Aspirin use is associated with the Risk of HCC Development in Patients with Compensated ALC

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Background/Aims: Aspirin therapy has shown protective effects against hepatocellular carcinoma (HCC) in preclinical studies. However, it is unclear whether aspirin therapy lowers the risk of HCC in patients with compensated alcoholic cirrhosis. Recent preclinical studies have suggested potential therapeutic applications of antiplatelet therapy in hepatitis B models. In epidemiological studies, however, the effect of aspirin on HCC prevention is controversial. A large population-based study in the National Institutes of Health Association of American Retired Persons Diet and Health Study cohort showed that aspirin use was associated with a 41% lower risk of HCC compared to non-use (3). We investigated whether aspirin therapy is associated with a reduction in HCC incidence in patients with compensated alcoholic liver cirhosis. **Methods:** A retrospective analysis of data from 993 consecutive patients with compensated alcoholic cirrhosis who abstained from alcoholic drinking was performed. Primary and secondary outcomes were development of HCC and bleeding events, respectively. Risk was compared between patients with aspirin treatment and patients who were not treated (non-aspirin group) using a time-varying Cox proportional hazards model for total population to minimize immortal time bias and propensity score-matching analysis. **Results:** During the study period of median duration of 4.6 years, 133 patients (13.6%) developed HCC. In time-varying Cox proportional analyses, the aspirin group showed a significantly lower risk of HCC. In bleeding risk, aspirin therapy was not associated with a higher bleeding risk. In propensity score-matched pairs, aspirin therapy significantly reduced the risk of HCC. In patients with FIB-4 index ≤3.25, HCC incidence rates in aspirin user were significantly different from those in non-aspirin user. In patients with FIB-4 index >3.25, HCC incidence rates in aspirin user were not significantly different from those in non-aspirin user. **Conclusions:** Aspirin therapy reduces the risk of HCC in patients with compensated alcoholic cirrhosis without significantly increasing bleeding risk.

Table 1. Baseline Characteristics

	Non-aspirin group (n=769)	Aspirin group (n=224)	*P* value
Age, yrs	58.05 ± 12.20	64.60 ± 10.77	<0.001
Male, N (%)	558 (72.56%)	150 (66.96%)	0.103
CTP score	5.36 ± 0.74	5.63 ± 1.02	<0.001
CTP class			<0.001
A	711 (92.46%)	189 (84.38%)	
B	57 (7.41%)	31 (13.84%)	
C	1 (0.13%)	4 (1.79%)	
MELD score	8.54 ± 3.38	9.86 ±5.33	0.001
AST, IU/L	31 [26, 37]	37 [28, 53]	<0.001
ALT, IU/L	18 [14, 26]	27 [17, 40]	<0.001
GGT, IU/L	31 [18, 56]	37 [19, 53]	0.305
Albumin, g/dL	4.0 [3.6, 4.2]	3.9 [3.4, 4.2]	0.011
Total bilirubin, mg/dL	0.8 [0.6, 1.0]	0.9 [0.6, 1.3]	0.013
Creatinine, mg/dL	0.8 [0.6, 1.0]	0.9 [0.7, 1.1]	<0.001
PT INR	1.04 [0.97, 1.14]	1.03 [0.95, 1.12]	0.076
Platelet, ×10³ /μL	173 [132, 227]	170 [126, 225]	0.419

Table 2. Time-varying Cox Proportional Hazards Regression Analysis for **HCC Development** in the Entire Cohort

	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, yrs	1.03 (1.01, 1.04)	<0.001	1.03 (1.01, 1.04)	<0.001
Male, N (%)	1.22 (0.84, 1.78)	0.303		
MELD score	1.01 (0.98, 1.05)	0.436		
CTP score	1.32 (1.14, 1.53)	<0.001	0.75 (0.55, 1.01)	0.057
ALT, IU/L	1.01 (0.998, 1.01)	0.157		
Albumin, g/dL	0.50 (0.38, 0.66)	<0.001	0.46 (0.29, 0.72)	0.001
Total bilirubin, mg/dL	1.15 (1.08, 1.23)	<0.001	1.20 (1.09, 131)	<0.001
Creatinine, mg/dL	0.89 (0.73, 1.09)	0.272		
PT INR	1.39 (0.73, 2.64)	0.311		
Platelet, ×10³ /μL	0.994 (0.991, 0.996)	<0.001	0.995 (0.99, 0.998)	<0.001
Aspirin therapy	**0.18 (0.07, 0.50)**	**0.001**	**0.15 (0.10, 0.27)**	**<0.001**

Table 3. Characteristics of Propensity Score-matched Cohorts

	Non-aspirin group (n=170)	Aspirin group (n=170)	*P* value
Age, yrs	65.04 ± 11.80	64.39 ± 10.53	0.478
Male, N (%)	108 (63.53%)	108 (63.53%)	1.000
CTP score	5.47 ± 0.76	5.52 ± 0.89	0.523
MELD score	8.63 ± 3.45	8.95 ± 3.92	0.416
AST, IU/L	32 [27, 40]	34.5 [26, 47]	0.863
ALT, IU/L	22 [16, 28.8]	23 [16, 31.8]	0.929
Albumin, g/dL	3.9 [3.5, 4.1]	3.9 [3.4, 4.2]	0.524
Total bilirubin, mg/dL	0.8 [0.6, 1.1]	0.8 [0.6, 1.2]	0.548
Creatinine, mg/dL	0.8 [0.6, 1.0]	0.9 [0.7, 1.1]	0.342
PT INR	1.04 [0.99, 1.14]	1.02 [0.95, 1.09]	0.208
Platelet, ×10³ /μL	172.5 [129, 221]	171 [126.8, 226.5]	0.967

Table 4. Time-varying Cox Proportional Hazards Regression Analysis for **Gastrointestinal Bleeding Events** in the Entire Cohort

	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, yrs	0.99 (0.97, 1.00)	0.116		
Male, N (%)	2.04 (1.30, 3.19)	0.002	2.01 (1.28, 3.16)	0.003
MELD score	1.04 (1.01, 1.08)	0.007	1.01 (0.97, 1.05)	0.590
CTP score	1.36 (1.18, 1.61)	<0.001	1.06 (0.79, 1.42)	0.715
ALT, IU/L	0.990 (0.978, 1.00)	0.116		
Albumin, g/dL	0.52 (0.39, 0.70)	<0.001	0.59 (0.38, 0.90)	0.015
Total bilirubin, mg/dL	1.05 (0.93, 1.19)	0.421		
Creatinine, mg/dL	1.01 (0.91, 1.12)	0.906		
PT INR	1.83 (1.01, 3.34)	0.048	1.23 (0.54, 2.78)	0.628
Platelet, ×10³ /μL	0.999 (0.997, 1.001)	0.263		
Aspirin therapy	**0.62 (0.33, 1.14)**	**0.126**		