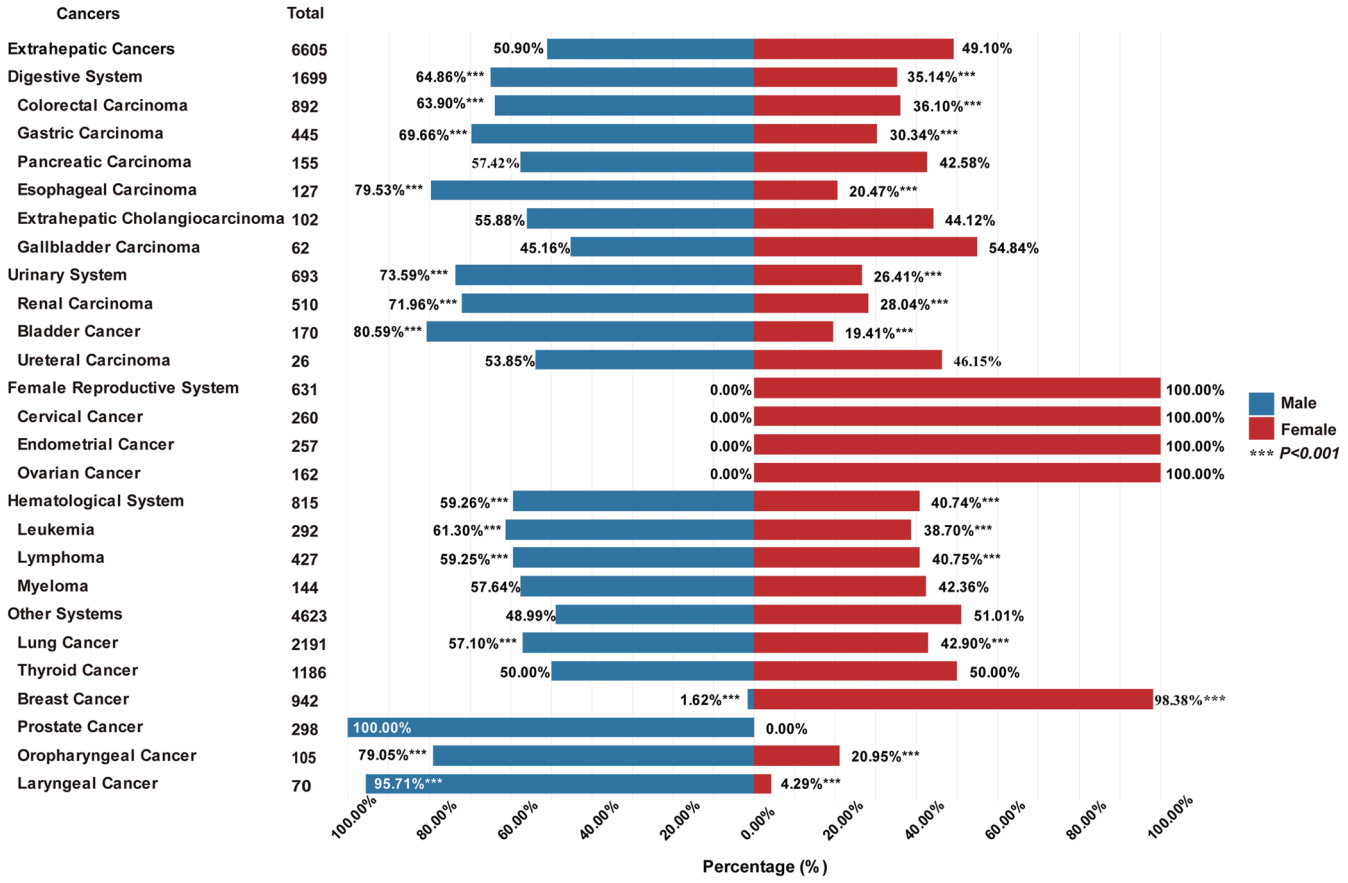

Fig. 2. Gender differences of extrahepatic cancers in the MASLD population. ***p < 0.001, MASLD, metabolic dysfunction–associated steatotic liver disease.

Risk factors	Extrahepatic cancers	Non cancer	OR (95% CI)	*P value*
Age<30	104	5913	Reference	
Age 30 to 39	376	15808	1.46 (1.17,1.82)	*<0.001*
Age 40 to 49	903	20226	2.75 (2.23,3.39)	*<0.001*
Age 50 to 59	2112	26342	4.58 (3.74,5.61)	*<0.001*
Age 60 to 69	1799	15574	6.47 (5.27,7.95)	*<0.001*
Age ≥70	1205	9202	7.47 (6.05,9.22)	*<0.001*
Female	3195	31468	1.41 (1.33,1.48)	*<0.001*
Hypertension	3189	42962	1.15 (1.04,1.26)	*0.0044*
Abnormal lipid metabolism	4208	77299	0.40 (0.37,0.42)	*<0.001*
Hyperglycemia	3232	38539	0.79 (0.75,0.84)	*<0.001*
AST>40U/L	1069	14370	1.25 (1.14,1.38)	*<0.001*
ALT>40U/L	1578	25242	1.19 (1.09,1.29)	*<0.001*
Abnormal liver function	504	9986	0.76 (0.69,0.84)	*<0.001*
Cirrhosis	45	1602	0.49 (0.36,0.67)	*<0.001*
CKD	257	7132	0.53 (0.47,0.61)	*<0.001*
CVD	3403	42649	0.74 (0.68,0.82)	*<0.001*
OSA	41	1480	0.51 (0.37,0.69)	*<0.001*
PCOS	6	313	0.68 (0.31,1.50)	*0.3363*
Viral hepatitis	227	8948	0.42 (0.37,0.48)	*<0.001*
Hp infection	83	1695	0.68 (0.54,0.85)	*<0.001*
Autoimmune hepatitis	7	285	0.30 (0.14,0.63)	*0.0013*
COPD	134	771	1.71 (1.41,2.07)	*<0.001*

Fig. 3. The association of metabolic dysfunctions, elevated liver enzymes, comorbidities, and extrahepatic cancers in the MASLD population. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; CVD, cardiovascular disease; MASLD, metabolic dysfunction–associated steatotic liver disease; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; COPD, chronic obstructive pulmonary disease.

Risk factors	Extrahepatic cancers	Non cancer	OR (95% CI)	P value
Age<30	104	5913	Reference	
Age 30 to 39	376	15808	1.47 (1.18,1.84)	<0.001
Age 40 to 49	903	20226	2.85 (2.32,3.51)	<0.001
Age 50 to 59	2112	26342	4.90 (4.00,6.00)	<0.001
Age 60 to 69	1799	15574	7.00 (5.70,8.60)	<0.001
Age ≥70	1205	9202	8.11 (6.57,10.01)	<0.001
Female	3195	31468	1.40 (1.33,1.48)	<0.001
Hypertension and Abnormal lipid metabolism	1739	29934	0.52 (0.47,0.57)	<0.001
Hypertension and Hyperglycemia	1553	20948	1.36 (1.22,1.51)	<0.001
Abnormal lipid metabolism and Hyperglycemia	1836	32621	0.64 (0.59,0.69)	<0.001
All three metabolic dysfunction	998	17768	0.96 (0.81,1.14)	0.6586
AST>40U/L	1069	14370	1.26 (1.15,1.38)	<0.001
ALT>40U/L	1578	25242	1.16 (1.07,1.25)	<0.001
Abnormal liver function	504	9986	0.75 (0.68,0.83)	<0.001
Cirrhosis	45	1602	0.49 (0.36,0.66)	<0.001
CKD	257	7132	0.54 (0.48,0.62)	<0.001
CVD	3403	42649	1.17 (1.09,1.26)	<0.001
OSA	41	1480	0.52 (0.38,0.71)	<0.001
PCOS	6	313	0.79 (0.36,1.73)	0.5510
Viral hepatitis	227	8948	0.40 (0.35,0.46)	<0.001
Hp infection	83	1695	0.69 (0.56,0.87)	0.0014
Autoimmune hepatitis	7	285	0.31 (0.15,0.64)	0.0016
COPD	134	771	1.70 (1.41,2.06)	<0.001

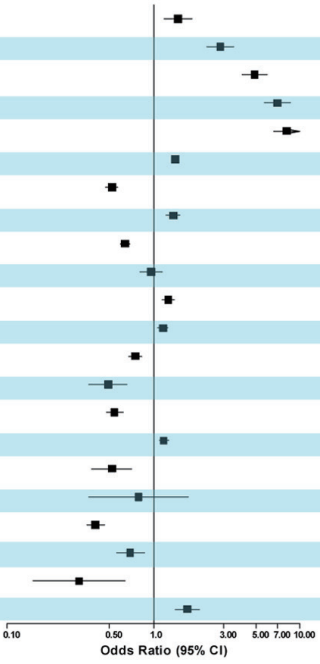

Fig. 4. The association of the combination of cardiometabolic dysfunction factors, elevated liver enzymes, comorbidities, and extrahepatic cancers in the MASLD population. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; CVD, cardiovascular disease; MASLD, metabolic dysfunction–associated steatotic liver disease; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; COPD, chronic obstructive pulmonary disease.

Table 2. The association of FIB-4 and extrahepatic carcinoma in the MASLD population

	Extrahepatic cancer	Non cancer	aOR (95% CI)	aOR (95% CI)
All MASLD				
Age from 35 to 64				
FIB-4 < 1.3	1,765	27,454	1.00	0.73 (0.68,0.79)**
FIB-4 1.3–2.66	1,155	11,776	1.37 (1.26,1.48)**	1.00
FIB-4 2.67–3.47	125	1,074	1.50 (1.23,1.82)**	1.10 (0.90,1.34)
FIB-4 ≥ 3.48	261	1,941	1.62 (1.40,1.87)**	1.18 (1.02,1.37)*
Age ≥ 65				
FIB-4 < 2	922	7,301	1.00	
FIB-4 ≥ 2	932	5,446	1.22 (1.10,1.35)**	
Hypertension subgroup				
Age from 35 to 64				
FIB-4 < 1.3	735	11,157	1.00	0.68 (0.60,0.77)**
FIB-4 1.3–2.66	529	5,126	1.47 (1.30,1.65)**	1.00
FIB-4 2.67–3.47	49	469	1.40 (1.02,1.92)*	0.95 (0.69,1.31)
FIB-4 ≥ 3.48	91	716	1.73 (1.35,2.21)**	1.78 (0.92,1.52)
Age ≥ 65				
FIB-4 < 2	599	5,088	1.00	
FIB-4 ≥ 2	595	3,764	1.25 (1.10,1.42)**	
Abnormal lipid metabolism subgroup				

(continued)

Table 2. *(continued)*

	Extrahepatic cancer	Non cancer	aOR (95% CI)	aOR (95% CI)
Age from 35 to 64				
FIB-4 < 1.3	1,240	23,888	1.00	0.71 (0.64,0.78)**
FIB-4 1.3–2.66	737	9,936	1.42 (1.29,1.56)**	1.00
FIB-4 2.67–3.47	87	874	2.04 (1.61,2.58)**	1.44 (1.13,1.83)*
FIB-4 ≥ 3.48	171	1,591	2.29 (1.91,2.74)**	1.61 (1.34,1.94)**
Age ≥ 65				
FIB-4 < 2	582	6,333	1.00	
FIB-4 ≥ 2	598	4,587	1.41 (1.25,1.60)**	
T2DM subgroup				
Age from 35 to 64				
FIB-4 < 1.3	572	9,248	1.00	0.67 (0.59,0.76)**
FIB-4 1.3–2.66	454	4,672	1.50 (1.31,1.71)**	1.00
FIB-4 2.67–3.47	51	491	1.46 (1.07,1.99)*	0.97 (0.71,1.33)
FIB-4 ≥ 3.48	131	969	1.90 (1.53,2.35)**	1.27 (1.02,1.58)*
Age ≥ 65				
FIB-4 < 2	434	3,748	1.00	
FIB-4 ≥ 2	440	2,726	1.28 (1.10,1.48)*	

All MASLD population adjustive factors: gender, hypertension, hyperlipidemia, type 2 diabetes mellitus, pre-diabetes, anti-metabolic dysfunction agents, abnormal blood pressure, abnormal lipid metabolism, hyperglycemia, the combination of metabolic dysfunction, hs-CRP, cardiovascular disease, cirrhosis, chronic obstructive pulmonary disease, metabolism, T2DM, using hypoglycemia treatment, hyperlipidemia, using lipid-adjusting agents, abnormal liver function, cirrhosis, chronic kidney disease, cardiovascular disease, obstructive sleep apnea, hypothyroidism, viral hepatitis, Hp. infection, chronic obstructive pulmonary disease. Abnormal lipid metabolism group adjustive factors: sex, hyperglycemia, hypertension, T2DM, using hypoglycemia treatment, pre-diabetes, hypertension (diagnosis), using hypertension treatment, hyperglycemia and hypertension, abnormal liver function, cirrhosis, chronic kidney disease, cardiovascular disease, osteoporosis, obstructive sleep apnea, polycystic ovarian syndrome, hypothyroidism, viral hepatitis, chronic obstructive pulmonary disease. T2DM subgroup adjustive factors: hypertension, abnormal lipid metabolism, hypertension diagnosis, using hypertension treatment, hyperlipidemia, using lipid-adjusting agents, hypertension and abnormal lipid metabolism, abnormal liver function, cirrhosis, chronic kidney disease, obstructive sleep apnea, polycystic ovarian syndrome, hypothyroidism, viral hepatitis, Hp. infection, chronic obstructive pulmonary disease. $^{**}p < 0.001$, $^{*}p < 0.05$; aOR 1.00 as reference; aOR, adjusted odds ratio. FIB-4, Fibrosis-4 index; hs-CRP, high-sensitivity C-reactive protein; T2DM, Type 2 diabetes mellitus; MASLD, metabolic dysfunction–associated steatotic liver disease.

lidinediones) might have exhibited robust protective associations against extrahepatic cancers. In stratified analyses by 10-year age groups, hypertension remained a significant risk factor in all strata above 30 years of age, and this association persisted across gender, hyperglycemia, abnormal lipid metabolism, and all FIB-4 subgroups. Our results added new data to a recent study showing that hypertension was associated with increased risks of all-cause mortality, cardiovascular events, progression of liver stiffness or fibrosis, and liver-related events in patients with MASLD.[16]Although extrahepatic cancers represent the first or second leading cause of death in this population,[6,17] evidence linking hypertension to specific cancer types has been limited. Prior studies have suggested elevated risks of thyroid, esophageal, colorectal, liver, renal cell, breast (in women), and endometrial cancers in individuals with hypertension.[8,18–21] Several plausible biological pathways may underlie these associations. First, androgens contribute to both hypertension and prostate cancer through shared mechanisms involving the renin–angiotensin system and enhanced sodium reabsorption.[22] Second, dysregulation of vascular endothelial growth factor establishes a bidirectional link, whereby elevated vascular endothelial growth factor levels in hypertensive patients promote tumor angiogenesis.[8,23] Additionally, chronic inflammation and oxidative stress—common to both conditions—drive endothelial dysfunction, sympathetic overactivity, and pro-proliferative signaling pathways.[8] Further mechanistic studies are warranted to elucidate these relationships. Our findings underscore the importance of rigorous hypertension screening and management in patients with MASLD, as effective control may potentially reduce adverse outcomes, including extrahepatic cancers. These results provide insights for future research and clinical practice, particularly the need to further establish the causal association between hypertension and extrahepatic cancers in patients with MASLD, and to evaluate the potential benefits of targeted hypertension management and enhanced extrahepatic cancer screening in specific subgroups, such as those stratified by age or severity of hypertension. Additionally, the combination of hypertension and hyperglycemia was identified as a risk factor associated with extrahepatic cancers without a significant interaction effect in this study. A previous study has demonstrated that the clustering of two or more cardiometabolic risk factors markedly heightens malignancy risk.[24] These findings further suggest that, on the basis of the established association between hypertension and extrahepatic cancers, concomitant hyperglycemia may confer additional risk, highlighting the importance of targeting this specific cardiometabolic combination in patients with MASLD.

To further confirm the association between hypertension and extrahepatic cancers and to elucidate the role of cardiometabolic factors in the context of liver disease, this study investigated these associations among patients with MASLD stratified by different FIB-4 thresholds. Such stratification

may reveal whether advanced liver fibrosis modifies the hypertension-related risk of extrahepatic cancers.

Our results demonstrated that the association between hypertension and extrahepatic cancers was observed in patients with FIB-4 scores ≥ 1.3 in the 35–64-year age group and ≥2.0 in those aged ≥ 65 years, but not in patients with FIB-4 scores below these respective thresholds. Priority should therefore be given to individuals with FIB-4 scores ≥ 1.3 or ≥2.0. Interventions and screening strategies should not be limited to cardiology departments but should also be integrated into hepatology, endocrinology, and other relevant departments. A recent study reported that FIB-4 ≥ 2.67 conferred a 16% higher risk in adults with MASLD.[25] Our findings further addressed the overlapping effect by demonstrating that the association was primarily observed in patients with higher FIB-4 scores. Other cardiometabolic risk factors warrant additional investigation to determine their independent or combined associations with extrahepatic cancers.

Our results also showed a sharp increase in ORs for extrahepatic cancers with advancing 10-year age strata among individuals over 40 years of age. Compared with a previous study on early-onset cancers in patients with MASLD,[26] our findings suggest that extrahepatic cancer screening should be considered even earlier in individuals with MASLD, particularly those with concomitant hypertension. Additionally, women exhibited a 44% higher cancer risk than men in this study, consistent with previous reports of advanced fibrosis and malignancy risk in female patients with MASLD.[27,28] Although women tend to be more active in cancer screening programs, these findings simultaneously suggest that men with MASLD and hypertension may warrant particular attention for enhanced extrahepatic cancer screening to address potential disparities in detection and outcomes.

Several limitations merit acknowledgment. First, MASLD was identified using ICD-10 codes; although the diagnosis of fatty liver disease was based on imaging, clinical, or pathological records confirmed by physicians, specific diagnostic modalities were unavailable. Second, data on obesity, overweight status, and alcohol consumption were lacking, precluding adjustment for these confounders. Further studies focusing on obesity and alcohol intake are required; notably, MASLD, rather than obesity, has been shown to be independently associated with malignancy.[29] Third, FIB-4 was the only noninvasive liver fibrosis score evaluated. As previous studies have indicated that FIB-4 may underestimate the degree of liver fibrosis in these populations,[13] future studies are needed to validate our findings using additional fibrosis scoring systems. Fourth, socioeconomic and educational data were unavailable due to the inherent limitations of hospital records; prior studies have linked lower socioeconomic and educational status to accelerated fibrosis progression and major liver outcomes, including hepatocellular carcinoma.[30]

The strengths of our study include the demonstration of an association between hypertension and extrahepatic cancers in patients with MASLD using a multicenter, large-scale MASLD cohort. We provide robust evidence that hypertension—alone and in combination with hyperglycemia—is significantly associated with extrahepatic cancers, a finding rarely reported for specific cardiometabolic clusters. Subgroup analyses further highlight the protective potential of metabolism-targeted therapies and the utility of FIB-4 and age stratifications as simple tools for cancer risk stratification in this population.

Conclusions

A total of 6,605 individuals with extrahepatic cancers were identified from a population of 103,652 patients with MASLD. Hypertension and the combination of hypertension and hyperglycemia were significantly associated with extrahepatic cancers. This association was further supported by the finding that metabolism-based treatments might be significantly linked to a protective role in the MASLD population. The association was observed in individuals with FIB-4 scores ≥ 1.3 among those aged 35 to 65 years and ≥2.0 among those aged over 65 years. Individuals with MASLD over 40 years of age may be recommended for extrahepatic cancer screening, especially those with hypertension and FIB-4 scores ≥ 1.3.

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Conflict of interest

LW consults for Hiskynedical, BI, Gilead, Kaiyin, MSD, Novo Nordisk, Pfizer, Roche, and VirsiRNA; is a speaker for GSK, Novo Nordisk, and Sanofi; and receives research grants from Amoytop, AZ, Gilead, GSK, Kaiyin, Pfizer, and Sanofi, but has nothing to declare for this manuscript. PH has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2026. LW and JJ have been Executive Associate Editors of *Journal of Clinical and Translational Hepatology* since 2013. XD has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. HR and FJ have been Editorial Board Members of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (XZ, LW), data acquisition (HD, SW, SG, FX, FJ, JJ, HR, XM, PH, XD, KX), data analysis (HD, SW, XZ), draft of the manuscript (XZ, LW), data interpretation, critical review and revision of manuscript (LW, MY, SG, DL, FJ, JJ, HR, XM, PH, XD, KX), and study supervision (LW). All authors participated in the preparation of the manuscript and have seen and approved the final version.

Ethical statement

This study was reviewed and approved by the Beijing Tsinghua Changgung Hospital Ethics Committee, which waived the need for informed consent since the study only used deidentified databases (ID for ethics approval: 25469-0-01), and was conducted in accordance with the Declaration of Helsinki

(as revised in 2024). We adhered to all recommendations and requirements set forth by the board.

Data sharing statement

The data were used under license for the current study and are therefore not publicly available.

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