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Is It Possible To Reduce the Risk of Hepatocellular Carcinoma by Taking Statin in Diabeties Mellitus Patients with HBV or HCV

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Abstract

Objectives: To determine the relationship between the dose effect of Statin and the risk of HCC.

Methods: This study was a case-control study. All participants were ≧ 50 years of age and were diagnosed with diabetes (ICD-9250.0x 0, 205.0 × 2) and were treated with an anti-diabetic agent for at least for 3 months according to the NHID, LHID2010 (longitudinal health insurance database 2010). We captured the use of a Statin before the index date in patients with type II diabetes. Patients diagnosed with a hepatoma (ICD-9:155) were defined as the case group.

Results: The risk of hepatoma was reduced in patients with higher cumulative DDDs statin use compared to statin non-users. (HBV population: cumulative dose>298 DDDs: OR=0.41; 95% CI:0.24-0.72; HCV population: cumulative dose>205 DDDs: [OR=0.25; 95% CI: 0.13-0.48]).

Conclusion: A dose-response relationship exists between lower risk of hepatoma and higher cumulative DDDs of statin use.

Keywords: Hepatocellular Carcinoma (HCC); Diabetes mellitus; Statin

Introduction

Research background and motivation

Current results by numerous epidemiological studies have indicated that the population of people with diabetes mellitus (DM) has a higher incidence of hepatocellular carcinoma (HCC). Research has also shown that statin drugs can reduce the risk of HCC in patients with hepatitis B and hepatitis C, and that aspirin can reduce the risks of colon cancer (although there are no consistent results in the risk prevention of aspirin toward other cancers). Moreover, although statin drugs may have potential protective effects on the incidence of cancers, studies on the relationship between statin drugs and HCC incidence in Taiwan are scarce. In response, this study recruited patients with DM and hepatitis B or hepatitis C who were taking statin drugs, and investigated whether the drugs had a protective effect against HCC or whether they increased HCC incidence.

Research purpose

To analyze the correlation between statin dose dependence and HCC risk among patients with DM and hepatitis B or hepatitis C.

Materials and Methods

Research framework

This study collected information from Taiwan's National Health Insurance database to conduct a case-control study. Specifically, patients with confirmed DM (International Classification of Diseases-Ninth Revision [ICD-9]: 250.XX) and were treated with an anti-diabetic agent for at least for 3 months according to the NHID between 2005 and 2010 were selected from the database for statistical analysis. After excluding those who were less than 50-years-old, the patients were divided into the HCC group and control group. The HCC group consisted of the patients who had received their first diagnosis of HCC (ICD-9:155), and the control group comprised the patients without a HCC diagnosis. Pairwise matching for age, sex, drug usage, and comorbidities was performed for all of the patients at a ratio of 1:2. The HCC group and control group were then subjected to cross analysis to elucidate the correlations between statin drug usage and dosage and HCC risk. Two additional subgroups of patients, namely those with hepatitis B and hepatitis C, were extracted for further analysis; accordingly, the subgroups were also divided into HCC groups comprising those who had received their first diagnosis of HCC (ICD-9:155), and control groups comprising the patients without a HCC diagnosis. The subgroups were then similarly subjected to cross analysis to determine the correlations between statin drug use and dosage and HCC risk (Figure 1).

Research hypotheses

Research purpose: Correlations of statin dose dependence and HCC risk among patients with diabetes mellitus and hepatitis B or hepatitis C.

Hypothesis 1: Patients with DM who received a higher dosage of statin drugs had a significantly reduced risk of developing HCC.

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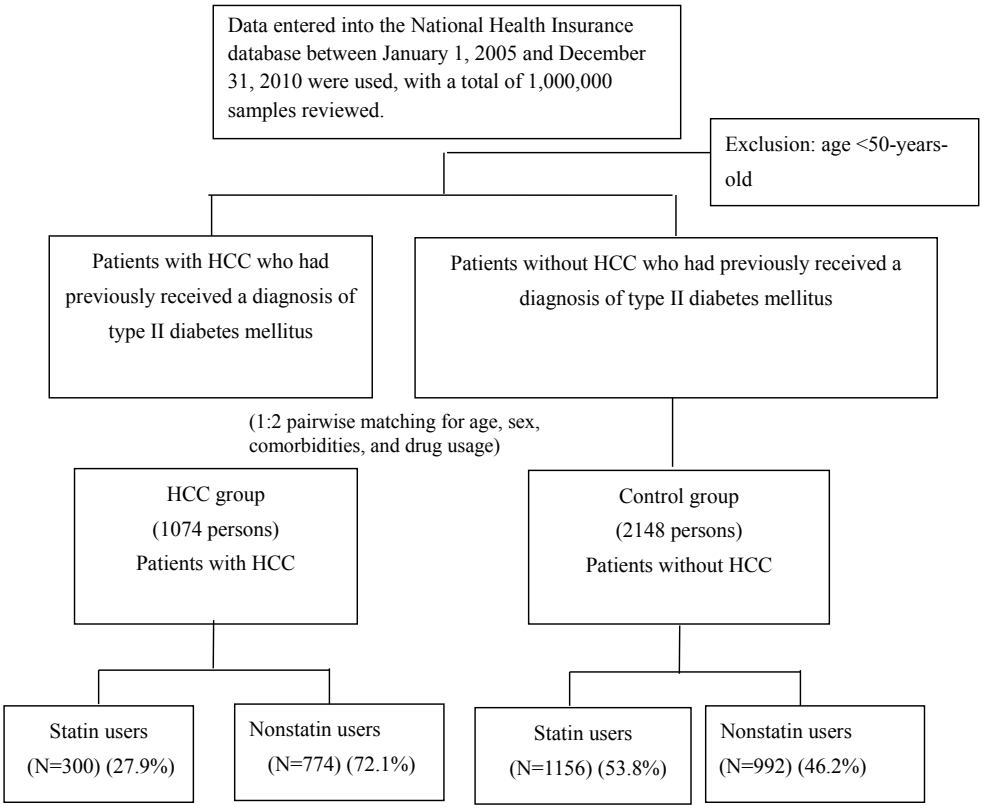

Figure 1: Research framework.

Hypothesis 2: Patients with DM and hepatitis B who received a higher dosage of statin drugs had a significantly reduced risk of developing HCC.

Hypothesis 3: Patients with DM and hepatitis C who received a higher dosage of statin drugs had a significantly reduced the risk of developing HCC.

Research samples

Definition of DM: ICD-9 code 250.XX and were treated with an anti-diabetic agent for at least for 3 months according to the NHID.

Definition of hepatocellular carcinoma: ICD-9 code 155 and patients who had received their first diagnosis of HCC.

Definition of hepatitis B: ICD-9 codes 070.22, 070.23, 070.32, 070.33, and V02.61; patients who had tested positive for HBsAg twice, with the second test being conducted at least 3 months after the previous test, who had also continuously received hepatitis B medication (e.g., tenofovir, lamivudine, telbivudine, adefovir, entecavir, or peginterferon alpha) for more than 1 year.

Definition of hepatitis C: ICD-9 codes 070.41, 070.44, 070.51, 070.54, and V02.62; patients who had tested positive for the hepatitis C virus antibody, who had also received ribavirin and interferon alpha medication for hepatitis C.

In total, 3222 patients who met the definition of DM between 2005 and 2010 were recruited for this study. Of these patients, 1074 were patients with confirmed HCC and 2148 without HCC. Additionally, 300 and 774 of the patients with HCC had received and not received statins, respectively, whereas 1156 and 992 of the patients without HCC had received and not received statins, respectively. Finally, 79 patients had both hepatitis B and HCC, 154 patients had hepatitis B but not HCC, 220 patients had both hepatitis C and HCC, and 433 patients had hepatitis C but not HCC.

Statistical Analysis

A chi-square test and Fisher's exact test were used to analyze the categorical variables of the patients' descriptive statistics, and two independent T-tests were used to analyze the continuous variables in order to determine the differences between the HCC group and control group. Propensity score matching was performed to ensure that there was a consistent distribution between the sexes, ages, comorbidities, and medication usage of the two groups. Moreover, tertiles were adopted as the cut-off points for the cumulative doses of low, medium, and high exposure to statin drugs, which were used to conduct a dose-effect analysis. Then, to compare the differences of statin exposure rate and cumulative exposure between the HCC and control groups, odds ratios and 95% confidence intervals of the two groups were estimated using multiple logistic regression; the variables of age, sex, comorbidities, and drug history were simultaneously adjusted. The statistical software SAS 9.3 was used to perform the data analyses in this study. Two-tailed tests were adopted for all p values, and statistical significance was set at $P<0.05$.

Results

Descriptive statistics of research samples

Patient characteristics: This study included 1074 patients with HCC (the HCC group) and 2148 patients without HCC (the control

group). All of the patients were pairwise matched according to age, sex, comorbidities, aspirin usage, nonsteroidal anti-inflammatory drug (NSAID) usage, and angiotensin-converting-enzyme inhibitor (ACEi) drug usage.

The HCC group consisted of 631 males (58.8%) and 433 females (41.2%) with an average age of 65.36 years. Liver cirrhosis (27.3%, N=293) and Hepatitis C (20.5%, N=220) were the most common comorbidities. Additionally, NSAIDs were the most commonly received drugs among the HCC group (67.1%, N=721), followed by ACEi (35.6%, N=382) and statins (27.9%, N=300).

The control group comprised 1266 males (58.9%) and 882 females (41.4%) with an average age of 65.53 years. Again, liver cirrhosis (27.3%, N=587) and Hepatitis C (20.2%, N=433) were the most common comorbidities. Moreover, NSAIDs were the most received drugs among the control group (67.5%, N=1449), followed by statins (53.8%, N=1156). Because all of the patients in this study were matched by age, sex, comorbidities, aspirin usage, NSAID usage, and ACEi usage, no difference between the two groups regarding these variables was observed.

The use of statins was the variable that displayed significant differences between the two groups, with atorvastatin being the most received drug (12.4%) in the HCC group, followed by lovastatin (11.2%); in the control group, atorvastatin was the most received drug (28.8%), followed by simvastatin (22.1%) (Table 1).

Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis B or hepatitis C

After adjusting the demographic variables, it was determined that the risk of developing HCC for the patients with DM who had received statin was 0.31 times that of the patients with DM who had not received statins (P<0.001) (Table 2). Moreover, the risk of HCC for the patients with DM and hepatitis C who had received statins was 0.35 times that of those who did not take statins (P<0.001), whereas there was no significant difference in the risk of HCC for the patients with DM and Hepatitis B who had and had not received statins (P=0.081). In terms of the cumulative daily doses, the risk of HCC for the patients with a <84 defined daily dose (DDD), 84-360.60 DDD, and >360.61 DDD of statins was 0.44 (P<0.001), 0.30 (P<0.001), and 0.21 (P<0.001) times that of the patients who had not received statins, respectively. In terms of the cumulative number of days of using statin (hereafter abbreviated as cumulative days), the risk of HCC development among the patients who had received statins for an accumulation of <1 year, 1-2 years, and >2 years was 0.36 (P<0.001), 0.35 (P<0.001), and 0.21 (P<0.001) times that of the patients who had not received statins, respectively. Finally, in terms of average daily dose, the risk of HCC development for the patients with a <0.49 DDD, 0.49-0.66 DDD, and >0.67 DDD was 0.43 (P<0.001), 0.27 (P<0.001), and 0.25 (P<0.001) times that of the patients who had not received statins, respectively. Notably, cumulative daily dose, cumulative days, and average daily dose all reached linear correlation (P<0.001). This result was consistent with the conditional logistic regression analysis of the correlation between statin drug usage and HCC risk among patients with DM and either hepatitis B or hepatitis C (Supplementary Table 1), which also obtained a linear correlation (P<0.001).

Variables	HCC group (N=1074)		Control group (N=2148)		P value
Age (years) (mean ± SD)	65.37	(± 9.40)	65.53	(± 9.67)	0.668
Sex					
Female	443	(41.2)	882	(41.4)	0.919
Male	631	(58.8)	1266	(58.9)	
Comorbidities (%)					
Hepatitis B	79	(7.4)	154	(7.2)	0.847
Hepatitis C	220	(20.5)	433	(20.2)	0.828
Hepatitis B and C	9	(0.8)	7	(0.3)	0.051
Alcoholic liver disease	69	(6.4)	146	(6.8)	0.690
Cirrhosis	293	(27.3)	587	(27.3)	0.978
Coronary heart disease	126	(11.7)	245	(11.4)	0.785
Cerebrovascular disease	38	(3.5)	72	(3.4)	0.784
Medications taken (%)					
Aspirin	38	(3.5)	75	(3.5)	0.946
NSAID	721	(67.1)	1449	(67.5)	0.852
ACEi	382	(35.6)	768	(35.8)	0.917
Statin					
Any statin	300	(27.9)	1156	(53.8)	<0.001
Lovastatin	120	(11.2)	392	(18.2)	<0.001
Pravastatin	69	(6.4)	221	(10.3)	<0.001
Rosuvastatin	44	(4.1)	340	(15.8)	<0.001
Fluvastatin	66	(6.1)	229	(10.7)	<0.001
Simvastatin	112	(10.4)	475	(22.1)	<0.001
Atorvastatin	133	(12.4)	619	(28.8)	<0.001

Table 1: Demographic characteristics of the patients with DM and hepatitis B or hepatitis C who received statin drugs (N=3222).

Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis B

After adjusting the demographic variables, it was determined that the following variables were not statistically different between the HCC and control groups: diagnosis of DM and hepatitis B+receipt of statins compared with diagnosis of DM and Hepatitis B+no receipt of statins (P=0.081); cumulative daily dose of <83.53 DDD (P=0.733) and >311.18 DDD (P=0.115); cumulative days of drug usage of <1 year (P=0.297) and 1-2 years (P=0.547); and average daily dose of <0.50 (p=0.138), 0.50-0.67 (P=0.464), and >0.67 (P=0.112). Table 3 presents an overview of these findings.

The risk of HCC development for the patients with a cumulative daily dose of statins of 83.53-311.18 DDD was 0.32 times of the patients who had not received statins (P=0.020). Moreover, the risk of HCC development for the patients who had received statins for an accumulation of >2 years was 0.29 times of the patients who had not received statins (P=0.036). Notably, cumulative daily dose and cumulative days of usage were linearly correlated (P<0.001). This result was consistent with the conditional logistic regression analysis of the correlation between statin drug usage and HCC risk among the patients with DM and Hepatitis B (Supplementary Table 2), which also achieved a linear correlation (P<0.001).

Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis C

After adjusting the demographic variables, the risk of HCC development among the patients with DM and Hepatitis C who had received statins was 0.35 times that of the patients who had not received statins (P<0.001). Additionally, the risk of HCC development among the patients with a cumulative daily dose of statins of <83.53 DDD, 83.53-311.18 DDD, and >311.18 DDD was 0.49 (P=0.014), 0.35 (P=0.001), and 0.21 (P<0.001) times that of the patients who had not received statins, respectively. The risk of HCC development among the patients who had received statins for an accumulation of <1 year, 1-2 years, and >2 years was 0.40 (P<0.001), 0.25 (P=0.006), and 0.30

Variables	Model I									Model II			
	HCC group		Control group		OR value (95% CI)	P value	Adjusetd OR (95% CI)			p value	Adjusetd OR (95% CI)		p value
Overall													
Statin not received	774	(43.8)	992	(56.2)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	300	(20.6)	1156	(79.4)	0.33	(0.28-0.39)	<0.001	0.31	(0.27-0.37)	<0.001	-	--	---
Hepatitis B population													
Statin not received	50	(39.1)	78	(60.9)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	29	(27.6)	76	(72.4)	0.60	(0.34-1.04)	0.067	0.60	(0.34-1.07)	0.081	--	--	--
Hepatitis C population													
Statin not received	178	(40.6)	260	(59.4)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	42	(19.5)	173	(80.5)	0.36	(0.24-0.52)	<0.001	0.35	(0.24-0.52)	<0.001			
Cumulative daily dose													
Statin not received	774	(43.8)	992	(56.2)	Ref.	--	--	Ref.	--	--		--	--
<84.00	129	(26.5)	358	(73.5)	0.46	(0.37-0.58)	<0.001	0.44	(0.35-0.55)	<0.001	Ref.	--	--
84.00-360.60	96	(19.8)	389	(80.2)	0.32	(0.25-0.40)	<0.001	0.30	(0.23-0.38)	<0.001	0.63	(0.46-0.86)	0.003
>360.61	75	(15.5)	409	(84.5)	0.24	(0.18-0.31)	<0.001	0.21	(0.16-0.28)	<0.001	0.44	(0.31-0.61)	<0.001
p for trend	--	--	--	--	--	<0.001	--	--	<0.001	--	--	<0.001	--
Cumulative number of days													
Statin not received	774	(43.8)	992	(56.2)	Ref.	--	--	Ref.	--	--	--	--	--
<1	179	(22.8)	605	(77.2)	0.38	(0.31-0.46)	<0.001	0.36	(0.30-0.44)	<0.001	Ref.	--	--
1-2	56	(22.7)	191	(77.3)	0.37	(0.27-0.51)	<0.001	0.35	(0.25-0.48)	<0.001	0.93	(0.66-1.32)	0.685
>2	65	(15.3)	361	(84.7)	0.23	(0.17-0.31)	<0.001	0.21	(0.16-0.28)	<0.001	0.53	(0.38-0.73)	<0.001
p for trend	--	--	--	--	--	<0.001	--	--	<0.001	--	--	<0.001	--
Average daily doses													
Statin not received	774	(43.8)	992	(56.2)	Ref.	--	--	Ref.	--	--	--	--	--
<0.49	126	(26.1)	357	(73.9)	0.45	(0.36-0.57)	<0.001	0.43	(0.34-0.54)	<0.001	Ref.	--	--
0.49-0.66	107	(18.2)	480	(81.8)	0.29	(0.23-0.36)	<0.001	0.27	(0.21-0.34)	<0.001	0.64	(0.48-0.86)	0.003
>0.67	67	(17.4)	319	(82.6)	0.27	(0.20-0.36)	<0.001	0.25	(0.19-0.34)	<0.001	0.60	(0.43-0.84)	0.003
p for trend	--	--	--	--	--	<0.001	--	--	<0.001	--	--	0.002	--
Adjusted age, gender, comorbidities (HBV, HCV, Alcoholic liver disease, Cirrhosis, Coronary heart disease)													

Table 2: Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis B or hepatitis C.

(P=0.004) times that of the patients who had not received statins, respectively. Finally, the risk of HCC development among the patients who received an average daily dose of statins of 0.49-0.67 and >0.67 was 0.21 (P<0.001) and 0.29 (P=0.001) times that of the patients who had not received statins, respectively; the patients who received an average daily dose of statins of <0.49 (P=0.053) did not display any significant difference from the patients who had not received statins. Similar to the previously discussed results, cumulative daily dose, cumulative days, and average daily dose were all linearly correlated (P<0.001). This result was again consistent with the conditional logistic regression analysis of the correlation between statin drug usage and HCC risk among the patients with DM and Hepatitis C, which also yielded a linear correlation (P<0.001).

Discussion

This research explored the correlations between statin drug usage and HCC risk among patients with DM and hepatitis B or hepatitis C. According to the results listed in Table 2, the patients with DM who received a higher dose of statins had a significantly reduced risk of developing HCC; thus, hypothesis 1 was supported. Similarly, as Table 3 reveals, the patients with DM and hepatitis B who received a higher dose of statins had a significantly reduced risk of developing HCC; thus, hypothesis 2 was also supported. Finally, as evidenced by the results presented in Table 4, the patients with DM and hepatitis C who received a higher dose of statins had a significantly reduced risk of developing HCC; thus, hypothesis 3 was also supported.

This study discovered a significantly reduced risk of developing HCC following high-dose statin usage among the patients with DM, as well as among the patients with DM and hepatitis C. Furthermore, a higher cumulative dose and longer accumulation of days of usage among the patients with DM and hepatitis B was associated with a significantly reduced risk of developing HCC. Notably, no significant differences were discovered between the average daily dose of statin usage among the patients DM and hepatitis B and HCC development risk, a result that may be attributed to an insufficient number of samples. These results are similar to those found by Chiu et al. [1], who stated that a higher statin dose resulted in lower HCC risk. Their study also discovered that an accumulated dose of statins of <215.4 DDD reduced HCC risk by 38% among patients, compared with those who did not receive statins. They concluded that an accumulated dose of statins of >215.4 DDD was not associated with any significant differences, which they similarly attributed to an inadequate sample size [2-4]. However, it was determined in the present study that cumulative daily dose, cumulative days, and average daily dose were all linearly correlated (P<0.001) regarding the correlation between statin drug usage and HCC risk among the patients with DM and either hepatitis B or hepatitis C. One possible reason for this discrepancy, in comparison to the study by Chiu et al. [1] did not focus solely on whether receiving statin drugs could reduce HCC risk among patients with DM.

In addition, Shao et al. [5] indicated that statin drug usage can reduce the mortality of patients with early-stage HCC, especially those with early-stage HCC that is related to hepatitis B. Elsewhere, Chen et al. [6] also noted that the receipt of statins or metformin drugs alone could protect patients with hepatitis B from developing cancer. This result was similar to the linear correlation of cumulative daily dose and cumulative

Variables								Model I			Model II		
	HCC group		Control group		OR value (95% CI)		P value	Adjusetd OR (95% CI)		p value	Adjusetd OR (95% CI)		p value
Overall													
Statin not received	50	(39.1)	78	(60.9)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	29	(27.6)	76	(72.4)	0.60	(0.34-1.04)	0.067	0.60	(0.34-1.07)	0.081	--	--	--
Cumulative daily dose													
Statin not received	50	(39.1)	78	(60.9)	Ref.	--	--	Ref.	--	--	--	--	--
<83.53	14	(40.4)	21	(60.0)	1.04	(0.49-2.23)	0.920	1.15	(0.52-2.52)	0.733	Ref.	--	--
83.53-311.18	6	(17.1)	29	(82.9)	0.32	(0.13-0.83)	0.019	0.32	(0.12-0.84)	0.020	1.15	(0.52-2.52)	0.733
>311.18	9	(25.7)	26	(74.3)	0.54	(0.23-1.25)	0.149	0.49	(0.21-1.19)	0.115	0.32	(0.12-0.84)	0.020
p for trend	--	--	--	--	--	0.028	--	--	0.024	--	--	0.024	--
Cumulative number of days													
Statin not received	50	(39.1)	78	(60.9)	Ref.	--	--	Ref.	--	--	--	--	--
<1	18	(30.0)	42	(70.0)	0.67	(0.35-1.29)	0.229	0.70	(0.36-1.37)	0.297	Ref.	--	--
1-2	7	(33.3)	14	(66.7)	0.78	(0.29-2.07)	0.617	0.73	(0.27-2.02)	0.547	0.70	(0.36-1.37)	0.297
>2	4	(16.7)	20	(83.3)	0.31	(0.10-0.97)	0.043	0.29	(0.09-0.92)	0.036	0.73	(0.27-2.02)	0.547
p for trend	--	--	--	--	--	0.039	--	--	0.034	--	--	0.034	--
Average daily dose													
Statin not received	50	(39.1)	78	(60.9)	Ref.	--	--	Ref.	--	--	--	--	--
<0.50	8	(23.5)	26	(76.5)	0.48	(0.20-1.14)	0.098	0.51	(0.21-1.25)	0.138	Ref.	--	--
0.50-0.67	12	(32.4)	25	(67.6)	0.75	(0.35-1.63)	0.464	0.74	(0.34-1.64)	0.464	0.51	(0.21-1.25)	0.138
>0.67	8	(24.2)	25	(75.8)	0.50	(0.21-1.19)	0.118	0.48	(0.20-1.19)	0.112	0.74	(0.34-1.64)	0.464
p for trend	--	--	--	--	--	0.095	--	--	0.100	--	--	0.100	--

Table 3: Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis B.

Variables								Model I			Model II		
	HCC group		Control group		OR value (95% CI)		P value	Adjusetd OR (95% CI)		p value	Adjusetd OR (95% CI)		p value
Overall													
Statin not received	178	(40.6)	260	(59.4)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	42	(19.5)	173	(80.5)	0.36	(0.24-0.52)	<0.001	0.35	(0.24-0.52)	<0.001	--	--	--
Cumulative daily dose													
Statin not received	178	(40.6)	260	(59.4)	Ref.	--	--	Ref.	--	--	--	--	--
<83.53	18	(24.4)	53	(74.6)	0.50	(0.28-0.88)	0.016	0.49	(0.28-0.87)	0.014	Ref.	--	--
83.53-311.18	14	(19.2)	59	(80.8)	0.35	(0.19-0.64)	0.001	0.35	(0.19-0.66)	0.001	0.49	(0.28-0.89)	0.014
>311.18	10	(14.1)	61	(85.9)	0.24	(0.12-0.48)	<0.001	0.23	(0.12-0.47)	<0.001	0.35	(0.19-0.66)	0.001
P for trend	--	--	--	--	--	<0.001	--	--	<0.001	--	--	<0.001	--
Cumulative number of days													
Statin not received	178	(40.6)	260	(59.4)	Ref.	--	--	Ref.	--	--	--	--	--
<1	29	(21.3)	107	(78.7)	0.40	(0.25-0.62)	<0.001	0.40	(0.25-0.63)	<0.001	Ref.	--	--
1-2	5	(15.2)	28	(84.8)	0.26	(0.10-0.69)	0.007	0.25	(0.09-0.67)	0.006	0.40	(0.25-0.63)	<0.001
>2	8	(17.4)	38	(82.6)	0.31	(0.14-0.68)	0.003	0.30	(0.14-0.68)	0.004	0.25	(0.09-0.67)	0.006
P for trend	--	--	--	--	--	<0.001	--	--	<0.001	--	--	<0.001	--
Average daily dose													
Statin not received	178	(40.6)	260	(59.4)	Ref.	--	--	Ref.	--	--	--	--	--
<0.50	23	(28.4)	58	(71.6)	0.58	(0.35-0.97)	0.039	0.59	(0.35-1.01)	0.053	Ref.	--	--
0.50-0.67	10	(12.5)	70	(87.5)	0.21	(0.11-0.42)	<0.001	0.21	(0.10-0.41)	<0.001	0.59	(0.35-1.01)	0.053
>0.67	9	(16.7)	45	(83.3)	0.29	(0.14-0.61)	0.001	0.29	(0.14-0.61)	0.001	0.21	(0.10-0.41)	<0.001
p for trend						<0.001			<0.001			<0.001	
Adjusted age, gender, comorbidities (HBV, HCV, Alcoholic liver disease, Cirrhosis, Coronary heart disease).													

Table 4: Correlation between statin drug usage and HCC risk among the patients with DM and hepatitis C.

days (P<0.001) regarding the correlation between statin drug usage and HCC risk among the patients with DM and hepatitis B achieved in the present study. By contrast, the patients with DM and hepatitis B who received an average daily dose of either <0.50 (P=0.138), 0.50-0.67 (P=0.464), or >0.67 (P=0.112) of statins were not at a statistically significant different level of risk for HCC than were those who had not received statins [7,8]. This result was possibly a result of hepatitis B carriers' long latency period, and the fact that most patients do not seek for medical treatment at hospitals unless they fall ill; thus, it is likely that there was an insufficient number of patients with hepatitis B in this study, which may have contributed to the nonsignificant difference in these statistical results.

Research Limitations

The present study aimed to conduct a more in-depth investigation on the impact of statin drug usage on the risks related to the occurrence rates of HCC among patients with DM and either hepatitis B or hepatitis C. However, due to hepatitis B carriers' long latency period,

Variables								Model I			Model II		
	HCC group		Control group		Crude OR (95% CI)		P value	Adjusetd OR (95%CI)		p value	Adjusetd OR (95%CI)		p value
Overall													
Statin not received	484	(70.2)	575	(41.5)	Ref.	--	--	Ref.	--	--	--	--	--
Statin received	205	(29.8)	810	(58.5)	0.30	(0.25-0.37)	<0.001	0.28	(0.23-0.34)	<0.001	--	----	--
Cumulative daily dose													
Statin not received	484	(70.2)	575	(41.5)	Ref.	--	--	Ref.	--	--	--	--	--
<93.33	88	(12.8)	249	(18.0)	0.42	(0.32-0.55)	<0.001	0.40	(0.30-0.53)	<0.001	Ref.	--	--
99.33-404.15	67	(9.7)	273	(19.7)	0.29	(0.22-0.39)	<0.001	0.27	(0.20-0.36)	<0.001	0.62	(0.43-0.91)	0.014
>404.16	50	(7.3)	288	(20.8)	0.21	(0.15-0.29)	<0.001	0.19	(0.14-0.26)	<0.001	0.43	(0.29-0.64)	<0.001
p for trend							<0.001			<0.001			<0.001
Cumulative number of days													
Statin not received	484	(70.2)	575	(41.5)	Ref.	--	--	Ref.	--	--	--	--	--
<1	117	(17.0)	404	(29.2)	0.34	(0.27-0.44)	<0.001	0.33	(0.26-0.41)	<0.001	Ref.	--	--
1-2	38	(5.5)	129	(9.3)	0.35	(0.24-0.51)	<0.001	0.33	(0.22-0.48)	<0.001	0.98	(0.64-1.51)	0.942
>2	50	(7.3)	277	(20.0)	0.21	(0.16-0.30)	<0.001	0.20	(0.14-0.27)	<0.001	0.54	(0.37-0.79)	0.002
p for trend	--	--	--	--	--	--	<0.001	--	--	<0.001	--	--	0.002
Average daily dose													
Statin not received	484	(70.2)	575	(41.5)	Ref.	--	--	Ref.	--	--	--	--	--
<0.48	86	(12.5)	238	(17.2)	0.43	(0.33-0.57)	<0.001	0.40	(0.30-0.53)	<0.001	Ref.	--	--
0.48-0.65	63	(9.1)	278	(20.1)	0.37	(0.20-0.36)	<0.001	0.25	(0.18-0.34)	<0.001	0.61	(0.42-0.88)	0.009
>0.66	56	(8.1)	294	(21.2)	0.23	(0.17-0.31)	<0.001	0.21	(0.16-0.29)	<0.001	0.55	(0.38-0.81)	0.003
p for trend	--	--	--	--	--	--	<0.001	--	--	<0.001	--	--	0.002
Adjusted age, gender, comorbidities (HBV, HCV, Alcoholic liver disease, Cirrhosis, Coronary heart disease).													

Table 5: Correlation analysis of statin drug usage and HCC risk for the patients with DM but without hepatitis B or hepatitis C (N=1,015)).

and because most patients do not seek medical treatment at hospitals unless they fall ill, it is likely that there was an insufficient number of patients with hepatitis B in this study, which may have contributed to the insignificant difference in some of the statistical results.

Conclusion and Recommendations

The risk analyses in this study revealed a lower HCC risk among the patients with DM, as well as the patients with DM and hepatitis C, who had received statins, compared with those who had not received statins. Specifically, the patients with DM displayed a 69% reduction in HCC risk following statin drug intake, whereas the HCC risk among the patients with DM and hepatitis C who had received statins was reduced by 64%. Additionally, an increase in the cumulative dose, cumulative days, and average daily dose of statin usage was associated with a decrease in HCC risk among the patients with DM, as well as the patients with DM and hepatitis C. A similar decrease in HCC risk was also observed among the patients with DM and hepatitis B following an increase in the cumulative dose and cumulative days of statin usage. In contrast to previous research that has solely explored the decline in HCC risk with an increase in cumulative statin dose, this study both investigated statin usage and HCC risk among patients with DM and either hepatitis B or hepatitis C and conducted a correlation analysis on the statin usage and HCC risk of those patients (Table 5). In the future, researchers are recommended to conduct further in-depth research on the varying strength of different statin drugs on cancer incidence rate reduction. Aside from some information supporting the fact that lipophilic statins possess stronger anticancer effects compared with their hydrophilic counterparts, lipophilic drugs are theoretically stronger in terms of cell membrane penetration, although they have not yet been subjected to a strength analysis.

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