MAJOR ARTICLE

Increased Risk of Cirrhosis and Its Decompensation in Chronic Hepatitis B Patients With Newly Diagnosed Diabetes: A Nationwide Cohort Study

Yi-Wen Huang,[1,2,3,4] Ting-Chuan Wang,[5] Shih-Chang Lin,[5] Han-Yu Chang,[1] Ding-Shinn Chen,[3,4] Jui-Ting Hu,[1,6] Sien-Sing Yang,[1,6] and Jia-Horng Kao[3,4,7,8]

[1]Liver Center, Cathay General Hospital Medical Center, [2]School of Medicine, Taipei Medical University, [3]Division of Gastroenterology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, [4]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, [5]Department of Medical Research, Cathay General Hospital Medical Center, [6]School of Medicine, Fu-Jen Catholic University College of Medicine, [7]Hepatitis Research Center, and [8]Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan

Background. The impact of diabetes on cirrhosis, its decompensation, and their time relationship in patients with chronic hepatitis B (CHB) remain unclear.

Methods. We conducted a nationwide cohort study by using the Taiwanese National Health Insurance Research Database, which was comprised of data from >99% of the entire population. Among 1 million randomly sampled enrollees, 14 523 adult CHB patients were identified from 1997 to 2009. Diabetes was defined as newly diagnosed in CHB patients who were given the diagnosis in the years 1998–2001 but not in 1996–1997 and with physician visits of at least twice per year. The cohorts of CHB with newly diagnosed diabetes (n = 351) and without diabetes (n = 7886) were followed up from the diagnosis of diabetes and from 2000 in the patients without diabetes until development of cirrhosis or its decompensation, withdrawal from insurance, or December 2009.

Results. Kaplan-Meier survival analysis showed a significantly higher cumulative incidence of cirrhosis (relative risk [RR] = 3.43; 95% confidence interval [CI], 2.62–4.49; $P < .001$, log-rank test) and decompensated cirrhosis (RR = 4.11; 95% CI, 2.95–5.70; $P < .001$, log-rank test) among patients with newly developed diabetes compared with those without diabetes. After adjustment for age, sex, CHB treatment, hepatocellular carcinoma, and comorbidity index by Cox proportional hazards model, diabetes was still an independent predictor for cirrhosis (hazard ratio [HR] = 2.015; 95% CI, 1.393–2.915; $P < .001$) and its decompensation (HR = 1.792; 95% CI, 1.192–2.695; $P = .005$).

Conclusions. Patients with CHB who develop diabetes are at an increased risk of liver cirrhosis and its decompensation over time.

Keywords. population; database; decompensated cirrhosis; time-relationship; comorbidity.

Hepatitis B virus (HBV) infection is a global health problem. Approximately 2 billion people in the world have been infected by HBV, 350 million of whom are chronic carriers of the virus [1]. The infection can cause acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma [1, 2]. HBV-related liver cirrhosis is one of the leading causes of death worldwide [3]. Diabetes mellitus is a very common disease and has been proposed as a risk factor for cirrhosis in patients with chronic hepatitis B [4–6]. The prevalence of diabetes increases with higher liver fibrosis score in chronic hepatitis B patients [7].

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Correspondence: Jia-Horng Kao, MD, PhD, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, No. 1, Chang-Te St, Taipei 10002, Taiwan (kaojh@ntu.edu.tw).

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However, the time relationship of diabetes for cirrhosis development of chronic hepatitis B patients in these studies remains largely unknown. Most, if not all, of these association studies between diabetes and cirrhosis in chronic hepatitis B patients were case-control studies. Because cirrhosis itself may lead to glucose intolerance and diabetes [8–10], whether the presence of diabetes will hasten cirrhosis development in hepatitis B virus carriers remains controversial. To study the impact of diabetes on cirrhosis development requires a longitudinal chronic hepatitis B cohort to enroll patients with newly diagnosed diabetes prior to the emergence of cirrhosis.

Taiwan is an HBV-endemic area. About half of Taiwanese chronic HBV carriers acquire the infection through perinatal transmission from carrier mothers to newborns [11], and the rest of them are infected early in life [12, 13]. The rate of spontaneous hepatitis B surface antigen clearance is extremely low [14–16]. Thus, although the diagnosis of chronic hepatitis B is made in adulthood, these patients have typically been infected for decades. In this large population-based cohort study, we evaluated the risk of cirrhosis and its decompensation in adult chronic hepatitis B patients who developed diabetes during long-term follow-up by using the National Health Insurance Research Database (NHIRD) in Taiwan.

METHODS

Ethics Statement

The procedures followed were in accordance with the ethical standards of the Institutional Review Board of the Cathay General Hospital (CGH-P101056) and with the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association. Informed consent was not obtained as the data were analyzed anonymously.

Databases

National Health Insurance in Taiwan is a nationwide health program introduced in March 1995. The NHIRD comprises of healthcare claims data from >99% of the 24 million inhabitants of Taiwan. NHIRD includes information on ambulatory and inpatient care, prescription drugs, and medical institutions. Diagnoses are coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*; Supplementary Table 1). For the precision of the claims data, the Bureau of National Health Insurance performs expert reviews on a random sample of every 50–100 ambulatory and inpatient claims in each hospital and clinic quarterly. False reports of diagnosis yield a severe penalty from the Bureau of National Health Insurance (BNHI).

Study Population

The study population included 1 million enrollees who were randomly sampled by BNHI from the original claims data of NHIRD. There was no significant difference in the sex ($P = .613$; http://w3.nhri.org.tw/nhird/en/Data_Subsets.html#S2) [17] and age distribution (http://nhird.nhri.org.tw/date_cohort.htm) between the patients in the randomly sampled data and the original NHIRD. Figure 1 depicts the flowchart of enrollment. We identified adult (>20 years of age) chronic hepatitis B patients by *ICD-9* codes (Supplementary Table 1) from 1997 to 2009. Newly diagnosed diabetes was defined as a diagnosis of diabetes in the years 1998–2001 but no such diagnosis during the years 1996–1997. To increase the accuracy of the diagnosis of diabetes, we enrolled diabetes patients with physician visits of at least twice per year. The nondiabetes cohort was comprised of chronic hepatitis B patients without an assigned diagnosis of diabetes from 1997 to 2009.

To increase the probability of capturing new (incident) cases of cirrhosis, we excluded patients with the diagnosis of cirrhosis or esophageal varices before the inception point for follow-up. We also excluded patients with the diagnosis of alcoholic cirrhosis or biliary cirrhosis. To increase the homogeneity of the study population, we excluded patients with alcoholic liver disease or hepatitis C infection. The time at risk of cirrhosis was measured from the inception point in the newly diagnosed diabetes cohort and from the year 2000 in the nondiabetes cohort until the development of cirrhosis, esophageal varices, withdrawal from insurance, or December 2009. Decompensated cirrhosis was defined as development of cirrhosis and encephalopathy, or cirrhosis and ascites, or inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD. One of the following criteria is required for cirrhotic patients to be registered in the RCIPD: (1) intractable ascites, (2) variceal bleeding, or (3) hepatic coma or liver decompensation. The time at risk of decompensated cirrhosis was measured from the inception point in the newly diagnosed diabetes cohort and from 2000 in the nondiabetes cohort until the development of decompensated cirrhosis, withdrawal from insurance, or December 2009.

We searched chronic hepatitis B patients receiving treatment by the Anatomical Therapeutic Chemical Classification System [18] (Supplementary Table 1): interferons, lamivudine, adefovir dipivoxil, telbivudine, and entecavir. In Taiwan, tenofovir was not reimbursed for the treatment of chronic hepatitis B in the entire study period. To adjust for the effect of comorbidities, we searched comorbid illnesses in the NHIRD to calculate the Deyo comorbidity index as a modification of the Charlson disease severity index [19]. The index comprises 12 diagnostic categories: myocardial infarction; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; rheumatic disease; peptic ulcer disease; hemiplegia or paraplegia; renal disease; any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin; metastatic solid tumor; and human

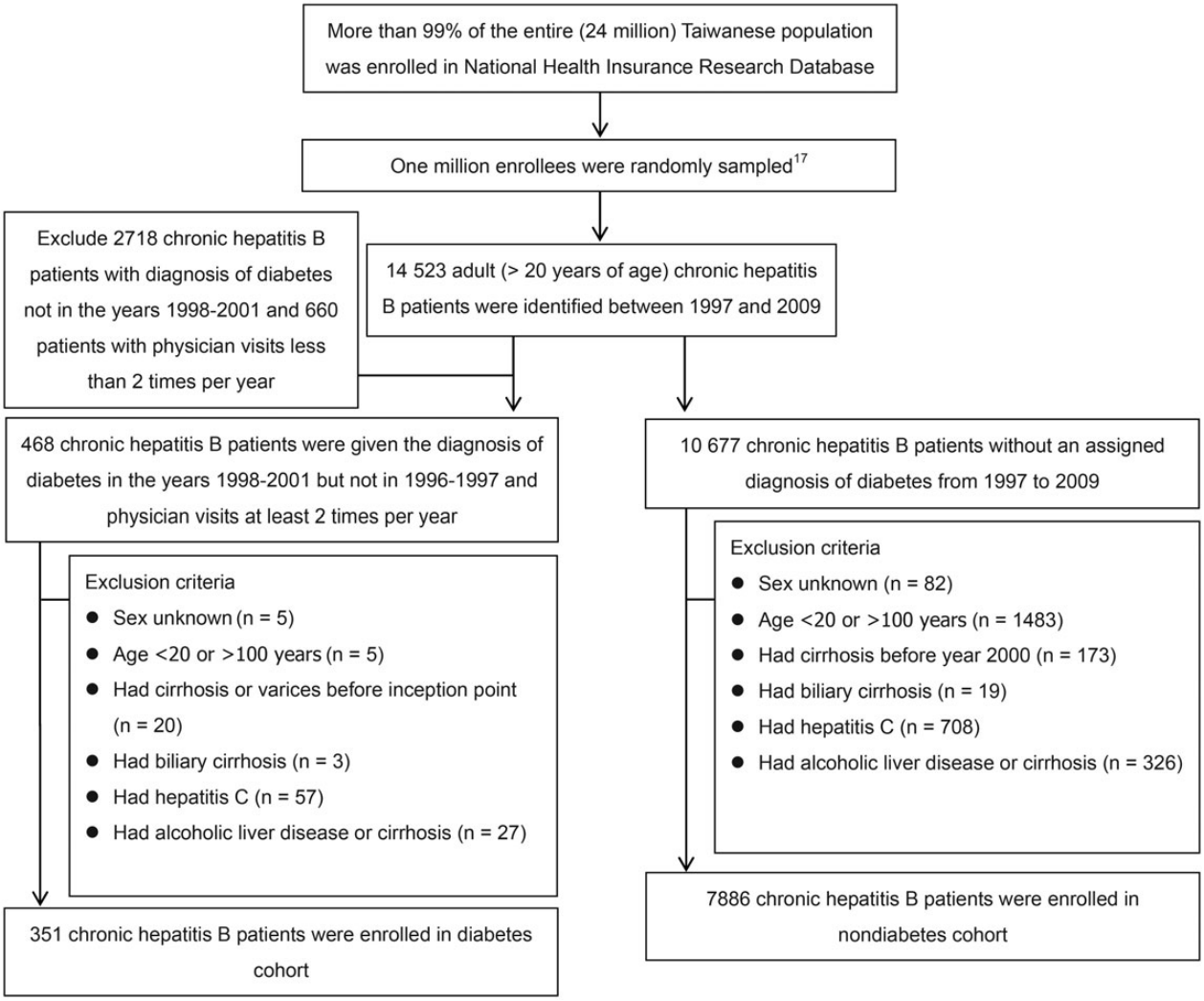

Figure 1. Flowchart of enrollment of chronic hepatitis B patients with newly diagnosed diabetes and those without diabetes (nondiabetes).

immunodeficiency virus/AIDS. In constructing the index, we did not include mild liver disease, moderate or severe liver disease, diabetes without chronic complication, or diabetes with chronic complication. The composite score for the modified Deyo comorbidity index was compared between the cohorts of chronic hepatitis B patients with newly diagnosed diabetes and those without diabetes, which was also included as a covariate in the Cox regression analysis.

Statistical Analyses

Demographics and clinical characteristics between chronic hepatitis B patients with newly diagnosed diabetes and those without diabetes were analyzed by χ^2 test for univariate comparisons between dichotomous variables, and Student *t* tests for continuous variables. All of the tests of significance were 2-tailed, and a *P* value of <.05 was considered statistically significant. The standardized incidence ratio and cumulative incidence of the study outcome were estimated in Kaplan-Meier survival analyses. The log-rank test was used to test the statistical significance for differences in the incidence rates of cirrhosis and its decompensation between patients with newly diagnosed diabetes and those without diabetes. The risks of cirrhosis and its decompensation were modeled in a Cox proportional hazards survival analysis that examined the risk associated with diabetes after adjustment for age in each incremental year, sex, chronic hepatitis B treatment, hepatocellular carcinoma (HCC), and comorbidity index. The SAS PROC LIFETEST package and SPSS software were used for the Kaplan-Meier survival analysis, and the SAS package PROC PHREG was used for the Cox proportional hazards model. All analyses were performed using SAS software version

Table 1. Comparison of Demographic and Clinical Characteristics Between Chronic Hepatitis B Patients With Newly Diagnosed Diabetes and Those Without Diabetes

Characteristics	Newly Diagnosed Diabetes (n = 351) No.	%	Nondiabetes (n = 7886) No.	%	*P* Value
Age, y, mean ± SD	49.04 ± 11.55		37.04 ± 11.96		<.001
20–39	74	21.1	5036	63.9	
40–59	211	60.1	2444	31.0	
60–79	64	18.2	394	5.0	
≥80	2	0.6	12	0.2	
Sex					.613
Male	209	59.5	4802	60.9	
Female	142	40.5	3084	39.1	
Follow-up, y, mean ± SD	9.34 ± 1.93		9.75 ± 1.13		<.001
Cirrhosis incidence	38	10.8	208	2.6	<.001
Comorbidity index score[a]	2.89 ± 2.60		1.64 ± 1.98		<.001
0	47	13.4	2307	29.3	
1	67	19.1	2489	31.6	
2	76	21.7	1494	18.9	
≥3	161	45.8	1596	20.2	
Myocardial infarction	7	2.0	51	0.6	.003
Congestive heart failure	31	8.8	213	2.7	<.001
Peripheral vascular disease	14	4.0	162	2.1	.014
Cerebrovascular disease	68	19.4	555	7.0	<.001
Dementia	10	2.8	69	0.9	<.001
Chronic pulmonary disease	169	48.1	2679	34.0	<.001
Rheumatologic disease	27	7.7	359	4.6	.006
Peptic ulcer disease	218	62.1	3800	48.2	<.001
Hemiplegia or paraplegia	8	2.3	59	0.7	.002
Renal disease	74	21.1	599	7.6	<.001
Any malignancy (including lymphoma and leukemia)	91	25.9	1139	14.4	<.001
Metastatic solid tumors	21	6.0	237	3.0	.002
HIV/AIDS	0	0.0	11	0.1	.484
Chronic hepatitis B treatment	28	8.0	617	7.8	.917
Hepatocellular carcinoma	21	6.0	197	2.5	<.001

Chronic hepatitis B treatment (Anatomical Therapeutic Chemical Classification System): interferons (L03AB, S01AD05), lamivudine (J05AF05), adefovir dipivoxil (J05AF08), telbivudine (J05AF11), and entecavir (J05AF10).

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

[a] Comorbidity index includes 12 disease categories described fully in the Methods section.

9.2 (SAS Institute, Cary, North Carolina) and SPSS program for Windows 10.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 14 523 adult chronic hepatitis B patients were identified. The diabetes cohort comprised 351 patients and the nondiabetes cohort 7886 patients (Figure 1). Table 1 showed the characteristics of patients in both cohorts. Patients with newly diagnosed diabetes were older by an average of 12 years than those without diabetes. Although patients without diabetes were followed up for an average of 0.4 years longer duration, a lesser proportion of them (2.6%) had cirrhosis as compared to patients with newly diagnosed diabetes (10.8%). Patients with newly diagnosed diabetes had a higher comorbidity index than those without diabetes (mean, 2.9 vs 1.6; $P < .001$). There were more HCCs in patients with newly diagnosed diabetes than in those without diabetes (6% vs 2.5%; $P < .001$). Cirrhosis preceded HCC in all patients with concomitant cirrhosis and HCC.

The Kaplan-Meier survival analysis showed that the standardized incidence ratio of cirrhosis was higher in chronic hepatitis B patients with newly diagnosed diabetes who were

Table 2. Risk Factors for Cirrhosis in a Population-Based Cohort of Chronic Hepatitis B Patients With Newly Diagnosed Diabetes and Those Without Diabetes

	Newly Diagnosed Diabetes (n = 351)		Nondiabetes (n = 7886)		
Variable	Cirrhosis, No.	SIR, %, Range	Cirrhosis, No.	SIR, %, Range	*P* Value[a]
Age					
20–39	3	4.05 (1.99–6.11)	53	1.05 (0.83–1.27)	.009
40–59	20	9.48 (6.42–12.54)	113	4.62 (4.16–5.08)	.002
60–79	15	23.44 (19.01–27.87)	42	10.66 (9.98–11.34)	.027
≥80	0	0	0	0	NA
Sex					
Male	26	12.44 (8.99–15.89)	165	3.44 (3.04–3.84)	<.001
Female	12	8.45 (5.54–11.36)	43	1.39 (1.13–1.65)	<.001
Chronic hepatitis B treatment					
Yes	8	28.57 (23.84–33.30)	66	10.70 (10.02–11.38)	.007
No	30	9.29 (6.25–12.33)	142	1.95 (1.64–2.26)	<.001
Hepatocellular carcinoma					
Yes	11	52.38 (31.02–73.74)	59	29.95 (23.55–36.35)	.036
No	27	1.94 (1.63–2.25)	149	8.18 (5.22–11.14)	<.001
Comorbidity index score[b]					
0	0	0	9	0.39 (0.25–0.53)	.696
1	1	1.49 (0.22–2.76)	25	1.00 (0.78–1.22)	.629
2	3	3.95 (1.91–5.99)	28	1.87 (1.57–2.17)	.146
≥3	34	21.12 (16.85–25.39)	146	9.15 (8.51–9.79)	<.001

Chronic hepatitis B treatment (Anatomical Therapeutic Chemical Classification System): interferons (L03AB, S01AD05), lamivudine (J05AF05), adefovir dipivoxil (J05AF08), and entecavir (J05AF10).

Abbreviations: CHB, chronic hepatitis B; NA, not applicable; SIR, standardized incidence ratio.

[a] Kaplan-Meier survival analysis with log-rank test.

[b] Comorbidity index includes 12 disease categories described fully in the Methods section.

between 20 and 79 years old, either men or women, either receiving chronic hepatitis B treatment or not, with concomitant HCC, and those with comorbidity index scores of ≥3, when compared to those without diabetes (Table 2). Furthermore, the Kaplan-Meier survival analysis also showed a significantly higher cumulative incidence of cirrhosis (log-rank test, $P < .001$; Figure 2), with a relative risk (RR) of 3.43 (95% confidence interval [CI], 2.62–4.49) as well as significantly higher cumulative incidence of decompensated cirrhosis (log-rank test, $P < .001$; Figure 3), with an RR of 4.11 (95% CI, 2.95–5.70) among chronic hepatitis B patients with newly diagnosed diabetes as compared to those without diabetes.

During the follow-up of 2900 person-years with newly diagnosed diabetes, 38 chronic hepatitis B patients developed cirrhosis (incidence rate, 1.31 per 10 000 person-years), whereas during the follow-up of 73 380 person-years without diabetes, 208 chronic hepatitis B patients developed cirrhosis (incidence rate, 0.28 per 10 000 person-years). Consistent with this increased incidence among chronic hepatitis B patients with newly diagnosed diabetes, the adjusted hazard ratios in the Cox proportional

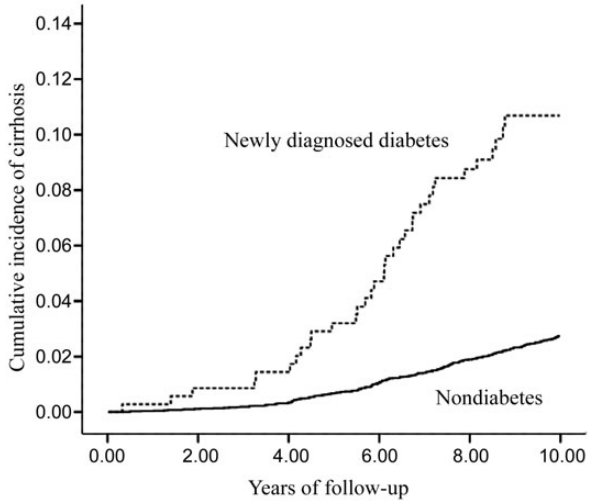

Figure 2. Cumulative incidence of cirrhosis in chronic hepatitis B patients with newly diagnosed diabetes and those without diabetes (nondiabetes).

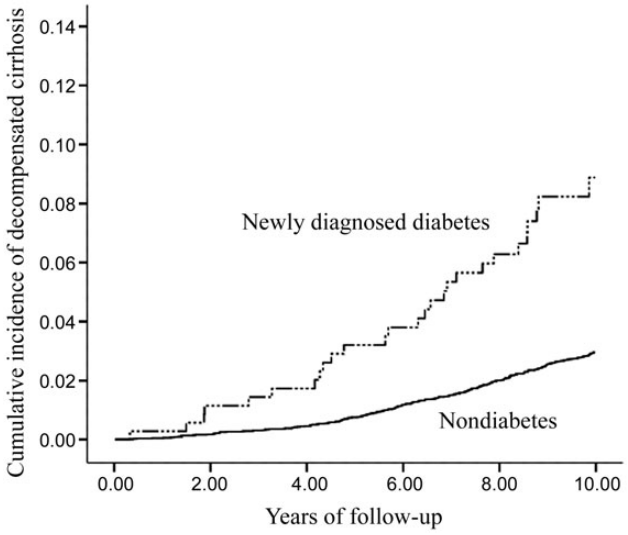

Figure 3. Cumulative incidence of decompensated cirrhosis in chronic hepatitis B patients with newly diagnosed diabetes and those without diabetes (nondiabetes).

hazards analysis for cirrhosis and its decompensation were 2.055 (95% CI, 1.420–2.975; $P < .001$) and 1.801 (95% CI, 1.198–2.708; $P = .005$), respectively, after controlling for differences in age, sex, chronic hepatitis B treatment, HCC, and comorbidity index (Tables 3 and 4, respectively). The Kaplan-Meier curves for cirrhosis and decompensated cirrhosis were superimposed in the nondiabetes cohort, suggesting that most of the diagnoses of cirrhosis were those of decompensated cirrhosis. However, new-onset diabetes not only increased the risk for decompensated cirrhosis but also compensated cirrhosis (Supplementary Figure 1 and Supplementary Table 2).

To further disentangle the effects of age and sex, we repeated the analysis in chronic hepatitis B patients (n = 1691) with newly diagnosed diabetes and those without diabetes by using a 1:4 ratio of age and sex random sample matching. After adjustment for differences in chronic hepatitis B treatment and comorbidity index, the risk for cirrhosis in the Cox proportional hazards analysis persisted. The hazard ratio was 1.700 (95% CI, 1.133–2.550; $P = .01$). Furthermore, the hazard rate ratio for cirrhosis persisted over time. The hazard rate ratio was 2.674 (95% CI, 0.756–9.456) at 3 years, 2.290 (95% CI, 1.329–3.947) at 6 years, and 2.306 (95% CI, 1.587–3.351) at 9 years.

Table 3. Risk Factors for Cirrhosis: Results of the Cox Proportional Hazards Analysis in a Population-Based Cohort of Chronic Hepatitis B Patients

Variable	Adjusted HR	95% CI	*P* Value
Newly diagnosed diabetes	2.055	1.420–2.975	<.001
Older age (per 1 y)	1.046	1.036–1.056	<.001
Men (vs women)	1.881	1.382–2.560	<.001
CHB treatment (vs no treatment)	3.642	2.743–4.835	<.001
Hepatocellular carcinoma	4.774	3.506–6.501	<.001
Comorbidity index[a]	1.195	1.146–1.246	<.001

All of these patients had no cirrhosis before the inception point and within 1 year of follow-up. All covariates included in the model are shown in the table. CHB treatment (Anatomical Therapeutic Chemical Classification System): interferons (L03AB, S01AD05), lamivudine (J05AF05), adefovir dipivoxil (J05AF08), telbivudine (J05AF11), and entecavir (J05AF10).

Abbreviations: CHB, chronic hepatitis B; CI, confidence interval; HR, hazard ratio.

[a] Comorbidity index includes 12 disease categories described fully in the Methods section.

Table 4. Risk Factors for Decompensated Cirrhosis: Results of the Cox Proportional Hazards Analysis in a Population-Based Cohort of Chronic Hepatitis B Patients

Variable	Adjusted HR	95% CI	*P* Value
Newly diagnosed diabetes	1.801	1.198–2.708	.005
Older age (per 1 y)	1.031	1.021–1.042	<.001
Men (vs women)	1.704	1.271–2.284	<.001
CHB treatment (vs no treatment)	5.015	3.834–6.560	<.001
Hepatocellular carcinoma	4.080	2.907–5.725	<.001
Comorbidity index[a]	1.118	1.068–1.171	<.001

All of these patients had no cirrhosis before the inception point and within 1 year of follow-up. All covariates included in the model are shown in the table. CHB treatment (Anatomical Therapeutic Chemical Classification System): interferons (L03AB, S01AD05), lamivudine (J05AF05), adefovir dipivoxil (J05AF08), telbivudine (J05AF11), and entecavir (J05AF10).

Abbreviations: CHB, chronic hepatitis B; CI, confidence interval; HR, hazard ratio.

[a] Comorbidity index includes 12 disease categories described fully in the Methods section.

DISCUSSION

This large population-based study in an HBV-endemic country with careful selection of patients with newly diagnosed diabetes strongly suggested that diabetes accelerates cirrhosis development and its decompensation in chronic hepatitis B patients. A causal relationship could be inferred by the findings of a temporal association by which diabetes preceded the development of liver cirrhosis and its decompensation.

Previous case-control studies reported that 21%–40% of patients with cirrhosis had diabetes [4, 5, 8, 9, 20, 21]; however, these studies failed to address the time relationship between diabetes and cirrhosis. The current study corroborated the significance of the correlation between diabetes and cirrhosis as well as its decompensation. Furthermore, our data showed that diabetes preceded cirrhosis development and its decompensation, in some cases by many years, providing strong support for a

causal association. In addition, the potential bias in determining the time relationship between diabetes and cirrhosis was minimized by the exclusion of patients with the diagnosis of cirrhosis or esophageal varices before the inception point for follow-up.

In previous case-control studies, it was difficult to determine the independent effect of diabetes due to inclusion of other strong risk factors for cirrhosis. We included homogeneous chronic hepatitis B patients with exclusion of comorbid illness of alcoholic liver diseases and hepatitis C virus infection in this large population study. Furthermore, we performed additional analyses in which the hazard ratio for cirrhosis and its decompensation was obtained while controlling for age, sex, chronic hepatitis B treatment, HCC, and comorbidity index. The results indicated that diabetes is a risk factor for cirrhosis and its decompensation, independent of the above-mentioned well-recognized risk factors.

Our study had several strengths. First, with the inclusion of 8237 chronic hepatitis B patients with a follow-up of up to 10 years in the analysis, we were able to demonstrate the increased risk of cirrhosis and its decompensation in newly diagnosed diabetes that might be over- or underestimated in a smaller study. Second, the use of the population-based Taiwanese NHIRD allowed the identification of a large cohort of chronic hepatitis B patients with good generalizability. Third, to our knowledge, this is the largest cohort study in the literature to evaluate the correlation between newly diagnosed diabetes and cirrhosis as well as its decompensation in chronic hepatitis B patients.

There were several limitations in this study. First, in large administrative datasets, there exists the possibility of misclassification of both the risk and the outcome of interest (diabetes and cirrhosis) such that the association cannot be verified. Taiwan National Health Insurance puts efforts into preventing false diagnosis by performing quarterly expert reviews on diagnosis and severe penalty on false diagnosis. Whereas most of the patients with diagnosis of diabetes are likely to have actual diabetes, those without diabetes diagnosis may have had diabetes but were underreported or underrecognized. Thus, this misclassification bias might tend to diminish the true effect of diabetes. Second, the validity of the *ICD-9* codes to define cirrhosis, esophageal varices, or decompensated cirrhosis was unknown. Nevertheless, errors in coding or recording tend to occur in random, as the same codes were used in both the diabetes and nondiabetes groups, and might have a limited effect on the calculated hazard ratios. Third, it is theoretically possible that cirrhosis, which itself could have driven development of diabetes, could have been detected later than the diabetes because it may have been clinically silent. However, this finding would not adequately explain the continued persistence of excess risk for cirrhosis seen as far as 9 years after diabetes diagnosis (Figure 2). Finally, potentially important variables related to diabetes might not be included in this study, such as the severity and treatment of diabetes, triglyceride level, and body mass index.

The mechanisms by which diabetes leads to fibrosis progression or cirrhosis in chronic hepatitis B remain unclear. The hypothesis of the detrimental effect of diabetes on cirrhosis has been linked to insulin resistance and hepatic steatosis [22, 23]. In chronic hepatitis B patients, diabetes independently correlates with grading of hepatic steatosis and fibrosis [7]. However, hepatic steatosis in HBV-infected patients is as frequent as in the general population and is not related to fibrosis [24]. Thus, diabetes, but not hepatic steatosis alone, may lead to fibrosis in patients with chronic hepatitis B. Further studies are needed to evaluate the underlying pathogenesis of diabetes in causing fibrosis progression or cirrhosis in chronic hepatitis B patients.

In summary, in a large population-based cohort study, after adjustment for age, sex, chronic hepatitis B treatment, HCC, and comorbidity index, newly diagnosed diabetes is still an independent predictor for cirrhosis development and its decompensation in patients with chronic hepatitis B. Chronic hepatitis B patients who develop diabetes during follow-up are at an increased risk of cirrhosis and its decompensation over time and should receive active management.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis, **2002**; 2:395–403.
2. Chen DS. From hepatitis to hepatoma: lessons from type B viral hepatitis. Science **1993**; 262:369–70.
3. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat **2004**; 11:97–107.

4. Huo TI, Wu JC, Lee PC, Tsay SH, Chang FY, Lee SD. Diabetes mellitus as a risk factor of liver cirrhosis in patients with chronic hepatitis B virus infection. J Clin Gastroenterol **2000**; 30:250–4.
5. Custro N, Carroccio A, Ganci A, et al. Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. Diabetes Metab **2001**; 27: 476–81.
6. Huo T, Wu JC, Hwang SJ, et al. Factors predictive of liver cirrhosis in patients with chronic hepatitis B: a multivariate analysis in a longitudinal study. Eur J Gastroenterol Hepatol **2000**; 12:687–93.
7. Papatheodoridis GV, Chrysanthos N, Savvas S, et al. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. J Viral Hepat **2006**; 13:303–10.
8. Megyesi C, Samols E, Marks V. Glucose tolerance and diabetes in chronic liver disease. Lancet **1967**; 2:1051–6.
9. Kingston ME, Ali MA, Atiyeh M, Donnelly RJ. Diabetes mellitus in chronic active hepatitis and cirrhosis. Gastroenterology **1984**; 87: 688–94.
10. Hsieh PS, Hsieh YJ. Impact of liver diseases on the development of type 2 diabetes mellitus. World J Gastroenterol **2011**; 17:5240–5.
11. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med **1975**; 292:771–4.
12. Ko YC, Li SC, Yen YY, Yeh SM, Hsieh CC. Horizontal transmission of hepatitis B virus from siblings and intramuscular injection among preschool children in a familial cohort. Am J Epidemiol **1991**; 133: 1015–23.
13. Hsu SC, Chang MH, Ni YH, Hsu HY, Lee CY. Horizontal transmission of hepatitis B virus in children. J Pediatr Gastroenterol Nutr **1993**; 16:66–9.
14. Liu J, Yang HI, Lee MH, et al. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. Gastroenterology **2010**; 139:474–82.
15. Tseng TC, Liu CJ, Su TH, et al. Serum hepatitis B surface antigen levels predict surface antigen loss in hepatitis B e antigen seroconverters. Gastroenterology **2011**; 141:517–25.
16. Tseng TC, Liu CJ, Yang HC, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology **2012**; 55:68–76.
17. National Health Insurance Research Database. Taiwan: data subsets. Available at: http://w3.nhri.org.tw/nhird/en/Data_Subsets.html#S2. Accessed 15 May 2011.
18. World Health Organization Collaborating Centre for Drug Statistics Methodology/ Norwegian Institute of Public Health. ATC/DDD Index 2013. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 4 January 2012.
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative databases. J Clin Epidemiol **1992**; 45:613–9.
20. Chen YW, Chen HH, Wang TE, et al. The dissociation between the diabetes and both Child-Pugh score and in-hospital mortality in cirrhotic patients due to hepatitis B, hepatitis C, or alcoholic. Hepatol Int **2011**; 5:955–64.
21. Amarapurkar D, Das HS. Chronic liver disease in diabetes mellitus. Trop Gastroenterol **2002**; 23:3–5.
22. Falchuk KR, Fiske SC, Haggitt RC, Federman M, Trey C. Pericentral hepatic fibrosis and intracellular hyalin in diabetes mellitus. Gastroenterology **1980**; 78:535–41.
23. El-serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology **2004**; 126:460–8.
24. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol **2011**; 26:1361–7.