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Short communication

Post-discharge use of antipsychotics in patients with hospital-acquired delirium and associated risk of mortality – A population-based nested case-control study

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ABSTRACT

Objective: To evaluate post-discharge use of antipsychotics in patients with incident hospital-acquired delirium and the associated risk of mortality.
Methods: We conducted a nested case-control study for patients newly diagnosed with hospital-acquired delirium and subsequently discharged from hospital using Taiwan's National Health Insurance Database (NHID) from 2011 to 2018.
Results: The use of antipsychotics after discharge did not increase the risk of mortality (adjusted OR: 1·03; 95% CI: 0·98–1·09).
Conclusions: The findings suggested that using antipsychotics after discharge in patients with hospital-acquired delirium may not increase the risk of mortality.

1. Introduction

Delirium is a common condition characterized by acute confusion, altered mental status, and/or metabolic encephalopathy in hospitalized elders (Marcantonio, 2017). Several studies have revealed the association between the use of antipsychotics and an increased risk of mortality among patients with hospital-acquired delirium (Agar et al., 2017; Basciotta et al., 2020; Collet et al., 2018; Girard et al., 2018; Swan et al., 2012). Swan et al. found that antipsychotic exposure was associated with longer hospitalization (Swan et al., 2012). However, a recent systematic review has shown conflicting results, suggesting that, compared with placebo, the use of haloperidol and second-generation antipsychotics did not increase the risk of mortality for patients with hospital-acquired delirium (Nikooie et al., 2019).

Approximately 24–40% of patients may be prescribed antipsychotics to control psychotic symptoms after they are discharged from hospital (Herzig et al., 2016; Kalisch Ellett et al., 2019; Rowe et al., 2015). However, previous studies have indicated that the use of antipsychotics may increase the risk of mortality (Gill et al., 2007; Swan et al., 2012), raising calls to reduce the use of antipsychotics for treatment after discharge (Herzig et al., 2016). However, antipsychotics may improve patients' quality of life by controlling psychotic symptoms (Taipale et al., 2020). Current evidence predominantly focuses on antipsychotics use during hospitalization, with only limited evidence available regarding the use of antipsychotics after discharge. Therefore, we analyzed a population-based database to evaluate the risk of mortality for patients with incident delirium during hospitalization and who did or did not receive antipsychotics after discharge. We hypothesized that the post-discharge use of antipsychotics was not associated with risk of mortality after considering patients' underlying diseases and baseline covariates.

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2. Materials and methods

2.1. Data sources

We used Taiwan's National Health Insurance Database (NHID) with a linkage to the Cause of Death Registry for this study. The details of NHID and Cause of Death Registry have been described elsewhere (Cheng et al., 2015; Hsieh et al., 2019) (Supplementary materials).

2.2. Study design

This is a nested case-control study analyzing patients who suffered a new episode of hospital-acquired delirium between 2011 and 2018 and were later discharged from hospital. We captured all records of delirium from the in-patient claims of NHID by using the International Classification of Diseases, Ninth Revision (ICD9) and International Classification of Diseases, Tenth Revision (ICD10) codes. The definition of ICD9 and ICD10 codes for delirium are listed in the supplementary materials. This definition of delirium was based on a previous study with a positive predictive value of 90% and modified by expert opinion (Kim et al., 2017). A new episode of hospital-acquired delirium was defined as having no record of delirium for a year before the first record of delirium. In addition, we excluded patients discharged against advice because the major reason for such discharge was termination of life. We also excluded patients with comorbid schizophrenia, depression and bipolar disorder to ensure that the antipsychotics were for the indication of delirium rather than for pre-existing psychiatric conditions. The detailed definition of diagnostic codes for the exclusion conditions are listed in the Supplementary materials.

2.3. Definition of case and control patients

We defined the index date as the date of death (Cheng et al., 2015), and defined the case group as those who died within 180 days after discharge from the hospital with incident delirium. We selected the control group using up to one:five matching by sex and age (± five years) on the date of admission. To improve comparability between case and control group, we assigned the control patients the same length of observation period (from discharge date to index date) as their respective case patients (Fig. 1).

2.4. Exposure definition

We defined exposure to antipsychotics as requiring at least one recorded prescription of antipsychotic medication after hospital discharge. Patients with no record of antipsychotics were classified as unexposed. We further classified exposed patients by the type of their prescribed antipsychotics including haloperidol, risperidone, quetiapine, olanzapine, while those who received two or more antipsychotics were classified as the combination group.

2.5. Statistical analysis

We selected covariates on the basis of literature review and expert opinion (Elie et al., 2009; Marcantonio, 2017; Oh et al., 2017). The details of covariates are presented in the supplementary materials. We performed multivariable conditional logistic regression models considering all covariates listed in Table 1 to assess the association between the use of antipsychotics after discharge and the risk of mortality. We considered the unexposed group as the reference group for all analyses. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were presented accordingly. The details regarding the methods for the

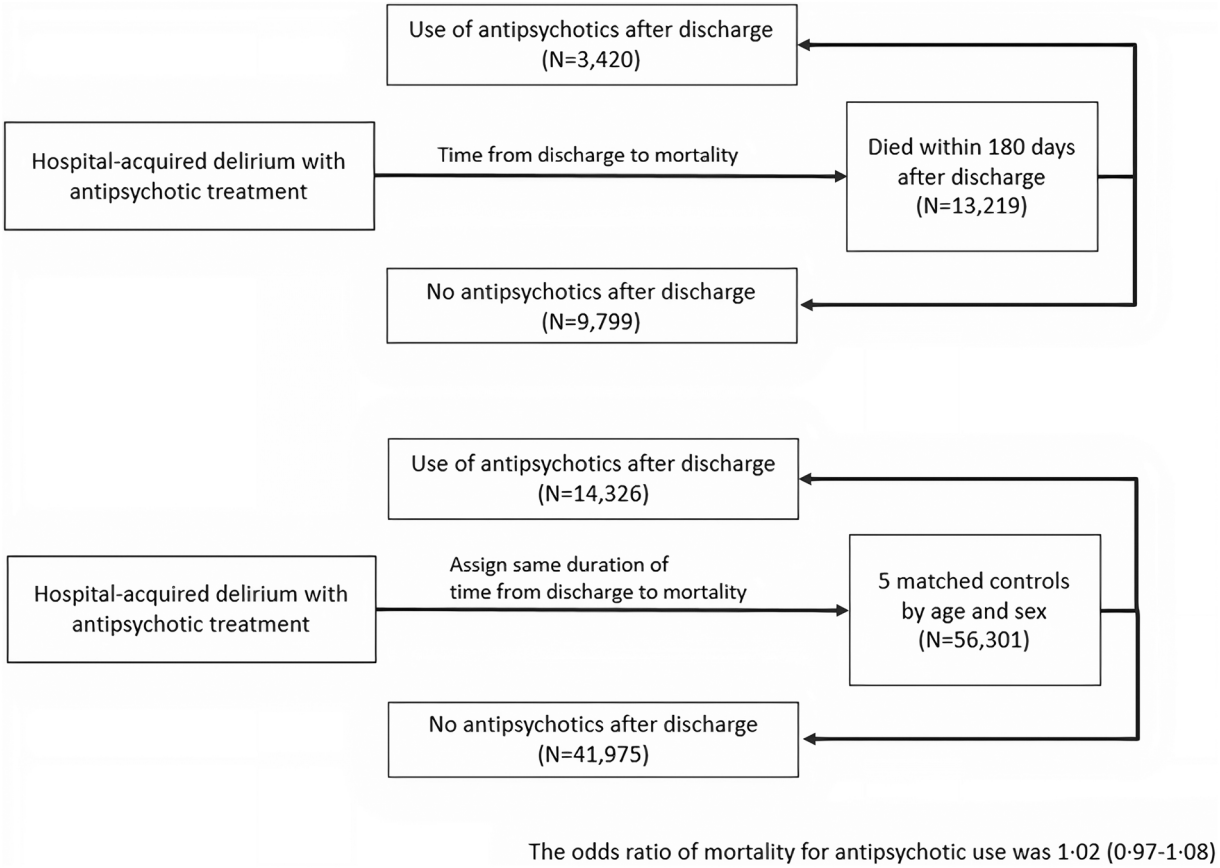

Fig. 1. The nested case control design and odds ratio of mortality with antipsychotic use.

Table 1
Characteristics of 180-day mortality cases and matched population controls.

Characteristics	Case (n = 13219)	Control (n = 56301)	SMD
Age, years, mean (SD)	80·3 (13·3)	78·9 (13·0)	0·11
Elderly (≥65 y), n (%)	11765 (89·0)	49,672 (88·2)	0·02
Male sex, n (%)	7494 (56·7)	30,914 (54·9)	0·04
Length of stay, day, mean (SD)	14·8 (32·6)	11·2 (27·6)	0·12
Comorbidities, n (%)			
Acute kidney injury	2400 (18·2)	3839 (6·8)	0·35
Anemia	4118 (31·2)	10,715 (19·0)	0·28
Arrhythmia	3376 (25·5)	8821 (15·7)	0·25
Asthma	1269 (9·6)	4508 (8·0)	0·06
Coronary artery disease	3324 (25·2)	12,122 (21·5)	0·09
Chronic kidney disease	4176 (31·6)	12,697 (22·6)	0·20
COPD	4005 (30·3)	11,525 (20·5)	0·23
Dementia	6623 (50·1)	30,718 (54·6)	-0·09
Diabetes	5251 (39·7)	20,183 (35·9)	0·08
Electrolyte imbalance	5498 (41·6)	13,616 (24·2)	0·38
Encephalopathy	2866 (21·7)	7982 (14·2)	0·20
Epilepsy	941 (7·1)	3667 (6·5)	0·02
Head injury	1848 (14·0)	8156 (14·5)	-0·01
Heart failure	3310 (25·0)	7440 (13·2)	0·30
Hemorrhagic stroke	1769 (13·4)	7462 (13·3)	0·00
Hepatic failure	826 (6·3)	1345 (2·4)	0·19
Hyperlipidemia	2247 (17·0)	13,309 (23·7)	-0·17
Hypertension	9097 (68·8)	39,463 (70·1)	-0·03
Insomnia	1754 (13·3)	8053 (14·3)	-0·03
Ischemic stroke	3447 (26·1)	15,611 (27·7)	-0·04
Osteoporosis	1126 (8·5)	6189 (11·0)	-0·08
Parkinson's disease	1308 (9·9)	6503 (11·6)	-0·05
Peptic ulcer	4945 (37·4)	17,370 (30·9)	0·14
Peripheral arterial occlusive disease	926 (7·0)	3078 (5·5)	0·06
Pneumonia	9447 (71·5)	24,848 (44·1)	0·58
Sepsis	6624 (50·1)	10,407 (18·5)	0·71
Solid tumor	4244 (32·1)	9199 (16·3)	0·37
Tuberculosis	639 (4·8)	1191 (2·1)	0·15
Urinary tract infection	852 (6·5)	3419 (6·1)	0·02
Valvular heart disease	971 (7·4)	3407 (6·1)	0·05
Ventilator support	4465 (33·8)	5479 (9·7)	0·61
Comedications, n (%)			
Antiarrhythmic agent	3302 (25·0)	6185 (11·0)	0·37
Antihypertensive agent	2134 (16·1)	7660 (13·6)	0·07
Anticholinergics	2263 (17·1)	8700 (15·5)	0·05
Antihistamine	9950 (75·3)	37,306 (66·3)	0·20
Bronchodilator	9975 (75·5)	28,082 (50·0)	0·55
Carbapenem	4367 (33·0)	5321 (9·5)	0·60
Cephalosporins	4733 (35·8)	6365 (11·3)	0·60
Cholinesterase inhibitor	432 (3·27)	4111 (7·3)	-0·18
Dextromethorphan	3375 (25·5)	12,680 (22·5)	0·07
H_2 receptor antagonist	8331 (63·0)	26,997 (48·0)	0·31
Muscle relaxant	4451 (33·7)	20,843 (37·0)	-0·07
NSAID	9025 (68·3)	38,571 (68·5)	-0·01
Opioid	7276 (55·0)	20,596 (36·6)	0·38
Propofol	604 (4·6)	1582 (2·8)	0·09
Proton Pump Inhibitor	7013 (53·1)	16,089 (28·6)	0·51
Statin	2287 (17·3)	12,848 (22·8)	-0·14
Sulfamethoxazole/ Trimethoprim	1484 (11·2)	4228 (7·5)	0·13
Trazodone	733 (5·6)	3192 (5·7)	-0·01
Valproic acid	1307 (9·9)	3536 (6·3)	0·13

Note: COPD, Chronic obstructive pulmonary disease; NSAID, Non-steroidal anti-inflammatory drug

sensitivity analysis are presented in the Supplementary materials. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

3. Results

Fig. 1 presents the flowchart of patient disposition. Table 2 presents the association between antipsychotics use after discharge and the risk of mortality with adjustment for the covariates. The risk of mortality was similar for those exposed to antipsychotics and those not exposed

Table 2
Evaluation of antipsychotic use and the risk of mortality.

			Crude		Adjusted[a]	
	Case	Control	OR	95% CIs	OR	95% CIs
No use of antipsychotics	9799	41,975	1·00	–	1·00	–
Antipsychotics	3420	14,326	1·02	0·97–1·06	1·03	0·98–1·09
Haloperidol	749	2993	1·09	1·00–1·19	1·06	0·95–1·19
Risperidone	155	777	0·85	0·71–1·02	0·78	0·62–0·98
Quetiapine	1391	6228	0·93	0·88–1·00	1·00	0·92–1·08
Olanzapine	38	192	0·88	0·62–1·25	0·87	0·57–1·30
Combination use	1085	4134	1·12	1·05–1·21	0·98	0·87–1·09
Groups by dosage of antipsychotics[b]						
Low dose	12,134	51,856	1·0	–	1·00	–
Medium dose	438	2013	0·93	0·84–1·03	1·12	0·96–1·30
High dose	647	2432	1·14	1·04–1·24	1·36	1·19–1·56

[a]Adjusted by all covariates listed in Table 1.
[b]Antipsychotic dosage was converted to haloperidol equivalent doses and divided into three groups: High (daily dose greater than 3·0 mg), Medium (1·5–3·0 mg/day), and Low (less than 1·5 mg/day).
[c]Ziprasidone group was not applicable because a number less than three was considered as an identifiable number.

(adjusted OR: 1·03, 95% CI: 0·98–1·09). Specifically, patients receiving haloperidol (crude OR: 1·09; 95% CI: 1·00–1·19) or a combination of antipsychotics (crude OR: 1·12; 95% CI: 1·05–1·21) had a higher risk of mortality compared to those not receiving antipsychotics; however, the difference in risk was eliminated after adjustment for the covariates (adjusted OR: 1·06; 95% CI: 0·95–1·09 for haloperidol and adjusted OR: 0·98; 95% CI: 0·87–1·09 for combination). The details of the sensitivity analysis are presented in the supplementary materials.

4. Discussion

Some evidence suggests patients with hospital-acquired delirium may require antipsychotic treatment in specific situations (Thom et al., 2017). However, data regarding continuous use of antipsychotics after discharge are limited. In this study, we evaluated the mortality risk for those who used antipsychotics after discharge, compared to those who did not, and found that antipsychotics use was not associated with a higher risk of mortality. Specifically, compared to those not receiving antipsychotics, we found the mortality risk was higher for those receiving haloperidol or a combination of two or more antipsychotics; however, these differences in risk were eliminated when we considered the dosages of the antipsychotics and patients' baseline covariates. The results should be interpreted carefully, especially since patients receiving a higher dose of antipsychotics had a greater length of hospitalization, suggesting that the severity of delirium conditions should be considered. However, data on the delirium severity, such as the Delirium Rating Scale–Revision-98 (DRS-R-98) and the CAM-Severity Scale (CAM-S) were not available in the NHID (Oh et al., 2017). Future studies using electronic health records or other databases that might contain the severity of delirium are suggested.

Antipsychotics use in the elderly and the association with mortality has been under discussion for decades (Gill et al., 2007). It has been reported that antipsychotics may cause elevated risk of mortality through several possible mechanisms, including metabolic changes, extrapyramidal symptoms, falls, pneumonia, QTc prolongation, and sudden cardiac death (Basciotta et al., 2020; Maust et al., 2015; Wang et al., 2021). However, some clinicians may consider antipsychotics to control psychotic symptoms, thus potentially reducing the caregiver burden and improving patients' quality of life (Taipale et al., 2020). These issues have raised considerable debate on the continuous use of antipsychotic treatment after discharge (Kalisch Ellett et al., 2019), mainly on concerns over the increased risk of mortality. Diverging from previous studies (Collet et al., 2018; Swan et al., 2012), our results indicated that antipsychotics use after discharge did not increase

mortality risk in patients with hospital-acquired delirium. One possible explanation for this discrepancy between our results and those of previous studies was that we use a relatively low dose of antipsychotics in Taiwan. The degree of control over a large number of covariates such as arrhythmia, dementia, and infectious disease may be another explanation because they were not considered in previous studies (Collet et al., 2018; Swan et al., 2012).

There were some limitations to this study. First, as in other claims database research, we did not have information about the severity of patients' delirium or delusional symptoms. We may have underestimated the benefit from receiving antipsychotics because those receiving antipsychotics may have had more severe conditions compared to those not receiving them. Our study considered a large number of covariates, including approximately 30 comorbidities and 20 co-medications, to minimize the impact of confounding by indication, but the effects of residual confounders could not be completely eliminated. Nonetheless, this may not have affected our conclusion that antipsychotics did not increase the risk of mortality. Second, the NHID did not provide information about the delirium subtypes. Antipsychotics may be more likely to be used for patients with hyperactive delirium, but patients with hypoactive delirium are associated with higher mortality (Avelino-Silva et al., 2018). Therefore, we could not completely eliminate potential bias because those not receiving antipsychotics could be cases of hypoactive delirium. To minimize bias, we included patients receiving antipsychotics before discharge from hospitalization. In this situation, most of the patients could have hyperactive delirium, unless the patients changed from hyperactive delirium to hypoactive delirium after discharge.

5. Conclusions

We analyzed a large population-based real-world dataset to minimize the effects of random error and provide more definite result estimates for clinical practice. The results showed no association between the use of antipsychotics after hospital discharge and increased mortality risk in patients with hospital-acquired delirium. Although we observed that patients receiving higher doses may be at higher risk of mortality, the increased risk associated with the high dose may be the result of patients' underlying diseases. These findings suggested that using antipsychotics after discharge in patients with hospital-acquired delirium may not increase the risk of mortality until disproven.

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DHTT, ECCL, WHC conceived and designed the study. DHTT analyzed the data and DHTT and ECCL wrote the first draft. DHTT and ECCL accessed and verified the data. All authors provided critical revisions. All authors read and approved the submitted manuscript. ECCL supervised the study.

Financial disclosure

None.

Declaration of conflicts of interest

We declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103533.

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