Evaluation of the relationship between central serous chorioretinopathy and liver cirrhosis: A nationwide, population-based study

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Abstract

Background: Central serous chorioretinopathy (CSCR) and liver cirrhosis share numerous risk factors and may have possible connections. We aimed to investigate whether patients with liver cirrhosis and the severity of cirrhosis have an increased incidence of CSCR.

Methods: This population-based retrospective cohort study was conducted by collecting data from the Taiwan National Health Insurance Research Database from January 1, 2000, to December 31, 2015. We included patients who were newly diagnosed with cirrhosis and selected an equal number of sex- and age-matched control subjects. The effect of cirrhosis on the risk of CSCR was examined via a Cox proportional hazard regression analysis. The cumulative incidence of CSCR was assessed with the Kaplan-Meier method and the log-rank test.

Results: Both groups in this study comprised a total of 25 925 individuals. The cirrhotic patients had a significantly higher cumulative risk of developing CSCR in following years than patients without cirrhosis (log-rank test < 0.001). Furthermore, compared with noncirrhotic patients, the risk of CSCR was increased 3.59-fold (95% confidence interval [CI], 2.31-5.28) in cirrhotic patients with complications, and 2.34-fold (95% CI, 1.27-3.24) in cirrhotic patients without complications. Additionally, male sex, springtime, diabetes mellitus, hepatitis B virus, and hepatitis C virus statistical significantly increased the incidence of CSCR.

Conclusion: Cirrhosis is an independent indicator of CSCR. Among the cirrhotic population, patients with ascites and other complications have a higher incidence of CSCR than those with uncomplicated cirrhosis. Physicians should be observant when managing cirrhotic patients with visual disturbances.

Keywords: Central serous chorioretinopathy; Cirrhotic-related complications; Liver cirrhosis

1. INTRODUCTION

Central serous chorioretinopathy (CSCR), a disease characterized by serous retinal detachment mostly confined to the posterior pole of the retina, is responsible for many cases of visual loss among middle-aged men.[1] The exact physiopathology of CSCR is not completely understood. It is believed that dilatation and hyperpermeability of choroidal vessels, as well as disruption of the retinal pigment epithelium (RPE), contribute to the characteristic accumulation of subretinal fluid that occurs in CSCR.[2,3] There are several risk factors strongly associated with CSCR; they include hypertension (HTN), coronary artery disease (CAD), heart failure, pregnancy, *Helicobacter pylori* (*H pylori*) infection, alcohol, tobacco use, exogenous corticosteroids and endogenous cortisol, autonomic dysfunction, type-A personality, and genetic susceptibility loci.[4–12]

Cirrhosis, a degenerative chronic liver disease characterized by fibrosis of normal liver tissue, is mostly caused by viral infection and alcoholic and nonalcoholic steatohepatitis. In Taiwan, the prevalence of liver cirrhosis is high and cirrhosis complications and hepatocellular carcinoma (HCC) are among the top 10 causes of death. In cirrhosis, portal HTN develops due to increased resistance within the liver and this change leads to increased splenic blood flow and peripheral arterial vasodilation. As the disease progresses, vasodilation and arterial underfilling stimulate systemic activation of the renin–angiotensin–aldosterone system (RAAS), resulting in sodium and water retention. The presence of ascites, which is the most common complication of cirrhosis, marks the advancement of the disease to the decompensated stage.[13–15] Apart from ascites, other complications of

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live cirrhosis include gastroesophageal varices, hepatic encephalopathy, HCC, and hepatorenal syndrome (HRS).[16] Diabetes mellitus (DM), male sex, alcohol, and tobacco consumption have been suggested as contributing factors for the development of liver cirrhosis.[17] In addition, several studies had shown that cirrhotic patients were associated with higher prevalence *H pylori* infection when compared with controls.[18]

Although cirrhosis and CSCR possess similar predisposing factors such as male sex, hyperlipidemia, DM, alcohol, and tobacco use, studies on the association between the two diseases are scarce. The available published data include studies on the relationship between chronic liver disease and several retinal pathologic features including vitamin A deficiency–related ocular diseases, color blindness, retinal hemorrhage, cotton wool spots, and increased formation of exudates[19,20]; only one report addressed a case of an alcoholic liver cirrhosis patient who suffered from CSCR.[21] Therefore, in this study, we used population-based data from the National Health Insurance Research Database (NHIRD) to determine the relationship between CSCR and liver cirrhosis in patients with and without cirrhotic-related complications.

2. METHODS

2.1. Database

This was a retrospective cohort study used the data from Longitudinal Health Insurance Database (LHID) of the years 2000 to 2015, which is composed of the claim data of one million beneficiaries randomly selected from the Taiwan National Health Insurance (NHI) Program. The government of Taiwan implemented a mandatory NHI Program for eligible residents since 1995. Around 23 million people (98% of the population in Taiwan) are covered in the system and this high coverage rate has made the NHI program one of the biggest nationwide population databases around the world. We assessed the recorded diagnoses and medical procedure of ascites drainage based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes adopted by NHIRD. The study protocol was approved by the institutional review board of Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (TSGHIRB No. 1-108-05-109).

2.2. Selection of patients and variables

In the present study, we tracked and assessed the risk of developing CSCR (ICD-9-CM 364.21) in adult patients (aged 20 years or above) diagnosed with liver cirrhosis without mention of alcohol (ICD-9-CM 571.5) between January 1, 2000, and December 31, 2015. Alcoholic liver cirrhosis (ICD-9-CM 571.2) was not included because alcohol use has been identified as a common risk factor for cirrhosis and CSCR. The enrolled inpatients or outpatients with liver cirrhosis were required to have visited the clinic more than three times. We defined the date of liver cirrhosis diagnosis as the index date. Patients who were diagnosed with liver cirrhosis before the index date and patients

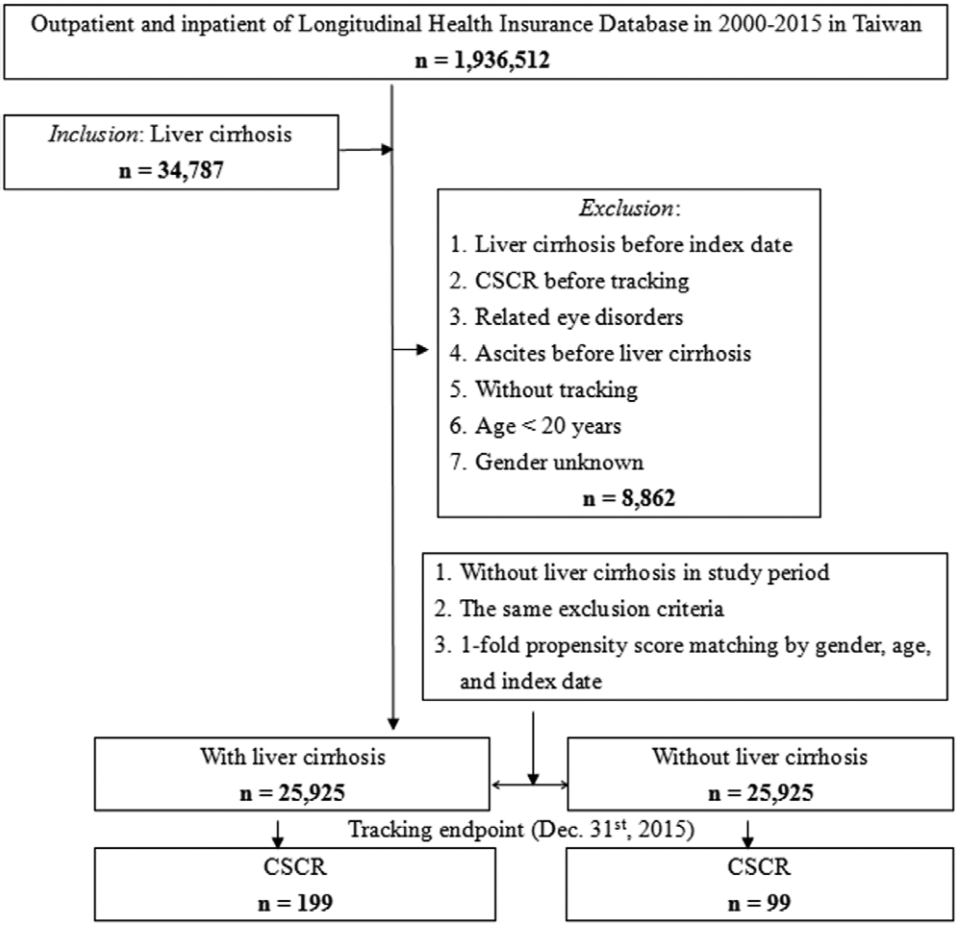


Fig. 1 Flowchart of the selection process of the study population from the National Health Insurance Research Database in Taiwan. CSCR = Central serous chorioretinopathy.

of unknown sex were excluded from the study. To increase the precision of the study, we also excluded patients diagnosed with CSCR before 2000 and those who suffered from related eye disorders with choroidal and RPE abnormalities including exudative senile macular degeneration (ICD-9-CM 362.52), macular hole (ICD-9-CM 362.54), myopic degeneration(ICD-9-CM 360.21), hemorrhagic RPE detachment (ICD-9-CM 362.43), focal and disseminated retinochoroiditis (ICD-9-CM 363.0, 363.1), hereditary retinal dystrophies (ICD-9-CM 362.7), Harada's disease (ICD-9-CM 363.22), angioid streak (ICD-9-CM 363.43), diabetic retinopathy (ICD-9-CM 362.01-362.06), diabetic macular edema (ICD-9-CM 362.07 must be used with a code for diabetic retinopathy [ICD-9-CM 362.01-362.06]), hypertensive retinopathy (ICD-9-CM 362.11), and hypertensive choroidopathy (ICD-9-CM 363.8 must be used with a code for essential HTN [ICD-9-CM 401] or secondary HTN [ICD-9-CM 405]) or choroidal malignancies (ICD-9-CM 190.6) within 1 year before or after the diagnosis of CSCR. The control cohort, which included subjects without liver cirrhosis during tracking period, shared the same exclusion criteria. The nonliver cirrhosis control cohort was 1-fold matched by sex, age, and index year. Therefore, both groups contained 25 925 individuals. The tracking endpoint was December 31, 2015 (Fig. 1).

We performed further subgroup analyses to investigate the risk of CSCR in cirrhotic patients with and without cirrhotic complications including ascites (ICD-9-CM code 789.5 or ICD-9 v3 Procedure Codes 54.91), gastroesophageal varices (ICD-9-CM 456.0, 456.1, 456.2, code first 571.5 or 572.3), hepatic encephalopathy (ICD-9-CM 572.2 0, 070.0, 070.2, 070.71), HCC (ICD-9-CM 155.0 and 155.2), and HRS (ICD-9-CM 572.4). In addition, each cirrhotic individual with complication often have more than one cirrhosis-related complications. To reduce the possibility of over-correction and interference of these factors, we classified patients with liver cirrhosis into complicated liver cirrhosis and uncomplicated liver cirrhosis. Complicated liver cirrhosis were defined as patients with a code for ascites or gastroesophageal varices, or hepatic encephalopathy, or HCC, or HRS, and all remaining cases were classified as uncomplicated liver cirrhosis. Patients diagnosed with complications before the date of cirrhosis diagnosis were excluded.

The covariates included sex, age group (20-29, 30-39, 40-49,50-59, ≥60 years), and monthly income (<18 000, 18 000-34 999, ≥35 000 [New Taiwan Dollars]). The history of drug use (including statin, metformin, proton pump inhibitor, aspirin, non-steroidal anti-inflammatory drugs, nonselective beta blocker, and antiviral therapy for hepatitis B virus [HBV] and hepatitis C virus [HCV]) of the individuals in this study was assessed.

With reference to previous reports that collected data from the NHIR, baseline comorbidities previously known as CSCR risk factors including peptic ulcer (ICD-9-CM codes 531-534), psychiatric disorders (ICD-9-CM codes 292-302, 304-309, 311), DM (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), HTN (ICD-9-CM codes 401–405), CAD (ICD-9-CM codes 410-414), chronic renal disease (CKD) (ICD-9-CM codes 582-586, 588), allergic respiratory diseases (ICD-9-CM codes 477, 493), and *H pylori* infection (ICD-9-CM 041.86) were recorded.[22] Cirrhotic etiology including HBV infection (ICD-9-CM codes 070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33, V02.61), HCV infection (ICD-9-CM 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62), nonalcoholic steatohepatitis (NASH) (ICD-9-CM codes 571.8), and cryptogenic cirrhosis (ICD-9-CM 571.9) was also recorded. The diseases mentioned above were confirmed by at least three clinical visits, which were all within 1 year of CSCR diagnosis.

Table 1

Baseline characteristics of the study population

Liver cirrhosis	Yes (N = 25 925) n (%)	No (N = 25 925) n (%)	*p*
Sex			0.999
Male	16 441 (63.42)	16 441 (63.42)	
Female	9484 (36.58)	9484 (36.58)	
Age (SD)	55.63 (14.77)	55.66 (14.98)	0.818
Age group, y			0.999
20-29	1031 (3.98)	1031 (3.98)	
30-39	2897 (11.17)	2897 (11.17)	
40-49	5672 (21.88)	5672 (21.88)	
50-59	6185 (23.86)	6185 (23.86)	
≧60	10 140 (39.11)	10 140 (39.11)	
Insurance premium (NT$)			0.146
<18 000	10 245 (39.52)	10 345 (39.90)	
18 000-34 999	11 706 (45.15)	11 497 (44.35)	
≧35 000	3974 (15.33)	4083 (15.75)	
Preexisting comorbidities			
Diabetes mellitus	2164 (8.35)	897 (3.46)	<0.001
Hyperlipidemia	797 (3.07)	582 (2.24)	<0.001
Hypertension	2186 (8.43)	1101 (4.25)	<0.001
Chronic renal disease	899 (3.47)	271 (1.05)	<0.001
Peptic ulcer	1386 (5.35)	597 (2.30)	<0.001
Psychiatric diseases	1050(4.05)	677 (2.61)	<0.001
Allergic respiratory diseases	378 (1.46)	497 (1.92)	<0.001
Coronary artery disease	501 (1.93)	310 (1.20)	<0.001
H. pylori infection	178 (0.69)	25 (0.10)	0.001
Medicine			
Statin	11 275 (43.49)	10 452 (40.32)	<0.001
Metformin	10 985 (42.37)	9986 (38.52)	<0.001
PPI	9899 (38.18)	9132 (35.22)	<0.001
Aspirin	13 401 (51.69)	11 240 (43.36)	<0.001
NSAID	17 989 (69.39)	15 103 (58.26)	<0.001
Nonselective beta blockers	8765 (33.81)	8012 (30.90)	<0.001
Antiviral therapy	16 975 (65.48)	15 134 (58.38)	<0.001
Etiology			
HBV	14 853 (57.29)	7298 (28.15)	<0.001
HCV	11 270 (43.47)	6513 (25.12)	<0.001
NASH	3536 (13.64)	2756 (10.63)	<0.001
Cryptogenic	186 (0.72)	13 (0.05)	<0.001
Complications			
Gastroesophageal varices	1865 (7.19)	1725 (6.65)	<0.001
Hepatic encephalopathy	973 (3.75)	701 (2.70)	<0.001
Hepatocellular carcinoma	7019 (27.07)	3861 (14.89)	<0.001
Hepatorenal syndrome	4112 (15.86)	2986 (11.52)	<0.001
Ascites	5827 (22.48)	1845 (7.12)	<0.001
Follow-up years (mean ± SD)	10.24 ± 7.24	11.86 ± 7.98	

HBV = hepatitis B virus; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis; NSAID = non-steroidal anti-inflammatory drugs; NT$ = new Taiwan dollars; PPI = proton pump inhibitor.

2.3. Statistical analysis

We conducted all analyses with IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). We utilized the chi-square test to estimate the categorical variables distributed between the cirrhosis group and the noncirrhosis control cohort and used the *t*-test for the analysis of the continuous variables.

The Kaplan-Meier method was used with the log-rank test to present the difference of the cumulative risk of CSCR between the cirrhosis group and the noncirrhosis group, and the stratification of cirrhotic patients with and without complications. In addition, we performed a multivariate Cox regression analysis with forward stepwise selection to assess the risk of CSCR and presented the result using adjusted hazard ratios (HRs) with

corresponding 95% confidence intervals (CIs). A two-tailed p value <0.05 indicated significance.

3. RESULTS

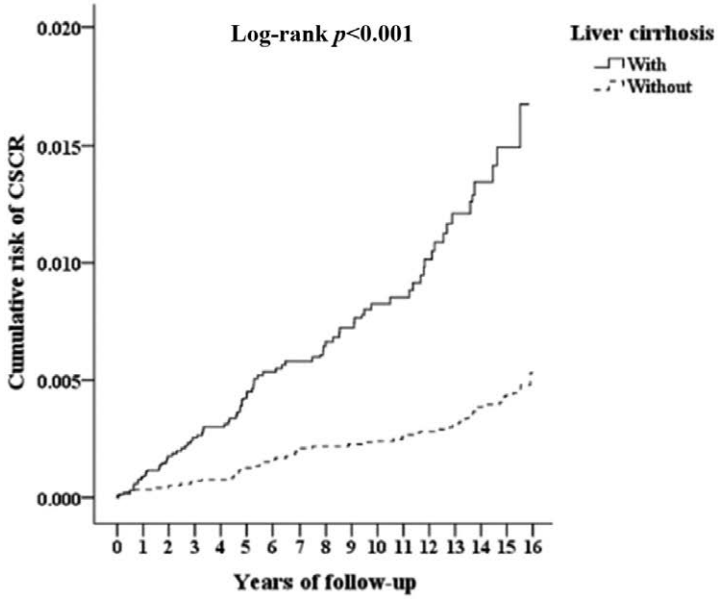
Figure 1 is the flow diagram illustrating the enrollment process of the patients in this study. Among 1 936 512 patients registered in the LHID, we identified 25 925 liver cirrhosis patients and 25 925 individuals without liver cirrhosis who were included in a sex-, age-, and index year–matched control cohort. The major baseline characteristics of the included patients are listed in Table 1. The average age of patients with and without cirrhosis was 55.63 ±14.77 years and 55.66±14.98 years, respectively. Most patients (39.11%) were aged ≥60 years and only 3.98% of the patients were younger than 30 years. Males accounted for majority (63.42 %) of the patients. After matching, no significant difference was noted in sex and age between the two groups. Certain comorbidities including DM, HTN, CKD, hyperlipidemia, peptic ulcer, psychiatric diseases, allergic respiratory diseases, CAD, and *H pylori* infection were more prevalent in the liver cirrhosis group at baseline ($p \leq 0.001$). Patients with cirrhosis also had higher rates of drug intake ($p < 0.001$) than controls. As for cirrhotic etiology and cirrhotic-related complication, HBV was present in 14 853 cirrhotic patients (57.29%) and 7298 controls (28.15%); HCV was present in 11 270 cirrhotic patients (43.47%) and 6513 controls (25.12%). Only 0.72% of patients with cirrhosis and 0.05% of controls were recorded as cryptogenic. Compared with controls, cirrhotic patients had higher rates of cirrhosis-related complications including ascites, gastroesophageal varices, hepatic encephalopathy, HCC, and HRS ($p < 0.001$). Cirrhosis patients on the average were followed up for 10.24 ± 7.24 years, whereas the noncirrhosis control subjects had an average follow-up period of 11.86 ± 7.98 years.

The cumulative incidences of developing CSCR at the end of the 16-year follow-up period were significantly higher for patients with liver cirrhosis than for patients without liver cirrhosis (61.61 cases per 100 000 person-years vs 30.47 cases per 100 000 person-years, $p \leq 0.001$). Analysis of the cumulative risk of developing CSCR during follow-up (Fig. 2) revealed that liver cirrhosis patients were associated with a higher incidence of CSCR than nonliver cirrhosis subjects; the difference between the two groups was significant from the first year to the end of study (log-rank test p <0.001).

The Cox regression analysis, which was used for comparing the risk of developing CSCR in cirrhotic and noncirrhotic patients, showed that the crude HR was 2.35 (95% CI, 1.31-3.83; p <0.05). After adjusting for age, sex, insurance premium, comorbidities, drug intake, and cirrhotic etiology, the HR was 2.95 (95% CI, 1.61-3.90; p <0.05) (Table 2). Males had a 1.52 times higher risk (95% CI, 1.13-2.17; p <0.05) of developing CSCR compared with females. Age, patient's income, and drug intake exhibited no significant association with CSCR after adjustment for other potential confounding factors. After conducting Cox regression analysis, only DM (HR, 1.89; 95% CI, 1.24-2.17; p <0.05) remained significant risk factors for CSCR. This depicted that HBV (HR, 1.80; 95% CI, 1.16-3.12; p <0.05) and HCV (HR, 1.92; 95% CI, 1.10-2.89; p <0.05) infection were significant risk factors for CSCR. In addition, CSCR development was noted to be more predominant in the spring.

Table 3 displays the results of the subgroup analysis by stratified sampling. The cirrhotic patients, irrespective of sex and age, were associated with a higher risk of developing CSCR than patients without cirrhosis. Cirrhotic patients with or without other comorbidities also had higher risks of developing CSCR than the subjects in the noncirrhotic cohort. In both groups, drug administered or not, the risk of CSCR was higher in those with cirrhosis than in those without cirrhosis.

In the cirrhotic group (25 925 individuals), 14 243 (54.9%) patients had at least one cirrhotic-related complications and 5827 patients had ascites (22.5%). Table 4 demonstrates the incidence rate and adjusted HR of CSCR in cirrhotic patients with and without complications relative to those of the control subjects. Complicated liver cirrhosis group had a 3.59-fold (95% CI, 2.31-5.28; $p < 0.001$) higher risk of developing CSCR than noncirrhotic patients, and uncomplicated cirrhotic patients had a 2.34-fold (95% CI, 1.27-3.24; $p < 0.001$) higher risk of developing CSCR than noncirrhotic patients. Additionally, those with ascites, esophageal varices, hepatic encephalopathy, HCC, and HRS are more prone to develop CSCR than those without complications ($p < 0.005$).



Liver cirrhosis	With (n=25,925)	Without (n=25,925)	Log-rank p
In the tracking of x year(s)	Numbers of CSCR/ Numbers at risk		
1	26/25,899	10/25,915	0.002
2	45/25,854	14/25,901	<0.001
3	59/25,795	16/25,885	<0.001
4	71/25,724	20/25,865	<0.001
5	86/25,638	31/25,834	<0.001
6	101/25,537	39/25,795	<0.001
7	113/25,424	45/25,750	<0.001
8	124/25,300	59/25,691	<0.001
9	137/25,163	63/25,628	<0.001
10	142/25,021	70/25,558	<0.001
11	150/24,871	74/25,484	<0.001
12	158/24,713	79/25,405	<0.001
13	163/24,550	85/25,320	<0.001
14	178/25,372	88/25,232	<0.001
15	187/25,185	93/25,139	<0.001
16	199/25,986	99/25,040	<0.001

Fig. 2 Kaplan-Meier curve for the cumulative risk of central serous chorioretinopathy (CSCR), stratified by liver cirrhosis using the log-rank test.

Table 2

Cox regression analysis of the relationship between baseline characteristics and central serous chorioretinopathy

Factors	Crude HR (95% CI)	Adjusted HR (95% CI)
Liver cirrhosis (reference: without)	2.35 (1.31-3.83)[a]	2.95 (1.61-3.90)[a]
Male (reference: female)	1.60 (1.13-2.20)[a]	1.52 (1.13-2.17)[a]
Age group, y		
20-29	Reference	Reference
30-39	1.87 (0.71-8.98)	1.95 (0.72-9.11)
40-49	1.72 (0.68-7.55)	1.84 (0.64-7.42)
50-59	1.28 (0.30-6.69)	1.32 (0.33-3.99)
≧60	0.98 (0.11-5.10)	1.08 (0.15-5.25)
Insurancepremium (NT$)		
<18 000	Reference	Reference
18 000-34 999	1.07 (0.70-2.00)	1.02 (0.69-1.71)
≧35 000	0.88 (0.59-1.87)	0.75 (0.43-1.69)
Comorbidities (reference: without)		
Diabetes mellitus	2.54 (1.38-3.21)[a]	1.89 (1.24-2.17)[a]
Hyperlipidemia	1.15 (0.38-2.99)	1.31 (0.44-2.98)
Hypertension	1.35 (0.52-3.33)	1.19 (0.56-3.00)
Chronic renal disease	2.75 (0.27-4.86)	2.14 (0.27-3.24)
Peptic ulcer	1.38 (0.86-1.99)	1.08 (0.59-1.78)
Psychiatric diseases	1.73 (1.01-2.65)[a]	1.41 (0.95-2.12)
Allergic respiratory diseases	2.90 (0.35-4.27)	2.24 (0.35-3.84)
Coronary artery disease	1.60 (0.34-2.70)	1.55 (0.81-2.87)
H. pylori infection	11.98 (0.04-394.47)	5.26 (0.02-178.82)
Medicine (reference: without)		
Statin	1.24 (0.48-1.76).	0.95 (0.40-1.57)
Metformin	1.14 (0.41-1.71)	0.82 (0.35-1.44)
PPI	0.94 (0.25-1.52)	1.03 (0.27-1.86)
Aspirin	0.76 (0.33-1.42)	0.88 (0.38-1.50)
NSAID	0.89 (0.43-1.56)	0.86 (0.41-1.55)
Nonselective beta blockers	0.85 (0.31-1.89)	0.80 (0.28-1.77)
Antiviral therapy	0.82 (0.25-1.72)	0.94 (0.34-1.84)
Etiology (reference: without)		
HBV	2.85 (1.42-4.26)[a]	1.80 (1.16-3.12)[a]
HCV	2.97 (1.56-4.31)[a]	1.92 (1.10-2.89)[a]
NASH	1.72 (0.84-2.65)	1.23 (0.55-2.27)
Cryptogenic	2.21 (1.11-2.76)[a]	1.84 (0.82-2.69)
Season		
Spring	Reference	Reference
Summer	0.67 (0.26-0.94)[a]	0.58 (0.25-0.91)[a]
Autumn	0.38 (0.13-0.67)[a]	0.39 (0.18-0.68)[a]
Winter	0.22 (0.10-0.37)[a]	0.24 (0.11-0.35)[a]

CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; NASH = non-alcoholic steatohepatitis; NSAID = non-steroidal anti-inflammatory drugs; NT$ = new Taiwan dollars; PPI = proton pump inhibitor.

[a]$p < 0.05$.

4. DISCUSSION

In this study, we revealed that liver cirrhosis is a significant indicator for CSCR after adjusting for age, sex, and other comorbidities. Another major finding of our study is that cirrhotic patients with cirrhotic-related complications including ascites, gastroesophageal varices, hepatic encephalopathy, HCC, and HRS are more prone to developing CSCR than those without cirrhotic-related complications, confirming the association between severity of liver cirrhosis and CSCR development. Regarding sex analyses, we found that males are more prone to developing CSCR than females. Moreover, subjects with DM, HBV, and HCV have an increased risk of developing CSCR.

Only few previous clinical reports on the associations between liver disease and retinopathy involved the use of indocyanine green angiography or optical coherence tomography, which are important imaging modalities in the diagnosis of CSCR[19,20]; this means that the incidence of CSCR in cirrhotic patients may be underreported. Gkotsi et al[21] later reported on the case of an alcoholic liver cirrhosis patient with ascites who presented with CSCR. However, since alcohol is known as a predisposing factor for CSCR, the incidence of CSCR in cirrhotic patients, especially in those with ascites, should be assessed further. To the best of our knowledge, this is the first nationally representative cohort study to evaluate the association between liver cirrhosis and CSCR after adjusting for confounding variables.

Regarding demographic findings that CSCR develops mainly in middle-aged males has been well documented. Results of the present study showed that males have a 1.52 times higher risk of developing CSCR than females; the sex ratio in the present study is similar to that of the previous population-based study conducted in Taiwan.[23] In our study, the peak incidence of CSCR was in the 20- to 29-year age group, followed by the 30- to 39-year age group; this is also consistent with the findings of previous published literature. Previous epidemiologic studies have shown that there is a seasonal variation in the prevalence of CSCR, with a higher prevalence recorded in spring[24]; in our study, CSCR was also found to occur predominantly in spring. The reason why CSCR tends to occur more in the spring remains to be determined.

Additionally, previous data indicated that commodities including HTN, CAD, heart failure, *H pylori* infection, and exogenous corticosteroids increase the risk of developing CSCR.[25] However, in this study, only DM was a significant risk factor for CSCR. Different inclusion criteria, study population, and methodological design may potentially contribute.

A meta-analysis conducted by Feng et al[18] showed that cirrhotic patients had higher *H pylori* infection rate in Europe, America, and Africa than controls but not in Asia. In this study, we analyzed *H pylori* infection as a covariate, and *H pylori* infection was significantly higher in patients with cirrhosis than in controls ($p = 0.001$). However, after adjusting for age, sex, and comorbidities, *H pylori* infection was not a significant risk factor for developing CSCR.

Choroidopathy and RPE epitheliopathy have been considered in the pathogenesis of CSCR. Endogenous and exogenous corticosteroids, as well as primary hyperaldosteronism, are known to trigger CSCR, and their affinity for mineralocorticoid receptors (MRs) has been implicated as a contributing factor to the development of CSCR.[3] Recently, with recent advances in molecular biology, MR has been identified in the neuroretina and choroidal vasculature, and a mineralocorticoid pathway involved in CSCR development had been proposed.[13,14] As for cirrhosis, aldosterone also plays a role in the disease pathophysiology. As cirrhosis progresses, sinusoidal pressure increases and leads to portal HTN, further inducing peripheral and splenic vasodilatation. Consequently, the decreased effective blood volume activates the RAAS, as well as the sympathetic nervous system.[15] Angiotensin increases aldosterone, and this subsequently leads to sodium and water retention. Thus, increased aldosterone and activation of MR, which are prevalent in in both cirrhotic patients and patients with CSCR, may be the potential common contributing factors for both diseases.

Inappropriate activation of MR and aldosterone is known to promote vascular fibrosis, inflammation, atherosclerosis, and endothelium dysfunction.[26,27] In the past, several cardiovascular diseases had been shown to increase the risk of CSCR by unknown mechanisms.[4,28,29] Emerging evidence addresses the possible relationship between cardiovascular events and CSCR may be associated with the harmful effect of aldosterone and over or improper activation of the MR pathway, thereby

Table 3

Stratified sampling of the factors associated with central serous chorioretinopathy using Cox regression analysis

Liver cirrhosis	With			Without			With vs without	
Stratified	Event	PYs	Rate[a]	Event	PYs	Rate[a]	Ratio	Adjusted HR (95% CI)
All	199	323015.12	61.61	99	324896.70	30.47	2.02	2.95 (1.61-3.90)[b]
Sex								
Male	111	202485.12	54.82	50	203706.12	24.55	2.23	3.26 (1.78-4.31)[b]
Female	88	120530.01	73.01	49	121190.58	40.43	1.81	2.64 (1.44-3.49)[b]
Age group, y								
20-29	24	3034.12	791.00	10	2928.12	341.52	2.32	3.39 (1.85-4.48)[b]
30-39	47	20986.54	223.95	22	20784.10	105.85	2.12	3.10 (1.69-4.09)[b]
40-49	65	52710.99	123.31	31	52825.72	58.68	2.10	3.07 (1.67-4.05)[b]
50-59	34	86975.20	39.09	18	88879.80	20.25	1.93	2.82 (1.54-3.73)[b]
≧60	29	159308.27	18.20	18	159478.96	11.29	1.61	2.35 (1.28-3.11)[b]
Diabetes mellitus								
Without	158	294218.00	53.70	88	303876.46	28.96	1.85	2.71 (1.48-3.58)[b]
With	41	28797.12	142.38	11	21020.24	52.33	2.72	3.97 (2.17-5.25)[b]
Hyperlipidemia								
Without	185	311135.58	59.46	95	316884.15	29.98	1.98	2.90 (1.58-3.83)[b]
With	14	11879.54	117.85	4	8012.55	49.92	2.36	3.45 (1.88-4.56)[b]
Hypertension								
Without	169	285034.90	59.29	91	304772.50	29.86	1.99	2.90 (1.58-3.83)[b]
With	30	37980.22	78.99	8	20124.20	39.75	1.99	2.91 (1.59-3.84)[b]
Chronic renal disease								
Without	179	313127.92	57.17	92	317609.50	28.97	1.97	2.88 (1.57-3.81)[b]
With	20	9887.20	202.28	7	7287.20	96.06	2.11	3.08 (1.68-4.07)[b]
Peptic ulcer								
Without	195	303227.92	64.31	97	304134.60	31.89	2.02	2.94 (1.61-3.89)[b]
With	4	19787.20	20.22	2	20762.10	9.63	2.10	3.07 (1.67-4.05)[b]
Psychiatric diseases								
Without	175	306442.91	57.11	89	309254.90	28.78	1.98	2.90 (1.58-3.83)[b]
With	24	16572.21	144.82	10	15641.80	63.93	2.27	3.32 (1.81-4.38)[b]
Allergic respiratory diseases								
Without	192	317043.72	60.56	96	318221.18	30.17	2.01	2.93 (1.60-3.88)[b]
With	7	5971.40	117.23	3	6675.52	44.94	2.61	3.81 (2.08-5.04)[b]
Coronary artery disease								
Without	192	317043.72	60.56	96	318221.18	30.17	2.01	2.93 (1.60-3.88)[b]
With	7	5971.40	117.23	3	6675.52	44.94	2.14	3.13 (1.71-4.13)[b]
H. pylori infection								
Without	197	321857.16	61.21	98	323870.95	30.26	2.02	2.95 (1.61-3.91)[b]
With	2	1157.96	172.72	1	1025.75	97.49	1.77	1.86 (1.06-2.94)[c]
HBV								
Without	101	144512.88	69.89	53	186443.84	28.43	2.46	3.59 (1.96-4.75)[b]
With	98	178502.24	54.90	46	138452.86	33.22	1.65	2.54 (1.22-3.24)[b]
HCV								
Without	95	135485.79	70.12	59	184694.69	31.94	2.19	3.21 (1.75-4.24)[b]
With	104	187529.33	55.46	40	140202.01	28.53	1.94	2.73 (1.85-3.22)[b]
NASH								
Without	166	257750.01	64.40	86	261194.56	32.93	1.96	2.86 (1.56-3.78)[b]
With	33	65265.11	50.56	13	63702.14	20.41	2.48	3.15 (1.97-3.76)[b]
Cryptogenic								
Without	197	321825.56	61.21	99	323844.26	30.57	2.00	2.95 (1.61-3.90)[b]
With	2	1189.56	168.13	0	1052.44	0.00	∞	-
Statin								
Without	123	135072.77	91.06	63	141445.50	44.54	2.04	2.99 (1.63-3.95)[b]
With	76	187942.35	40.44	36	183451.20	19.62	2.06	2.83 (1.52-3.36)[b]
Metformin								
Without	154	143190.00	107.55	72	147239.41	48.90	2.20	3.21 (1.75-4.25)[b]
With	45	179825.12	25.02	27	177657.29	15.2	1.65	2.04 (1.48-2.73)[b]
PPI								
Without	166	154262.47	107.61	79	166171.05	47.54	2.26	3.31 (1.80-4.37)[b]
With	33	168752.65	19.56	20	158725.65	12.60	1.55	1.62 (1.10-2.00)[c]
Aspirin								
Without	150	151272.44	99.16	71	163144.37	43.52	2.28	3.33 (1.82-4.40)[b]
With	49	171742.68	28.53	28	161752.33	17.31	1.65	1.79 (1.24-2.35)[b]
NSAID								
Without	147	135989.36	108.10	68	138470.77	49.11	2.20	3.21 (1.75-4.25)[b]
With	52	187025.76	27.80	31	186425.93	16.63	1.67	1.98 (1.22-3.15)[b]
Nonselective beta blockers								
Without	139	153292.56	90.68	69	153354.06	44.99	2.02	2.94 (1.61-3.89)[b]
With	60	169722.56	35.35	30	171542.64	17.49	2.02	2.51 (1.46-3.92)[b]
Antiviral therapy								
Without	161	146472.67	109.92	85	168924.39	50.32	2.18	3.19 (1.74-4.22)[b]
With	38	176542.45	21.52	14	155972.31	8.98	2.40	2.19 (1.65-3.29)[b]

CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; NASH = non-alcoholic steatohepatitis; NSAID = non-steroidal anti-inflammatory drugs; PPI = proton pump inhibitor; PYs = person-years.

[a]Rate: incidence rate (per 100 000 PYs).

[b]$p < 0.001$.

[c]$p < 0.05$.

Table 4

Comparison of the incidence and the HRs of central serous chorioretinopathy between cirrhotic patients with and without ascites and noncirrhotic patients

	n	Event	PYs	Rate[a]	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Without cirrhosis	25 925	99	324896.70	30.47	Reference	
With cirrhosis	25 925	199	323015.12	61.61	2.95 (1.61-3.90)[b]	
No complications	11 682	78	159102.44	49.03	2.34 (1.27-3.24)[b]	Reference
Complications	14 243	121	163912.68	73.82	3.59 (2.31-5.28)[b]	1.50 (1.21-2.16)[b]
No ascites	20 098	155	263216.45	58.89	2.72 (1.49-3.71)[b]	Reference
ascites	5827	44	59798.67	73.58	3.40 (1.97-4.96)[b]	1.30 (1.05-1.87)[c]
No gastroesophageal varices	24 060	180	303292.00	59.35	2.73 (1.50-3.72)[b]	Reference
Gastroesophageal varices	1865	19	19723.12	96.33	3.82 (2.20-5.10)[b]	1.24 (1.06-1.75)[c]
No hepatic encephalopathy	24 952	198	321949.95	61.50	2.89 (1.58-3.89)[b]	Reference
Hepatic encephalopathy	973	1	1065.17	93.88	3.74 (2.18-5.02)[b]	1.38 (1.10-1.92)[c]
No HCC	18 906	140	250219.70	55.95	2.57 (1.32-3.56)[b]	Reference
HCC	7019	59	72795.42	81.05	3.56 (1.99-4.97)[b]	1.54 (1.23-2.21)[b]
No HRS	21 813	161	282004.17	57.09	2.66 (1.44-3.64)[b]	Reference
HRS	4112	38	41010.95	92.66	3.68 (2.01-4.99)[b]	1.42 (1.15-2.01)[b]

Adjusted HR = adjusted hazard ratio: adjusted variables listed in Table 2; CI = confidence interval; HCC = hepatocellular carcinoma; HR = hazard ratio; HRS = hepatorenal syndrome; PYs = person-years.
[a]Rate: incidence rate (per 100 000 PYs).[b]$p < 0.001$.
[c]$p < 0.05$.

contributing to systemic vascular dysfunction.[27,30] MR antagonists, including spironolactone and eplerenone, have been widely used in various diseases such as HTN, heart failure, and CAD. Plasma aldosterone is notably more elevated in decompensated cirrhosis with the presence of ascites, and MR antagonists have been the first-line medication for refractory ascites. In addition, based on the postulation of a mineralocorticoid pathway-mediated CSCR, therapeutic MR antagonism has been utilized for the treatment of cases of nonresolving CSCR and has shown promising treatment efficacy.[30] The beneficial effects of MR antagonists in both CSCR and liver cirrhosis also imply that mineralocorticoid activation is a potential common pathogenic pathway of CSCR and liver cirrhosis.

Considering MR antagonists as treatments for both CSCR and liver cirrhosis and mineralocorticoid activation is a potential common pathogenic pathway of CSCR and liver cirrhosis, we conducted analysis of MR antagonists (spironolactone and eplerenone) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers treatments and the risk of CSCR in cirrhotic groups. The Kaplan-Meier analysis showed no significant difference in the cumulative risk of CSCR stratified by MR antagonists ($p = 0.694$; Supplementary Fig. 3, http://links.lww.com/JCMA/A76) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers ($p = 0.602$; Supplementary Fig. 4, http://links.lww.com/JCMA/A76) with log-rank test (Supplementary Figs. 3 and 4, http://links.lww.com/JCMA/A76). It was possible that the relatively small sample size and event numbers had low statistical power (Supplementary Figs. 1 and 2, http://links.lww.com/JCMA/A76).

Furthermore, we postulated that some other pathophysiological mechanisms may be involved in the association of CSCR and cirrhosis. Chronic hepatic inflammation accelerates tissue damage and fibrosis, leading to cirrhosis and even tumorigenesis. Increased inflammatory cytokines and reactive oxygen species have been noted in various liver diseases. In liver cirrhosis, systemic arterial dilation due to overproduction of nitric oxide in splenic vasculature and increased inflammatory cytokines are believed to exert hyperdynamic circulation and increase vascular permeability.[31] Furthermore, hypoalbuminemia, ascribed to decreased albumin synthesis in cirrhotic patients, lowers vascular osmotic pressure. These effects favor interstitial fluid volume expansion and may potentially contribute to alternated choroid vessel permeability and lead to accumulation of subretinal fluid in CSCR.

Moreover, higher serum levels of complement factor H (CFH) and CFH gene polymorphism are associated with CSCR. CFH binds to adrenomedullin, a peptide that elicits vasodilatation and hyperpermeability of choroidal blood vessels.[32,33] On the other hand, cirrhotic patients tend to have higher plasma adrenomedullin levels and this phenomenon is especially prominent in cirrhotic patients with ascites.[34] It has been proposed that adrenomedullin contributes to the activation of the RAAS and the sympathetic nervous system, ultimately leading to the synthesis of ascites.[35] Elevated adrenomedullin and increase in sympathetic activity is an additional probable mechanism for the association between cirrhosis and CSCR.

The present study has several strengths. It was a nationwide population-based cohort study, which had significant statistical power due to the large sample size and the long-term follow-up period. Variables such as age and sex were controlled with matching in cases, and confounding factors including insurance premium, HTN, DM, hyperlipidemia, CKD, CAD, peptic ulcer, psychiatric diseases, drug intake, cirrhotic etiology, and cirrhotic-related complications were adjusted in this study, making our results more reliable. We also used cirrhotic-related complications as indicators of the severity of cirrhosis and found a positive correlation between severity of cirrhosis and CSCR development.

Our study has some limitations as well. First, blood test data including complete blood count, and biochemistry exams such as albumin, bilirubin, and prothrombin time could not be identified from data collected from the NHIRD. Thus, the commonly used severity index and prognostic indicators for liver cirrhosis, including the Child-Pugh score and the Model for End-Stage Liver Disease score, could not be identified and the effect of the severity of liver disease on CSCR could not be assessed. We supposed that the presence of complications such as ascites in cirrhotic patients reflects a more advanced disease and indicates that the patients were in the decompensated stage of the disease. Second, certain characteristics of the subjects such as genetics, personality pattern, psychological stress, tobacco, and alcohol consumption were not included in the NHIRD and these variables may be confounding factors related to CSCR occurrence. Third, the NHIRD does not contain imaging data; therefore, we could only rely on ICD-9 codes to identify CSCR cases. To ameliorate the probability of misdiagnosis, we used similar exclusion criteria adopted by previous studies

to exclude other disease entities that result in the accumulation of sub-retinal fluid.[4,36] In addition, liver cirrhosis is the late stage of liver disease and is associated with relatively short life expectancy and the life expectancy of decompensated patients with ascites is significantly shorter than that of compensated cirrhosis patients.[37] Patients with severe cirrhosis may be too ill to report any visual disturbance or to undergo ocular examination. This may have been why the average years of follow-up for the liver cirrhosis patients in our study was much shorter than that of the control cohort; this may contribute to the incidence of CSCR being underestimated. Therefore, we calculated the death number during the follow-up period (Supplementary Table 1), showing that the mortality of patients with liver cirrhosis was significantly higher than patients without liver cirrhosis ($p < 0.001$). We further conducted Cox regression using death as a competing risk (Supplementary Table 2) and revealed that cirrhotic group had a 3.01 times higher risk for CSCR compared with controls (95% CI, 1.68-4.02; $p < 0.05$) after adjusting the competing risk of mortality, which was mildly higher than the adjusted HR without considering death as a competing event.

In conclusion, this study revealed that cirrhotic patients are at a higher risk of developing CSCR. Furthermore, cirrhotic patients with complications have higher risks of developing CSCR than noncirrhotic population and are at increased risk of developing CSCR than uncomplicated cirrhotic group. Further molecular signaling pathways involved in both CSCR and cirrhosis should be explored to enhance the understanding of the association between these two diseases. When treating cirrhotic patients with vision problems, physicians should be alert to the possibility of CSCR being present.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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