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# Paliperidone is associated with reduced risk of severe hepatic outcome in patients with schizophrenia and viral hepatitis: A nationwide population-based cohort study

Chun-Hung Chang[a,b,c], Hsien-Yuan Lane[a,b,d,e,1,*], Chieh-Yu Liu[f], Shaw-Ji Chen[g,h], Chieh-Hsin Lin[a,d,i,1,*]

[a] Department of Psychiatry, Institute of Clinical Medical Science, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan
[b] Department of Psychiatry & Brain Disease Research Center, China Medical University Hospital, Taichung, Taiwan
[c] An Nan Hospital, China Medical University, Tainan, Taiwan
[d] Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
[e] Department of Psychology, College of Medical and Health Sciences, Asia University, Taichung, Taiwan
[f] Biostatistical Consulting Lab,Department of Speech Language Pathology and Audiology, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan
[g] Department of Psychiatry, Mackay Memorial Hospital Taitung Branch, Taitung, Taiwan
[h] Department of Medicine, Mackay Medical College, New Taipei, Taiwan
[i] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No 123, Dapi Rd, Niaosong District, Kaohsiung 833, Taiwan

A B S T R A C T

*Objective:* Paliperidone, a second-generation antipsychotic, has been found to have minimal hepatotoxicity in patients with schizophrenia. However, long-term hepatic outcome in patients with schizophrenia and viral hepatitis remains unclear.
*Methods:* Data obtained from the Taiwan National Health Insurance Research Database was used to enroll newly diagnosed schizophrenic patients between January 2007 and December 2013. Patients with schizophrenia and viral hepatitis who were receiving paliperidone were allocated to the paliperidone group while those who were not receiving paliperidone were allocated to the control group. Using a 1:2 ratio, we matched the age, sex, and index year to select the control participants. Patients with severe hepatic outcomes (SHOs) before enrollment were excluded. The two groups were studied until December 31, 2013. The primary endpoint was the occurrence of SHOs including liver failure, liver decompensation, liver transplantation, or liver cancer.
*Results:* We identified 134 patients with schizophrenia and viral hepatitis who received paliperidone and 268 matched patients who did not receive paliperidone. Of the 402 patients, 22 (5.47%) developed SHOs during a mean follow-up period of 3.57 ± 1.62 years, including 2 (1.49%) from the paliperidone cohort and 20 (7.46%) from the control group. Furthermore, the Cox multivariate proportional hazards analysis revealed that the risk decreased with paliperidone use (adjusted hazard ratio [HR]: 0.155, 95% confidence interval [CI]: 0.032–0.737, $p = 0.019$) after adjusted for confounding factors.
*Conclusion:* Paliperidone treatment was associated with a reduced risk of SHOs in patients with schizophrenia and viral hepatitis.

## 1. Introduction

Schizophrenia is a chronic psychiatric disorder characterized by cognitive deficits that place a heavy burden on patients, their families, and society (Owen et al., 2016). The lifetime prevalence of schizophrenia is approximately 0.30–0.66% per 10,000 person-years (McGrath et al., 2008). Comorbid viral hepatitis, including hepatitis B virus (HBV) and hepatitis C virus (HCV), among patients with schizophrenia is a growing concern (Hughes et al., 2016). Several studies have investigated the prevalence of viral hepatitis in patients with schizophrenia (Chiu et al., 2017; Freudenreich et al., 2007; Hung et al., 2012; Sockalingam et al., 2010; Wang et al., 2016; Zhu et al., 2015). 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 (Hung et al., 2012). Another study, however, found an HCV prevalence of 2.7% in 110 patients with schizophrenia in Canada (Sockalingam et al., 2010). A high risk of liver cancer, particularly hepatocellular carcinoma, is associated with patients with viral hepatitis (Liaw and Chu, 2009; Webster et al., 2015). However, previous studies have focused on the general population and have not examined patients with schizophrenia.

Second-generation (atypical) antipsychotics are widely used in the

* Corresponding authors.
*E-mail addresses:* hylane@gmail.com (H.-Y. Lane), cyndi36@gmail.com (C.-H. Lin).
[1] Hsien-Yuan Lane and Chieh-Hsin Lin contributed equally in this manuscript as corresponding authors.

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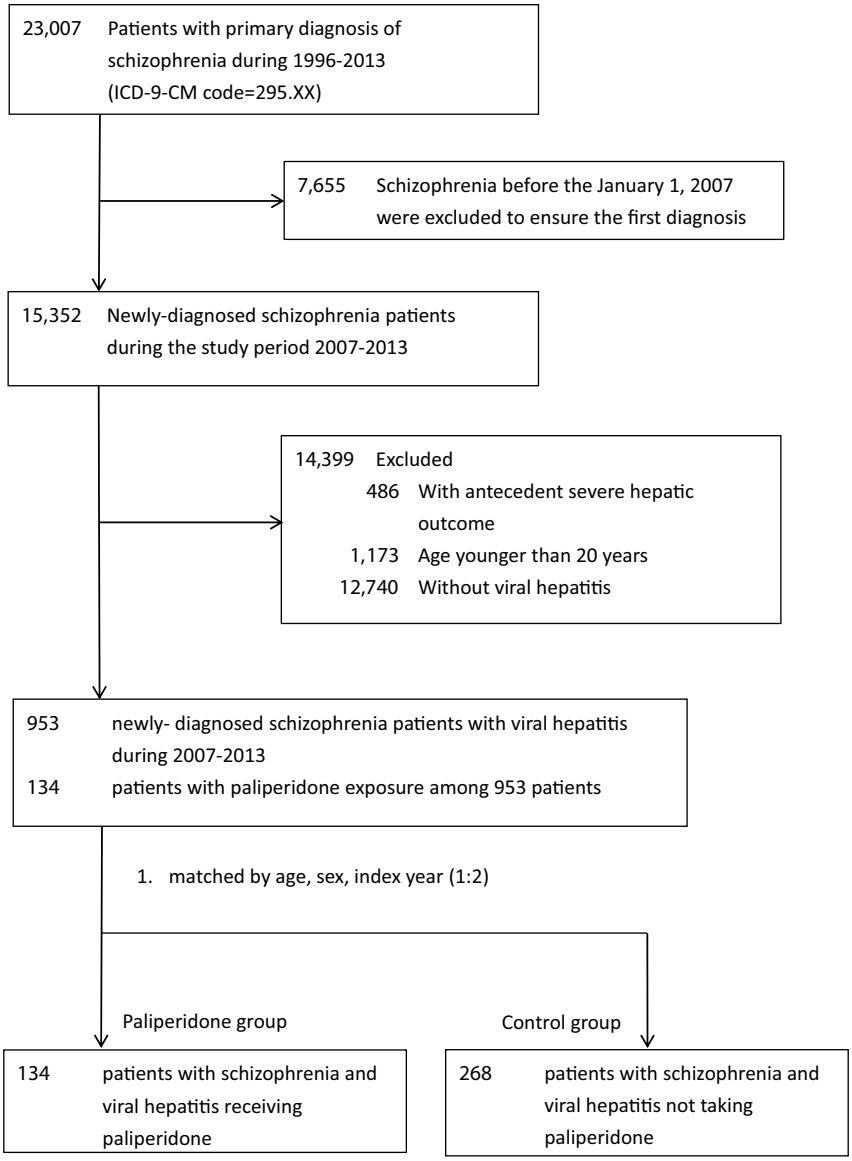


**Fig. 1.** Selection of study patients.

treatment of schizophrenia. Most antipsychotics, including typical and atypical antipsychotics, are metabolized by the hepatic system (Leucht et al., 2012; Owen et al., 2016). Paliperidone, a second-generation antipsychotic, is the primary active metabolite of risperidone (Harvey et al., 2016; Lindenmayer and Kaur, 2016; Mauri et al., 2017). Two case reports have revealed that paliperidone may improve the status of liver enzymes during drug-induced hepatitis or liver cirrhosis (Chou and Chen, 2013; Paulzen et al., 2010). Paulzen et al. reported the case of a 43-year-old woman with schizophrenia and drug-induced hepatitis (Paulzen et al., 2010). After discontinuing risperidone and starting paliperidone at 9 mg per day, her elevated liver enzymes improved. For example, 1159 U/L for gamaglutamyltransferase (normal range: 6–42 U/L) decreased to 112 U/L after 4 weeks of paliperidone treatment. Chou et al. reported the case of a 54-year-old man with schizophrenia and liver cirrhosis (Chou and Chen, 2013). They first prescribed risperidone at 2 mg per day, but the level of his liver enzymes (specifically aspartate aminotransferase/alanine aminotransferase) increased from 34/20 to 91/64 U/L (normal range: < 40/41 U/L) within 5 days. Therefore, risperidone was replaced with paliperidone at 6 mg per day and subsequently titrated up to 9 mg per day after a week. This decreased the enzyme level to 29/4 U/L.

On the basis of these studies, we hypothesize that patients with schizophrenia and viral hepatitis who received paliperidone treatment may have a lower risk of hepatic complications compared to those who do not. We used a real-world database to evaluate the incidence and risk of severe hepatic outcomes (SHOs) including liver cancer, liver failure, and liver decompensation among patients with schizophrenia and viral hepatitis who were treated with paliperidone.

## 2. Methods

### 2.1. Data source

The National Health Insurance Research Database (NHIRD), which was based on the National Health Insurance (NHI) program implemented by the Taiwanese government in March 1995, was used for the study. The NHI program covered more than 99.5% of the population by the year 2010 (Hsieh et al., 2019; Hsing and Ioannidis, 2015). The NHIRD is a de-identified database that consists of medical data for insurance reimbursement in an electronic format, including disease diagnoses, prescription details, clinic visits, hospitalization, examinations, procedures, payments, and locations. The diagnostic codes are

**Table 1**
Demographic profiles of study patients ($n$ = 402).

| | Paliperidone cohort ($n$ = 134) M ± SD/n(%) | Control cohort ($n$ = 268) M ± SD/n(%) | $p$-value |
|---|---|---|---|
| Age (yrs) | 39.10 ± 8.90 | 39.15 ± 8.97 | 0.965 |
| Male | 79 (59.0) | 158 (59.0) | 1.000 |
| Follow-up, y | 3.65 ± 1.59 | 3.52 ± 1.64 | 0.441 |
| Outpatient visits per person per year | | | 0.106 |
| > 0 and ≤10 | 15 (11.2) | 52 (19.4) | |
| > 10 and ≤20 | 51 (38.1) | 106 (39.6) | |
| > 20 and ≤30 | 29 (21.6) | 53 (19.8) | |
| > 30 | 39 (29.1) | 57 (21.3) | |
| Major coexisting diseases | | | |
| Hypertension | 18 (13.4) | 44 (16.4) | 0.435 |
| Diabetes | 13 (9.7) | 20 (7.5) | 0.441 |
| Coronary disease | 13 (9.7) | 18 (6.7) | 0.290 |
| COPD | 34 (25.4) | 58 (21.6) | 0.401 |
| Chronic Kidney disease | 6 (4.5) | 20 (7.5) | 0.251 |
| Asthma | 14 (10.4) | 22 (8.2) | 0.459 |
| Autoimmune diseases | 8 (6.0) | 10 (3.7) | 0.306 |
| Cerebrovascular disease | 6 (4.5) | 15 (5.6) | 0.634 |
| HBV | 68 (50.7) | 125 (46.6) | 0.437 |
| HCV | 21 (15.7) | 54 (20.1) | 0.277 |
| Alcohol liver disease | 5 (3.7) | 20 (7.5) | 0.144 |
| Cirrhosis | 1 (0.7) | 14 (5.2) | 0.026 |
| Hyperlipidemia | 9 (6.7) | 17 (6.3) | 0.886 |
| Atypical Antipsychotics | | | |
| Risperidone | 97 (72.4) | 173 (64.6) | 0.115 |
| Olanzapine | 67 (50.0) | 93 (34.7) | 0.003 |
| Quetiapine | 64 (47.8) | 131 (48.9) | 0.832 |
| Amisulpride | 47 (35.1) | 60 (22.4) | 0.007 |
| Aripiprazole | 46 (34.3) | 56 (20.9) | 0.004 |
| Ziprasidone | 21 (15.7) | 22 (8.2) | 0.022 |
| Zotepine | 21 (15.7) | 38 (14.2) | 0.690 |
| Clozapine | 11 (8.2) | 25 (9.3) | 0.711 |
| Typical Antipsychotics | 110 (82.1) | 219 (81.7) | 0.927 |
| Charlson comorbidity score | 0.40 ± 1.64 | 0.37 ± 1.33 | 0.864 |

Abbreviations: COPD = chronic obstructive pulmonary disease; HBV = hepatitis B virus; HCV = hepatitis C virus.

recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

We followed the guidelines of the Declaration of Helsinki. Because the data were de-identified, information that could identify individual patients was encrypted by the Ministry of Health and Welfare of Taiwan. Because this approach ensured that the study did not violate participants' privacy rights, it was exempted from obtaining informed consent from participants. The study was approved by the Institutional Review Board of the China Medical University Hospital (CMUH105-REC2-087).

### 2.2. Study group

We defined the study group (paliperidone group) as patients with schizophrenia and viral hepatitis receiving paliperidone. From NHIRD, we identified patients (aged 20–99 years) diagnosed with schizophrenia (ICD-9-CM codes 295.XX) and viral hepatitis (ICD-9-CM codes 070.XX) between January 2007 and December 2013. Patients with a prior diagnosis of schizophrenia before enrollment were excluded. The enrollment date was defined as the date of receipt of initial diagnosis of schizophrenia. In Taiwan, a diagnosis of schizophrenia was made according to the ICD-9-CM code and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) by board-certified psychiatrists. In this study, only those patients who have been admitted or received at least three corresponding diagnoses at an outpatient clinic were designated as having schizophrenia for superior diagnostic validity.

### 2.3. Matching process and control group

The control group was defined as patients with schizophrenia and viral hepatitis not taking paliperidone. We used a 1:2 ratio and matched the age, sex, and index year to select control participants. Matching for age and year of enrollment was allowed within a tolerance range ( ± 1 year). For the control group, the start date of follow-up was defined as the date of first admission to a medical facility in the enrollment year (Fig. 1).

### 2.4. Main outcome measures

We defined the endpoint as the occurrence of SHOs, namely, 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) (Kaye et al., 2010; Wu et al., 2012; Yu et al., 2016). In both the groups, patients with a medical history of SHOs before enrollment were excluded. All patients were observed from the enrollment date until either the first SHO diagnosis or the study end date of December 31, 2013. Mortality was defined as death during hospitalization.

### 2.5. Statistical analysis

We used MY Structured Query Language for extraction, linkage, and processing of the data. In this study, we performed all statistical analyzes using IBM SPSS statistical software (version 20.0 for Windows; IBM Corp., New York, NY, USA). The demographic characteristics and comorbidities of the paliperidone group and control group were compared using Pearson's $\chi^2$ test for categorical variables and the unpaired Student's $t$-test for continuous variables. We used the Kaplan–Meier analysis to evaluate the cumulative incidence of SHOs and log-rank test to evaluate the significance. A Cox proportional hazard model was used for multivariate adjustments. Adjusted parameters included age, sex, outpatient visits, comorbidities, Charlson comorbidity score, atypical antipsychotics, and typical antipsychotics. We used the Charlson comorbidity score to evaluate the severity of comorbidity diseases (Charlson et al., 1987). Statistical significance was defined as a 2-sided $p$ value of $<0.05$.

## 3. Results

### 3.1. Demographic characteristics

The paliperidone cohort (the study cohort) included 134 patients with schizophrenia and viral hepatitis who received paliperidone, whereas the control cohort included 268 patients with schizophrenia and viral hepatitis matched for age, sex, and index year who did not receive paliperidone. The basic characteristics of the schizophrenia cohort and the matched control group are shown in Table 1. The percentages on formulation (oral paliperidone) were 100%. The patients in the paliperidone cohort received oral paliperidone. The three leading second-generation antipsychotics were risperidone, olanzapine, and quetiapine. In both groups, the patients were predominately male (59.0%). No significant difference in major coexisting diseases except cirrhosis was observed between the two groups.

### 3.2. Cumulative incidences of severe hepatic outcome

During a mean follow-up period of 3.57 ± 1.62 years, a lower incidence of SHO was observed in the paliperidone cohort compared to the control group (4.08 vs 21.15 per 1000 person-years) (Table 2). Patients with schizophrenia and viral hepatitis receiving paliperidone exhibited a significantly lower risk compared to the control group (HR = 0.194, log-rank test, $p$ = 0.0135, Fig. 2). The fully adjusted hazard ratio was 0.155 (95% confidence interval [CI]: 0.032–0.737;

**Table 2**
Incidences and hazard ratios for SHOs in patients with schizophrenia and hepatitis (2007–2013, $n$ = 402).

| Severe hepatic outcome during follow-up | Total sample | Comparison group | Paliperidone group |
|---|---|---|---|
| Incidence of SHO (per 1000 person-years) | 15.34 | 21.18 | 4.08 |
| No. of occurrences | 22 | 20 | 2 |
| Observed person-years | 1433.84 | 944.07 | 489.77 |
| Crude hazard ratio (95% CI) | | 1.00 | 0.194(0.045–0.829)[a] |
| Adjusted hazard ratio (95% CI)[b] | | 1.00 | 0.155(0.032–0.737)[a] |

Abbreviations: CI = confidence interval.
[a] $p < 0.001$.
[b] Adjusted for age, sex, outpatient visits per year, major coexisting diseases, Charlson comorbidity score, atypical antipsychotics, and typical antipsychotics.

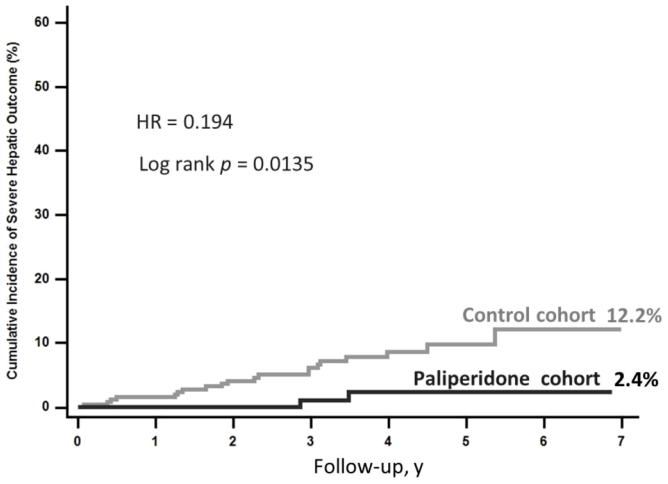


**Fig. 2.** Cumulative incidence of SHOs in two cohorts.

**Table 3**
Serial multivariate adjustment showing paliperidone exposure as a protective factor for SHOs.

| Adjustment Model | Hazard ratio | 95% CI | $p$ Value |
|---|---|---|---|
| Crude, unadjusted | 0.194 | 0.045–0.829 | 0.006 |
| Model 1[a] | 0.194 | 0.045–0.832 | 0.027 |
| Model 2[b] | 0.206 | 0.047–0.911 | 0.037 |
| Model 3[c] | 0.189 | 0.042–0.852 | 0.030 |
| Model 4[d] | 0.156 | 0.033–0.734 | 0.019 |
| Model 5[e] | 0.155 | 0.032–0.737 | 0.019 |

[a] Adjusted for age, sex, and outpatient visits.
[b] Adjusted for variables in Model 1 plus comorbidities in Table 1.
[c] Adjusted for variables in Model 2 plus Charlson comorbidity score in Table 1.
[d] Adjusted for variables in Model 3 plus atypical antipsychotics.
[e] Adjusted for variables in Model 4 plus typical antipsychotics.

$p$ = 0.019) (Table 3). Furthermore, early use of paliperidone was associated with a lower risk of SHOs because none of the paliperidone cohort developed SHOs if they received paliperidone treatment within 180 days (schizophrenia to paliperidone use, median: 174.0 days, mean: 361.8 days). Moreover, the paliperidone cohort exhibited a lower risk of mortality, though not significant (HR: 0.759; 95% CI: 0.392–1.472; $p$ = 0.437).

The Cox multivariate proportional hazards analysis showed that typical antipsychotics and atypical antipsychotics, including amisulpride, aripiprazole, olanzapine, risperidone, ziprasidone, and zotepine, were associated with an increased risk of SHOs, though not significant (Fig. 3).

### 3.3. Severe hepatic outcome analysis

Among the 22 patients with schizophrenia and viral hepatitis who developed SHO, 15 (68.2%) were men. SHOs occurred within 3 years following schizophrenia in 15 of the total 22 patients (first year, 4 (18.2%); second year, 6 (27.3%); third year, 5 (22.7%); fourth year, 5 (22.7%); and more than 5 years, 2 (9.1%)) (Fig. 4). The three leading subgroups of SHOs were liver decompensation (11/22 (50.0%)), liver failure (6/22(27.3%)), and liver cancer (5/22(22.7%)).

## 4. Discussion

To our knowledge, this is the first study to analyze subsequent risk of SHOs and paliperidone administration in patients with schizophrenia and viral hepatitis. The results show that (1) receiving paliperidone treatment was associated with a reduced risk of SHOs in patients with schizophrenia and viral hepatitis (aHR: 0.155; 95% CI: 0.032–0.737; $p$ = 0.019); (2) early use of paliperidone was associated with a lower risk of SHOs; (3) more than 90% of SHOs were developed within 5 years following schizophrenia diagnosis.

Paliperidone treatment has been reported in patients with schizophrenia and drug-induced hepatitis and liver cirrhosis (Chou and Chen, 2013; Paulzen et al., 2010). They noted that abnormal liver function returned to normal after shifting risperidone to paliperidone. In our study, we found that risperidone was associated with an increased risk of SHOs (nonsignificant), including liver failure, liver decompensation, liver transplantation, and liver cancer. By contrast, paliperidone administration in patients with schizophrenia and viral hepatitis was associated with a lower risk of SHOs.

Why risperidone may be associated with hepatotoxicity? Risperidone is metabolized to active metabolite compound (9-OH-risperidone) via cytochrome P450 (CYP) 2D6 (Rattehalli et al., 2016). The differences in the pharmacokinetic properties of these two compounds (risperidone and 9-OH-risperidone) might increase the risk of hepatotoxicity (Benazzi, 1998). On the other hand, why paliperidone is associated with reduced risk of SHOs? This may be attributed to the mechanism of metabolite action. Paliperidone is the primary active metabolite of risperidone. It has a high affinity for dopamine type 2 (D2) and serotonin 5-HT2 receptors. Paliperidone does not undergo significant hepatic metabolism (Dolder et al., 2008; Schoretsanitis et al., 2018a, b). In our study, paliperidone is associated with lower risk of SHO than other antipsychotics (Fig. 3). Over 1000 drugs have been considered responsible for hepatic adverse effects, and 16% of these agents were neuropsychopharmacologic medications (Dumortier et al., 2002). Psychiatrists and physicians should be aware about the hepatic tolerance of second-generation antipsychotics.

We found that the mean duration from the schizophrenia diagnosis to paliperidone administration was 361.8 days. Patients who received paliperidone treatment within 180 days did not develop SHOs. This finding may suggest that early use of paliperidone may reduce the risk of severe liver complications. Additionally, early use of long-acting injectable antipsychotics has proven to be efficacious in recently diagnosed schizophrenia (Si et al., 2017; Stevens et al., 2016). Long-acting paliperidone may be suggested for patients with recently diagnosed schizophrenia with viral hepatitis. However, further trials with large samples and superior study design are warranted to evaluate such findings. Our study showed that the leading SHO was liver

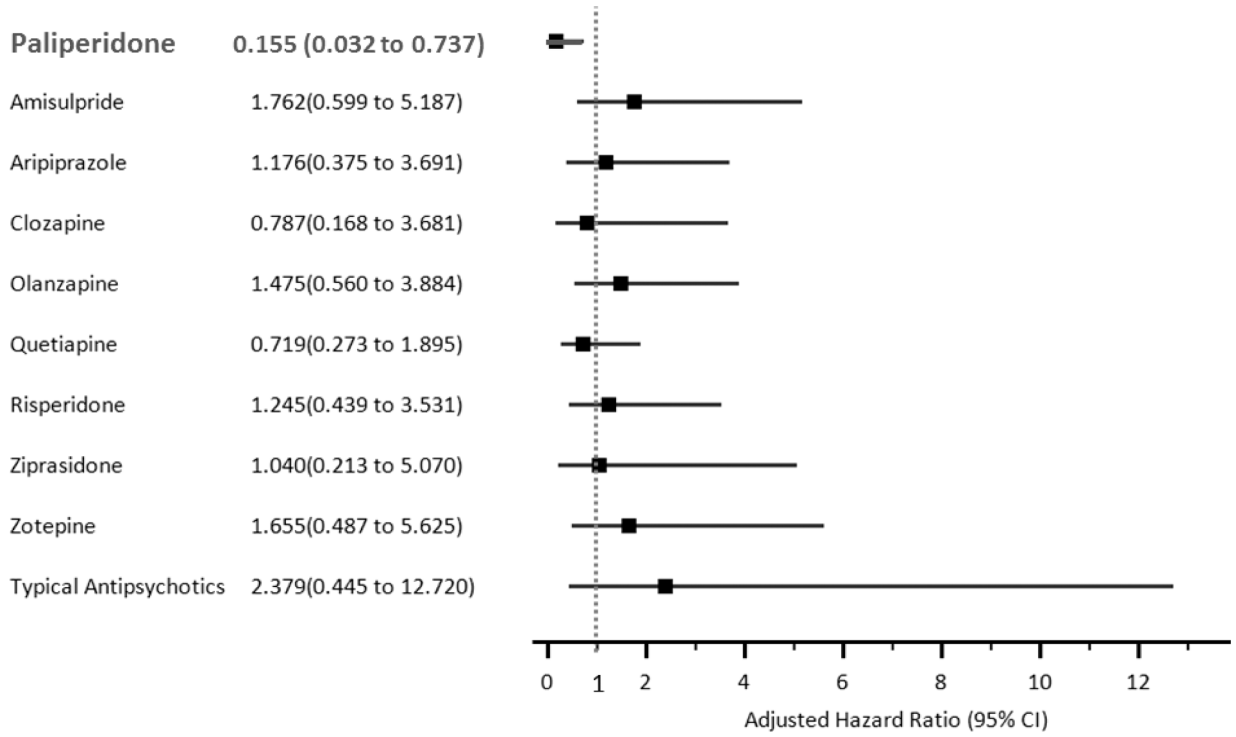


**Fig. 3.** Multivariate Cox analysis for factors associated with SHOs in patients with schizophrenia and viral hepatitis who received antipsychotics.

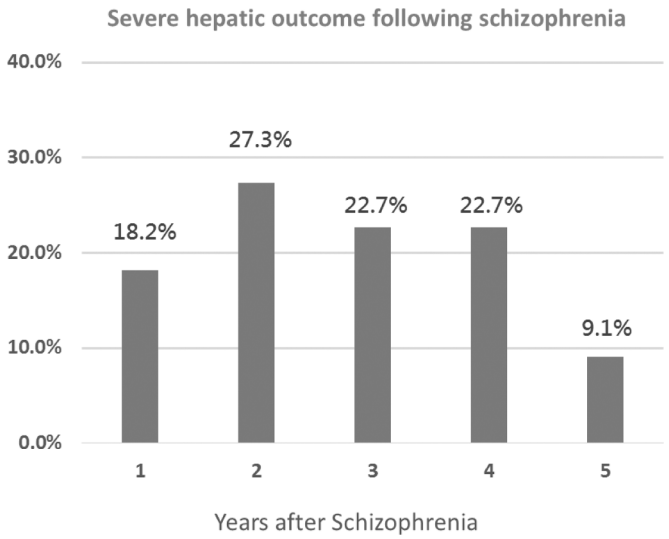


**Fig. 4.** Follow-up duration among 22 patients with schizophrenia and viral hepatitis who developed SHOs.

decompensation (11/22 (50.0%)). More than 90% of the SHOs were developed within 5 years following a schizophrenia diagnosis. Previous studies have shown that in patients with chronic HBV or HCV, the cumulative incidence of decompensation at 5 years ranges from 7.5% to 15% (Benvegnu et al., 2004; Fattovich et al., 2008; Trinchet et al., 2015). A study of 312 patients with HBV or HCV found that during a median follow-up of 93 (range 14–194) months, 102 (32.6%) patients developed at least one complication (Benvegnu et al., 2004). Our findings suggest patients with schizophrenia may develop complications earlier than the normal population. One of the possible reasons is that people with severe mental illnesses, such as schizophrenia, may receive poorer medical care, encounter more obstacles within the medical system, and exhibit a higher degree of medical morbidity (Chochinov et al., 2012; Viron and Stern, 2010).

### 4.1. Strength and implications

This is the first study to evaluate the association between paliperidone treatment and hepatic outcome in patients with schizophrenia and viral hepatitis. We found that receiving paliperidone treatment was associated with a reduced risk of SHOs in patients with schizophrenia and viral hepatitis. We also noted that the early use of paliperidone may be associated with a lower risk of SHOs. Atypical antipsychotics are the main pharmacologic treatment for schizophrenia (Freedman, 2003) and physicians must be aware of adverse effects, such as metabolic syndrome and cardiovascular diseases (Pringsheim et al., 2017). In a recent study, hepatic adverse effects were found to have caused more concerns because of the increasing use of atypical antipsychotics (Slim et al., 2016). Our findings implicate that paliperidone may be the first choice for patients with schizophrenia and viral hepatitis to reduce the risk of liver failure, liver decompensation, and liver cancer.

Our study has limitations. First, no hepatic functionality parameters were available in our database. Till date, no trial on paliperidone for patients with schizophrenia and viral hepatitis has been reported. In fact, it is difficult to conduct such a trial because clinical trials often exclude comorbidities such as hepatitis to reduce the effect of confounding factors (Miskulin et al., 2001). Additionally, it is difficult for any single research center to include a sufficient number of patients with schizophrenia and viral hepatitis. Therefore, we used this dataset and SHOs as the endpoint to evaluate the prognosis. Second, information about dosages was not available in our datasets. For instance, it is known that long-acting paliperidone provides a more stable plasma-drug concentration than oral paliperidone (Mathews et al., 2019). Additional studies may need to investigate the comparative effects of the two different formulations in patients with schizophrenia and viral hepatitis. Third, the treatment and severity of viral hepatitis may affect hepatic outcomes. However, disease severity has not been examined using the claims-based data. Further research should explore patients with differing hepatitis therapies, disease severities, and clinical variables. Fourth, amisulpride (Komossa et al., 2010), which is not eliminated by the liver, does not exhibit a significantly lower risk of SHOs compared to other antipsychotics. This finding may be misleading

because only a few patients received amisulpride in the study. The three leading antipsychotics were risperidone, olanzapine, and quetiapine. Therefore, additional studies using a larger sample size and comprehensive variables that affect hepatic complications are warranted.

In conclusion, this study demonstrated a reduced risk of SHOs in patients with schizophrenia and viral hepatitis who were treated with paliperidone. Our findings suggest that the early use of paliperidone treatment may benefit this category of patients by reducing the risk of liver failure, liver decompensation, and liver cancer.

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The authors have indicated they have no relevant financial relationships to disclose for this article.

## CRediT authorship contribution statement

**Chun-Hung Chang:** Conceptualization, Formal analysis. **Hsien-Yuan Lane:** Visualization, Writing - review & editing. **Chieh-Yu Liu:** Data curation, Writing - review & editing. **Shaw-Ji Chen:** Data curation, Writing - review & editing. **Chieh-Hsin Lin:** Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112597.

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