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ORIGINAL ARTICLE

The association between metabolic risk factors, nonalcoholic fatty liver disease, and the incidence of liver cancer: a nationwide population-based cohort study

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Abstract

Background and aims Liver cancer is a detrimental complication in patients with chronic viral hepatitis and alcoholic or nonalcoholic fatty liver disease (NAFLD). However, metabolic risk factors underlying NAFLD usually cause substantial differences in their clinical outcomes. Recently, several studies have used a novel definition of metabolic dysfunction-associated fatty liver disease (MAFLD) to reassess patients with NAFLD and pointed out the importance of metabolic risk factors. Since patients with NAFLD, MAFLD, or metabolic syndrome (MetS) have different burden of metabolic risk factors, it is crucial to decipher the risk of developing hepatic complications in these populations.

Methods Through a longitudinal nationwide cohort study, the risk of liver cancer was investigated in patients with MetS alone, NAFLD alone, overlap NAFLD/MAFLD, and coexisting MetS and NAFLD. The general characteristics, comorbidities, and incidence of liver cancer were also compared.

Results Intriguingly, patients diagnosed with MetS alone did not have a significant risk of developing HCC compared to control individuals, while patients with NAFLD alone, NAFLD/MAFLD, and coexisting NAFLD and MetS exhibited 6.08-, 5.81-, and 15.33-fold risks of developing HCC, respectively. Apart from metabolic risk factors, renal function status and liver cirrhosis were the independent risk factors for the development of HCC among these groups.

Conclusion Our data emphasize that metabolic dysfunction has a significant impact on hepatocarcinogenesis in patients with NAFLD. Moreover, coexisting multiple metabolic risk factors would dampen the risk of developing HCC in patients with NAFLD. Closely tracing HCC formation through laboratory examination or imaging is crucial in these patients.

Keywords Metabolic syndrome · Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Hepatocellular carcinoma · Epidemiology · Clinical research · Cirrhosis of liver · National Health Insurance Research Database

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy among all cancer types and causes one-third of cancer-associated deaths worldwide [1, 2]. Geographically, Asian countries such as China, Japan and Taiwan are endemic areas for liver cancers in comparison to Western countries, which could be explained by hepatotropic viruses such as hepatitis B and hepatitis C [3].

Apart from virus-derived HCC, nonalcoholic fatty liver disease (NAFLD) has become an emerging cause of HCC in Western and Asian countries. Based on community studies in Taiwan, the prevalence of NAFLD varied from approximately 11.5% to 57.8% [4, 5]. The current diagnostic criteria for NAFLD are established by excluding all known causes of hepatitis, such as viruses, toxic autoimmune disorders, or excessive alcohol consumption. It is not mandatory for the presence of metabolic risk factors in patients with NAFLD. Accordingly, serum biomarkers, imaging, and histopathological examinations are required to confirm this diagnosis [6]. Many epidemiological studies have demonstrated a steady increase in the incidence and prevalence of HCC in patients with NAFLD globally, and currently, NAFLD-derived HCC has become the third leading cause of HCC in the USA. It is anticipated that it will become the most common cause of HCC after two decades [7]. Another retrospective study in the UK that included 632 HCC cases demonstrated a similar trend: the incidence of NAFLD-derived HCC increased five times more than that of HCC derived from other causes of liver disease between 2000 and 2010 [8]. In Asian countries, lifestyle changes have led to gradually increasing numbers of NAFLD and nonalcoholic steatohepatitis (NASH), the most severe form of NAFLD-derived HCC [9]. A population-based cohort study conducted in Taiwan demonstrated that NAFLD is an important and easily ignored risk factor in Taiwan apart from virus-driven HCC [10].

Since patients with NAFLD have broad-spectrum diseases ranging from NAFLD or simple steatosis to nonalcoholic steatohepatitis, intra/extrahepatic complications and outcomes vary among patients with NAFLD [11]. Recently, metabolic dysfunction-associated liver disease (MAFLD), proposed by the international consensus, highlights the impact of several metabolic risk factors on the intra/extrahepatic complications and outcomes in patients with fatty liver diseases [6, 11–13]. In the current definition, MAFLD is diagnosed on the basis of the following criteria: patients with hepatic steatosis simultaneously presented with one or more following status: (1) overweight/obesity, (2) type 2 diabetes mellitus, or (3) at least two metabolic dysregulations (e.g., hypertension, dyslipidemia, and waist circumference ≥ 90 and 80 cm in men and women, respectively, and so on). According to the statistical results, the prevalence rate of MAFLD varies between 12 and 30% in different Asian countries [12, 14, 15]. Regarding MAFLD-derived complications, a population-based study from the USA showed an increased risk of all-cause mortality, especially in cardiovascular complications, and associated mortality was observed in patients with MAFLD, whereas this notion was not found in patients with NAFLD [16]. Additionally, MAFLD-derived HCC accounts for approximately 2% and 12.2% of all HCC cases in Japan and South Korea, respectively [17, 18].

Metabolic syndrome (MetS), a cluster of multiple metabolic risk factors, has also been considered as a predictor of NAFLD [9, 19] and recognized as a risk factor for the development of colon cancer, breast cancer, etc., despite the fact that the incidence of HCC in patients with MetS is still controversial. Intriguingly, a part of the patients with MAFLD did not meet the criteria for MetS because they only had fewer metabolic risk factors (less burden of metabolic dysfunction) than those with MetS according to the ATPIII MetS diagnostic criteria. It raised an interesting question on whether the severity of metabolic risk factors would affect the risk of developing HCC. Furthermore, it remains unclear whether the risk of HCC increased in the population with coexisting MetS and NAFLD compared to the population with less metabolic risk factors only (MetS alone) or fatty liver disease only (NAFLD alone). This study aimed to determine the risk of HCC among different groups consisting of patients with fatty liver disease or different severities of metabolic risk factors using a large longitudinal database.

Methods

Database description

The National Health Insurance (NHI) Program was established on March 1, 1995, and covers more than 99% of the 23.72 million people in Taiwan. The Longitudinal Health Insurance Database (LHID) of the NHI Research Database in Taiwan includes one million individuals randomly selected from the Registry for Beneficiaries, which contains the complete medical records of each case. Regarding disease coding, the LHID was released by the NHRI, and the institute provides detailed examinations of International Classification of Diseases, Ninth Revision (ICD-9-CM) codes. Additionally, this database has reported that there is no significant difference in age, sex, or health-care costs between the selected cohort in the present study and other cases enrolled in the NHI program.

Sampled participants and study design

Identification of the NAFLD group without metabolic risk factors (NAFLD alone)

The selection criteria of NAFLD group in NHIRD was used according to a previous literature [10]. Generally, we selected patients 18 years of age or older with a first diagnosis of NAFLD by using ICD-9-CM codes 571.40, 573.3, and 571.8 from the LHID. For exclusion criteria, individuals with other causes of hepatitis (ICD codes ICD-9-CM 303.9, 571.0–571.3, V11.3, and V79.1), those with viral hepatitis (070, 573.1, V02.6, and V05.3), those with human immunodeficiency virus infection and infectious hepatitis (042 and 573.2) and other causes such as toxic hepatitis (573.3), primary biliary cirrhosis (571.6) and autoimmune hepatitis (571.42) from these cohorts, or age less than 18 years old before the index dates were excluded. To augment the precision of diagnosis of NAFLD, the diagnostic codes mentioned above for NAFLD were confirmed at least three times during the period of this study. In addition, we excluded cases with missing age or sex information at baseline for meeting the current diagnostic criteria of NAFLD. Otherwise, all cases with any metabolic risk factors including hypertension, type 2 diabetes, obesity, and dyslipidemia were excluded. The index date for each NAFLD case was the date of diagnosis.

Identification of metabolic syndrome in the NHIRD

Metabolic syndrome (MetS) consists of increasing blood pressure/hypertension, dyslipidemia (increased triglycerides and lowered high-density lipoprotein cholesterol), elevated fasting glucose and central obesity. Since there is no ICD-9 CM code for MetS in the NHIRD, the identification of MetS in the NHIRD was used by combining all different disease codes below, which was also implemented by a previous study [20]. These disease codes contain (1) hypertension (ICD-9 codes 401–405), defined as a blood pressure $\geq$ 130/85 mmHg, (2) diabetes mellitus (DM; ICD-9 code 250.x) and insulin resistance (ICD-9 code 277.7), defined as a fasting plasma glucose $\geq$ 110 mg/dL, (3) coronary artery diseases (ICD-9 codes 414.0, 414.0x, 414.2, 414.3, 414.4, 414.8 and 414.9) and (4) hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.4 and 272.9), defined as fasting triglycerides $\geq$ 150 mg/dL. If the cases were coded with some disease codes before the index date, they were excluded from this study. The inclusion criterion of obesity was defined by the ICD9-CM code (278.0) [21]. The patients who received the following surgical approaches such as open gastroplasty (OP44.69), laparoscopic vertical banded gastroplasty (OP44.68), laparoscopic adjustable gastric band (OP44.95), and sleeve gastrectomy (OP43.89) were excluded from this study. Additionally, all disease codes of the cases enrolled in this study were identified at least three times within 1 year, which avoids miscoding.

Identification of the overlap of the NAFLD and MAFLD group

Since there was no direct ICD-9 CM code for the diagnosis of MAFLD in our database, the coexisting NAFLD and MAFLD group in this study was classified on the basis of the consensus guideline: the cases were diagnosed as (1) coexisting NAFLD and hypertension/hyperlipidemia, (2) NAFLD and type 2 diabetes, or (3) NAFLD and obesity. All ICD-9 CM codes were mentioned previously, and these codes were confirmed at least three times during the study period. Moreover, we excluded cases with missing age or sex information at baseline.

Study design, events, and comorbidities assessment

According to the method and ICD code for identification, our study group was defined as the cohort diagnosed with metabolic syndrome (MetS) and NAFLD together. The comparison groups were classified into four different populations: the population with either MetS or NAFLD or overlap NAFLD/MAFLD and the individuals without MetS and NAFLD (control population). The detailed design, inclusion and exclusion criteria and tracking time are described in Fig. 1. Follow-up was calculated in person-years for each patient until any hepatocellular carcinoma was diagnosed (ICD-9-CM codes: 155.0), the patient withdrew from the insurance system, or until the end of 2013. All comorbidities in this study were listed as below: COPD (ICD-9-CM codes 491, 492, 496), heart failure (ICD-9-CM code 428), stroke (ICD-9-CM codes: 430–438), thrombocytopenia (ICD-9-CM codes: 287.5), hyperbilirubinemia (ICD-9-CM codes: 782.4), cirrhosis of liver (ICD-9-CM codes: 571.5) chronic renal failure, (ICD-9-CM codes:585.9), end-stage renal disease/ESRD (ICD-9-CM codes:V45.11 and 585.6). Additionally, the comorbidities were also scored by the Charlson Comorbidity Index removing the parameters of metabolic syndrome (CCI_R).

Statistical analysis

The statistical software is the Statistical Product and Service Solutions 20th edition (Armonk, NY: IBM Corp.). Categorical variables were compared by the Chi-square or

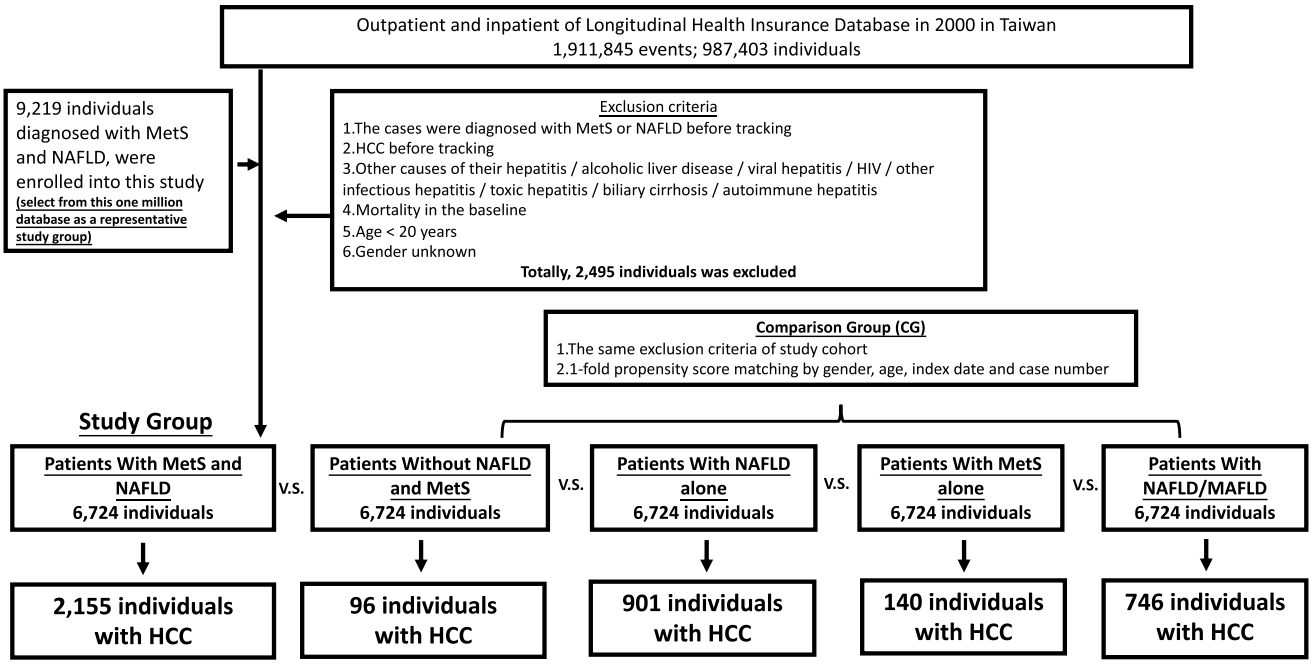

Fig. 1 The flowchart of study design from national health insurance database in Taiwan

Fisher exact test, and continuous variables were compared by one-way ANOVA among these groups. The cumulative risk of hepatocellular carcinoma was demonstrated by Kaplan–Meier curves and verified by the log-rank test. *p* values less than 0.05 were regarded as statistically significant. The adjusted hazard ratios of hepatocellular carcinoma for the parameters were presented by applying the Cox regression hazard model.

Results

Initially, 9219 individuals were enrolled by the inclusion criteria. After excluding subjects based on certain criteria, the study arm in this study included a total of 6724 patients who had NAFLD and MetS. Regarding the demographic characteristics among all groups, there was no significant difference in the age and gender distribution, while in terms of the CCI-R scores, apparently, the study population that had MetS and NAFLD together had higher scores than those in the other populations. Otherwise, the incidence of most comorbidities, including liver cirrhosis, COPD, heart failure, stroke, thrombocytopenia, hyperbilirubinemia, chronic renal failure, and ESRD, was higher in the population with coexisting MetS and NAFLD than in those with MetS alone or control individuals (Table 1).

The mean follow-up was 7.16 years (SD = 8.69), 8.62 years (SD = 9.37), 6.17 years (SD = 4.82) and 8.29 years (SD = 9.48) in the study group (MetS and NAFLD), the patients with NAFLD alone, the patients with MetS alone and control individuals, respectively. Regarding the incidence of HCC, 2155, 901, 746, 140, and 96 cases were diagnosed with HCC in the NAFLD/MetS population, NAFLD alone population, NAFLD/MAFLD population, MetS alone population and control individuals during their tracing period, respectively. Since patients with MetS and NAFLD had the worst outcome than that in other groups, we examined the risk of developing HCC between these two factors–MetS and NAFLD. Table 2 reveals the hazard ratio of developing HCC as analyzed by the joint effect between NAFLD and MetS after adjusting for age, sex, other comorbidities, and CCI_R. Individuals with MetS and NAFLD exhibited a 15.33-fold increased risk (95% CI 12.08–18.24, $p < 0.001$) of developing HCC compared with the individuals without metabolic risk factors and NAFLD. Otherwise, among individuals with NAFLD alone, the aHR for HCC was a 6.08-fold increased risk in comparison with the control individuals (95% CI 4.91–7.62). This result emphasized that coexisting MetS in NAFLD patients dampens the risk of developing HCC. We also examined different components of MetS in the NHIR database to assess the impact of different metabolic risk factors on the incidence of HCC. Clearly, the aHR for HCC had a 3.4-fold, 7.26-fold, 2.64-fold, and 11.82-fold increase among groups with obesity, hypertension, dyslipidemia, and type 2 diabetes, respectively (Supplementary Table 1).

In Fig. 2, apparently, the mean time for developing HCC in individuals with MetS and NAFLD was 0.65 years

Table 1 Baseline characteristics of the study participants

Groups	NAFLD (+) MetS (+)		NAFLD (−) MetS (−)			NAFLD (+) MetS (−)			NAFLD (−) MetS (+)			NAFLD (+) MAFLD (+)		
Variables	*n*	%	*n*	%	*p* value	*n*	%	*p* value	*n*	%	*p* value	*n*	%	*p* value
Overall	6,724		6,724			6,724			6,724			6,724		
Sex					0.999			0.999			0.999			0.999
Male	4,140	61.57	4,140	61.57		4,140	61.57		4,140	61.57		4,140	61.57	
Female	2,584	38.43	2,584	38.43		2,584	38.43		2,584	38.43		2,584	38.43	
Age (years)	58.44 ± 14.01		58.30 ± 14.30		0.567	58.71 ± 13.89		0.245	58.74 ± 13.95		0.134	58.35 ± 14.20		0.711
Comorbidities														
Cirrhosis of liver	1,906	28.35	128	1.90	< 0.001	680	10.11	< 0.001	125	1.86	< 0.001	723	10.75	< 0.001
COPD	686	10.20	134	1.99	< 0.001	620	9.22	0.055	572	8.51	0.001	155	2.31	< 0.001
Heart failure	452	6.72	88	1.31	< 0.001	411	6.11	0.149	400	5.95	0.066	84	1.25	< 0.001
Stroke	1,786	26.56	397	5.90	< 0.001	1,456	21.65	< 0.001	1,389	20.66	< 0.001	296	4.40	< 0.001
Thrombocytopenia	76	1.13	13	0.19	< 0.001	72	1.07	0.741	66	0.98	0.399	24	0.36	0.704
Hyperbilirubinemia	35	0.52	10	0.15	< 0.001	33	0.49	0.808	29	0.43	0.452	25	0.37	0.913
Chronic renal failure	1,265	18.81	275	4.09	< 0.001	1,012	15.05	< 0.001	996	14.81	< 0.001	311	4.63	< 0.001
ESRD	989	14.71	206	3.06	< 0.001	913	13.58	0.060	883	13.13	0.008	692	10.29	0.102
CCI_R	1.03 ± 1.41		0.25 ± 0.70		< 0.001	0.84 ± 0.98		< 0.001	0.62 ± 0.95		< 0.001	0.45 ± 0.81		< 0.001
Level of care														
Hospital center	2,347	34.90	2,523	37.52		1,459	21.70		2,494	37.09		2,507	37.28	
Regional hospital	2,566	38.16	2,303	34.25		2,702	40.18		2,261	33.63		2,339	34.79	
Local hospital	1,811	26.93	1,898	28.23		2,563	38.12		1,969	29.28		1,878	27.93	

CCI_R Charlson Comorbidity Index score, revised, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease

Reference category is the group diagnosed with MetS and NAFLD

Table 2 Joint effect between MetS and NAFLD in association with HCC

Variables		N	Events	Events %	Adjusted HR (95% CI)[a]	*p* value
MetS	NAFLD					
Without	Without	6,724	96	1.43	1 (Reference)	
With	Without	6,724	140	2.08	1.04 (0.63–1.11)	0.554
Without	With	6,724	901	13.40	6.08 (4.73–7.48)	< 0.001
With	With	6,724	2,155	32.05	15.33 (12.08–18.24)	< 0.001

HR hazard ratio, *CI* confidence interval

[a]Model was adjusted for age and sex and other comorbidities

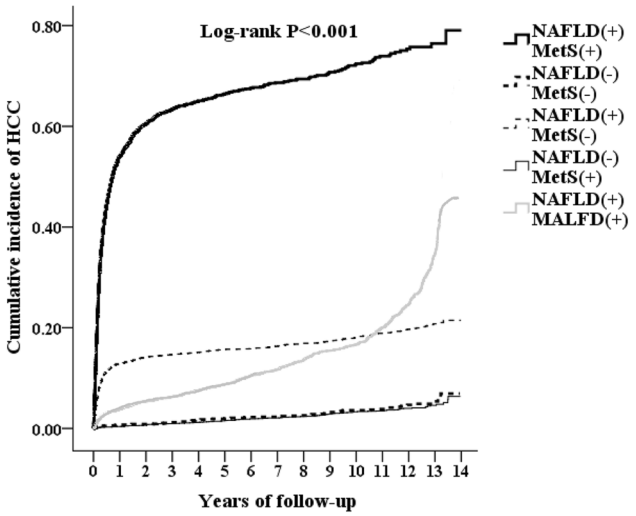

Fig. 2 Kaplan–Meier analysis of the cumulative risk of HCC among patients aged 20 and over stratified by different study groups with the log-rank test. Study cohort: with MetS, with NAFLD. Comparison cohort 1: Patients with NAFLD alone. Comparison cohort 2: Patients with MetS alone. Comparison cohort 3: Cases without NAFLD/MetS. Comparison cohort 4: Cases without NAFLD/MAFLD. Log-rank test: study cohort (patients with NAFLD and MetS) vs. Comparison Group 3 (patients without NAFLD/MetS): $P < 0.001$; Comparison Group 1 (Patients with NAFLD alone) vs. Comparison Group 3 (patients without NAFLD/MetS): $P < 0.001$; Comparison Group 2 (patients with MetS alone) vs. Comparison Group 3 (Patients without NAFLD/MetS): $P = 0.894$

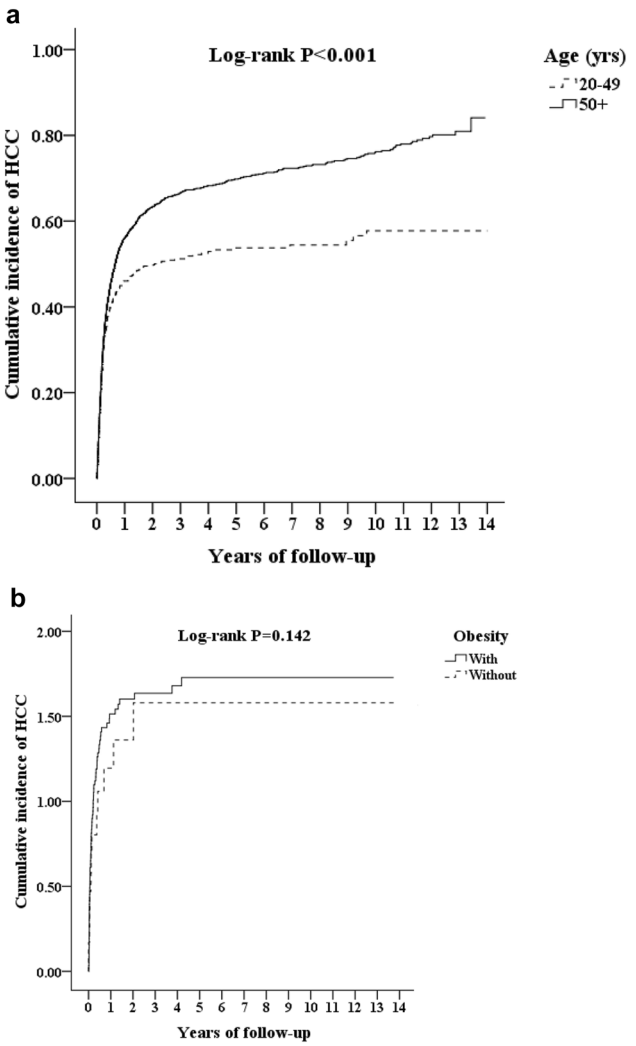

Fig. 3 Kaplan–Meier analysis of the cumulative risk of HCC among patients with NAFLD and MetS stratified by age (**a**) or obesity (**b**)

(SD = 1.55), while this time in the groups with NAFLD alone, MetS alone and the reference group was 1.49 years (SD = 2.92), 5.38 years (SD = 3.94) and 4.35 years (SD = 3.94), respectively. According to the results of a previous epidemiological study, age was an important predisposing factor in the development of HCC in patients with NAFLD. Supplementary Table 2 demonstrates the distribution of HCC cases stratified by different age groups. In the groups whose ages were approximately 50–59, 60–69, and 70–79 years, the incidence rates of HCC were 35.09%, 41.25% and 31.98%, respectively. Approximately, 80% of HCC cases were observed in NAFLD and MetS individuals aged more than 50 years. Figure 3a shows that the incidence rate of developing HCC is significantly higher in patients with MetS and NAFLD aged more than 50 years than in the younger population (age less than 50 years).

Table 3 reveals the HR of developing HCC among different populations after adjusting gender, age CCI_R and multiple comorbidities. Patients with coexisting MetS NAFLD had a 15.01-fold increased risk of HCC compared

Table 3 Multivariable analysis of demographic factors and comorbidities associated with the risk of developing HCC among different study groups

Predictors	With NAFLD vs. Without NAFLD in MetS population		With MetS vs. Without MetS in NAFLD population		With MetS and NAFLD vs. Without MetS and NAFLD	
	Multivariable analysis		Multivariable analysis		Multivariable analysis	
	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Overall	9.97 (6.33–13.99)	< 0.001	2.40 (2.11–2.65)	< 0.001	15.01 (12.14–19.67)	< 0.001
Male gender[a]	1.42 (1.28–1.53)	< 0.001	1.41 (1.30–1.59)	< 0.001	1.38 (1.25–1.56)	< 0.001
Age (years)	0.98 (0.95–1.03)	0.351	0.97 (0.94–1.02)	0.284	0.99 (0.94–1.03)	0.092
CCI_R (per score)	1.12 (1.09–1.17)	< 0.001	1.17 (1.14–1.20)	< 0.001	1.24 (1.12–1.37)	< 0.001
Cirrhosis of liver[b]	5.82 (3.31–8.74)	< 0.001	5.83 (3.37–8.79)	< 0.001	5.84 (3.10–8.82)	< 0.001
COPD[b]	1.14 (0.86–1.55)	0.286	1.26 (0.84–1.59)	0.297	1.21 (0.85–1.67)	0.276
Heart failure[b]	0.98 (0.75–1.24)	0.332	0.88 (0.52–1.17)	0.492	0.92 (0.66–1.18)	0.385
Stroke[b]	1.25 (0.72–1.69)	0.341	1.36 (0.79–1.84)	0.301	1.29 (0.77–1.72)	0.341
Thrombocytopenia[b]	1.12 (0.45–1.97)	0.587	1.18 (0.52–1.99)	0.483	1.15 (0.51–1.84)	0.496
Hyperbilirubinemia[b]	1.06 (0.52–1.84)	0.425	1.11 (0.29–3.37)	0.786	1.35 (0.22–3.16)	0.772
Chronic renal failure[b]	1.79 (1.31–2.25)	< 0.001	1.73 (1.38–2.11)	< 0.001	1.94 (1.42–2.48)	< 0.001
ESRD[b]	2.01 (1.88–2.97)	< 0.001	1.96 (1.52–2.39)	< 0.001	2.50 (1.97–3.07)	< 0.001

CCI_R Charlson Comorbidity Index score, revised, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease

[a]Reference category is female patients

[b] Reference category is the group without this variable

to the group without NAFLD and MetS, while the aHR only achieved a 2.40-fold increased risk of HCC in the patients with NAFLD and MetS compared to the patients with NAFLD only. Additionally, the presence of NAFLD had a 9.97-fold increased risk of developing HCC in the patients diagnosed of MetS compared to that in the group with MetS alone. In multivariable analysis, male gender, high CCI_R score, status of cirrhosis, renal function impairment had a significant impact on the incidence rate of HCC among these three comparisons. Since obesity is also a crucial factor in MetS, to investigate the effect of obesity on developing HCC in the population with MetS and NAFLD, different ICD9-CM codes and operative codes were utilized for subgroup analysis. In Fig. 3b, there was no significant difference in the incidence of HCC between the obese and nonobese groups of patients with NAFLD and MetS.

MAFLD has been proposed as an appropriate classification of fatty liver diseases [13]. In line with this, we examined the risk of developing HCC among the overlap NAFLD/MAFLD cases compared to NAFLD alone and control populations. As shown in Table 4, there was a 6.08-fold and 5.81-fold increased risk of developing HCC among patients diagnosed with NAFLD alone and NAFLD/MAFLD, respectively. Regarding the risk of liver cirrhosis, NAFLD alone and NAFLD/MAFLD cases had a 4.58-fold and 3.57-fold increased risk, respectively. Given that renal function has been shown to be an independent risk factor for developing HCC among our study populations, we stratified the overlap NAFLD/MAFLD populations by their renal function. As shown in Supplementary Table 3, patients with renal function impairment (mild to moderate) and end-stage renal disease presented with a higher risk of developing HCC or liver cirrhosis. Since

Table 4 Multivariable analysis of demographic factors and comorbidities associated with the risk of hepatic complications among the control, NAFLD alone and overlapping NAFLD/MAFLD population

Group	Events	HCC				Cirrhosis of liver			
	Population	*N*	%	Adjusted HR (95% CI)[a]	*p* value	*N*	%	Adjusted HR (95% CI)[a]	*p* value
Control	6724	96	1.43	1 (Reference)		125	1.86	1 (Reference)	
NAFLD alone	6724	901	13.40	6.08 (4.73–7.48)	< 0.001	999	14.86	4.58 (3.55–5.65)	< 0.001
NAFLD/MAFLD	6724	746	11.09	5.81 (4.60–7.36)	< 0.001	723	10.75	3.57 (2.72–4.37)	< 0.001

HR hazard ratio, *CI* confidence interval, control means the population without NAFLD and metabolic risk factors

[a] Model was adjusted for age and sex and other comorbidities

there was a correlation between renal function and FIB-4 fibrotic score in the NAFLD population [22, 23], we also examined the association between renal function status and the risk of HCC and liver cirrhosis in patients with NAFLD/MAFLD. As shown in Supplementary Table 4, there was also a positive correlation between impairment of renal function and risk of developing these detrimental complications in patients with NAFLD/MAFLD.

Discussion

The current study utilized a large sample size and sufficient tracking time to elucidate the incidence of hepatic complications among populations with different severities of metabolic risk factors. We demonstrated that there was no statistical significance in the risk of developing HCC in patients with MetS alone compared to the control individuals, whereas the risks of developing HCC in patients with NAFLD alone and patients with coexisting NAFLD and MetS was higher than that in the control individuals, with aHR values of 6.08 and 15.33, respectively. Furthermore, the risk of developing cirrhosis of the liver or HCC among patients diagnosed with NAFLD alone and NAFLD/MAFLD was similar. Collectively, our data emphasize that metabolic risk factors are an important predisposing factor in patients with NAFLD for the development of HCC. Coexisting NAFLD in patients with multiple metabolic risk factors (Metabolic syndrome status) would dampen the risk of HCC compared to that in the MetS alone population.

MetS containing multiple metabolic risk factors, has been recognized as a common predisposing factor for ischemic heart disease, cerebrovascular diseases, and several malignancies [24, 25]. The systemic effect of MetS was proposed to occur through hyperinsulinemia, insulin resistance, chronic inflammatory cytokine production or apoptotic suppression. Insulin resistance causes metabolic stress and several systemic consequences in different tissues and organs, such as subcutaneous/visceral adipose tissues, liver, muscle, and pancreas [26, 27]. Accordingly, overnutrition causes lipid accumulation in muscle, liver, and adipose tissue, which drives lipotoxicity and insulin resistance. Subsequently, the chronic inflammatory response derived from inflammatory cytokines and innate and adaptive immune cells aggravates these consequences and forms a vicious cycle.

The risk of developing all kinds of cancer in MetS population has been considered and investigated. A meta-analysis of 38,940 patients with cancer demonstrated that MetS exhibited a 1.43-, 1.25- and 1.10-fold increased risk of developing liver cancer, colorectal cancer and bladder cancer, respectively [28]. Another meta-analysis that analyzed 18 cohorts and 1 case–control study also revealed that the relative risk of developing HCC in patients with MetS was 1.76 from 11 studies [29]. Although these data provided evidence regarding the positive association between MetS and the incidence of HCC, there are still several large sample size studies demonstrating no significant association between MetS and HCC [30–32]. The possible explanation for this difference could be considered that some previous studies did not entirely exclude NAFLD/NASH or hepatitis in their MetS cohorts, which might interfere with their results. Intriguingly, our results also indicated that patients diagnosed with MetS alone did not have a significantly greater risk of developing HCC compared to the control individuals, whereas the risk of developing HCC significantly increased in patients with NAFLD alone, NAFLD/MAFLD, and coexisting MetS/NAFLD. These data suggest that NAFLD could be a possible prerequisite in the MetS group during the development of HCC. Accordingly, it also points out that NAFLD-derived chronic hepatic inflammation would be a necessary step for hepatocarcinogenesis, while metabolic risk factors serve as aggravated factors for dampening this process.

Our study also demonstrated that patients with coexisting NAFLD/MAFLD or NAFLD alone had a similar trend in the risk for developing HCC or liver cirrhosis, whereas the risk for developing HCC in our NAFLD population with coexisting MetS was higher than that in patients with NAFLD/MAFLD or NAFLD alone. A possible explanation would be that more comorbidities were defined in our MetS population than in the MAFLD population. This also reflects that the different metabolic stresses aggravate the risk of developing HCC in the NAFLD population. Furthermore, several studies demonstrated patients with NAFLD alone did not have an increased risk for developing hepatic complications such as cirrhosis of liver [33, 34], which is different from the result in our study. The possible reason for this result could be considered that most NAFLD only cases in this study would be steatohepatitis patients or cases already had hepatic features such as elevated liver enzymes due to the method we used for defining NAFLD, which also means most of asymptomatic NAFLD cases (steatosis only) might be missed in this study.

During mean follow-up of 7.16–8.62 years, the mean time for HCC development in patients with NAFLD alone and coexisting NAFLD and MetS were 1.65 years and 0.65 year, respectively.(Fig. 2) This data demonstrated that most HCCs were found during the first 2 years in both cohorts. It was also anticipated that this time was shortened by approximately 0.65 years in patients with coexisting MetS and NAFLD, which could be explained by our MetS population had many predisposing factors for developing HCC such as hypertension, diabetes, and hyperlipidemia etc. Additionally, our NAFLD alone, MetS

alone or coexisting NAFLD/MetS populations could visit hospital frequently due to hepatic manifestations or multiple comorbidities, which indirectly increase the chance for HCC identification. Collectively, even though there were still some bias in study population selection, these data supported the evidence that hepatic manifestation-metabolic risk factor could be an important predisposing factor for HCC formation either in the normal population or in the NAFLD population.

Obesity is an important metabolic risk factor and serves as a component of MAFLD or MetS. A meta-analysis reviewed 11 different cohort studies in Europe, the United States and Asia and revealed that overweight and obese status were significant risk factors for developing HCC [35]. Despite this evidence between obesity and HCC, some patients with NAFLD who had severe abnormalities in their metabolic profiles, such as lipids or glucose, did not present any overweight or obesity (lean NAFLD) [36–38]. In line with this, it is worth understanding the impact of obesity on the risk of HCC between normal weight group and obese populations among the patients with coexisting NAFLD/MetS. Our data indicated that this risk is similar between the two subgroups, which means that regardless of obese status, early recognition of HCC by imaging and tumor marker examination is required in NAFLD patients with metabolic risk factors. Furthermore, as shown in Supplementary Table 3, the subgroup analysis demonstrated that the aHR increased among the patients with overlap NAFLD/MAFLD with renal function impairment and ESRD. Accordingly, patients with worse renal function have a higher risk of developing HCC. Previously, few studies have demonstrated a positive correlation between renal function and FIB-4 fibrosis score. It is worth establishing a scoring system for these metabolic risk factors to predict the risk of hepatocarcinogenesis or liver cirrhosis.

There are several limitations and missing information in this study. First, the NHIR database does not contain detailed information for patients with MetS or NAFLD regarding smoking habits, body mass index, physical inactivity (sedentary lifestyle), waist circumference, central obesity and cytogenetic or molecular testing results for prognosis markers, which means some MetS cases with less severity could be missed. Alternatively, we used the obesity ICD9-CM code and relative surgical procedure codes, such as gastric bypass surgery, which was only performed in obese patients based on the criteria of the national health system in Taiwan. Second, our study lacked a detailed laboratory assessment for MetS and for NAFLD, including blood glucose, lipid data (triglyceride, cholesterol, HDL/LDL), biochemistry data, white blood cell counts, hemoglobin levels, and platelet values. Third, there were no imaging data, pathological severity scores, fibrosis status, or therapeutic strategies for the NAFLD population in this study, which means that few patients with early-stage NASH were still in our NAFLD population. However, due to the large sample sizes in this study, the results in this study still provide evidence of confidence in establishing the association between MetS, NAFLD, MAFLD, and HCC. Finally, this retrospective cohort study has relatively lower statistical quality and evidence than detailed registry studies, despite the strict ICD-9-CM coding.

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Author contributions All authors made substantive intellectual contributions to this study to qualify as authors. CWY and YGC designed the study. CWC and CHC performed statistical analysis. An initial draft of the manuscript was written by YGC. WLC, CLH, CHC, and CWC redrafted parts of the manuscript and provided helpful advice on the final revision. All authors were involved in writing the manuscript. All authors have read and approved the final manuscript.

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Declarations

Conflict of interest Yu-Guang Chen, Chih-Wei Yang, Chi-Hsiang Chung, Ching-Liang Ho, Wei-Liang Chen and Wu-Chien Chien declare no competing financial interests.

Ethical approval The study design, case enrollment and data analysis were approved by the Institutional Review Board (IRB) of Tri-Service General Hospital, Taiwan, Republic of China. The registration number is TSGH-IRB No. B-109–26.

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