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ORIGINAL RESEARCH

Statin Monotherapy Not Inferior to Aspirin or Combined Aspirin and Statins Reducing the Incidences of Cirrhosis, HCC, and Mortality in MAFLD/MASH Patients: A Population Cohort Study

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Purpose: Metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatohepatitis (MASH) pose significant risks for liver cirrhosis and hepatocellular carcinoma (HCC). Daily aspirin and statins could reduce HCC in patients with MAFLD/MASH. We aimed to clarify whether combined aspirin and statins exert a synergistic effect on prevention of cirrhosis and HCC in patients with MAFLD/MASH.

Patients and Methods: Patients and their clinical data were collected from the National Health Insurance Research Database (NHIRD), encompassing about 20 million population. A total of 735,574 MAFLD/MASH patients between January 1, 2009, and December 31, 2020 were identified. After applying exclusion criteria, 662,004 cases were enrolled, with a follow-up period of 3 years. Propensity score matching was employed for comparative analysis.

Results: Our findings indicate that combined statin and aspirin use significantly reduced the incidence of liver cirrhosis ($p < 0.001$) compared to statin or aspirin alone, or non-use of both drugs. However, the combined therapy did not confer additional benefits in reducing mortality rates and HCC. Furthermore, statin monotherapy exhibited a more pronounced effect in reducing mortality and HCC compared to aspirin alone or combined therapy.

Conclusion: Our study underscores that statin monotherapy was not inferior to aspirin or aspirin-statin combined therapies in terms of chemoprevention of cirrhosis, HCC, and overall mortality in MAFLD/MASH patients.

Keywords: MAFLD, MASH, statin, aspirin, cirrhosis, hepatocellular carcinoma

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is characterized by the accumulation of >5% fat in liver tissue without other chronic liver diseases, leading to liver inflammation and potentially progressing to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, or hepatocellular cancer (HCC).[1,2] Worldwide prevalence estimates for MAFLD range from 6.3% to 33%, with a median of 20% and MASH ranges from 3% to 5% in the general population.[3] MAFLD is included of non-alcoholic fatty liver (NAFL) and MASH.[4] Concomitant diseases associated with MAFLD/MASH include obesity (51%), type 2 diabetes (41%), hyperlipidemia (69%), hypertension (39%), and metabolic syndrome in 42% of cases.[5,6]

Meta-analyses indicate that statins and aspirin use is associated with a significant reduction in HCC risk.[7] Aspirin exhibits anti-platelet and anti-inflammatory effects, leading to lower indices of liver fibrosis[8]. Aspirin also demonstrates a

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chemopreventive effect on chronic hepatitis B and hepatitis C, as well as the progression of MAFLD/MASH to HCC.[9,10] Similarly, statins reported to have a chemopreventive effect on chronic hepatitis B and C, as well as cirrhosis before.[11,12] Statin initiators have a 53% lower risk of developing HCC compared to non-users among patients with MAFLD.[13] Additionally, a study by Fatima et al suggests that statins may significantly reduce the risk of developing MAFLD by 31% and improve liver histology in patients with MAFLD.[14] Statin use might be associated with reducing hepatic decompensation, mortality, and portal hypertension in patients with chronic liver diseases.[15]

Sarcopenia is closely linked to MAFLD, liver cirrhosis, and HCC. Patients using statins were observed to have a lower likelihood of sarcopenia. Valdivieso et al hypothesized that this association could be attributed to the pleiotropic effects of statins, which enhance endothelial function and subsequently improve muscle perfusion, thereby supporting better neuromuscular fitness. This mechanism may contribute to the prevention of sarcopenia and the progression of MAFLD.[16]

Newly discovered substances start being considered. These specific stem cells are essential for skeletal muscle regeneration, and a reduction or dysregulation in the mSC pool may accelerate the loss of muscle mass commonly observed in the elderly. Tarantino et al proposed that muscle satellite cells (mSCs) play a crucial role in maintaining muscle health into old age.[17]

In the metabolic or cardiovascular domain, aspirin use is associated with reducing 20% cancer incidence.[18] Historical cohort studies show that statin and aspirin users had significantly lower HCC risk, with reductions of 33% and 19%, respectively, in a nested case-control study.[19] Both aspirin and statins have been proposed as anticancer agents due to their anti-inflammatory, anti-proliferative, and pro-apoptotic effects, despite variations in their biological mechanisms of action.[20] Early chemoprevention of HCC occurrence or recurrence is crucial.[21] Therefore, this study investigates whether daily combined statin and aspirin use is more effective than daily single-drug use (statin or aspirin) in reducing cirrhosis, HCC incidence, and outcomes in MAFLD/MASH patients within a nationwide cohort. This comprehensive discussion highlights the nuanced relationship between MAFLD, cirrhosis, and HCC, as well as the potential benefits of aspirin and statin therapy in mitigating liver disease progression.

Materials and Methods

Ethics

Our study was conducted following the protocol approved by the Chang Gung Medical Foundation's Institutional Review Board (IRB), with approval number: 202100464B0.

Data Sources

All data were collected retrospectively from the National Health Insurance Research Database (NHIRD), covering nearly 99% of the general population in Taiwan. MAFLD/MASH patients (n = 735,574) were identified from the NHIRD between January 1, 2009, and December 31, 2020.

Patients

A cohort of 662,004 cases using aspirin and statins was enrolled, with a follow-up period of 3 years. Exclusion criteria included a diagnosis of cancer, including GI tract cancer, before the index date (n = 408,526), age <18 years old (n = 5191), missing data on sex (n = 3558), diagnosis of outcome before index (n = 6602), follow-up <90 days (n = 9128), duration of statin or aspirin use <90 days after MAFLD/MASH diagnosis (n = 51,948), and index year before 2009 or after 2019 (n = 156,905). After 1:1 propensity score matching by sex, 5-year age group, index year, and each comorbidity, the following groups were analyzed: combined statin with aspirin use (n = 1995), statin alone (n = 1508), aspirin alone (n = 1116), and non-aspirin and non-statin (n = 4619) (Figure 1 and Table 1). The definition of disease and comorbidity followed the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for the period 1997–2015 and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for the period after 2016 (Table S1). Drug codes were selected according to ATC (Table S2). Comorbidities were defined as patients having been admitted or visited the outpatient department at least 5

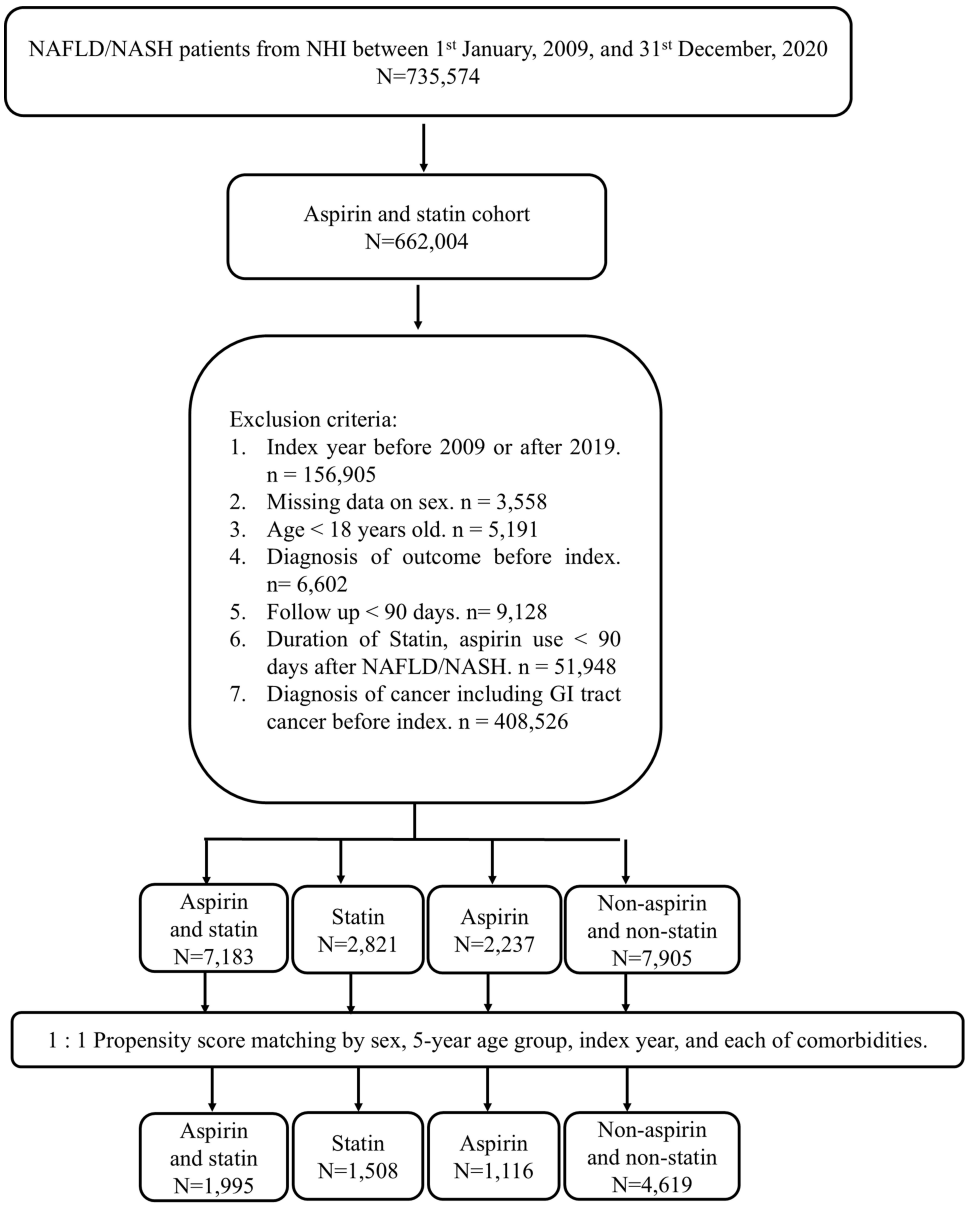

Figure 1 Flow chart.

times. The index date was defined as the initial date of diagnosed MAFLD/MASH. Patients were follow-up over 3 years. Charlson comorbidity index was defined concurrent condition such as co-morbidities bases on the ICD-9 and ICD-10.

Main Outcomes

The main outcomes included cirrhosis, HCC, and death. A disease was considered a baseline comorbidity if a patient's medical records contained the relevant ICD-9-CM or ICD-10-CM code around the index date (Table S1).

Statistical Analysis

A chi-square test was used to assess the difference of the categorical variables such as sex, stratified age, comorbidities and medications between four cohorts. The difference of mean ages between the four cohorts were tested by the student's *t* test. Univariate and multivariate Cox regression hazard model analyses were conducted to assess confounding risk factors between patients with MAFLD or MASH who were taking daily statins and/or aspirin versus those who were not.

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Table 1 Baseline Characteristics of Patients with MAFLD/MASH Across Cohorts of Non-Statin & Aspirin Use, Statin Use, Aspirin Use, and Statin & Aspirin Use

Variables	Non- Statin & Aspirin		Statins		Aspirin		Statins & Aspirin		*p*-value	SMD
	(n=4619)		(n=1508)		(n=1116)		(n=1995)			
	n	%	n	%	n	%	n	%		
Gender										
Female	1851	40.07	692	45.89	411	36.83	759	38.05	<0.0001	0.005
Male	2768	59.93	816	54.11	705	63.17	1236	61.95		
Age, years										
18–50	784	16.97	422	27.98	106	9.50	253	12.68	<0.0001	0.002
51–60	1380	29.88	572	37.93	238	21.33	579	29.02		0.004
>60	2455	53.15	514	34.08	772	69.18	1163	58.30		0.003
Comorbidities										
Cardiovascular disease	2928	63.39	566	37.53	924	82.80	1443	72.33	<0.0001	0.002
Stroke	362	7.84	31	2.06	135	12.10	188	9.42	<0.0001	0.006
Diabetes mellitus	1502	32.52	506	33.55	263	23.57	796	39.90	<0.0001	0.029
Hyperlipidemia	2030	43.95	709	47.02	152	13.62	1101	55.19	0.3183	0.03
Obesity	116	2.51	30	1.99	19	1.70	49	2.46	<0.0001	0.026
Chronic kidney disease	222	4.81	32	2.12	45	4.03	118	5.91	<0.0001	0.028
Viral hepatitis	1253	27.13	332	22.02	379	33.96	521	26.12	<0.0001	0.01
Metabolic syndrome	707	15.31	97	6.43	99	8.87	485	24.31	<0.0001	0.016
Medication										
H2 receptor antagonists	2155	46.66	538	35.68	617	55.29	1087	54.49	<0.0001	0.038
Proton pump inhibitors	1284	27.80	311	20.62	346	31.00	625	31.33	<0.0001	0.001
Age, years	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	p-value	SMD
	61.90	11.98	56.55	10.79	66.97	12.26	62.99	11.28	<0.0001	0.004
Follow-up time (years)	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	**mean ±**	**SD[a]**	p-value	SMD
Hepatocellular carcinoma	4.26	2.81	6.35	3.31	4.31	2.81	5.10	2.90	<0.0001	0.357
Cirrhosis	4.48	2.81	6.56	3.26	4.65	2.83	5.33	2.91	<0.0001	0.366
All-cause mortality	4.50	2.82	6.56	3.26	4.65	2.82	5.34	2.91	<0.0001	0.36

Notes: [a]t-test; Chi-square test.

Abbreviations: MAFLD, Metabolic dysfunction-associated fatty liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; SD, standard deviation; SMD, standardized mean difference.

Estimates for crude hazard ratios (cHRs) and adjusted HRs (aHRs), along with their relevant 95% confidence intervals (95% CIs), were derived using Cox proportional hazards regression models, with or without adjusting for age, sex, or confounding factors. Risk factors were analyzed for liver cirrhosis, HCC, and all cause of mortality using forest plots stratification. Three main outcomes were evaluated using a propensity score to determine the correlation between daily statin and/or aspirin use and liver cirrhosis, HCC, and mortality risks. The Kaplan–Meier method investigated the

cumulative incidence of liver cirrhosis or HCC and survival rate during follow-up between MAFLD or MASH patients with daily statin and/or aspirin use or not, and the Log rank test examined the differences. Statistical analysis was performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA), with a two-tailed p-value < 0.05 considered statistically significant. Additionally, differences in all variables among the four groups of patients were also compared by the standardized mean difference (SMD), if the SMD value was less than 0.1, the differences among the four groups are considered negligible.

To ensure the robustness of our results, we conducted a proportional hazards assumption test to verify the validity of the Cox regression model. Cox-Snell residuals were utilized, with cumulative hazard function plots against these residuals examined. A close alignment with a 45-degree line indicated that the Cox model met the proportional hazards assumption (Figures S1–S3).

Results

Liver Cirrhosis

Compared to non-statin and non-aspirin groups, statins (p = 0.0033, aHR: 0.23, 95% CI: 0.09–0.62), aspirin (p = 0.0147, aHR: 0.23, 95% CI: 0.07–0.75), and combined statin with aspirin use (p < 0.001, aHR: 0.17, 95% CI: 0.06–0.46) all demonstrated the ability to reduce cirrhosis incidence in MAFLD/MASH patients. Conversely, certain comorbidities increased the incidence of liver cirrhosis, such as diabetes mellitus (DM) (p = 0.0218, aHR: 2.01), alcoholism (p < 0.001, aHR: 7.14), and metabolic syndrome (p = 0.0427, aHR: 2.89) (Table 2). According to the Log rank test, the cumulative incidence of liver cirrhosis was significantly lower in the combination of statin and aspirin use cohort than in statin, aspirin, or non-statin and non-aspirin cohort (P < 0.001, Figure 2). Accordingly, combined statin with aspirin use might

Table 2 Incidences and Hazard Ratios of Cirrhosis in Patients with MAFLD/MASH Across Cohorts

Variables	Cirrhotic			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Exposure									
Non-Statin&Aspirin	46	20708	2.22	1.00	(reference)	–	1.00	(reference)	–
Statin	5	9888	0.51	0.22	(0.08, 0.58)	0.0021	0.23	(0.09, 0.62)	0.0033
Aspirin	3	5186	0.58	0.26	(0.08, 0.84)	0.0239	0.23	(0.07, 0.75)	0.0147
Statin&Aspirin	4	10630	0.38	0.17	(0.06, 0.48)	<0.001	0.17	(0.06, 0.46)	<0.001
Gender									
Female	19	19435	0.98	1.00	(reference)	–	1.00	(reference)	–
Male	39	26977	1.45	1.45	(0.84, 2.52)	0.1816	0.90	(0.50, 1.63)	0.7255
Age, years									
18–50	15	9101	1.65	1.00	(reference)	–	1.00	(reference)	–
51–60	14	15333	0.91	0.54	(0.26, 1.13)	0.1022	0.57	(0.27, 1.19)	0.1328
>60	29	21978	1.32	0.75	(0.40, 1.40)	0.3690	0.92	(0.47, 1.80)	0.8012
Comorbidities									
Cardiovascular disease									
No	22	19679	1.12	1.00	(reference)	–	1.00	(reference)	–
Yes	36	26733	1.35	1.14	(0.67, 1.95)	0.6335	0.73	(0.39, 1.37)	0.3279

(*Continued*)

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Table 2 (Continued).

Variables	Cirrhotic			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Stroke									
No	54	43645	1.24	1.00	(reference)	–	1.00	(reference)	–
Yes	4	2767	1.45	1.10	(0.40, 3.04)	0.8571	0.53	(0.17, 1.63)	0.2702
Diabetes mellitus									
No	26	32290	0.81	1.00	(reference)	–	1.00	(reference)	–
Yes	32	14122	2.27	2.76	(1.64, 4.63)	<0.001	2.01	(1.11, 3.66)	0.0218
Hyperlipidemia									
No	39	27091	1.44	1.00	(reference)	–	1.00	(reference)	–
Yes	19	19322	0.98	0.67	(0.38, 1.16)	0.1485	0.39	(0.19, 0.80)	0.0099
Obesity									
No			1.23	1.00	(reference)	–	1.00	(reference)	–
Yes			2.05	1.61	(0.39, 6.61)	0.5073	1.10	(0.24, 4.94)	0.9051
Chronic kidney disease									
No			1.25	1.00	(reference)	–	1.00	(reference)	–
Yes			1.23	0.91	(0.22, 3.75)	0.8998	0.50	(0.11, 2.26)	0.3675
Viral hepatitis									
No	43	34441	1.25	1.00	(reference)	–	1.00	(reference)	–
Yes	15	11971	1.25	0.99	(0.55, 1.78)	0.9746	0.90	(0.49, 1.62)	0.7154
Metabolic syndrome									
No	44	40949	1.07	1.00	(reference)	–	1.00	(reference)	–
Yes	14	5464	2.56	2.22	(1.21, 4.06)	0.0101	2.89	(1.04, 8.07)	0.0427
Medication									
H2 receptor antagonists									
No	28	26545	1.05	1.00	(reference)	–	1.00	(reference)	–
Yes	30	19868	1.51	1.37	(0.81, 2.30)	0.2418	0.99	(0.56, 1.74)	0.9653
Proton pump inhibitors									
No	35	35086	1.00	1.00	(reference)	–	1.00	(reference)	–
Yes	23	11326	2.03	1.96	(1.15, 3.33)	0.0129	1.58	(0.89, 2.80)	0.1193

Notes: Adjusted HR: Adjusted for sex, age, comorbidities, and medications in the Cox proportional hazards model.
Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1000 person-years; MAFLD, Metabolic dysfunction-associated fatty liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; PY, person-years.

potentially further reduce cirrhosis development. Comparison between statin alone versus combined statin and aspirin yielded a p-value of 0.65, with an adjusted hazard ratio (aHR) of 1.37 (95% CI: 0.35–5.30). Similarly, the comparison between aspirin alone versus combined statin and aspirin resulted in a p-value of 0.59, with an aHR of 1.52 (95% CI: 0.34–6.90). For further details, refer to Tables 2 and S3.

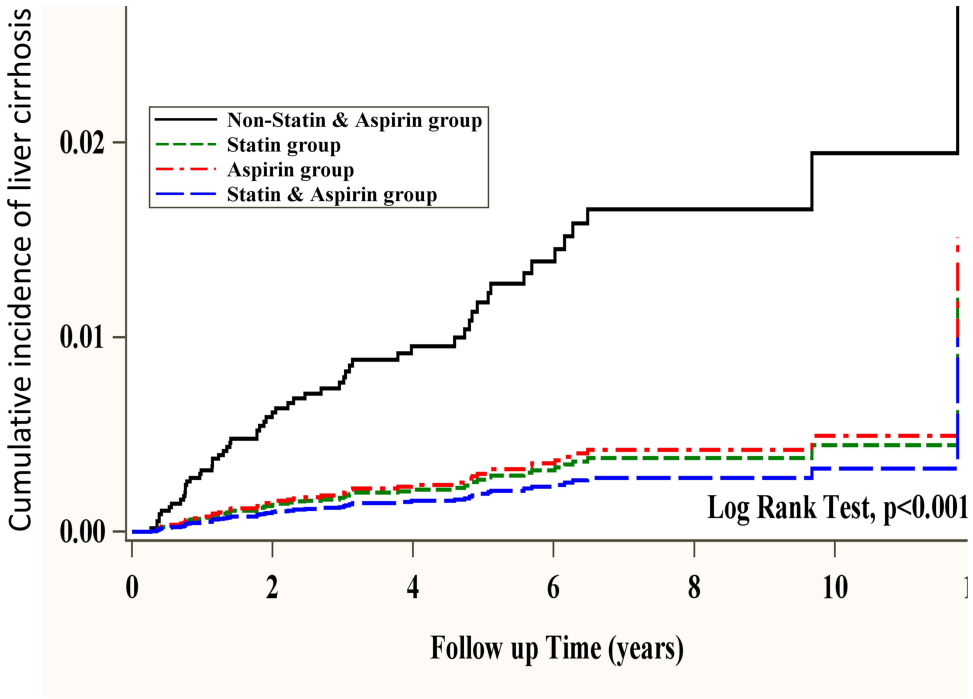

Figure 2 Kaplan-Meier curves depict the cumulative incidence rate of liver cirrhosis during the follow-up period among four groups: non-statin and aspirin group, statin group, aspirin group, and combined statin and aspirin group. Comparison between statin alone versus combined statin and aspirin yielded a p-value of 0.65, with an adjusted hazard ratio (aHR) of 1.37 (95% CI: 0.35–5.30). The comparison between aspirin alone versus combined statin and aspirin resulted in a p-value of 0.59, with an aHR of 1.52 (95% CI: 0.34–6.90). For further details, refer to Tables 2 and S3.

Hepatocellular Carcinoma

Compared to non-statin and non-aspirin groups, statin use ($p < 0.001$, aHR: 0.50, 95% CI: 0.43–0.60), aspirin use ($p = 0.0167$, aHR: 0.83, 95% CI: 0.72–0.97), and combined aspirin with statin use ($p < 0.001$, aHR: 0.61, 95% CI: 0.53–0.69) all demonstrated the potential to reduce HCC incidence in NAFLD/NASH patients. Risk factors increasing HCC incidence included male gender ($p < 0.001$, aHR: 1.36), age over 60 ($p < 0.001$, aHR: 2.19), cardiovascular disease ($p = 0.0044$, aHR: 1.20), DM ($p < 0.001$, aHR: 1.58), viral hepatitis ($p < 0.001$, aHR: 4.39), alcoholism ($p = 0.0144$, aHR: 1.25), metabolic syndrome ($p = 0.0150$, aHR: 1.29), and H2 receptor antagonists ($p < 0.001$, aHR: 1.24). (Table 3)

Table 3 Incidences and Hazard Ratios of Hepatocellular Carcinoma in Patients with MAFLD/MASH Across Cohorts

Variables	Hepatocellular carcinoma			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Exposure									
Non-Statin&Aspirin	854	19663	43.43	1.00	(reference)	–	1.00	(reference)	–
Statin	169	9577	17.65	0.39	(0.33, 0.46)	<0.001	0.50	(0.43, 0.60)	<0.001
Aspirin	236	4810	49.06	1.13	(0.98, 1.31)	0.0909	0.83	(0.72, 0.97)	0.0167
Statin&Aspirin	297	10173	29.19	0.66	(0.58, 0.76)	<0.001	0.61	(0.53, 0.69)	<0.001
Gender									
Female	540	18633	28.98	1.00	(reference)	–	1.00	(reference)	–
Male	1016	25590	39.70	1.38	(1.24, 1.53)	<0.001	1.36	(1.22, 1.51)	<0.001

(*Continued*)

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Table 3 (Continued).

Variables	Hepatocellular carcinoma			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Age, years									
18–50	156	8922	17.48	1.00	(reference)	–	1.00	(reference)	–
51–60	408	14663	27.83	1.59	(1.32, 1.91)	<0.001	1.34	(1.12, 1.62)	0.0019
>60	992	20639	48.06	2.80	(2.36, 3.32)	<0.001	2.19	(1.84, 2.61)	<0.001
Comorbidities									
Cardiovascular disease									
No	477	18903	25.23	1.00	(reference)	–	1.00	(reference)	–
Yes	1079	25321	42.61	1.74	(1.56, 1.94)	<0.001	1.20	(1.06, 1.35)	0.0044
Stroke									
No	1431	41596	34.40	1.00	(reference)	–	1.00	(reference)	–
Yes	125	2628	47.56	1.40	(1.17, 1.69)	<0.001	1.06	(0.87, 1.29)	0.5903
Diabetes mellitus									
No	861	30944	27.82	1.00	(reference)	–	1.00	(reference)	–
Yes	695	13279	52.34	1.90	(1.71, 2.10)	<0.001	1.58	(1.4, 1.77)	<0.001
Hyperlipidemia									
No	1055	25479	41.41	1.00	(reference)	–	1.00	(reference)	–
Yes	501	18745	26.73	0.65	(0.58, 0.72)	<0.001	0.62	(0.55, 0.71)	<0.001
Obesity									
No	1540	43252	35.61	1.00	(reference)	–	1.00	(reference)	–
Yes	16	971	16.48	0.46	(0.28, 0.76)	0.0023	0.56	(0.34, 0.92)	0.0220
Chronic kidney disease									
No	1465	42691	34.32	1.00	(reference)	–	1.00	(reference)	–
Yes	91	1532	59.40	1.76	(1.42, 2.18)	<0.001	1.19	(0.95, 1.50)	0.1296
Viral hepatitis									
No	634	33657	18.84	1.00	(reference)	–	1.00	(reference)	–
Yes	922	10567	87.25	4.74	(4.28, 5.25)	<0.001	4.39	(3.97, 4.87)	<0.001
Metabolic syndrome									
No	1278	38983	32.78	1.00	(reference)	–	1.00	(reference)	–
Yes	278	5240	53.05	1.65	(1.45, 1.89)	<0.001	1.29	(1.05, 1.58)	0.0150

(*Continued*)

Table 3 (Continued).

Variables	Hepatocellular carcinoma			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Medication									
H2 receptor antagonists									
No	746	25393	29.38	1.00	(reference)	–	1.00	(reference)	–
Yes	810	18831	43.01	1.50	(1.35, 1.66)	<0.001	1.24	(1.11, 1.38)	<0.001
Proton pump inhibitors									
No	1136	33444	33.97	1.00	(reference)	–	1.00	(reference)	–
Yes	420	10780	38.96	1.16	(1.04, 1.30)	0.0087	0.94	(0.83, 1.06)	0.2919

Notes: Adjusted HR: Adjusted for sex, age, comorbidities, and medications in the Cox proportional hazards model.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-years; IR, incidence rate per 1000 person-years.

Univariate and multivariate risk factor stratification analysis are shown in the forest plot of adjusted HRs for the risk of hepatocellular carcinoma (Figure 3). Kaplan–Meier curves illustrating the cumulative incidence of hepatocellular carcinoma during the follow-up between the non-statin-aspirin, statin alone, aspirin alone, and combined aspirin with statin use. As shown in Figure 4, the analysis indicated that statin alone was not inferior to either aspirin alone or combined aspirin and statin in reducing the incidence of HCC. (P < 0.001). The comparison between statin alone and combined statin and aspirin yielded a p-value of 0.07, with an adjusted hazard ratio (aHR) of 0.83 (95% CI: 0.69–1.01). Similarly, the comparison between aspirin alone and combined statin and aspirin resulted in a p-value of <0.001, with an aHR of 1.39 (95% CI: 1.16–1.65). Refer to Tables 3 and S4 for detailed data.

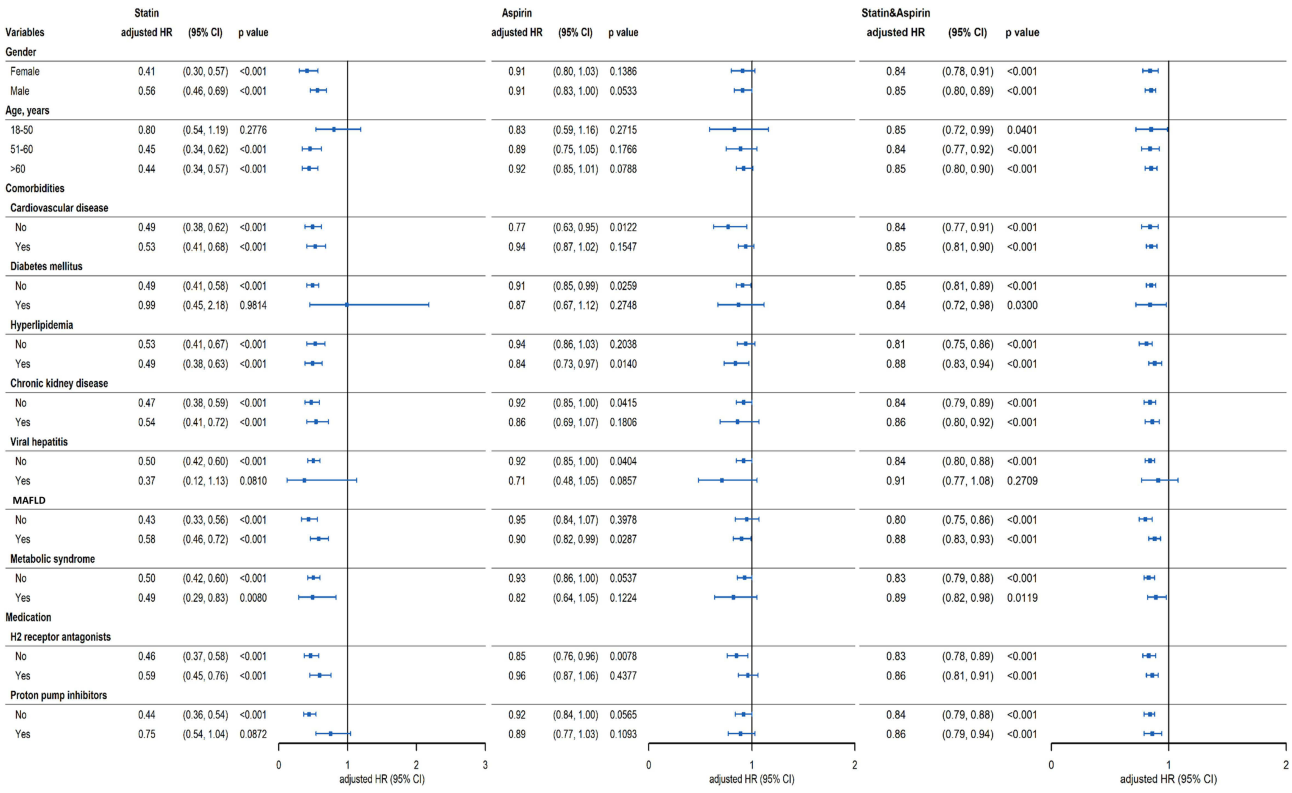

Figure 3 Multivariable stratified analyses were conducted to examine the association between hepatocellular carcinoma and the use of statin and aspirin among individuals in the MAFLD/ MASH groups.

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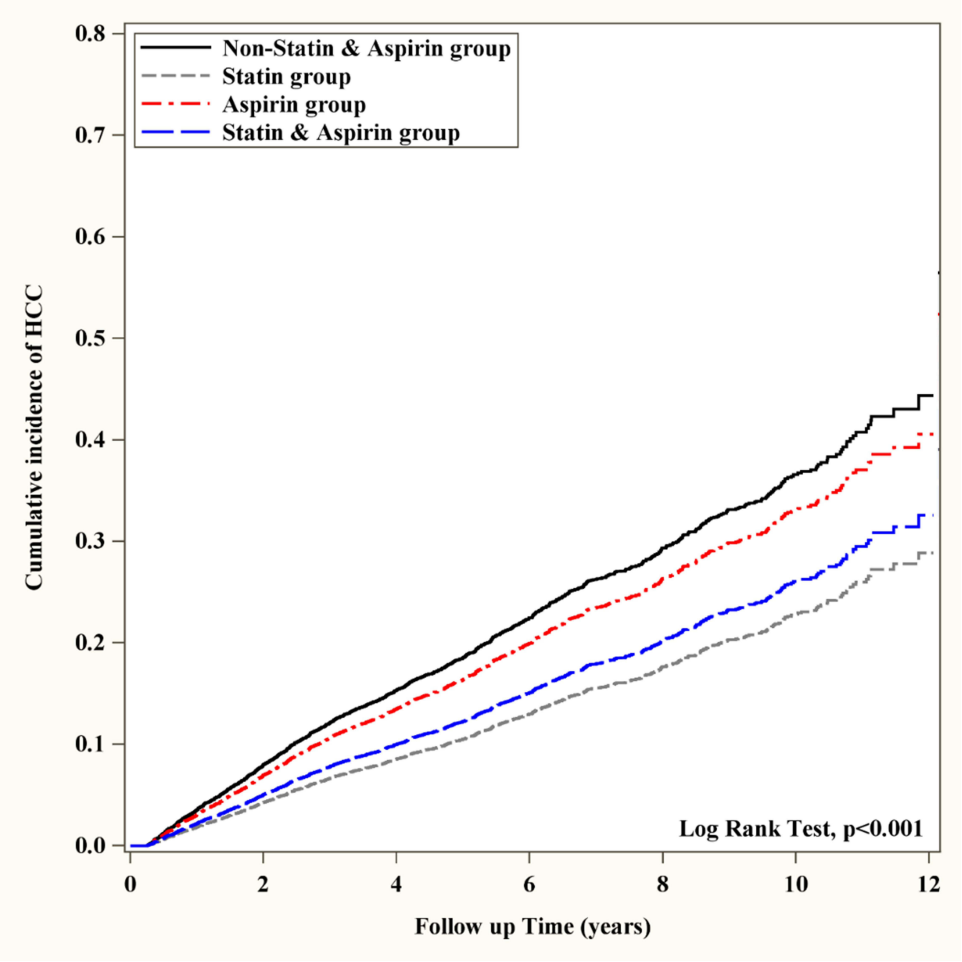

Figure 4 Kaplan-Meier curves illustrate the cumulative incidence rate of Hepatocellular Carcinoma (HCC) during the follow-up period across four groups: non-statin and aspirin, statin alone, aspirin alone, and combined statin and aspirin. The analysis indicated that statin alone was not inferior to either aspirin alone or combined aspirin and statin in reducing the incidence of HCC. The comparison between statin alone and combined statin and aspirin yielded a p-value of 0.07, with an adjusted hazard ratio (aHR) of 0.83 (95% CI: 0.69–1.01). The comparison between aspirin alone and combined statin and aspirin resulted in a p-value of <0.001, with an aHR of 1.39 (95% CI: 1.16–1.65). Refer to Tables 3 and S4 for detailed data.

Overall Mortality

All-cause mortality incidences and hazard ratios were decreased for statin, aspirin, and combined statin with aspirin use compared with non-statin and non-aspirin. Statin ($p < 0.001$, aHR: 0.41, 95% CI: 0.36–0.46), aspirin ($p = 0.026$, aHR: 0.85, 95% CI: 0.77–0.95), and combined statin with aspirin use ($p < 0.001$, aHR: 0.53, 95% CI: 0.48–0.58) all demonstrated the potential to reduce mortality incidence in MAFLD/MASH patients. Risk factors increasing mortality incidence in MAFLD/MASH patients included male gender ($p < 0.001$, aHR: 1.40), age over 60 ($p < 0.001$, aHR: 2.15), cardiovascular disease ($p < 0.001$, aHR: 1.19), stroke ($p < 0.001$, aHR: 1.51), DM ($p < 0.001$, aHR: 1.22), and alcoholism ($p < 0.001$, aHR: 1.51). (Table 4) Univariate and multivariate risk factor stratification analysis showed a reduction in mortality in the forest plot of aHRs for the risk of all-cause mortality (Figure 5). Kaplan–Meier curves showed that both aspirin and statin could reduce mortality incidence. However, the combined use of statin with aspirin was not superior to the use of statin alone in reducing mortality. (Figure 6, $p < 0.001$). When comparing statin alone versus combined statin and aspirin, the p-value was <0.001, with an adjusted hazard ratio (aHR) of 0.77 (95% CI: 0.67–0.89). Similarly, comparing aspirin alone versus combined statin and aspirin yielded a p-value of <0.001, with an aHR of 1.63 (95% CI: 1.44–1.84). Refer to Tables 4 and S5 for more detailed information.

One limitation of our study is the use of propensity score matching (PSM), which addresses only measured confounders, leaving unmeasured confounders unaccounted for. We acknowledge this limitation and recognize its

Table 4 Incidences and Hazard Ratios of All-Cause Mortality in Patients with MAFLD/MASH Across Cohorts

Variables	All-cause mortality			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Exposure									
Non-Statin&Aspirin	1922	20803	92.39	1.00	(reference)	–	1.00	(reference)	–
Statin	324	9892	32.75	0.34	(0.30, 0.39)	<0.001	0.41	(0.36, 0.46)	<0.001
Aspirin	486	5190	93.64	1.01	(0.92, 1.12)	0.8330	0.85	(0.77, 0.95)	0.0026
Statin&Aspirin	571	10645	53.64	0.57	(0.52, 0.63)	<0.001	0.53	(0.48, 0.58)	<0.001
Gender									
Female	1095	19466	56.25	1.00	(reference)	–	1.00	(reference)	–
Male	2208	27064	81.58	1.45	(1.35, 1.56)	<0.001	1.40	(1.30, 1.51)	<0.001
Age, years									
18–50	378	9149	41.32	1.00	(reference)	–	1.00	(reference)	–
51–60	788	15364	51.29	1.25	(1.10, 1.41)	<0.001	1.20	(1.06, 1.36)	0.0040
>60	2137	22017	97.06	2.39	(2.15, 2.67)	<0.001	2.15	(1.92, 2.41)	<0.001
Comorbidities									
Cardiovascular disease									
No	1066	19736	54.01	1.00	(reference)	–	1.00	(reference)	–
Yes	2237	26794	83.49	1.57	(1.46, 1.69)	<0.001	1.19	(1.10, 1.30)	<0.001
Stroke									
No	2949	43756	67.4	1.00	(reference)	–	1.00	(reference)	–
Yes	354	2775	127.57	1.93	(1.73, 2.15)	<0.001	1.51	(1.34, 1.71)	<0.001
Diabetes mellitus									
No	2097	32344	64.83	1.00	(reference)	–	1.00	(reference)	–
Yes	1206	14186	85.01	1.32	(1.23, 1.42)	<0.001	1.22	(1.13, 1.33)	<0.001
Hyperlipidemia									
No	2232	27176	82.13	1.00	(reference)	–	1.00	(reference)	–
Yes	1071	19354	55.34	0.67	(0.62, 0.72)	<0.001	0.72	(0.66, 0.79)	<0.001
Obesity									
No	3257	45548	71.51	1.00	(reference)	–	1.00	(reference)	–
Yes	46	982	46.84	0.66	(0.49, 0.88)	0.0048	0.81	(0.60, 1.08)	0.1539
Chronic kidney disease									
No	3140	44903	69.93	1.00	(reference)	–	1.00	(reference)	–
Yes	163	1627	100.18	1.45	(1.24, 1.70)	<0.001	1.12	(0.95, 1.33)	0.1805

(*Continued*)

Table 4 (Continued).

Variables	All-cause mortality			cHR	(95% CI)	*p*-value	aHR	(95% CI)	*p*-value
	Event	PY	IR						
Viral hepatitis									
No	2430	34529	70.38	1.00	(reference)	–	1.00	(reference)	–
Yes	873	12002	72.74	1.03	(0.96, 1.12)	0.4048	0.98	(0.90, 1.06)	0.5706
Metabolic syndrome									
No	2796	41039	68.13	1.00	(reference)	–	1.00	(reference)	–
Yes	507	5491	92.33	1.38	(1.25, 1.51)	<0.001	1.12	(0.97, 1.29)	0.1267
Medication									
H2 receptor antagonists									
No	1833	26596	68.92	1.00	(reference)	–	1.00	(reference)	–
Yes	1470	19934	73.74	1.08	(1.00, 1.15)	0.0403	0.97	(0.90, 1.04)	0.3639
Proton pump inhibitors									
No	2389	35153	67.96	1.00	(reference)	–	1.00	(reference)	–
Yes	914	11377	80.34	1.19	(1.10, 1.28)	<0.001	1.08	(1.00, 1.18)	0.0529

Notes: Adjusted HR: Adjusted for sex, age, comorbidities, and medications in the Cox proportional hazards model.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-years; IR, incidence rate per 1000 person-years.

potential impact on the robustness of our findings. To mitigate concerns about overfitting, we initially matched solely on the index year and subsequently conducted an additional matching approach that included index year, sex, and age. Importantly, the results from both matching strategies were consistent with our current findings, further supporting the validity of our conclusions (Tables S6–S13).

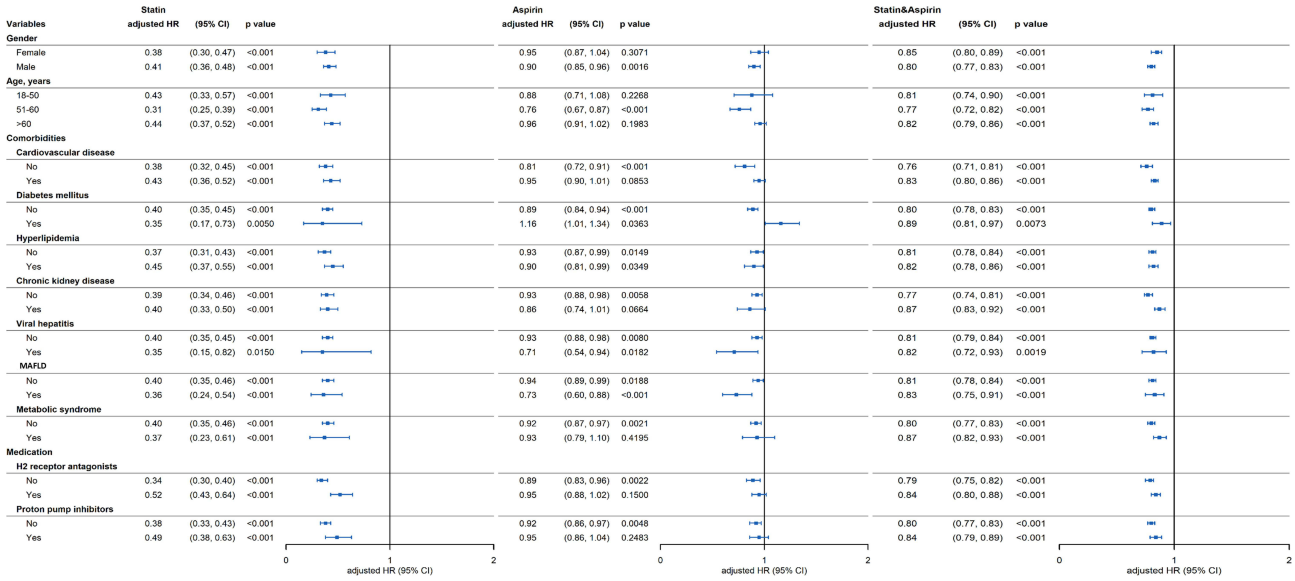

Figure 5 Multivariable stratified analyses were conducted to assess the association between all-cause mortality and the use of statins and aspirin in the MAFLD/MASH groups.

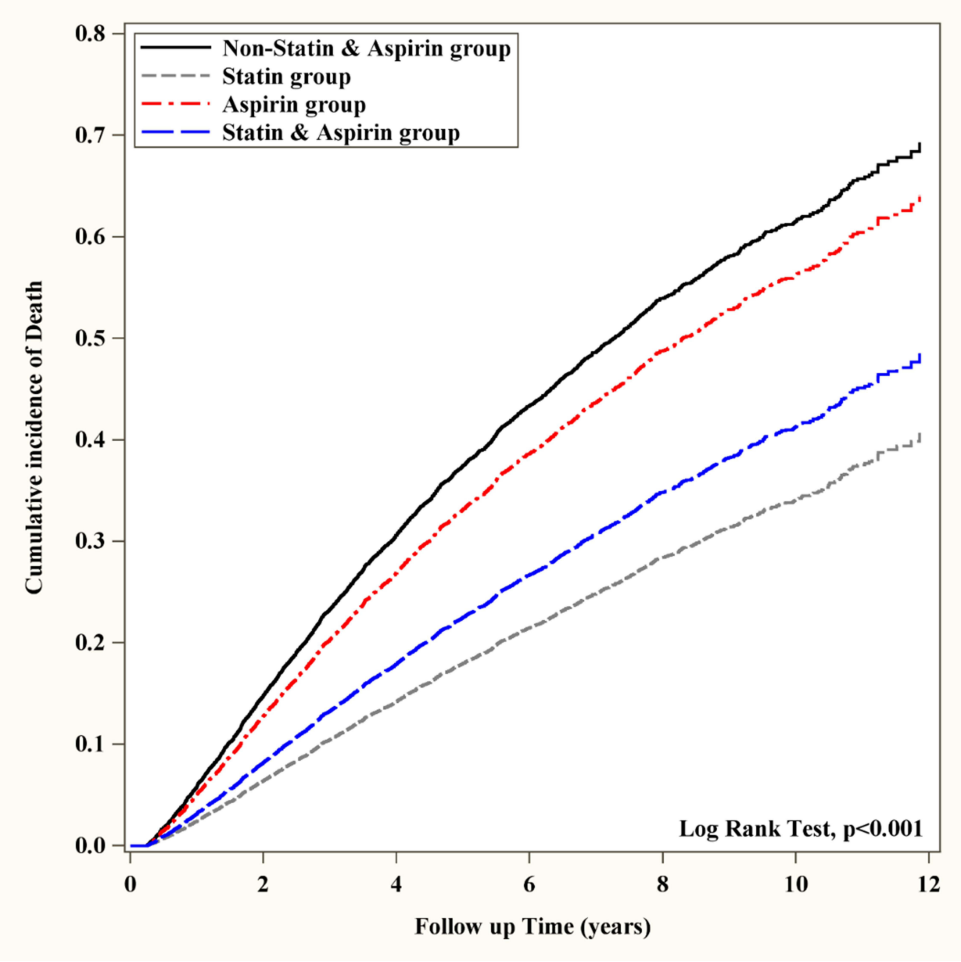

Figure 6 Kaplan-Meier curves display the cumulative incidence rate of all-cause mortality during the follow-up period among four groups: non-statin and aspirin, statin alone, aspirin alone, and statin and aspirin. The combined use of statin with aspirin was not superior to the use of statin alone in reducing mortality. When comparing statin alone versus combined statin and aspirin, the p-value was <0.001, with an adjusted hazard ratio (aHR) of 0.77 (95% CI: 0.67–0.89). Comparing aspirin alone versus combined statin and aspirin yielded a p-value of <0.001, with an aHR of 1.63 (95% CI: 1.44–1.84). Refer to Tables 4 and S5 for more detailed information.

Discussion

Many HCC cases develop in cryptogenic cirrhosis, which may be attributable to MAFLD and MASH.[22] Most HCC patients are 80–90% correlated with liver cirrhosis.[23,24] However, MAFLD-associated HCC may occur in non-cirrhotic patients.[23] The prevalence of HCC in non-cirrhotic MASH was 38.0%, significantly higher than in non-cirrhotic patients with others etiologies.[23] Liver cirrhosis is an insidious process, making it challenging to accurately determine incidence rates, which may explain why liver cirrhosis incidence is lower than HCC incidence in our findings.

Among 1654 HCC cases, 371 (22%) were non-cirrhotic, with the incidence of non-cirrhotic HCC increasing by 61% between 2009 and 2020. Notably, 39% of non-cirrhotic HCC cases had cryptogenic origins in a Dutch referral center. Advanced stages of cryptogenic non-cirrhotic HCC showed elevated serum interleukin-6 levels compared to non-cirrhotic HCC with known etiologies. Comparative analysis between cryptogenic and MAFLD non-cirrhotic HCC cohorts and controls revealed similar circulating immune biomarker profiles and PNPLA3 polymorphisms.[25]

MAFLD and ALD share similarities in pathogenesis, with three specific miRNAs (miR-34a, miR-122, and miR-155) implicated in both conditions. This overlap reinforces the notion of a common disease mechanism between MAFLD and ALD, highlighting the pleiotropic effects of these miRNAs.[26]

The proportion of fibrosis progression and mean annual rate of progression in MASH were 40.76% (95% CI: 34.69–47.13) and 0.09 (95% CI: 0.06–0.12),[6] respectively. Aspirin and other anti-platelet agents inhibiting platelet aggregation provided protection against hepatic fibrosis and were associated with a 32% decreased odds of hepatic fibrosis (adjusted pooled OR

0.68; CI 0.56–0.82, p = 0.0001).[8,27] In chronic liver diseases, portal hypertension develops as a result of increased intrahepatic vascular resistance due to the dysregulation of liver sinusoidal endothelial cells and hepatic stellate cells.[28] The anti-inflammatory action of some anti-platelet agents like aspirin inhibits the transcription of NF-κB in endothelial cells, preventing the adhesion of macrophages and T-lymphocytes and reducing levels of inflammatory cytokines including interleukin-6, tumor necrosis factor-β, and PDGF.[27,29] Antiplatelet agents can prevent injury to sinusoidal endothelial cells by inhibiting platelet aggregation, thereby reducing chemotherapy-induced sinusoidal lesions.[27,30]

Studies have shown that statins may significantly reduce the risk of developing MAFLD and decrease ALT/AST levels, as well as significant fibrosis.[14] Statins also reduce portal pressure, improve liver sinusoidal endothelial and hepatic microvascular dysfunction, decrease fibrogenesis, and offer protection against ischemia/reperfusion injury, among other benefits.[12] In the Cox proportional hazard model, chronic hepatitis B patients receiving statin therapy exhibit a dose-dependent reduction in the risk of cirrhosis and its decompensation.[31]

In our study, statins (p = 0.0033, aHR: 0.23), aspirin (p = 0.0147, aHR: 0.23), and combined statin with aspirin use (p < 0.001, aHR: 0.17) all demonstrated the potential to reduce cirrhosis incidence in MAFLD/MASH patients. Combined statin and aspirin use seemed to potentially have an additional effect, warranting further validation studies.

HCC incidence among MAFLD patients was 0.44 per 1000 person-years, HCC increases up to 5.29 per 1000 person-years after MAFLD-to- MASH transition.[6]

Statins and aspirin have various mechanisms of action that potential to reduce HCC incidence. Statins have anti-inflammatory, anti-tumor, and immunomodulatory properties. It has been shown that statins can affect the 5′-adenosine monophosphate-activated protein kinase (AMPK) pathway in differing physiological and pathological ways, resulting in anti-cancer and cardio-protective effects.[32] Statin data suggests that statin use was associated with a 20–43% lower risk of HCC compared to statin nonusers.[33,34] Aspirin's mechanism includes anti-inflammation and anti-platelet effects, inhibiting platelet coagulopathy, hemostasis, and reducing tumor development, recurrence, and metastasis. Aspirin use alone was associated with a decreased incidence of HCC.[35,36] In the Cancer and Cause of Death registries in Swedish adults with chronic hepatitis B or hepatitis C infection. A reduction of the estimated cumulative incidence of HCC was 31% at 7.9 years of follow-up aspirin users versus nonusers.[37,38]

Singh et al reported that the combined use of statin with aspirin was associated with a decreased hazard of HCC, statistically significant in the multivariable model [HR (CI): 0.113 (0.026–0.483); p = 0.0033] in a prospective cohort of patients with liver cirrhosis.[39] I In a large cohort study, it is evident that overweight and obesity significantly increase the risk of HCC in Koreans,[40] Non-cirrhotic patients with nonalcoholic fatty liver disease and hyperlipidemia show a significant association with the development of HCC.[41] Obesity and hyperlipidemia were significantly in reducing HCC associated with statin and aspirin use compared to non-use in our study. We hypothesize that statin and aspirin use may confer a stronger chemopreventive effect in high-risk populations.

Statin use was associated with an overall reduced risk of HCC (HR: 0.52; 95% CI: 0.37–0.72), including in subgroup analyses for cirrhosis, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease, as well as in studies that accounted for concurrent use of aspirin, metformin, and lipophilic statins. Similarly, aspirin use was linked to a reduced overall risk of HCC (HR: 0.48; 95% CI: 0.27–0.87). Although both statin and aspirin use were associated with a decreased HCC risk, only statin use remained statistically significant in subgroup analyses that considered concurrent medication use.[7]

Our results indicate that statin use alone is not inferior to the combined use of statins and aspirin in reducing HCC in patients with MAFLD/MASH. We hypothesize that statins may offer a more significant anti-inflammatory effect, decrease hyperlipidemia, and provide greater protection against HCC than aspirin in patients with non-alcoholic fatty liver and chronic hepatitis.

Approximately 10–20% of MAFLD patients may progress to MASH, potentially leading to cirrhosis and liver-related mortality.[6] Overall mortality among MAFLD and MASH were 11.77 per 1000 person-years (range, 7.10–19.53), and 25.56 per 1000 person-years (range, 6.29–103.80), respectively. Incidence risk ratios for overall mortality for MAFLD were 1.05 (range, 0.70–1.56).[6] In a meta-analysis, statin use was associated with a lower risk of all-cause mortality in HCC compared to non-use, with an HR of 0.80 (95% CI 0.68–0.94, P < 0.0001).[34] Statins could reduction of oxidative stress, inflammation, improvement in vascular function, and reorganization of the extracellular matrix in cirrhosis, increase in nitric oxide products (NOx) in the hepatic vein, decreasing portal pressure, and the hepatosinusoidal-protective effects has been strongly correlated

with improved outcomes.[12] The risk of overall mortality was significantly lower in MAFLD patients using statins compared to those not using statins (HR: 0.87, 95% CI: 0.76–0.99, p = 0.04). Similarly, cancer-related mortality was also significantly lower in statin users (SHR: 0.73, 95% CI: 0.54–0.99, p = 0.04).[42]

Aspirin, anti-platelet, and anti-inflammation effect, that could prevent thromboembolism for reducing cardiovascular death, and also prevent cancer develop, recurrent, and metastasis.[43–45] In the Cancer and Cause of Death registries among Swedish adults with chronic hepatitis B or C, liver-related mortality was found to be reduced by 27% in aspirin users compared to non-users.[37,38]

Statin use was particularly associated with a significant decrease in mortality rates than aspirin use, combined statin and aspirin use in our study. We suppose statins had a much more significant greater chemopreventive effect on mortality rates, and the others effect than aspirin use in patients with MAFLD/MASH.

Limitations

Our study has several limitations, including its retrospective design and dependence on administrative databases, which lack clinical examination results. This reliance makes it challenging to access detailed socioeconomic information, lifestyle factors, health behaviors, and potentially unhealthy habits. The NHIRD's strict privacy regulations further restrict the ability to link de-identified data with external sources, which limits comprehensive data analysis. Despite these constraints, our findings emphasize the potential of aspirin and statins in mitigating liver disease burden in MAFLD/MASH patients. Combined statin and aspirin therapy may offer additional benefits for cirrhosis prevention but does not appear to provide incremental advantages in reducing HCC incidence or mortality. Future research should aim to explore the mechanisms at play and optimize treatment strategies to improve patient outcomes in MAFLD/MASH.

Conclusion

Both aspirin and statins could reduce the incidence of cirrhosis, HCC, and mortality. However, combining statin with aspirin use might potentially offer additional reduction in cirrhosis development, but not in reducing HCC and mortality in MAFLD/MASH patients. It appears that statins may have a more pronounced chemopreventive effect compared to aspirin in these patients. Our findings underscore that the combined use of statin and aspirin was not superior to statin use alone for preventing HCC and mortality in MAFLD/MASH patients. This highlights a promising therapeutic strategy in this high-risk population.

Data Sharing Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Informed Consent Statement

As this was a retrospective study based on the assessment of existing data, the committee waived the requirement for informed consent from the patients. All personal data were only available to investigators and were secured by delinking the recognition information from the main dataset.

Acknowledgments

We acknowledge the support of the NHIRD and funding agencies for their contributions to this study. The authors declare no conflicts of interest, and the datasets used are available upon request. Ethical approval was obtained, and informed consent was waived due to the retrospective nature of the study. The contributions of the authors to the study are outlined, and relevant ORCID identifiers are provided for reference.

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Disclosure

The authors declare no conflicts of interest in this work.

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