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Hepatitis C virus and hepatitis B virus in patients with schizophrenia

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Abstract

This study evaluated the severe hepatic outcome (SHO) in patients with schizophrenia and viral hepatitis who received antipsychotics.

Using the nationwide Taiwan National Health Insurance Research Database, patients first diagnosed with schizophrenia between 2002 and 2013 were identified. Patients diagnosed with schizophrenia who had viral hepatitis, including hepatitis B virus (HBV) or hepatitis C virus (HCV), were designated as the viral hepatitis group. A control group without viral hepatitis was matched for age, sex, and index year in a 2:1 ratio. Patients with severe hepatic outcomes before enrollment were excluded. The 2 cohorts were observed until December 31, 2013. The primary endpoint was occurrence of a SHO, including liver cancer, liver failure, liver decompensation, or transplantation.

Among the 16,365 patients newly diagnosed with schizophrenia between January 2002 and December 2013, we identified 614 patients with viral hepatitis and 1228 matched patients without viral hepatitis. Of these 1842 patients, 41 (2.22%) developed SHOs, including 26 (4.23%) in the viral hepatitis group and 15 (1.22%) in the control group, during the mean follow-up period of 3.71 ± 2.49 years. Cox proportional hazard analysis indicated that the SHO risk increased by 3.58 (95% confidence interval [CI]: 1.859–6.754; $P < .001$) in patients with schizophrenia and viral hepatitis. Moreover, patients with schizophrenia having HCV had a higher SHO risk than those without viral hepatitis (hazard ratio: 5.07, 95% CI: 1.612–15.956; $P < .0001$). Patients having both schizophrenia and viral hepatitis, especially HCV, had a higher risk of SHOs.

Abbreviations: aHR = adjusted hazard ratio, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FGAs = first-generation antipsychotics, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, SGAs = second-generation antipsychotics, SHO = severe hepatic outcome.

Keywords: antipsychotics, liver cancer, liver failure, schizophrenia, viral hepatitis

1. Introduction

Viral hepatitis, including that caused by hepatitis B virus (HBV)[1] and hepatitis C virus (HCV),[2] is the leading cause of liver inflammation diseases.[3] It has increasingly been reported to be related to severe mental illness,[4] such as schizophrenia, which is a chronic psychiatric disorder characterized by cognitive impairment.[5] Several studies have investigated the prevalence of viral hepatitis, especially HBV and HCV, in patients with schizophrenia.[6–11] Hung et al[6] reported that the seroprevalence of HBV and anti-HCV surface antigens was 10.4% and 1.9%, respectively, among 590 patients with schizophrenia in Taiwan, whereas Sockalingam et al[10] found an HCV prevalence (antibody and viremia positivity) of 2.7% in 110 patients with schizophrenia in Canada. Patients with viral hepatitis, including HBV and HCV, have a high risk of liver cancer, especially hepatocellular carcinoma (HCC).[12,13] In patients with HBV and liver cirrhosis, the 5-year cumulative risk of HCC is 17% in East Asia and 10% in Western Europe and the United States.[14] HCV is the leading cause of HCC in Western countries; it accounts for approximately 34% of HCC cases in the United States.[2,15] However, these studies have investigated the general population rather than focusing on patients with schizophrenia. Long-term hepatic outcomes, such as liver cancer,[16,17] liver failure,[18,19] and liver decompensation,[20] in patients with schizophrenia and viral hepatitis remain unclear.

Antipsychotics are the main psychopharmacologic treatment for schizophrenia, including first-generation antipsychotics

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(FGAs) and second-generation antipsychotics (SGAs).[21] SGAs have better tolerability and less extra-pyramidal symptoms, therefore, are increasing used than FGAs.[22] SGAs have been well known the association with greater risk of metabolic syndrome such as dyslipidemia compared with FGAs.[5,23–26] However, hepatic adverse effects of SGAs have been reported. Esposito et al[27] reported that a 28-year-old Caucasian man with paranoid schizophrenia developed elevated levels of serum aspartate aminotransferase (AST) (83 U/L) and alanine aminotransferase (ALT) (123 U/L) after 7-week of risperidone monotherapy.

The long-term hepatic outcomes in patients with schizophrenia and viral hepatitis receiving SGAs remain uncertain. Therefore, this population-based study assessed the incidence and risk of severe hepatic outcomes (SHOs), such as liver cancer, failure, and decompensation, among patients with schizophrenia who had viral hepatitis and were receiving SGAs.

2. Methods

2.1. Data source

The National Health Insurance program, launched by the Taiwanese government on March 1, 1995, currently covers >98.29% of Taiwan's residents. Comprehensive information including prescription details, clinic visits, and diagnostic codes, is recorded in the National Health Insurance Research Database (NHIRD).[28] We used the Psychiatric Inpatient Medical Claims database, a subset of the NHIRD, to identify patients hospitalized for psychiatric disorders between 2000 and 2013. This database contains patients with at least one psychiatric inpatient record and one discharge diagnosis for mental disorders coded according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 290–319. Patients' demographic characteristics, diagnoses, medical expenditures, and prescription claims are recorded in the database.[29]

2.2. Ethics statement

This study was approved by the Institutional Review Board (IRB) of China Medical University Hospital (CMUH105-REC2–087). In this study, information in the database that could identify individual patients was encrypted by the Ministry of Health and Welfare of Taiwan. This study involved analysis of only encrypted, noninvasive data. Therefore, this study was exempted from the requirement to obtain the written consent of study subjects by the IRB of China Medical University Hospital. Because the IRB of China Medical University Hospital and the NHI Administration guarantee patient privacy.

2.3. Study sample and control group

In this study, we enrolled patients aged 20 to 99 years who received a new diagnosis of schizophrenia (ICD-9-CM code: 295.XX) with viral hepatitis (ICD-9-CM code: 070.XX) from 2002 to 2013 as the study cohort (viral hepatitis group). The date of enrollment was defined as the date when schizophrenia was initially diagnosed. A group of patients with schizophrenia without viral hepatitis that was matched for age, sex, and index year served as the control group. In both groups, patients with a medical history of SHOs prior to enrollment were excluded.

2.4. Variables

In this study, general data such as age, sex, and index year were retrieved and matched between groups. Based on other studies, risk factors for SHOs and major comorbid conditions were analyzed.

2.5. Matching

The control group was matched with the viral hepatitis group at a 2:1 ratio for age, sex, and enrollment year; matching for the age and year of enrollment included a tolerance range of ±1 year. For the control group, the follow-up start date was defined as the first date of admission to a medical facility in the enrollment year.

2.6. Main outcome measures

The endpoint of the study was defined as the occurrence of severe hepatic outcomes (SHO). In this study, SHOs included liver failure (ICD-9-CM codes: 570.XX), liver decompensation (ICD-9-CM codes: 789.5, 572.2, 572.4, 456.0, 456.20, 567.XX), liver transplantation (ICD-9-CM codes: 996.82), and liver cancer (ICD-9-CM codes: 155.XX).[30–32] Besides, patients were observed from the enrollment date until either the first SHO diagnosis or the study's end date of December 31, 2013.

2.7. Statistical analysis

We used MySQL for data extraction, linkage, and processing. All statistical analyses were performed using SPSS (version 20.0 for Windows; IBM, New York, NY). Data are expressed as means ± standard deviations or as percentages, unless otherwise stated. Comparisons between the 2 groups were made using independent Student *t* test for continuous variables and Pearson chi-square test for categorical variables, as appropriate. Survival analysis was performed using the Kaplan–Meier method, with significance determined using the log-rank test. A Cox proportional hazard model was used for multivariate adjustments, which were performed to better elucidate dependent risk factors for SHOs. Hazard ratios (HRs) were obtained after adjustment for age, sex, and comorbidities (Table 1). Statistical significance was defined as 2-sided $P < .05$.

3. Results

A total of 15,914 patients were newly diagnosed with schizophrenia between January 1, 2007, and December 31, 2013. Among them, 614 patients with viral hepatitis and 1228 matched controls without viral hepatitis were included in the analysis. Figure 1 illustrates the flowchart of enrollment and follow-up. Table 1 presents the included patients' basic characteristics. The mean age was 40.13 ± 9.67 years. Patients in both groups were predominately men (63.8%). The viral hepatitis group had a higher rate of major comorbidities. Risperidone was the most common SGA.

3.1. Higher SHO risk in patients with schizophrenia and viral hepatitis

During the follow-up period, a higher incidence and risk of SHOs were observed in the viral hepatitis group than in the control group (incidence: 11.66 vs 3.25 per 1000 person-years; Table 2; risk: HR: 3.58, log-rank test, $P < .001$; Fig. 2). The fully adjusted

Table 1

Patients' demographic profile (n = 1842).

	Matched cohort (n = 1228) M ± SD/n (%)	Viral hepatitis cohort (n = 614) M ± SD/n (%)	*P*-value
Age, yrs	40.13 ± 9.66	40.13 ± 9.67	1.000
Male	784 (63.8)	392 (63.8)	1.000
Follow-up, y	3.76 ± 2.51	3.63 ± 2.44	.427
Outpatient visits per person per year			<.001
>0 and ≤10	391 (31.8)	95 (15.5)	
>10 and ≤20	476 (38.8)	226 (36.8)	
>20 and ≤30	185 (15.1)	129 (21.0)	
>30	176 (14.3)	164 (26.7)	
Major coexisting diseases			
Hypertension	162 (13.2)	125 (20.4)	<.001
Diabetes	82 (6.7)	72 (11.7)	<.001
Coronary disease	53 (4.3)	53 (8.6)	<.001
COPD	166 (13.5)	150 (24.4)	<.001
Chronic kidney disease	50 (4.1)	44 (7.2)	.004
Asthma	74 (6.0)	56 (9.1)	.015
Autoimmune diseases	28 (2.3)	33 (5.4)	<.001
Cerebrovascular disease	58 (4.7)	54 (8.8)	.001
Alcohol liver disease	30 (2.4)	54 (8.8)	<.001
Cirrhosis	10 (0.8)	36 (5.9)	<.001
Hyperlipidemia	63 (5.1)	61 (9.9)	<.001
Atypical antipsychotics			
Amisulpride	259 (21.1)	139 (22.6)	.477
Aripiprazole	250 (20.4)	133 (21.7)	.516
Clozapine	88 (7.2)	45 (7.3)	.899
Quetiapine	460 (37.5)	293 (47.7)	<.001
Olanzapine	345 (28.1)	208 (33.9)	.011
Paliperidone	158 (12.9)	92 (15.0)	.211
Risperidone	777 (63.3)	389 (63.4)	.973
Zotepine	159 (12.9)	78 (12.7)	.883
Typical antipsychotics	960 (78.2)	515 (83.9)	.004

COPD = chronic obstructive pulmonary disease.

HR was 2.57 (95% confidence interval [CI]: 1.255–5.251; $P = .010$; Table 2). Furthermore, 465 of 614 patients in the viral hepatitis group had HBV and 182 had HCV. Patients with schizophrenia having HCV had a higher cumulative SHO incidence than did those having HBV or controls (17.3%, 11.2%, and 2.4%, respectively; Fig. 3).

3.2. Liver cirrhosis is the leading risk factor for severe hepatic outcome

Cox multivariate proportional hazard analysis indicated that liver cirrhosis was an independent risk factor for SHO in patients with schizophrenia and viral hepatitis (adjusted HR: 5.536, 95% CI: 1.663–18.429, $P = .005$; Table 3). Typical and atypical antipsychotics were also analyzed, with Cox multivariate proportional hazard analysis indicating that paliperidone, an atypical antipsychotic, was nonsignificantly associated with the lowest SHO risk (aHR: 0.352, 95% CI: 0.045–2.729, $P = .318$; Table 3).

3.3. SHO occurrence within 5 years of schizophrenia diagnosis

Of the 26 patients in the viral hepatitis group who developed SHOs, 17 (65.38%) were men, and 19 (73.08%) developed SHOs within 5 years of their schizophrenia diagnosis (first year: 4/26 [15.38%], second year: 4/26 [15.38%], third year: 4/26 [15.38%], fourth year: 6/26 [23.08%], fifth year: 1/26 [3.84%], and over 5 years: 7/26 [26.92%]; Fig. 4). SHOs were mainly liver decompensation (20/26 [76.9%]), liver failure (3/26 [11.5%]), and liver cancer (3/26 [11.5%]; Fig. 5).

4. Discussion

The results of this nationwide population-based cohort study indicated that patients with schizophrenia and viral hepatitis had a significantly higher SHO risk than those without viral hepatitis; patients with schizophrenia having HCV had a higher cumulative SHO incidence than those with HBV and controls; and patients in the viral hepatitis group receiving paliperidone had the lowest SHO risk compared with those receiving other atypical antipsychotics, but this finding was not significant.

Our findings are in agreement with those of previous studies. Hung et al reported a 10.4% seroprevalence of the surface antigen for HBV and a 1.9% seroprevalence of that for HCV among 590 patients with schizophrenia in Taiwan [6]. In our study, the prevalence of viral hepatitis, including HBV and HCV, in patients with schizophrenia was 6.4% (1015/15,914). The prevalence of HBV among the general population in Taiwan ranges from 6.6% to 17.3%,[32,33] whereas that of HCV ranges from 0.1% to 34.1%.[34] This difference may result from

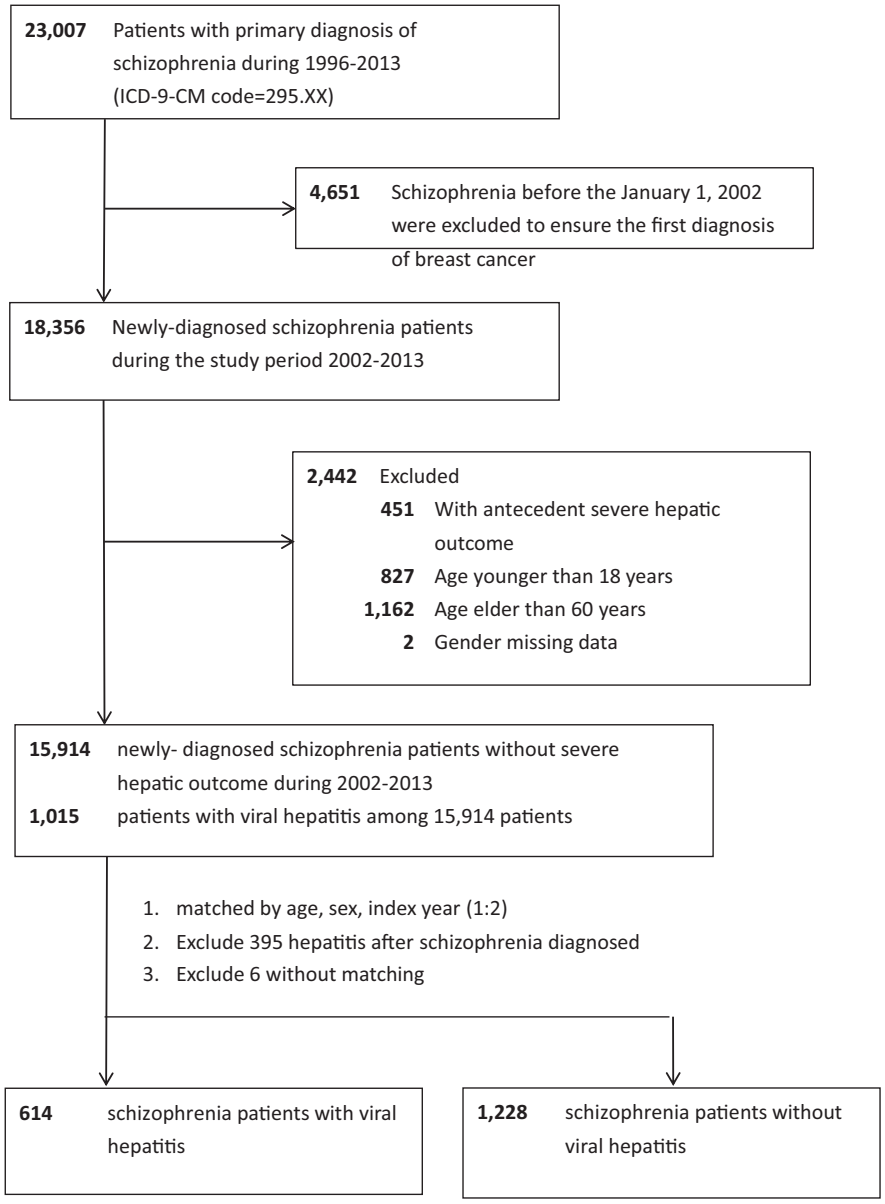

Figure 1. Flowchart of patient selection.

Table 2

SHO incidence and HRs in patients with schizophrenia having hepatitis (2002–2013, n = 1842).

Severe hepatic outcome during follow-up	Total sample	Comparison group	Viral hepatitis group
Incidence of SHO (per 1000 person-years)	5.99	3.25	11.66
No. of occurrences	41	15	26
Observed person-years	6841.56	4611.30	2230.26
Crude hazard ratio (95% CI)		1.00	3.58 (1.859–6.754)[a]
Adjusted hazard ratio (95% CI)[*]		1.00	2.57 (1.255–5.251)[b]

CI = confidence interval, HR = hazard ratio, SHO = severe hepatic outcome.

[a] $P < .001$.

[b] $P = .010$.

[*] Adjusted for age, sex, outpatient visits per year, major coexisting diseases, atypical antipsychotics, and typical antipsychotics.

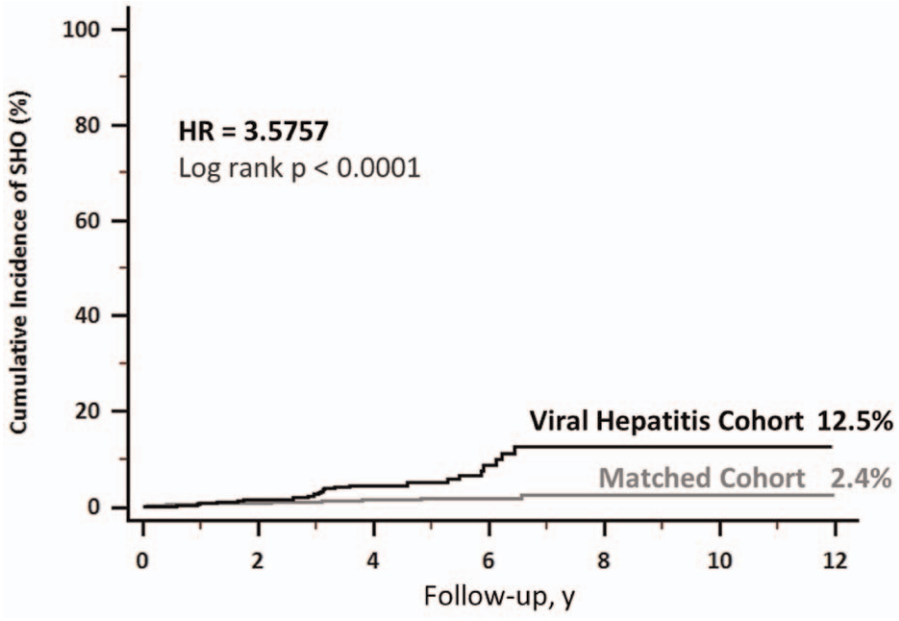

Figure 2. Cumulative SHO incidence in matched cohort and viral hepatitis cohort. SHO = severe hepatic outcome.

different study designs in terms of age, institution, and community.

Moreover, we found that patients with schizophrenia and viral hepatitis had a higher risk of SHOs, such as hepatic failure or liver cancer. One study reported that 152 of 3454 (4.40%) HBsAg-positive men developed HCC during the mean follow-up of 8.9 years.[35] In our study, 3 of 614 (0.49%) patients with schizophrenia and viral hepatitis developed liver cancer during the mean follow-up of 3.63 years. This discrepancy may be because our sample size was small (614 vs 3454) and the follow-up period was short (3.36 vs 8.9). Moreover, patients with schizophrenia may receive inadequate medical care and have

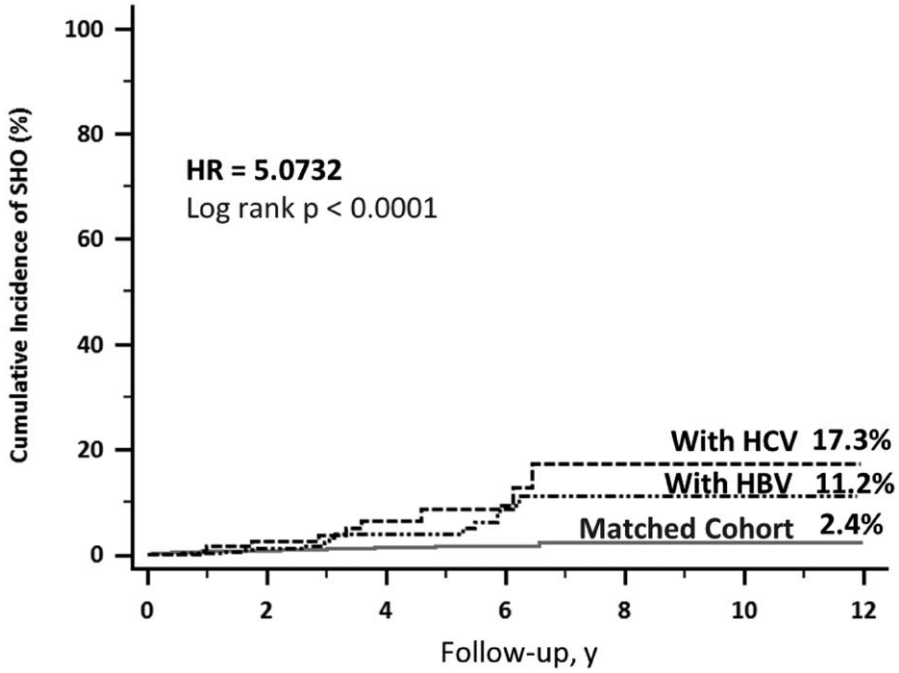

Figure 3. Cumulative SHO incidence in matched cohort, HBV cohort, and HCV cohort. HBV = hepatitis B virus, HCV = hepatitis C virus, SHO = severe hepatic outcome.

Table 3

Univariate and multivariate survival analysis for factors associated with SHOs in patients with schizophrenia having viral hepatitis.

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI of HR**	***P*-value**	**aHR**	**95% CI of aHR**	***P*-value**
Age, yrs	1.025	0.986–1.065	.207	1.013	0.965–1.064	.590
Sex						
Women	1.000					
Men	1.113	0.496–2.498	.795	0.764	0.287–2.035	.590
Visits per year	1.008	0.991–1.025	.369	1.012	0.991–1.034	.262
Major coexisting diseases						
Hypertension	1.465	0.584–3.678	.416	1.070	0.301–3.701	.915
Diabetes	1.483	0.509–4.317	.470	1.313	0.307–5.613	.713
Coronary disease	1.370	0.411–4.563	.608	1.387	0.274–7.027	.693
COPD	0.589	0.203–1.712	.331	0.574	0.151–1.981	.358
Chronic kidney disease	0.045	0.000–68.926	.408	0.000	0.000 to <0.001	.978
Asthma	0.510	0.069–3.772	.509	0.475	0.045–5.020	.536
Autoimmune diseases	2.438	0.572–10.392	.228	1.057	0.193–5.778	.949
Cerebrovascular disease	0.942	0.223–3.985	.935	0.237	0.032–1.763	.160
Alcohol liver disease	5.155	2.158–12.315	<.001	2.947	0.978–8.881	.055
Cirrhosis	6.100	2.440–15.249	<.001	5.536	1.663–18.429	.005
Hyperlipidemia	0.977	0.230–4.149	.975	1.188	0.226–6.251	.839
Atypical Antipsychotics						
Amisulpride	0.725	0.290–1.815	.492	1.064	0.377–2.999	.907
Aripiparzole	0.394	0.118–1.318	.130	0.610	0.164–2.275	.462
Clozapine	1.324	0.397–4.415	.648	1.595	0.413–6.162	.498
Quetiapine	0.609	0.276–1.344	.219	0.499	0.205–1.211	.124
Olanzapine	0.475	0.190–1.186	.111	0.691	0.257–1.857	.463
Paliperidone	0.208	0.028–1.535	.124	0.352	0.045–2.729	.318
Risperidone	0.741	0.336–1.634	.457	0.872	0.370–2.051	.753
Zotepine	0.575	0.171–1.934	.371	0.422	0.096–1.858	.254
Typical Antipsychotics	2.837	0.380–21.157	.309	3.146	0.389–25.413	.282

aHR = adjusted hazard ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, SHO = severe hepatic outcome.

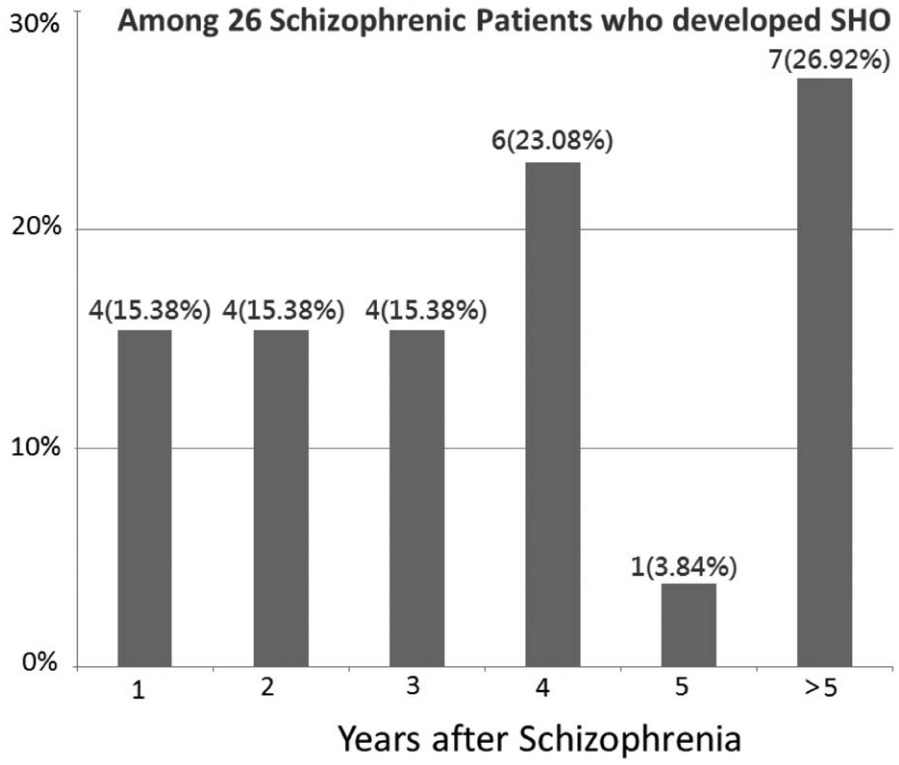

Figure 4. Follow-up of 26 patients with schizophrenia and viral hepatitis who developed SHOs. SHOs = severe hepatic outcomes.

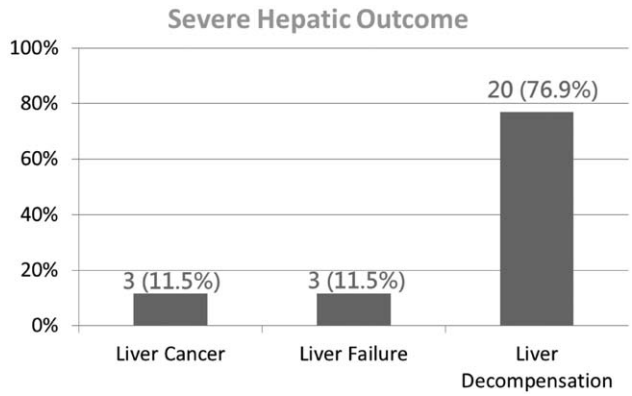

Figure 5. Types of SHOs among patients with schizophrenia and viral hepatitis. SHOs = severe hepatic outcomes.

fewer opportunities to be screened for liver cancer than the general population.[36,37] Furthermore, they have a shorter lifespan and may die before they are diagnosed with liver cancer.[5] Further studies with larger sample sizes and longer follow-up periods are required.

We found that patients with schizophrenia and HBV had a lower SHO risk than those with schizophrenia and HCV (11.2% and 17.3%, respectively). This may be because of several reasons. First, the Taiwanese government provides more resources for HBV treatment. In Taiwan, the government and scientists have cooperated together to control HBV infection and improve its treatment.[38] Second, new drugs, such as direct-acting antivirals for HCV, were not available until 2017.[2] The main medications for HCV are interferon-α and nucleotide analogues.[1] Our study period was from 1996 to 2013, and antiviral medications specific for HCV were not available in the study period. Future studies should investigate the relationship between these new antiviral drugs and hepatic prognosis in patients with schizophrenia and viral hepatitis.

Liver cirrhosis was the leading risk factor for SHOs, such as liver decompensation, according to our findings. In highly endemic HBV regions such as Taiwan, the 5-year cumulative incidence of cirrhosis in patients with HBeAg-positive hepatitis ranges from 13% to 38%. The 5-year cumulative incidence of liver decompensation among patients with cirrhosis has been estimated to be 15%.[14,39] However, approximately 20% of patients with chronic HCV develop liver cirrhosis within 20 to 30 years. Patients with cirrhosis have a higher rate of HCC development (1–4% annually) than those with cirrhosis.[40]

Our data also revealed that paliperidone was associated with a lower SHO risk compared with typical and atypical antipsychotics such as amisulpride, aripiprazole, olanzapine, risperidone, and zotepine (Fig. 3). Paliperidone may improve drug-induced hepatitis and liver cirrhosis in patients with schizophrenia.[41,42] A study reported that patients with schizophrenia and viral hepatitis who received paliperidone had a lower risk of SHO than those who did not (adjusted HR: 0.155, 95% CI: 0.032–0.737, $P = .019$) after adjustment for confounding.[43] This may be mainly associated with the metabolism of paliperidone. Paliperidone, with high affinity for dopamine type 2 and serotonin 5-HT2 receptors, is the primary active metabolite of risperidone.[44] It is metabolized through CYP2D6 and 3A4, with additional minor metabolism (<10% each) through dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission.[45,46]

4.1. Strengths and implication

Atypical antipsychotics are the main pharmacological treatment for schizophrenia,[21,47] and physicians should be aware of adverse effects such as metabolic syndrome and cardiovascular diseases.[48] Hepatic adverse effects currently cause greater concern because of increasing atypical antipsychotic use.[49]

4.2. Limitations

First, no biochemistry data including liver enzymes were available in our database. Second, no trials with patients with schizophrenia and viral hepatitis have been reported. Such clinical trials are difficult to perform because they often exclude comorbidities such as hepatitis to reduce confounding factors.[50] Third, it is difficult to recruit a large enough sample containing patients with both schizophrenia and viral hepatitis from a single center. Therefore, we used a national medical database to evaluate long-term hepatic outcomes in patients with viral hepatitis. Fourth, no biomedical laboratory test is diagnostic for schizophrenia; rather, diagnosis is based on the observation of many psychotic symptoms over a certain period. Reliable and valid measures of schizophrenia remain a concern. In Taiwan, schizophrenia is diagnosed by certified psychiatrists according to ICD-9 CM codes and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. To ensure higher diagnostic validity in this study, only patients who were hospitalized or had at least 3 corresponding outpatient clinic diagnoses were designated as having schizophrenia. Fifth, the onset of hepatitis, the viral load, the concomitant use of drugs such as valproate, and the sue of medications for viral hepatitis were not considered in our study. Further research with a larger sample size should investigate these factors.

5. Conclusions

Our findings indicate that patients with schizophrenia and viral hepatitis, especially HCV, have a higher risk of SHOs, including liver cancer, failure, or decompensation. Among antipsychotics, paliperidone use is associated with the lowest SHO risk, although this was not significant in this study. Further evaluation of hepatic function and antiviral drug use in patients with schizophrenia and viral hepatitis is required.

Author contributions

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Writing – original draft: Chun-Hung Chang, Hsin-Chi Tsai.
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