Hepatitis C virus and hepatitis B virus in patients with schizophrenia

Chun-Hung Chang, MD, PhD, Chieh-Yu Liu, PhD, Shaw-Ji Chen, MD, PhD, Hsin-Chi Tsai, MD, PhD

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 Outcome 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 (2.2%) 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]: 1.85–6.75; 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: 1.61–15.95; 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) and hepatitis C virus (HCV), is the leading cause of liver inflammation diseases. It has increasingly been reported to be related to severe mental illness, such as schizophrenia, which is a chronic psychiatric disorder characterized by cognitive impairment. Several studies have investigated the prevalence of viral hepatitis, especially HBV and HCV, in patients with schizophrenia. Hung et al 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 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). 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. HCV is the leading cause of HCC in Western countries; it accounts for approximately 34% of HCC cases in the United States. However, these studies have investigated the general population rather than focusing on patients with schizophrenia. Long-term hepatic outcomes, such as liver cancer and liver failure, and liver decompensation in patients with schizophrenia and viral hepatitis remain unclear.

Antipsychotics are the main psychopharmacologic treatment for schizophrenia, including first-generation antipsychotics.
(FGAs) and second-generation antipsychotics (SGAs).\textsuperscript{[21]} SGAs have better tolerability and less extra-pyramidal symptoms, therefore, are increasing used than FGAs.\textsuperscript{[22]} SGAs have been well known the association with greater risk of metabolic syndrome such as dyslipidemia compared with FGAs.\textsuperscript{[13,23–26]} However, hepatic adverse effects of SGAs have been reported. Esposito et al.\textsuperscript{[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).\textsuperscript{[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.\textsuperscript{[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).\textsuperscript{[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
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

| Table 1 | Patients’ demographic profile (n=1842). |
| --- | --- |
| | Matched cohort (n=1228) | Viral hepatitis cohort (n=614) | \( P \)-value |
| Age, yrs | M ± SD/n (%) | M ± SD/n (%) |  |
| 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 |
| Anipirazole | 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 (15.9) | .211 |
| Risperidone | 777 (63.3) | 389 (63.4) | .973 |
| Zipatine | 159 (12.9) | 78 (12.7) | .883 |
| Typical antipsychotics | 960 (78.2) | 515 (83.9) | .004 |

COPD = chronic obstructive pulmonary disease.
Patients with primary diagnosis of schizophrenia during 1996-2013 (ICD-9-CM code=295.XX)

Schizophrenia before the January 1, 2002 were excluded to ensure the first diagnosis of breast cancer

Newly-diagnosed schizophrenia patients during the study period 2002-2013

Excluded
- 451 With antecedent severe hepatic outcome
- 827 Age younger than 18 years
- 1,162 Age elder than 60 years
- 2 Gender missing data

Newly-diagnosed schizophrenia patients without severe hepatic outcome during 2002-2013

Patients with viral hepatitis among 15,914 patients

1. matched by age, sex, index year (1:2)
2. Exclude 395 hepatitis after schizophrenia diagnosed
3. Exclude 6 without matching

Schizophrenia patients with viral hepatitis

Schizophrenia patients without viral hepatitis

Figure 1. Flowchart of patient selection.

Table 2

| 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) | 2.57 (1.255–5.251) |
| Adjusted hazard ratio (95% CI)* | 1.00 | 3.58 (1.859–6.754) | 2.57 (1.255–5.251) |

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

* $P<.001$.

$P=.010$.

* Adjusted for age, sex, outpatient visits per year, major coexisting diseases, atypical antipsychotics, and typical antipsychotics.
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.\textsuperscript{[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 2.** Cumulative SHO incidence in matched cohort and viral hepatitis cohort. SHO = severe hepatic outcome.

**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.

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | 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    |
| Aripiprazole                     | 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    | 0.409   | 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.
fewer opportunities to be screened for liver cancer than the general population.\[136,137\] 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.\[138\] Second, new drugs, such as direct-acting antivirals for HCV, were not available until 2017.\[139\] The main medications for HCV are interferon-α and nucleotide analogues.\[140\] 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.\[140\]

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, \(P=0.019\)) 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.\[144\] 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 use 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
Conceptualization: Chun-Hung Chang, Hsin-Chi Tsai.
Data curation: Chun-Hung Chang, Chieh-Yu Liu, Shaw-Ji Chen, Hsin-Chi Tsai.
Formal analysis: Hsin-Chi Tsai.
Funding acquisition: Hsin-Chi Tsai.
Investigation: Chun-Hung Chang, Hsin-Chi Tsai.
Methodology: Chun-Hung Chang, Chieh-Yu Liu, Hsin-Chi Tsai.
Project administration: Hsin-Chi Tsai.
Resources: Chieh-Yu Liu, Shaw-Ji Chen, Hsin-Chi Tsai.
Software: Chieh-Yu Liu, Shaw-Ji Chen, Hsin-Chi Tsai.
Supervision: Chieh-Yu Liu, Hsin-Chi Tsai.
Validation: Hsin-Chi Tsai.
Visualization: Hsin-Chi Tsai.

Figure 5. Types of SHOs among patients with schizophrenia and viral hepatitis. SHOs = severe hepatic outcomes.
Writing – original draft: Chun-Hung Chang, Hsin-Chi Tsai.
Writing – review & editing: Hsin-Chi Tsai.

References

[1] Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet 2018;392:2313–24.

[2] Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: a narrative review. J Clin Transl Hepatol 2018;6:79–84.

[3] Razavi H. Global epidemiology of viral hepatitis. Gastroenterol Clin North Am 2020;49:179–89.

[4] Hughes E, Bassi S, Gilbody S, Bland M, Martin F. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. Lancet Psychiatry 2016;3:40–8.

[5] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet 2016;388:86–97.

[6] Chang et al. Medicine (2021) 100:22