PRELIMINARY COMMUNICATION

ONLINE FIRST

Association Between Nucleoside Analogues and Risk of Hepatitis B Virus–Related Hepatocellular Carcinoma Recurrence Following Liver Resection

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Context Tumor recurrence is a major issue for patients with hepatocellular carcinoma (HCC) following curative liver resection.

Objective To investigate the association between nucleoside analogue use and risk of tumor recurrence in patients with hepatitis B virus (HBV)–related HCC after curative surgery.

Design, Setting, and Participants A nationwide cohort study between October 2003 and September 2010. Data from the Taiwan National Health Insurance Research Database. Among 100 938 newly diagnosed HCC patients, we identified 4569 HBV-related HCC patients who received curative liver resection for HCC between October 2003 and September 2010.

Main Outcome Measures The risk of first tumor recurrence was compared between patients not taking nucleoside analogues (untreated cohort, n=4051) and patients taking nucleoside analogues (treated cohort, n=518). Cumulative incidences and hazard ratios (HRs) were calculated after adjusting for competing mortality.

Results The treated cohort had a higher prevalence of liver cirrhosis when compared with the untreated cohort (48.6% vs 38.7%; $P<.001$), but lower risk of HCC recurrence (n=106 [20.5%] vs n=1765 [43.6%]; $P<.001$), and lower overall death (n=55 [10.6%] vs n=1145 [28.3%]; $P<.001$). After adjusting for competing mortality, the treated cohort had a significantly lower 6-year HCC recurrence rate (45.6%; 95% CI, 36.5%-54.6% vs untreated, 54.6%; 95% CI, 52.5%-56.6%; $P<.001$). Six-year overall mortalities for treated cohorts were 29.0% (95% CI, 20.0%-38.0%) and for untreated 42.4% (95% CI, 40.0%-44.7%; $P<.001$). On modified Cox regression analysis, nucleoside analogue use (HR, 0.67; 95% CI, 0.55-0.81; $P<.001$), statin use (HR, 0.68; 95% CI, 0.53-0.87; $P=.002$), and nonsteroidal anti-inflammatory drugs or aspirin use (HR, 0.80; 95% CI, 0.73-0.88; $P<.001$) were independently associated with a reduced risk of HCC recurrence. Multivariable stratified analyses verified the association in all subgroups of patients, including those who were noncirrhotic (HR, 0.56; 95% CI, 0.42-0.76) and diabetic (HR, 0.52; 95% CI, 0.31-0.89).

Conclusion Nucleoside analogue use was associated with a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection.

JAMA. 2012;308(18):1906-1913
Published online November 12, 2012. doi:10.1001/2012.jama.11975 www.jama.com

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SURGERY IS CONSIDERED THE STANdard curative treatment option for hepatocellular carcinoma (HCC). However, the rate of long-term disease-free survival after liver resection remains unsatisfactory due to persistent high incidences of HCC recurrence.[1] Many factors affect HCC recurrence risk after liver resection, including tumor size and stage, serum α-fetoprotein level, cirrhosis, hepatitis B e antigen (HBeAg) status, and hepatitis B virus (HBV) viral load.[2-4] Among these factors, HBV viral load is the most clinically controllable.

Higher HBV viral load has been reported to be an independent risk factor for HCC recurrence in patients with HBV-related HCC.[5,6] Nucleoside analogues are effective in suppressing HBV replication and in ameliorating HBV-related liver disease.[7,8] They have been shown to be associated with a lower risk of HCC and other cirrhosis-related complications in those with chronic hepatitis[9,10] and cirrhosis.[11] However, studies on the effectiveness of nucleo-

For editorial comment see p 1922.

side analogue use in HCC recurrence have been relatively limited and have yielded conflicting results.[12-14] In Taiwan, under the National Health Insurance (NHI) program, reimbursement for nucleoside analogues for HBV patients meeting certain criteria began on October 1, 2003 (eTable 1 and eTable 2 available at http://www.jama.com).

The purpose of this study was to examine the association between use of nucleoside analogues and risk of HCC recurrence among patients with HBV-related HCC after curative liver resection. We also examined this association among different subpopulations and calculated the number needed to be treated (NNT) for 1 less HCC recurrence.

METHODS

Study Design

We conducted a nationwide cohort study by retrieving all patients receiving curative liver resection for HCC from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD has been described in detail in previous studies.[15-17] In brief, it consists of detailed health care data from more than 25 million enrollees, representing more than 99% of Taiwan's entire population. The accuracy of diagnosis of major diseases in the NHIRD, such as stroke and acute coronary syndrome, has been validated.[17,18] This study has been approved by the ethical review board of the National Health Research Institutes, Taiwan.

Study Population

We identified all hospitalized patients who were admitted with a primary diagnosis of HCC (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 155.0, 155.2) for the first time and who received curative liver resection between October 1, 2003, and September 30, 2010. The diagnostic accuracy of HCC was confirmed by both specific admission *ICD-9* codes and inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD.[15,16] Surgical pathological confirmation or typical image presentation of HCC is required for patients to be registered in the RCIPD.

Only HCC patients with HBV infection (*ICD-9* codes 070.2, 070.3, and V02.61) were included in our study cohorts. Patients were excluded if diagnosed with hepatitis C (*ICD-9* codes 070.41, 070.44, 070.51, 070.54, and V02.62), other viral hepatitis (*ICD-9* code V02.69), malignant tumor (*ICD-9* codes 104-208), or if they received antiviral treatments for more than 3 months before the index admission. Patients were also excluded if they received liver resection, transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation, or liver transplantation before the index hospitalization.

Study Cohorts

Patients who were newly diagnosed with HBV-related HCC and who received curative liver resection were divided into 2 cohorts based on their use of nucleoside analogues. The untreated cohort comprised patients who never received nucleoside analogues and the treated cohort was patients who received nucleoside analogues for at least 90 days. Those receiving antiviral treatments for less than 90 days during the observation period or prior to the observation period were excluded. Information regarding patients' medications was retrieved from the pharmacy prescription database. Reliability of the retrieved information was verified independently by 2 statisticians. Nucleoside analogues included lamivudine, entecavir, and telbivudine. For each nucleoside analogue prescription, the number of days of use was calculated. Then, the numbers of days of use for each prescription were added together to determine the total number of days of nucleoside analogue use.

Main Outcome Measurements

Hepatocellular carcinoma recurrence was defined as rehospitalization with a primary diagnosis of HCC after the index admission date and a treatment modality for HCC recurrence, such as surgery, transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation, or liver transplantation during the study period. Patients with HCC recurrence in the first 3 months after the index hospitalization for liver resection were excluded. We used the incident user design with follow-up for each patient beginning on the date of first prescription of nucleoside analogue in the treated cohort.[19,20] The follow-up for the untreated cohort began on the first day after the index hospitalization for liver resection. Both cohorts were followed up until the date of HCC recurrence, death, or the end of 2010. Death was defined as withdrawal of the patient from the NHI program. Causes of death were defined according to the primary diagnosis of hospitalization in the 3 months preceding death.

Covariate Assessment

Propensity score was calculated using logistic regression as proposed by Rosenbaum and Rubin[21,22] to estimate the probabilities of assigning a patient to the treated cohort given the background variables including age, sex, extent of resection, liver cirrhosis, other comorbidities listed in TABLE 1, and use of statins, nonsteroidal anti-inflammatory drugs (NSAIDs), and metformin. The mean and median propensity scores were compared between the 2 cohorts.

Since the chance of HCC recurrence can be confounded by competing risk of mortality, we identified comorbidities that may be associated with mortality based on diagnostic codes from both outpatient and inpatient datasets prior to the outcome of interest. All diseases included in the Charlson Comorbidity Index were analyzed except for human immunodeficiency virus, metastatic solid tumor, and cancer, because patients with these conditions were excluded from the present study.[23] Comorbidities, listed by *ICD-9* code, included acute coronary syndrome (410-414), cerebrovascular accident (430-438), chronic obstructive pulmonary disease (490-496), diabetes mellitus (250), liver cirrhosis (571.5), liver failure (570), renal failure (584-586), hypertension (401-405), hyperlipidemia (272.0-272.2), and peptic ulcer disease (531-534).

Certain drugs, including statins, aspirin, NSAIDs, and metformin, which might alter the risk of recurrent HCC, were analyzed. Exposure to these drugs was defined as frequency of use of more than 1 tablet per month during the observation period. Liver resection modalities for treatment of the original HCC, including major resection (extensive and partial hepatic lobectomy with at least 3 segmental resections of liver parenchyma) and minor resection (extensive and partial hepatectomy with 2 or fewer segmental resections of liver), were also analyzed.

Table 1. Study Cohorts Following Liver Resection

Characteristics	No. (%)[a] Untreated[b] (n = 4051)	Treated[b] (n = 518)	*P* Value
Age, mean (SD), y	54.6 (12.5)	54.4 (11.8)	.80
Sex			
Women	716 (17.7)	83 (16.0)	.39
Men	3335 (82.3)	435 (84.0)	
Resection[c]			
Major	1431 (35.3)	139 (26.8)	<.001
Minor	2620 (64.7)	379 (73.2)	
Follow-up, y			
Mean (SD)	2.18 (1.77)	2.64 (1.74)	<.001
Median (IQR)	1.57 (0.77-3.15)	2.18 (1.21-3.69)	<.001
Interval to start therapy, y			
Mean (SD)		1.19 (1.38)	
Median (IQR)		0.66 (0.14-1.84)	
Antiviral therapy duration, y	-		
Mean (SD)		1.45 (1.38)	
Median (IQR)		0.95 (0.48-1.94)	
Hospital visits			
Mean (SD)	56.54 (57.77)	74.37 (58.17)	<.001
Median (IQR)	37 (19-73)	60 (32.25-99.75)	<.001
Drug users[d]			
Statins	158 (3.9)	17 (3.3)	.55
NSAIDs or aspirin	2181 (53.8)	271 (52.3)	.51
Metformin	498 (12.3)	60 (11.6)	.72
Major coexisting diseases			
Cirrhosis	1569 (38.7)	252 (48.6)	<.001
Hypertension	978 (24.1)	109 (21.0)	.13
Diabetes	663 (16.4)	72 (13.9)	.16
Peptic ulcer diseases	603 (14.9)	78 (15.1)	.90
COPD	206 (5.1)	19 (3.7)	.20
Acute coronary syndrome	178 (4.4)	14 (2.7)	.08
Cerebral vascular disease	147 (3.6)	9 (1.7)	.03
Renal failure	83 (2.0)	5 (1.0)	.12
Hypercholesterolemia	35 (0.9)	2 (0.4)	.43
Propensity score			
Mean (SD)	0.11 (0.03)	0.12 (0.03)	<.001
Median (IQR)	0.11 (0.08-0.14)	0.12 (0.10-0.15)	<.001
Charlson score[e]			
Mean (SD)	1.20 (1.68)	1.22 (1.53)	.84
Median (IQR)	1 (0-1)	1 (0-2)	.16

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Values are shown as No. (%) unless otherwise indicated.
[b] Treated and untreated categories indicate patients with hepatitis B virus who are receiving nucleoside analogues, and those who are not, respectively.
[c] Major resection indicates extensive and partial hepatic lobectomy with at least 3 segmental resections of liver parenchyma; minor resection indicates extensive and partial hepatectomy with 2 or fewer segmental resections of liver.
[d] Drug users indicate patients using drugs at least 1 day per month on average.
[e] Charlson score represents degree of health. A higher score indicates a worse health condition.

Statistical Analysis

Death prior to tumor recurrence was considered a competing risk event. The death-adjusted cumulative incidences of HCC recurrence were calculated using a 2-step process and tested for equality among the study cohorts. Calculation and comparison of cumulative incidences in competing risk data ratios were conducted using modified Kaplan-Meier method[24] and Gray method.[25] We tested differences in the full time-to-event distributions between the study groups using log-rank test.

To determine the independent risk factors for HCC recurrence, multivariable analyses and stratified analyses using hazard ratios (HRs) were carried out with modified Cox proportional hazards models in the presence of competing risk event after adjusting for age, sex, resection modality, liver cirrhosis, diabetes, propensity score, and use of statins, NSAIDs or aspirin, and metformin.[24] To assess the dose-dependent association of recurrence with nucleoside analogue use, we further conducted multivariable analysis with nucleoside analogue use as a continuous variable. On multivariable stratified analyses, the association between nucleoside analogue use and the risk of HCC recurrence was examined in different subgroups. All subgroup comparisons were preplanned to control for potential confounding factors reported in previous studies.

The NNT represented the number of patients who needed to be treated for 1 less HCC recurrence or mortality; it was calculated by the inverse of the absolute risk reduction. All results in the present study originated from a nationwide registry database. Hepatocellular carcinoma is defined as a major disease and HCC patients can apply for a catastrophic illness certificate, which grants exemption from co-payment. It is nearly impossible for these HCC patients to withdraw from the NHI program before death. Therefore, there were no missing data or loss of follow-up in our study population.

All data management was performed using SAS 9.2 software (SAS Institute Inc). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the "cmprsk"

package of R (http://cran.r-project.org/web/packages/cmprsk/index.html). Calculated results were expressed as the estimated number together with the 95% confidence interval. Based on statistical power at 0.9, type I error rate at .05, and our case numbers in both cohorts, the detectable risk difference was estimated to be 0.02.

RESULTS

Demographic Characteristics of the HCC Cohort

We first identified 100 938 potentially eligible HCC patients admitted for the first time and registered in the RCIPD. We excluded 78 948 patients who did not receive liver resection and 8173 patients who received liver resection before October 1, 2003. In addition, 7870 patients without HBV infection or coinfection with hepatitis C or other hepatitis were excluded. Those using antiviral agents 3 months before liver resection or for less than 3 months were also not enrolled. There were 1019 patients who received other liver therapy or with another type of tumor before liver resection who were excluded. Another 359 patients with follow-up for less than 3 months were not included in the study. Therefore, 4569 patients were enrolled into the study cohorts (untreated, 4051 patients; treated, 518 patients) (FIGURE 1). In the treated cohort, 487 patients received only 1 nucleoside analogue, including 159 patients who received lamivudine, 292 patients who received entecavir, and 36 patients who received telbivudine. The remaining patients received more than 1 nucleoside analogue.

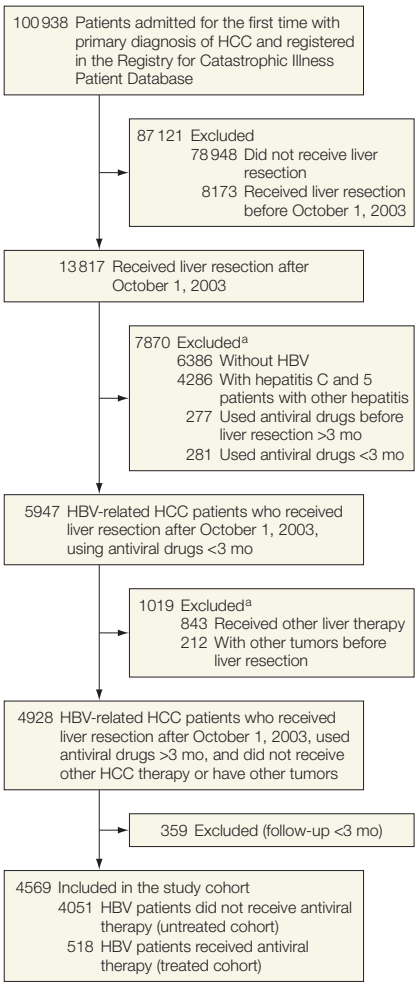
Demographic characteristics, confounding drugs, comorbidities, and follow-up durations of the study cohorts are presented in Table 1. The follow-up durations for the untreated cohort were a mean (SD) of 2.18 (1.77) years and a median (interquartile range [IQR]) of 1.57 (0.77-3.15) years, and for the treated cohort, a mean (SD) of 2.64 (1.74) years and a median (IQR) of 2.18 (1.21-3.69) years. The mean (SD) interval to start of antiviral therapy after liver resection was 1.19 (1.38) years and the median (IQR) was 0.66 (0.14-1.84) years. The mean (SD) duration of nucleoside analogue use in treated patients was 1.45 (1.38) years and the median (IQR) was 0.95 (0.48-1.94) years. The mean (SD) propensity score for the untreated cohort was 0.11 (0.03) and the median (IQR) was 0.11 (0.09-0.14), and for the treated cohort, the mean (SD) was 0.12 (0.03) and the median (IQR) was 0.12 (0.10-0.15). The treated cohort had a significantly higher prevalence of liver cirrhosis (48.6%) when compared with the untreated cohort (38.7%) ($P<.001$).

Six-Year Cumulative Incidences of HCC Recurrence and Overall Mortality

Among the 359 patients excluded with follow-up of less than 3 months there were 226 HCC recurrences and 93 deaths. During the observation period, 1765 patients in the untreated cohort (43.6%) and 106 patients in the treated cohort (20.5%) developed HCC recurrence. Death before the recurrence of HCC was defined as competing mortality. Compared with the untreated cohort (451 deaths; 11.1%), only 26 patients (5.0%) died before HCC recurrence in the treated cohort. The major identifiable causes of competing mortality in the untreated cohort were HCC or HCC treatment–related mortality (314 patients), liver cirrhosis (14), pneumonia (12), sepsis (9), and gastrointestinal bleeding (7). The identifiable causes of competing mortality in the treated cohort included HCC or HCC treatment–related mortality (20 patients), pneumonia (2), liver cirrhosis (1), and sepsis (1). During the follow-up period, overall deaths for the untreated and treated cohorts were 1145 (28.3%) and 55 (10.6%), respectively. For overall mortality, the major identifiable causes of death in the untreated cohort were HCC or HCC treatment–related mortality (832 patients), liver cirrhosis (47), sepsis (28), pneumonia (22), and gastrointestinal bleeding (21). The major identifiable causes of overall mortality in the treated cohort were HCC or HCC treatment–related mortality (38 patients), liver cirrhosis (5), pneumonia (5), and sepsis (3).

In FIGURE 2, cumulative incidences of HCC recurrence after adjustment for competing mortality are shown. The risk of HCC recurrence was significantly lower for patients in the treated cohort (6-year cumulative incidence, 45.6%; 95% CI, 36.5%-54.6%) than for patients in the untreated cohort (54.6%; 95% CI, 52.5%-56.6%) ($P<.001$). The difference in 6-year cumulative incidence was 9%. The unadjusted NNT associated with 1 less HCC recurrence within 6 years was 12 (95% CI, 7.4-22.6). This implies that use of nucleoside analogues in 12 HCC patients af-

Figure 1. Selection of Study Patients



HBV indicates hepatitis B virus; HCC, hepatocellular carcinoma.
[a] Numbers for exclusions may not sum because of patients fulfilling more than 1 criterion.

ter liver resection is associated with 1 less HCC recurrence within 6 years.

In the eFigure, we stratified patients by liver cirrhosis and NSAID use. We found that nucleoside analogue use was associated with lower risk of HCC recurrence in noncirrhotic patients, but not in cirrhotic patients. For NSAID users and nonusers, use of nucleoside analogues was associated with reduced risk of HCC recurrence.

Likewise, the risk of overall mortality was significantly lower in patients in the treated cohort (6-year cumulative incidence, 29.0%; 95% CI, 20.0%-38.0%) than in patients in the untreated cohort (42.4%; 95% CI, 40.0%-44.7%) ($P<.001$) (Figure 2). The difference in 6-year overall mortality was 13.4%. The unadjusted NNT associated with 1 less death within 6 years was 8 (95% CI, 5.7-11.0). This implies that use of nucleoside analogues in 8 HCC patients after liver resection is associated with 1 less death within 6 years.

Multivariable Analysis

Compared with the untreated cohort, the treated cohort was associated with a significantly lower risk of HCC recurrence (HR, 0.67; 95% CI, 0.55-0.81; $P<.001$). Use of statins (HR, 0.68; 95% CI, 0.53-0.87; $P=.002$) and use of NSAIDs or aspirin (HR, 0.80; 95% CI, 0.73-0.88; $P<.001$) were significantly associated with lower risk of tumor recurrence. Liver cirrhosis was found to be an independent risk factor for HCC recurrence (HR, 1.23; 95% CI, 1.12-1.35; $P<.001$) (TABLE 2). Each incremental year of use of nucleoside analogues was associated with reduced risk of HCC recurrence (HR, 0.59; 95% CI, 0.51-0.68; $P<.001$) (eTable 3).

Multivariable Stratified Analysis

The treated cohort was found to be associated with a reduced risk of HCC recurrence on all stratified analyses, including for noncirrhotic patients (HR, 0.56; 95% CI, 0.42-0.76) and diabetic patients (HR, 0.52; 95% CI, 0.31-0.89) (FIGURE 3). These observations further confirmed the association between nucleoside analogue use and attenuated risk of HCC recurrence in HBV-related HCC patients after liver resection.

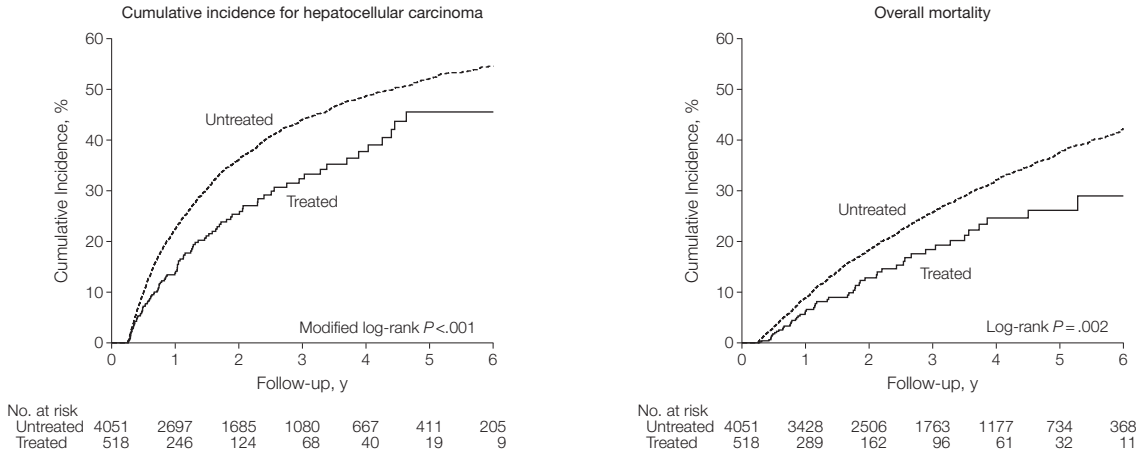
COMMENT

The roles of HBV in HCC recurrence have been widely investigated. Kubo et al[5] first reported that high viral load is an independent risk factor for HCC recurrence after liver resection in HBV-related HCC patients. Hung et al[6] found that HBV viral load of greater than 2000 IU/mL is associated with an odds ratio as high as 22.3 for HCC recurrence after liver resection. The association between serum HBV loads and risk of HCC recurrence after liver resection or transcatheter arterial embolization has been confirmed in previous studies.[3,26,27]

In the present study, we did not have data regarding a patient's HBV viral load or liver function. However, Taiwan's NHI program has strict regulations regarding reimbursement for nucleoside analogues. Reimbursement is granted only to patients in high-risk populations (eTable 1). Under such regulations, patients in the treated cohort should have a higher baseline HBV viral load, higher ALT level, or higher prevalence of liver decompensation than those in the untreated cohort to be eligible for reimbursement. In the present study, the treated cohort had higher prevalence of liver cirrhosis. If higher HBV viral load is associated with higher risk of HCC recurrence, higher baseline HBV viral load in the treated patients may have led to a more conservative estimation of the association in the present study.

Although it is generally accepted that HBV viral load plays an important role

Figure 2. Cumulative Incidences of HCC Recurrence and Overall Mortality Following Liver Resection



Data were compiled after adjustment for competing mortality. For cumulative incidences of hepatocellular carcinoma (HCC), calculation and comparison in competing risk data ratios were conducted using modified Kaplan-Meier and Gray methods. For overall mortality, Kaplan-Meier method was used. Recurrences (for cumulative incidences of HCC) and deaths (for overall mortality) during the first 3 months were excluded. Treated and untreated categories indicate patients with hepatitis B virus who are receiving nucleoside analogues, and those who are not, respectively.

in HCC recurrence, studies regarding the effectiveness of nucleoside analogues in HCC recurrence have been very limited and have produced conflicting results.[28] Based on a study of 14 patients receiving lamivudine and 10 control participants, Kubo et al[13] found a lower 5-year HCC disease-free survival rate after surgery in the lamivudine-treated patients. Chan et al[14] reported that the 5-year tumor free survival rates in the lamivudine or entecavir-treated group (42 participants; 51.4%) were significantly higher than in the control group (94 participants; 33.8%). In contrast, Li et al[29] found no significant differences in the 1-year tumor-free survival after curative hepatectomy between the lamivudine (43 participants; 23.3%) and control (36 participants; 8.3%) groups. Kuzuya et al[12] demonstrated that 5-year cumulative recurrence rates of HCC do not differ in a study of 16 patients receiving lamivudine and 33 control participants. In the present study, we confirmed the association between nucleoside analogue use and reduced risk of HCC recurrence in HBV patients after liver resection based on a nationwide database. However, reimbursement for oral antiviral agents for HBV infection is strictly limited to specified indications in Taiwan, and HCC does not qualify as an indication. Therefore, most of the HBV-infected HCC patients in the present study did not fulfill the NHI criteria for oral antiviral therapy.

Table 2. Risk of HCC Recurrence After Adjusting for Competing Mortality[a]

	No.	HCC Recurrence No.	HR (95% CI)[b]	*P* Value
Treated vs untreated[c]				
Untreated	4051	1765	1 [Reference]	
Treated	518	106	0.67 (0.55-0.81)	<.001
Age				
<50 y	1568	655	1 [Reference]	
50-59 y	1466	590	0.96 (0.83-1.10)	.53
≥60 y	1535	626	1.01 (0.90-1.13)	.92
Sex				
Women	799	306	1 [Reference]	
Men	3770	1565	1.08 (0.95-1.23)	.22
Resection[d]				
Minor	2999	1228	1 [Reference]	
Major	1570	643	1.04 (0.90-1.20)	.61
Liver cirrhosis				
No	2748	1046	1 [Reference]	
Yes	1821	825	1.21 (1.04-1.40)	.01
Diabetes				
No	3834	1554	1 [Reference]	
Yes	735	317	1.18 (0.99-1.41)	.07
Statin use[e]				
No	4394	1814	1 [Reference]	
Yes	175	57	0.68 (0.53-0.87)	.002
NSAID or aspirin use[e]				
No	2117	932	1 [Reference]	
Yes	2452	939	0.80 (0.73-0.88)	<.001
Metformin use[e]				
No	4011	1634	1 [Reference]	
Yes	558	237	1.01 (0.84-1.21)	.92
Propensity score				
Each incremental 10%	4569	1871	1.05 (0.78-1.41)	.74

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.
[a] Multivariable analysis is by Cox proportional hazards model.
[b] Adjusted for covariate factors, including age, sex, resection extent, liver cirrhosis, diabetes, and use of statins, NSAIDs, aspirin, and metformin.
[c] Treated and untreated categories indicate patients with hepatitis B virus who are receiving nucleoside analogues, and those who are not, respectively.
[d] Major resection indicates extensive and partial hepatic lobectomy with at least 3 segmental resections of liver parenchyma; minor resection indicates extensive and partial hepatectomy with 2 or fewer segmental resections of liver.
[e] Drug users indicate patients using a drug at least 1 day per month on average.

In previous studies, HCC with cirrhosis has been associated with decreased overall survival compared with HCC without cirrhosis after curative liver resection.[2] However, the outcome of patients with HBV-related compensated cirrhosis has not been shown to be worse than that of noncirrhotic patients.[4] In the present study, nucleoside analogue use was not only associated with improved disease-free survival, but also with improved overall survival in HBV-related HCC after liver resection. The higher prevalence of cirrhosis in the treated cohort was the main reason that the absolute difference in HCC recurrence rates (54.6% vs 45.6%) was much smaller than the HR (0.67) observed on multivariable analysis.

On multivariable analysis, we found that statin and NSAID or aspirin use were associated with a lower risk of HCC recurrence. The protective role of statins in HBV-infected HCC has been reported in a recent study.[30] The potential mechanisms involve AMP-activated protein kinase, p21 expression, endoplasmic reticulum stress, and autophagy.[31] The association between the use of NSAIDs or aspirin and a lower risk of HCC recurrence is a novel finding. Aspirin has been reported to induce cell cycle arrest and apoptosis, mediated by increased metabolic and oxidative stress.[32] An in vivo study showed that aspirin results in tumor growth inhibition.[33] More recently, Sitia et al demonstrated that aspirin diminishes the number of intrahepatic HBV-specific CD8(+) T cells and HBV-nonspecific inflammatory cells, the severity of liver fibrosis, and the development of HCC in an HBV transgenic mouse model.[34] Based on prior studies and our results, we postulated that NSAIDs, including aspirin, may be beneficial for reducing tumor recurrence in HCC patients. Future randomized controlled trial studies are necessary to clarify this issue.

There are several limitations to the present study. First, a causal associa-

tion between a drug of interest and risk of HCC recurrence cannot be inferred based on an observational study. Confounding by indication may exist and account for differences in outcomes. The patients in the study cohorts may differ in many measured and unmeasured ways. We did not have personal information for our patients such as lifestyle, family history of malignant diseases, body mass index, or laboratory parameters including HBV DNA viral load, which may contribute to tumor recurrence risk. To avoid these biases, we selected only patients receiving curative liver resection because resectable patients are comparable in terms of disease extent and remnant liver function. We analyzed propensity scores and Charlson scores to examine the comparability of these 2 cohorts. Multivariable analysis was performed to adjust for potential confounders. Furthermore, we conducted multivariable stratified analysis to examine the risk of HCC recurrence after liver resection for the study cohorts in different strata. Although unmeasured confounders may still exist, we believe the methodology used in the present study is solid and robust.

Second, coding error is possible in a database. We were unable to check the accuracy of nucleoside analogue use in the NHIRD. However, the information regarding insurance-paid nucleoside analogues was accurate because every prescription is strictly regulated and only patients fitting specific criteria are eligible to receive reimbursement.

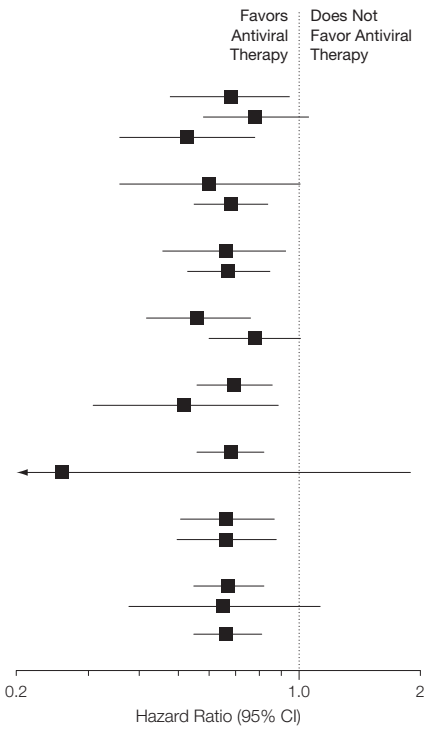
Third, some patients may have used self-paid nucleoside analogues and thus may have been inappropriately classified into the untreated cohort. Conversely, nucleoside analogue users in the treated cohort may have poor compliance. These potential misclassifications may have led to an underestimation of the association.

Fourth, HCC recurrence was defined as rehospitalization with a primary diagnosis of HCC and further HCC therapy. It is possible that some incidence of HCC recurrence might have been missed, for example if a patient did not receive therapy for the recurrence. Since all enrolled participants were able to undergo curative resection, the majority of them were unlikely to give up therapy for a recurrence. Furthermore, such misclassification would have underestimated the incidence of recurrent HCC in both cohorts and biased the results toward null difference.

Fifth, information about adverse events of nucleoside analogues was not available from the NHIRD. However,

Figure 3. Multivariable Stratified Analyses for the Association Between Nucleoside Analogue Use and HCC Recurrence

Subgroup	Untreated, No. Patients	Untreated, No. Recurrence	Treated, No. Patients	Treated, No. Recurrence	Hazard Ratio (95% CI)
Age, y					
<50	1418	619	150	36	0.68 (0.48-0.95)
50-59	1267	546	199	44	0.78 (0.58-1.06)
≥60	1366	600	169	26	0.53 (0.36-0.78)
Sex					
Male	716	291	83	15	0.60 (0.36-1.01)
Female	3335	1474	435	91	0.68 (0.55-0.84)
Resection					
Major	1431	612	139	31	0.66 (0.46-0.93)
Minor	2620	1153	379	75	0.67 (0.53-0.85)
Cirrhosis					
No	2482	1000	266	46	0.56 (0.42-0.76)
Yes	1569	765	252	60	0.78 (0.60-1.01)
Diabetes					
No	3388	1462	446	92	0.69 (0.56-0.86)
Yes	663	303	72	14	0.52 (0.31-0.89)
Statin					
No	3893	1709	501	105	0.68 (0.56-0.82)
Yes	158	56	17	1	0.26 (0.04-1.89)
NSAIDs or aspirin					
No	1870	878	247	54	0.66 (0.51-0.87)
Yes	2181	887	271	52	0.66 (0.50-0.88)
Metformin					
No	3553	1540	458	94	0.67 (0.55-0.82)
Yes	498	225	60	12	0.65 (0.38-1.13)
Overall	4051	1765	518	106	0.66 (0.55-0.81)



Among hepatitis B virus–related patients with hepatocellular carcinoma (HCC), nucleoside analogue use (treated cohort) was found to be associated with reduced risk of HCC recurrence on nearly all analyses (stratified by age, sex, extent of liver resection, liver cirrhosis, diabetes, and use of statins, nonsteroidal anti-inflammatory drugs [NSAIDs], and metformin). Some hazard ratios were not statistically significant due to a small number of cases. Recurrences during the first 3 months were excluded. Treated and untreated categories indicate patients with hepatitis B virus who are receiving nucleoside analogues, and those who are not, respectively. Major resection indicates extensive and partial hepatic lobectomy with at least 3 segmental resections of liver parenchyma; minor resection indicates extensive and partial hepatectomy with 2 or fewer segmental resections of liver.

there is evidence of excellent short-term safety profiles for the available nucleoside analogues for chronic hepatitis B.[35] Therefore, adverse events associated with oral anti-HBV therapy were very unlikely to substantially influence clinical outcomes in the present study. Sixth, we did not treat nucleoside analogue use as a time-dependent variable in the Cox model. Instead, we used the incident user design in this study, in which exposure time begins with the start of new antiviral agents. This minimizes the potential for immortal person-time bias prior to treatment exposure, which may result in a downward trend toward underestimation of the risk rate ratios.

In conclusion, nucleoside analogue use was associated with a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection.

Published Online: November 12, 2012. doi:10.1001/2012.jama.11975

Author Contributions: Dr C.-Y. Wu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs C.-Y. Wu and Chen contributed equally to this article as first authors; Drs C.-Y. Wu and Lin are both corresponding authors.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: The National Health Research Institutes provided access to the National Health Insurance Research Database (NHIRD) and financial support for the hiring of a research assistant. This work was supported by Taiwan's National Health Research Institute (PH-101-PP-23). This study is based on data from the NHIRD provided by the Bureau of National Health Insurance, Department of Health, and managed by the NHIRD, Taiwan.

Role of the Sponsor: The NHRI had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclaimer: The interpretations and conclusions contained in this article do not represent those of the Bureau of National Health Insurance, Department of Health, or the NHRI. National Health Insurance Research Database, Taiwan. http://www.nhri.org.tw/nhird/en/index.htm.

Online-Only Material: eTables 1 to 3 and an eFigure are available at http://www.jama.com.

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