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Title:

Demographic and clinical characteristics of patients with delirium: analysis of a nationwide Japanese medical database

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ABSTRACT

Objectives: Delirium commonly occurs during hospitalization and is associated with increased mortality, especially in elderly patients. This study aimed to determine the demographic and clinical characteristics of patients with delirium in the Japanese real-world clinical setting using a nationwide database comprising claims and discharge abstract data.

Design: This was an observational, cross-sectional, retrospective study in hospitalized patients with an incident delirium identified by a diagnosis based on International Classification of Diseases, 10th revision codes or initiating antipsychotics recommended for delirium treatment in Japan during their hospitalization.

Setting: Patients from the Medical Data Vision database including more than 400 acute care hospitals in Japan were evaluated from admission to discharge.

Participants: Of the 32,910,227 patients who were included in the database between April 2012 and September 2020, 145,219 patients met the criteria for delirium.

Primary and secondary outcome measures: Demographic and baseline characteristics, comorbidities, clinical profiles, and pharmacological treatments were evaluated in patients with delirium.

Results: The mean (standard deviation [SD]) patient age was 76.5 (13.8) years. More than half of the patients (n=82,159; 56.6%) were male. The most frequent comorbidity was circulatory disease, observed in 81,954 (56.4%) patients. Potentially inappropriate medications (PIMs) with risk of delirium including benzodiazepines and opioids were prescribed to 76,798 (52.9%) patients. Approximately three-fourths of these patients (56,949; 74.2%) were prescribed ≥4 PIMs. The most prescribed treatment for delirium was injectable haloperidol (n=82,490; 56.8%). Mean (SD) length of hospitalization was 16.0 (12.1) days.

Conclusions: The study results provide comprehensive details of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. In this patient population, the prescription rate of injectable haloperidol and PIMs was high, suggesting the need for improved understanding among healthcare providers about the appropriate management of delirium, which may benefit patients.

ARTICLE SUMMARY - Strengths and limitations of this study

- This was the first nationwide study that comprehensively assessed the clinical characteristics of patients with delirium in the real-world setting of acute care hospitals in Japan.
- Analysis of the nationwide claims and discharge abstract database, using an algorithm adapted to the Japanese clinical setting, enabled identification of a large sample of patients with delirium in acute care hospitals in Japan.
- The results of the sensitivity analysis demonstrated outcomes consistent with those of the main analyses, reinforcing the robustness of the study results.
- Data were identified from the Medical Data Vision database, which is designed to capture claims and discharge abstracts in Japan and is not for research use; therefore, misclassification of the International Classification of Diseases, 10th revision codes may occur, given that no quality check is performed.

KEYWORDS: Acute care hospitals, Antipsychotics, Delirium, Medical record database, Real-world evidence

INTRODUCTION

Delirium is an acute condition characterized by fluctuating disturbances in attention, awareness, and cognition.[1] It frequently occurs in hospitalized elderly patients in an acute care setting, especially those in intensive care units (ICUs), and in postoperative care settings.[2,3] The prevalence of delirium is reported as 10%–31% among hospitalized patients within 24 hours of admission.[4] Among elderly patients, the prevalence is reported as 15%–53% after surgery [5,6] and 80% in those admitted to the ICU.[5] Previous studies have shown that delirium is associated with prolonged hospital stay and institutionalization [2,7] and increased mortality in nonsurgical and surgical patients in general wards, emergency departments, and ICUs.[7,8] Furthermore, long-term cognitive and functional decline is associated with delirium, often lasting up to a year following hospital discharge.[7,9] Consequently, delirium increases economic burden by raising healthcare expenditure and imposing costs related to loss of well-being.[3]

Despite its high prevalence and poor prognosis, delirium remains unrecognized in a substantial proportion of old patients. In a prospective clinical epidemiological study, even nursing personnel was unable to recognize delirium in up to two-thirds of the hospitalized elderly patients.[10] Recent evidence suggests that antipsychotics and multicomponent interventions can notably reduce the incidence of delirium and improve clinical outcomes,[11-13] emphasizing the need for early intervention and prevention in the hospitalized or postoperative elderly population that is at risk of delirium.[14]

Antipsychotics are widely used for the treatment of delirium, although no standard clinical pathway for the management of delirium has been established. The Japanese Ministry of Health, Labour and Welfare (MHLW) issued a notification in 2011, permitting the reimbursement of off-label oral and injectable haloperidol, oral perospirone, quetiapine, and risperidone for the treatment of delirium, psychomotor agitation, and irritability associated with organic diseases.[15] In addition, the Japanese Society of General Hospital Psychiatry recommended the use of several antipsychotics in a pharmacotherapy algorithm for delirium.[16] However, few studies have quantitatively investigated the use of antipsychotics for the treatment of patients with delirium in real world clinical practice in Japan.[17,18]

A limited number of studies have examined the characteristics of patients experiencing delirium based on a medical database.[17-25] This is because identification of delirium through a medical database is quite challenging, given the inconsistent and poor documentation of records.[26] Moreover, the identification of delirium requires bedside cognitive assessments and application of validated diagnostic tools such as the Confusion Assessment Method (CAM) [27] or the Diagnostic and Statistical Manual of Mental Disorders criteria.[1] Therefore, delirium is not routinely evaluated in acute care hospitals,[26,28] and the information on delirium diagnosis rarely gets recorded in healthcare utilization databases (e.g., claims data or hospital clinical data repository).

Although several medical database studies in the USA [19] and Japan [24] have used International Classification of Diseases, 9th revision (ICD-9) or ICD, 10th revision (ICD-10) codes to identify patients with a diagnosis of delirium, only around 2% of patients with

delirium (postoperative in Japan) could be identified. On the other hand, several medical database studies have employed antipsychotic use to identify patients with delirium.[21,23,25] However, either of these criteria, when used exclusively, may be inadequate in obtaining a comprehensive and true picture of delirium patients in the real-world clinical setting in Japan.

To date, few studies have investigated the overall profile of delirium patients in the real-world clinical setting in Japan. The present study aimed to assess the demographic characteristics, comorbidities, clinical profiles, and treatments in patients with delirium during hospitalization in Japan from a nationwide database comprising claims and discharge abstract data. In this study, delirium was defined using the algorithms that were recommended in the recently published claims-based database studies with slight modifications.[22,24]

METHODS

Study design

This was a retrospective, cross-sectional, observational study using a nationwide administrative database, Medical Data Vision (MDV; MDV Co., Ltd., Tokyo, Japan), with data collected from April 1, 2012, to September 30, 2020. The MDV database contains anonymized administrative data of more than 30 million patients from over 400 hospitals, which cover approximately 24% of all acute care hospitals in Japan. The MDV database includes claims data and discharge abstract data collected from inpatient and outpatient visits.

Study ethics

This study utilized de-identified data from the MDV database and ethics approval was not required, in line with the Ethical Guidelines for Epidemiological Research from the MHLW, Japan. Therefore, no ethics or institution review board approval was obtained.

Patient selection

In this study, patients admitted to general wards and ICUs were included. Patients meeting the prespecified delirium identification algorithm criteria who were hospitalized for surgery or an emergency and those who were discharged, transferred to other hospitals, or died after hospitalization during the study period were included in the analyzed data set.

The delirium identification algorithm in this study was based on that recently reported by Kim et al. [22]. Kim et al. proposed an algorithm that defines delirium based on ICD diagnosis codes or antipsychotic use and has a modestly better profile (30% sensitivity; 97% specificity) than existing algorithms such as either ICD diagnosis codes alone or antipsychotic use alone. In this study, patients were identified and included as the study participants based on the following criteria: a confirmed diagnosis of delirium during hospitalization, coded as F05 per ICD-10 (criterion 1) or prescription of at least one antipsychotic agent (haloperidol, olanzapine, perospirone, quetiapine, or risperidone) between the index date (admission date) and the next 7 days (criterion 2). The algorithm was modified to adjust with the clinical setting in Japan. Patients with a minimum stay of 3 days, including at least 2 antipsychotic-free days, were included in the study [23]. This “two-day washout” period after hospitalization allowed the exclusion of patients who already had a prescription of the selected antipsychotic because of pre-existing conditions. Patients who were hospitalized for less than 3 days; who had schizophrenia spectrum disorder (F20-29 codes per ICD-10), bipolar disorder (F30-31 codes per ICD-10), or delirium (F05 code per ICD-10) as “admission-precipitating diagnosis” or “comorbidities present on admission;” who were prescribed antipsychotics on the hospitalization date or the next day; and who were prescribed olanzapine in combination with cisplatin for nausea within 1 week from the index date were excluded from the analyses.

Patients hospitalized multiple times were evaluated only at the first hospitalization when the inclusion criteria were met. Repeated episodes of delirium in the same patient were not tracked or included in the analysis. The observation period was from the index date (date of hospitalization) to the end of hospitalization, defined as discharge, hospital transfer, or death of the patient.

Outcomes

The following demographic and baseline characteristics, clinical profiles, and comorbidities of patients with delirium were assessed from the MDV database: patients' baseline characteristics (sex, age, activities of daily living score calculated using the Barthel Index [29] cognitive impairment [assessed as "present" if the patient was previously diagnosed with dementia or prescribed anti-dementia medications or had a low degree of independence]), inpatient departments, comorbidities, type of clinical practice (delirium-associated PIM use [identified based on the Beers Criteria,[30] the Guidelines for medical treatment and its safety in the elderly from the Japan Geriatrics Society Working Group,[31] and the report from Noshiro et al.,[32]] type of surgery [sites or duration of anesthesia], duration of hospitalization and ICU stay), hospitalization information (type of hospitalization [surgery or emergency hospitalization], number of beds), prescription pattern for each antipsychotic, and patient outcomes (transfer to other hospitals/nursing homes, death).

Statistical analysis

The aim of this study was descriptive; therefore, no sample size calculations were performed. Data were summarized as mean (standard deviation [SD]) or number and frequency (%). All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis

As many assumptions were made while creating the delirium identification algorithm, two sensitivity analyses were conducted for patients selected in the main analyses to confirm how different assumptions on the analyzed populations might have influenced the outcomes. As some patients could have undergone surgery several days after their admission and the criteria used to identify patients to be included in the main analysis do not allow their inclusion, patients who had a prescription of any of the "selected" antipsychotics between the 3rd day of hospitalization and the day of discharge (or transfer or death) were included in the sensitivity analysis 1 (SA1). Furthermore, as some patients may undergo surgery immediately after the emergency admission and have delirium on the next day and the criteria set for the main analysis do not allow their inclusion, patients who had a prescription of the specified antipsychotics between the 2nd and 8th day of hospitalization were included in the sensitivity analysis 2 (SA2).

Patient and public involvement

Patients were not involved in any phase of this retrospective study, and data were collected from de-identified administrative claims database.

RESULTS

Identification of patients with delirium

Of the 32,910,227 patients who were included in the MDV database during the study period, 145,219 were identified as having delirium (Figure 1). Among patients who were hospitalized for surgery or an emergency (n=7,221,643), 2.0% were identified as having delirium. Overall, 9,898 (6.8%) patients who met the delirium identification algorithm criteria were diagnosed with delirium based on ICD-10 codes and did not receive any of the selected antipsychotic treatments during their hospitalization; 128,095 (88.2%) patients were identified because they had been prescribed any of the selected antipsychotics, and 7,226 (5.0%) patients who met the delirium identification algorithm criteria had both a diagnosis of delirium and an antipsychotic prescription (Figure 1). Most (n=14,801; 86.4%) of the 17,124 patients with an ICD-10 coded diagnosis had "delirium" (code F05.9), followed by "nocturnal delirium" (code F05.9), "delirium superimposed on dementia" (code F05.1), and "delirium not superimposed on dementia" (code F05.0; Supplemental Table 1).

Patient demographics and baseline characteristics

Mean (SD) patient age was 76.5 (13.8) years, and approximately 65% of patients were ≥75 years of age; more than 50% (n=82,159) of patients were male. Approximately half (n=76,422; 52.6%) of the patients with delirium were categorized as "dependent (need someone's help)" based on the Barthel Index score (Table 1). Cognitive impairment was noted in 40,376 (27.8%) patients (Table 1; Supplemental Table 2). Circulatory disease was the most common comorbidity, observed in 81,954 (56.4%) patients, followed by endocrine, nutritional, and metabolic diseases (n=59,955; 41.3%) and gastrointestinal disorders (n=59,691; 41.1%; Table 1; Supplemental Table 3).

Clinical practice

Around half (n=85,492; 58.9%) of the patients with delirium underwent any surgery, of whom approximately one-third (n=28,557) were anesthetized for more than 2 hours (Table 2). There was a wide distribution of surgical sites, with the abdomen being the most common site (n=38,898; 26.8%; Supplemental Table 4).

Mean (SD) duration of hospitalization was 16.0 (12.1) days; 55,709 (38.4%) patients were hospitalized for 1–2 weeks (Table 2). Overall, 33,718 (23.2%) patients were admitted to the ICU for a mean (SD) of 3.4 (3.1) days, of whom 4,379 (3.0%) spent at least 7 days in the ICU (Table 2).

PIMs were prescribed to 76,798 (52.9%) patients, including benzodiazepines in 31,324 (21.6%) patients and opioids in 29,268 (20.2%) patients. Approximately three-fourths (n=56,949; 74.2%) of these patients were prescribed ≥4 PIMs. Multiple classes of PIMs were used by 38.6% of patients to whom PIMs were prescribed (Table 2).

Treatment for delirium

Injectable haloperidol was the most prescribed antipsychotic (n=82,490; 56.8%) for the treatment of delirium, followed by risperidone solution (n=34,282; 23.6%), quetiapine tablet (n=19,830; 13.7%), risperidone orodispersible tablet (n=7,645; 5.3%), and risperidone tablet (n=4,958; 3.4%; Table 3). The mean (SD) duration of these antipsychotic prescriptions was 5.4 (8.1) days (Table 3).

Hospitalizations and patient outcome

Assessment of patients with delirium by hospital department showed that the departments where at least 5% of patients experienced delirium were surgery (n=28,656; 19.7%), internal medicine (n=28,232; 19.4%), gastroenterology (n=15,445; 10.6%), cardiology (n=12,337; 8.5%), orthopedics (n=11,302; 7.8%), and neurosurgery (n=8,144; 5.6%; Table 1; Supplemental Table 4). In general, 52,766 (36.3%) patients with delirium were hospitalized for planned elective surgery, whereas 59,727 (41.1%) patients were hospitalized due to an emergency (without subsequent surgery) and 32,726 (22.5%) patients were hospitalized due to an emergency and underwent surgery (Supplemental Table 4). A total of 15,556 (10.7%) patients died while in hospital, and 22,081 (15.2%) were transferred to other hospitals or clinics (Table 4).

Sensitivity analysis

The results of the sensitivity analyses identified 184,817 patients with delirium in SA1 and 213,844 in SA2 (Supplemental Figure 1). Patients' mean (SD) age was 76.1 (13.8) years in SA1 and 76.3 (14.1) years in SA2. A total of 96,591 (52.3%) patients in SA1 and 113,005 (52.8%) patients in SA2 were classified as dependent (Supplemental Table 5).

The proportion of patients prescribed one or more antipsychotics to treat their delirium was 95.5% in SA1 and 95.4% in SA2. The proportion of injectable haloperidol prescriptions was 58.1% in SA1 and 60.1% in SA2, while the proportion of prescriptions for risperidone solution was 24.8% in SA1 and 23.5% in SA2 and that for risperidone tablets was 4.0% in SA1 and 3.5% in SA2 (Supplemental Table 5).

DISCUSSION

The present study was the first nationwide database study that assessed the clinical characteristics of patients with delirium in acute care hospitals in Japan. To identify patients with delirium from the hospital database, the study used the delirium identification algorithm which consists of diagnoses based on ICD-10 codes and prescriptions of antipsychotics frequently used in the treatment of delirium.[22] The prevalence of delirium obtained in our study was 2.0% among patients who were hospitalized for surgery or an emergency, which was lower than the incidence of new delirium per admission (3%–29%) reported in a systematic review of the literature.[4] The low prevalence of delirium determined using our criteria might be due to the sensitivity of the algorithm used in our study; however, it also suggests issues such as the lack of awareness of delirium among many physicians and inability to manage delirium appropriately.

In our study, most patients were ≥65 years of age (84.7%), 27.8% of patients had cognitive impairment, and 52.6% had functional dependence, which are known predisposing factors of delirium.[8,33] Approximately one-fourth (23.2%) of the patients included in this study were admitted to the ICU during the index hospitalization period. Although we did not assess the prevalence of delirium in patients in the ICU in this study, previous studies have shown a high incidence (70%–87%) of delirium in patients in the ICU,[34] suggesting that the management of delirium in these patients is also important for physicians and nurses. While about half of the patients (n=85,492; 58.9%) in the present study underwent surgery during their hospital stay, delirium was also identified among nonsurgical patients in general medical wards such as internal medicine, gastroenterology, and cardiology. A systematic literature review reported the prevalence of delirium among patients admitted to general medical and geriatric wards as 18%–35%.[8] Taken together, these data suggest that physicians and nurses from all clinical departments should be trained to diagnose and manage patients with delirium.

Drug classes such as benzodiazepines, opioids, and H2 blockers were selected as PIMs, which are reported to be associated with the onset of delirium in guidelines[30,31] and several studies.[32,33,35-37] In our study, more than half (52.9%) of the patients were prescribed a PIM of any type; approximately one-fifth of patients were prescribed either benzodiazepines or opioids (21.6% and 20.2%, respectively). Benzodiazepine and opioids are associated with an increased risk of delirium in medical and surgical patients.[35] In a single center study in Canada, the risk was more than doubled within 28 days of hospitalization in patients with cancer who were receiving benzodiazepines (>2 mg/day) and opioids (>90 mg/day).[38] Moreover, Japan is one of the countries with an increasing rate of consumption of benzodiazepine-type sedative hypnotics (>1 defined daily dose for statistical purposes).[39] Furthermore, at least 4 PIMs were prescribed in 74.2% of patients with delirium. Polypharmacy with ≥3 drugs is reported to increase the risk of delirium by 2.9 times in elderly patients during hospitalization.[40] Our findings suggest that polypharmacy with PIMs such as benzodiazepines/opioids, a known precipitating factor for delirium, is commonly observed in a real-world clinical setting. The frequent use of PIMs that increase the risk of delirium in the real world, particularly in elderly patients, reaffirms the need for the better understanding of the benefit-risk profile of such medications. On the other hand, opioids are necessary for the control of severe pain. Pain is also known to be associated with a risk of delirium[16] thus, suggesting the importance of delirium control in combination with pain control.

In our study, injectable haloperidol was the most frequently prescribed (56.8%) antipsychotic, followed by risperidone solution (23.6%) and quetiapine tablets (13.7%) in patients with delirium. The outcomes are similar to those from a recent database study in Japan, where haloperidol infusion was the most frequently used treatment in postoperative patients with delirium.[17] These results are also consistent with a questionnaire-based cross-sectional study in which more than two-thirds of Japanese experts recommended intravenous haloperidol (if an intravenous line was placed during hospitalization), and the oral use of atypical antipsychotics such as risperidone or quetiapine for hyperactive delirium.[41] Risperidone solution and olanzapine orodispersible tablets could be useful for patients who have difficulties in taking medicines.[16] In our study, a relatively high proportion of patients were prescribed risperidone solution (23.6%); however, only 0.6% were prescribed olanzapine orodispersible tablets. The low proportion of olanzapine prescription could be due to the long half-life of olanzapine and its contraindication in patients with diabetes in Japan.[16] Overall, our findings suggest that injectable haloperidol is the major treatment modality for delirium in an acute care setting likely because it can be used as needed for the treatment of delirium in such a setting. Unlike psychiatrists, the majority of physicians who treat patients with delirium are likely to be unfamiliar with use of atypical antipsychotics. However, in a broader clinical context, the risk of death in the elderly was reported to be 2.26-fold higher with haloperidol versus olanzapine[42], and the likelihood of overall survival was 1.73-fold higher with placebo in a randomized control trial.[43] Moreover, the incidence of adverse events, particularly extrapyramidal symptoms, is reportedly higher with haloperidol versus risperidone, although their efficacy is reportedly similar.[44,45]

The greatest strength of this study is the large size of the MDV database, which enabled the identification of a large number of patients with delirium. The use of our algorithm optimized for the Japanese clinical setting led to an increased number of patients being retrieved from hospital databases, thus highlighting the utility of this algorithm in real-world scenarios. More importantly, outcomes of the sensitivity analyses, which considered different treatment time frames in determining index, were consistent with those of the main analysis reinforcing the robustness of our study results. The prevalence of delirium obtained by identifying patients using an ICD-coded diagnosis was only 0.2% among patients who were hospitalized for surgery or an emergency in our study, which is similar to that reported in previous studies in Japan.[18,24] However, this low prevalence may not be a true reflection of the occurrence of delirium in the real world, as observed in a prospective study that compared the sensitivity and specificity of various delirium identification algorithms.[22] According to Sakakibara et al., delirium is recorded on the claims receipt only for patients with severe delirium requiring more medical resources, but not for those with mild-to-moderate delirium.[24] Our results confirm that the majority of Japanese patients with delirium can be identified from a Japanese claims database based on prescription of an antipsychotic during their hospital stay; 88.2% of patients with delirium were identified based on an antipsychotic prescription. A recent study employing a Japanese national inpatient database used the daily nursing necessity score (dangerous behavior or misunderstanding of nursing instructions) as the criterion of delirium, but reported a prevalence of delirium of approximately 1% (n=21,182) among 2,070,000 postoperative patients.[17] The results of the present study show the feasibility of using administrative databases for identifying patients with delirium in an acute care hospital setting in Japan.

This study has several limitations. First, the data were extracted from the MDV database, which is designed primarily for insurance purposes and not for research; therefore, no quality checks for data are performed and there is a likelihood of misclassification of ICD-10 coding. Second, as the data of patients transferred to other hospitals were not registered in this

database, patients who were moved to or hospitalized in a different hospital after the index hospitalization could not be identified. This could have led to multiple hospitalizations of the same high-risk patients, with multiple episodes of delirium at different times being identified as separate events and possibly increasing the number of identified cases. Third, the number of prescribed antipsychotics may be inflated because some patients with psychotic disorders may have been included from the database during analysis although the present study excluded patients with schizophrenia or bipolar disease. Lastly, the sensitivity and specificity of the modified delirium identification algorithm used in this study have not yet been validated in Japan. The recent addition of a medical fee for the care of high-risk patients with delirium in the medical reimbursement revision of 2020 in Japan may increase the accuracy of identification of patients with delirium from the medical database. For future research, the delirium identification algorithm used in our study needs to be validated.

In conclusion, the results of the present study provide comprehensive details of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. The results reinforce the need to consider the risk of delirium in hospitals, especially in high-risk patients, and provide useful information for healthcare professionals to understand the clinical profile of patients who are likely to experience delirium when hospitalized. The study reveals two important findings in this patient population: 1) the high prescription rate of injectable haloperidol and 2) the frequent use of PIMs in patients with delirium. Thus, there is a need for improved understanding among healthcare providers about appropriate management of delirium in an acute care setting, which may benefit patients.

COMPETING INTERESTS

NU, MI, KO, HS, KT, ST and SO are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. ZPQ is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. AO and YO have received funding from MSD K.K., Tokyo, Japan for research consulting.

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AUTHOR CONTRIBUTIONS

SO, HS, KT, ZPQ, ST, AO and YO conceptualized the study. NU, MI, KO, and SO conducted the study designing and data analysis planning. HS, KT, ZPQ, and ST contributed to the study designing. KT, AO, and YO provided advice on study design and contributed to the interpretation of the findings from the viewpoint of the clinical scientist, the physician and the epidemiologist, respectively. All authors contributed to interpretation of data and approved the final version of the manuscript. NU and SO are guarantors and accept full responsibility for the work.

DATA SHARING STATEMENT

The Medical Data Vision database analyzed in this study is not publicly accessible, and the data cannot be shared with external researchers according to the contract with Medical Data Vision Co., Ltd.

Table 1 Patient demographic and baseline characteristics.

		Number of patients N (%)	
Number of patients		145,219	
Age (years)	Mean (SD)	76.5 (13.8)	
	≤64	22,168	(15.3)
	65–74	28,371	(19.5)
	75–84	49,739	(34.3)
	≥85	44,941	(30.9)
Sex	Male	82,159	(56.6)
	Female	63,060	(43.4)
ADL score (point)*	Dependent group (0–59)	76,422	(52.6)
	Independent group (60–100)	66,381	(45.7)
	Unknown	2,416	(1.7)
Cognitive impairment†	Yes	40,376	(27.8)
	No	104,843	(72.2)
Inpatient department	Surgery	28,656	(19.7)
	Internal Medicine	28,232	(19.4)
	Gastroenterology	15,445	(10.6)
	Cardiology	12,337	(8.5)
	Orthopedics	11,302	(7.8)
	Neurosurgery	8,144	(5.6)
	Urology	7,031	(4.8)
	Cardiovascular Surgery	6,042	(4.2)
	Respiratory Medicine	5,506	(3.8)
	Gastrointestinal Surgery	4,093	(2.8)
	Emergency Medicine	3,414	(2.4)

	Neurology	3,008	(2.1)
	Others	11,573	(8.0)
Comorbidities	Circulatory disease	81,954	(56.4)
(ICD-10 major category)‡	Endocrine, nutritional, and metabolic diseases	59,955	(41.3)
	Gastrointestinal disorders	59,691	(41.1)
	Malignant neoplasms	41,710	(28.7)
	Respiratory disease	36,958	(25.4)

*Barthel Index will be used for evaluation.

†Cognitive Impairment was assessed as "present" if the patient was previously diagnosed with dementia or prescribed anti-dementia drugs or had a low degree of independence.

‡Top 5 major ICD-10 categories are presented.

ADL, activity of daily living; ICD-10, International Classification of Diseases, 10th revision; SD, standard deviation.

Table 2 Clinical practice.

		Number of patients N (%)	
Number of patients		145,219	
Prescription of PIM	Yes (any type of PIM)	76,798	(52.9)
	Antidepressants	299	(0.2)
	Anticholinergic drugs	163	(0.1)
	Benzodiazepines	31,324	(21.6)
	Non-benzodiazepines	10,582	(7.3)
	Corticosteroids	16,879	(11.6)
	H1-receptor antagonists	10,283	(7.1)
	H2-receptor antagonists	17,360	(12.0)
	Opioids	29,268	(20.2)
	Number of PIMs (drugs)	76,798	(100.0)
	1	5,268	(6.9)
	2	7,232	(9.4)
	3	7,349	(9.6)
	≥4	56,949	(74.2)
	Number of PIMs (classes)	76,798	(100.0)
	1	47,128	(61.4)
	2	21,637	(28.2)
	3	6,561	(8.5)
	≥4	1,472	(1.9)
Surgery	Yes	85,492	(58.9)
	Anesthesia type/duration:	85,492	(100.0)
	Surgery + no anesthesia/local anesthesia/light general anesthesia	35,048	(41.0)

	Surgery + general anesthesia (<2 hours)	21,887	(25.6)
	Surgery + general anesthesia (≥2 hours)	28,557	(33.4)
Duration of hospitalization (days)	Mean (SD)	16.0 (12.1)	
	≤1 week	22,542	(15.5)
	>1 week to ≤2 weeks	55,709	(38.4)
	>2 weeks to ≤3 weeks	38,342	(26.4)
	>3 weeks to ≤4 weeks	17,004	(11.7)
	4> weeks to ≤12 weeks	11,046	(7.6)
	>12 weeks	576	(0.4)
Use of ICU	Yes	33,718	(23.2)
Duration of ICU (days)	Mean (SD)	3.4 (3.1)	
	1 day	12,218	(8.4)
	2 days	5,970	(4.1)
	3 days	4,247	(2.9)
	4 days	3,104	(2.1)
	5 days	2,192	(1.5)
	6 days	1,608	(1.1)
	≥7 days	4,379	(3.0)

ICU, intensive care unit; PIM, potentially inappropriate medication; SD, standard deviation.

Table 3 Antipsychotics used for treating delirium.

			Number of patients N (%)	
Number of patients			145,219	
Antipsychotics used for delirium	Yes		135,321	(93.2)
Type of drug formulation	Haloperidol	INJ	82,490	(56.8)
		TAB	1,913	(1.3)
		FGR	192	(0.1)
		SOL	13	(0.0)
	Risperidone	SOL	34,282	(23.6)
		ODT	7,645	(5.3)
		TAB	4,958	(3.4)
		FGR	257	(0.2)
		INJ	6	(0.0)
	Quetiapine	TAB	19,830	(13.7)
		FGR	652	(0.4)
		SRT	20	(0.0)
	Olanzapine	TAB	2,262	(1.6)
		ODT	915	(0.6)
		FGR	156	(0.1)
		INJ	11	(0.0)
	Perospirone	TAB	2,210	(1.5)
Duration of prescription (days)	Mean (SD)		5.4 (8.1)	

FGR, fine granule; INJ, injectable; ODT, orodispersable tablet; SD, standard deviation; SOL, solution; SRT, sustained-release tablet; TAB, tablet.

Table 4 Patient outcome - Transfer to other hospitals/nursing homes and death.

		Number of patients N (%)	
Number of patients		145,219	
Transfer to other hospitals/nursing homes	Yes	32,651	(22.5)
	Transfer to other hospitals or clinics	22,081	(15.2)
	Admission to social welfare facilities or fee-based homes for the elderly, etc.	5,070	(3.5)
	Admission to facilities covered by public aid providing long-term care to the elderly	3,017	(2.1)
	Admission to long-term care health facilities	2,472	(1.7)
	Nursing home	11	(0.0)
Death	Yes	15,556	(10.7)
	No	129,637	(89.3)

FIGURE LEGENDS

Figure 1 Patient selection flowchart.

DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th revision; MDV, Medical Data Vision.

Supplemental Figure 1 Patient selection flowchart for the sensitivity analysis.

MDV, Medical Data Vision.

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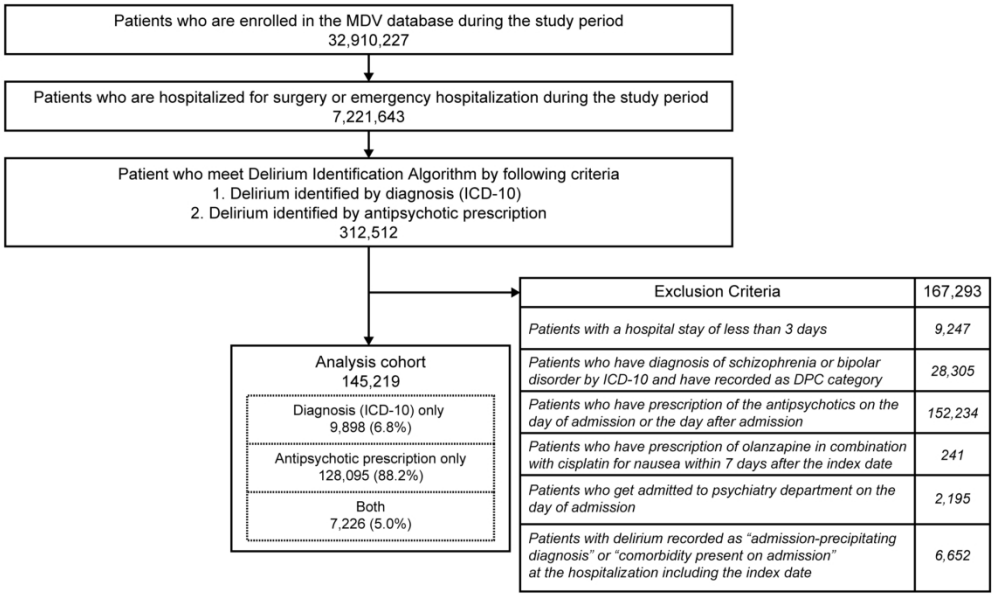


Figure 1 Patient selection flowchart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th revision; MDV, Medical Data Vision.

173x104mm (300 x 300 DPI)

Supplemental Table 1 ICD-10 codes for delirium diagnosis.

		Number of patients N (%)	
Number of delirium patients identified by diagnosis (ICD-10)	Total	17,124	(11.8)
	Delirium not superimposed on dementia (F05.0)	977	(0.7)
	Delirium superimposed on dementia (F05.1)	1,447	(1.0)
	Other delirium (F05.8)	37	(0.0)
	Subacute infection psychosis	0	(0.0)
	Subacute organic reaction	0	(0.0)
	Subacute organic psychiatric syndrome	0	(0.0)
	Subacute cerebral syndrome	5	(0.0)
	Acute infectious psychosis	1	(0.0)
	Acute organic reaction	3	(0.0)
	Acute organic psychiatric syndrome	2	(0.0)
	Acute confusional state	14	(0.0)
	Acute brain syndrome	11	(0.0)
	Nonalcoholic acute confusional state	1	(0.0)
	Delirium, unspecified (F05.9)	14,801	(10.2)
	Delirium	11,828	(8.1)
	Nocturnal delirium	2,494	(1.7)
	Senile nocturnal delirium	498	(0.3)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 2 Definition of cognitive impairment.

		Number of patients N (%)	
Number of patients		145,219	
Cognitive impairment	Yes	40,376	(27.8)
	Diagnosis of dementia (ICD-10)	21,498	(14.8)
	Prescription of anti-dementia drugs	12,032	(8.3)
	Low degree of independence in daily life for the elderly with dementia	25,537	(17.6)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 3 Comorbidities (diseases present in ≥3% of patients with delirium in each category).

Category	Disease	ICD-10	Number of patients N (%)
Number of patients			145,219
Circulatory disease			81,954 (56.4)
	Essential (primary) hypertension	I10	47,887 (33.0)
	Heart failure	I50	23,214 (16.0)
	Atrial fibrillation and flutter	I48	12,774 (8.8)
	Angina pectoris	I20	11,296 (7.8)
	Sequelae of cerebrovascular disease	I69	8,759 (6.0)
	Cerebral infarction	I63	6,577 (4.5)
	Aortic aneurysm and dissection	I71	4,432 (3.1)
Endocrine, nutritional, and metabolic diseases			59,955 (41.3)
	Type 2 diabetes mellitus	E11	23,809 (16.4)
	Disorders of lipoprotein metabolism and other lipidemia	E78	17,530 (12.1)
	Volume depletion	E86	13,698 (9.4)
	Other disorders of fluid, electrolyte, and acid-base balance	E87	4,896 (3.4)
	Unspecified diabetes mellitus	E14	4,364 (3.0)
Gastrointestinal disorders			59,691 (41.1)
	Gastroesophageal reflux disease	K21	13,242 (9.1)
	Other functional intestinal disorders	K59	10,515 (7.2)
	Gastric ulcer	K25	9,864 (6.8)
	Cholelithiasis	K80	8,230 (5.7)
	Paralytic ileus and intestinal obstruction without hernia	K56	5,276 (3.6)

	Gastritis and duodenitis	K29	5,025	(3.5)
	Other diseases of the biliary tract	K83	4,850	(3.3)
Malignant neoplasms			41,710	(28.7)
	Malignant neoplasm of stomach	C16	7,644	(5.3)
	Malignant neoplasm of colon	C18	7,163	(4.9)
	Secondary malignant neoplasm of respiratory and digestive organs	C78	5,631	(3.9)
	Malignant neoplasm of bronchus and lung	C34	4,433	(3.1)
Respiratory disease			36,958	(25.4)
	Respiratory failure, not elsewhere classified	J96	14,385	(9.9)
	Pneumonia, organism unspecified	J18	7,004	(4.8)
	Pneumonitis due to solids and liquids	J69	6,991	(4.8)
Nervous system disorders			28,557	(19.7)
	Alzheimer disease	G30	9,659	(6.7)
	Sleep disorders	G47	9,351	(6.4)
Genitourinary diseases			25,617	(17.6)
	Chronic kidney disease	N18	8,208	(5.7)
	Benign prostatic hyperplasia	N40	5,360	(3.7)
Mental and behavioral disorders			20,047	(13.8)
	Unspecified dementia	F03	8,934	(6.2)
Musculoskeletal / connective tissue disease			17,523	(12.1)
Injury			15,866	(10.9)
	Fracture of femur	S72	6,427	(4.4)
Blood disease			13,458	(9.3)
	Iron deficiency anemia	D50	6,881	(4.7)

Infectious disease (excluding parasitic disease)	-		12,442	(8.6)
Skin/subcutaneous tissue disease	-		4,094	(2.8)
Eye disease	-		1,565	(1.1)
Poisoning	-		806	(0.6)
Ear disease	-		624	(0.4)
Others			39,232	(27.0)
	Somnolence, stupor, and coma	R40	6,943	(4.8)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 4 Hospitalization information.

		Number of patients N (%)	
Number of patients		145,219	
Type of hospitalization	Hospitalization with elective surgery	52,766	(36.3)
	Emergency hospitalization without surgery	59,727	(41.1)
	Emergency hospitalization with surgery	32,726	(22.5)
Number of beds	0–199 beds	6,760	(4.7)
	200–499 beds	79,995	(55.1)
	≥500 beds	58,464	(40.3)
Inpatient department	Surgery	28,656	(19.7)
	Internal Medicine	28,232	(19.4)
	Gastroenterology	15,445	(10.6)
	Cardiology	12,337	(8.5)
	Orthopedics	11,302	(7.8)
	Neurosurgery	8,144	(5.6)
	Urology	7,031	(4.8)
	Cardiovascular Surgery	6,042	(4.2)
	Respiratory Medicine	5,506	(3.8)
	Gastrointestinal Surgery	4,093	(2.8)
	Emergency Medicine	3,414	(2.4)
	Neurology	3,008	(2.1)
	Pulmonary Surgery	1,734	(1.2)
	Obstetrics & Gynecology	1,528	(1.1)
	Otolaryngology	1,416	(1.0)
	Nephrology	1,252	(0.9)
	Hematology	729	(0.5)

	Endocrinology, Metabolism & Diabetology	706	(0.5)
	Reconstructive Surgery	625	(0.4)
	Ophthalmology	606	(0.4)
	Others	2,977	(2.1)
	Unknown	436	(0.3)
Surgery	Yes	85,492	(58.9)
	Surgery sites:		
	Abdomen	38,898	(26.8)
	Heart and blood vessels	15,240	(10.5)
	Musculoskeletal system, extremities, and trunk	10,424	(7.2)
	Thoracic	6,061	(4.2)
	Urinary system and adrenal glands	4,893	(3.4)
	Nervous system and cranial	3,708	(2.6)
	Skin or subcutaneous tissue	3,076	(2.1)
	Genital	2,557	(1.8)
	Ear, nose, and throat	1,113	(0.8)
	Face, mouth, and neck	738	(0.5)
	Eyes	606	(0.4)

Supplemental Table 5 Sensitivity analyses: Delirium identification algorithm, patient characteristics, clinical practice, delirium treatment with antipsychotics, and patient outcomes.

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Number of subjects		184,817		213,844	
Delirium identification algorithm					
Patients meeting criteria	Diagnosis (ICD-10) only	8,401	(4.5)	9,874	(4.6)
	Antipsychotic prescription only	167,756	(90.8)	193,507	(90.5)
	Both	8,660	(4.7)	10,463	(4.9)
Patient demographic and baseline characteristics					
Age (years)	Mean (SD)	76.1 (13.8)		76.3 (14.1)	
	≤64	29,659	(16.0)	34,204	(16.0)
	65–74	37,770	(20.4)	41,091	(19.2)
	75–84	62,820	(34.0)	71,825	(33.6)
	≥85	54,568	(29.5)	66,724	(31.2)
Sex	Male	105,167	(56.9)	120,696	(56.4)
	Female	79,650	(43.1)	93,148	(43.6)
ADL score (point)	Dependent group (0–59)	96,591	(52.3)	113,005	(52.8)
	Independent group (60–100)	85,101	(46.0)	97,296	(45.5)
	Unknown	3,125	(1.7)	3,543	(1.7)
Cognitive impairment	Yes	49,445	(26.8)	60,930	(28.5)
	Diagnosis of dementia (ICD-10)	26,470	(14.3)	33,014	(15.4)
	Prescription of anti-dementia drugs	15,214	(8.2)	18,685	(8.7)
	Low degree of independence*	30,820	(16.7)	38,575	(18.0)
Inpatient department	Surgery	36,983	(20.0)	38,799	(18.1)
	Internal Medicine	33,955	(18.4)	40,868	(19.1)
	Gastroenterology	20,135	(10.9)	26,557	(12.4)
	Cardiology	14,845	(8.0)	19,516	(9.1)
	Orthopedics	14,769	(8.0)	15,886	(7.4)
	Neurosurgery	10,039	(5.4)	12,943	(6.1)
	Urology	8,619	(4.7)	10,501	(4.9)
	Cardiovascular Surgery	7,953	(4.3)	7,405	(3.5)
	Respiratory Medicine	7,056	(3.8)	7,484	(3.5)
	Gastrointestinal Surgery	5,427	(2.9)	4,905	(2.3)
	Emergency Medicine	4,047	(2.2)	5,245	(2.5)
	Neurology	3,598	(1.9)	4,648	(2.2)
	Pulmonary Surgery	2,134	(1.2)	2,297	(1.1)
	Obstetrics & Gynecology	2,034	(1.1)	2,274	(1.1)
	Otolaryngology	2,033	(1.1)	2,047	(1.0)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
	Nephrology	1,728	(0.9)	1,755	(0.8)
	General Medicine	1,272	(0.7)	1,574	(0.7)
	Hematology	1,024	(0.6)	974	(0.5)
	Endocrinology, Metabolism & Diabetology	859	(0.5)	1,037	(0.5)
	Reconstructive Surgery	905	(0.5)	958	(0.4)
	Ophthalmology	720	(0.4)	1,040	(0.5)
	Others	4,093	(2.2)	4,550	(2.1)
	Unknown	589	(0.3)	581	(0.3)
Comorbidities	Circulatory disease	103,602	(56.1)	119,306	(55.8)
	Endocrine, nutritional, and metabolic diseases	77,200	(41.8)	86,310	(40.4)
	Gastrointestinal disorders	76,319	(41.3)	88,300	(41.3)
	Malignant neoplasms	56,282	(30.5)	58,680	(27.4)
	Others	51,859	(28.1)	57,420	(26.9)
	Respiratory disease	47,586	(25.7)	52,118	(24.4)
	Nervous system disorders	36,193	(19.6)	42,476	(19.9)
	Genitourinary diseases	32,942	(17.8)	36,993	(17.3)
	Mental and behavioral disorders	24,824	(13.4)	30,773	(14.4)
	Musculoskeletal/connective tissue disease	22,601	(12.2)	24,732	(11.6)
	Injury	20,340	(11.0)	23,901	(11.2)
	Blood disease	18,251	(9.9)	19,041	(8.9)
	Infectious disease (excluding parasitic disease)	16,392	(8.9)	17,308	(8.1)
	Skin/subcutaneous tissue disease	5,688	(3.1)	5,836	(2.7)
	Eye disease	1,960	(1.1)	2,445	(1.1)
	Poisoning	876	(0.5)	1,399	(0.7)
	Ear disease	793	(0.4)	927	(0.4)
Hospitalization information					
Type of hospitalization	Hospitalization for elective surgery	52,647	(28.5)	64,141	(30.0)
	Emergency hospitalization without surgery	71,805	(38.9)	88,286	(41.3)
	Emergency hospitalization with surgery	44,391	(24.0)	48,568	(22.7)
	Unknown	15,974	(8.6)	12,849	(6.0)
Number of beds	0–199	8,992	(4.9)	9,895	(4.6)
	200–499	101,596	(55.0)	117,555	(55.0)
	≥500	74,229	(40.2)	86,394	(40.4)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Clinical practice					
Prescription of PIM	Yes	94,998	(51.4)	69,827	(32.7)
	Antidepressants	371	(0.2)	254	(0.1)
	Anticholinergic drugs	194	(0.1)	137	(0.1)
	Benzodiazepines	38,988	(21.1)	28,269	(13.2)
	Non-benzodiazepines	12,954	(7.0)	8,780	(4.1)
	Corticosteroids	21,746	(11.8)	13,734	(6.4)
	H1-receptor antagonists	12,388	(6.7)	6,959	(3.3)
	H2-receptor antagonists	21,028	(11.4)	15,246	(7.1)
	Opioids	35,588	(19.3)	19,253	(9.0)
Prescription of PIM (number of PIM drugs)	1	5,640	(3.1)	4,728	(2.2)
	2	7,794	(4.2)	6,064	(2.8)
	3	7,985	(4.3)	6,451	(3.0)
	≥4	73,579	(39.8)	52,584	(24.6)
Prescription of PIM (number of PIM classes)	1	58,500	(31.7)	51,123	(23.9)
	2	26,719	(14.5)	15,136	(7.1)
	3	8,011	(4.3)	3,089	(1.4)
	≥4	1,768	(1.0)	479	(0.2)
Surgery	Yes	113,012	(61.1)	125,558	(58.7)
	Surgery sites:				
	Skin or subcutaneous tissue	4,477	(2.4)	4,672	(2.2)
	Musculoskeletal system, extremities, and trunk	13,859	(7.5)	14,564	(6.8)
	Nervous system and cranial	4,825	(2.6)	5,695	(2.7)
	Eyes	704	(0.4)	1,060	(0.5)
	Ear, nose, and throat	1,895	(1.0)	1,570	(0.7)
	Face, mouth, and neck	874	(0.5)	1,192	(0.6)
	Thoracic	7,613	(4.1)	9,017	(4.2)
	Heart and blood vessels	21,172	(11.5)	21,846	(10.2)
	Abdomen	51,061	(27.6)	57,020	(26.7)
	Urinary system and adrenal gland	6,173	(3.3)	7,365	(3.4)
	Genital	2,964	(1.6)	3,933	(1.8)
	Anesthesia type/duration:				
	Surgery + no/local/light general anesthesia	49,357	(26.7)	58,743	(27.5)
	Surgery + general anesthesia (<2 hours)	27,276	(14.8)	32,179	(15.0)

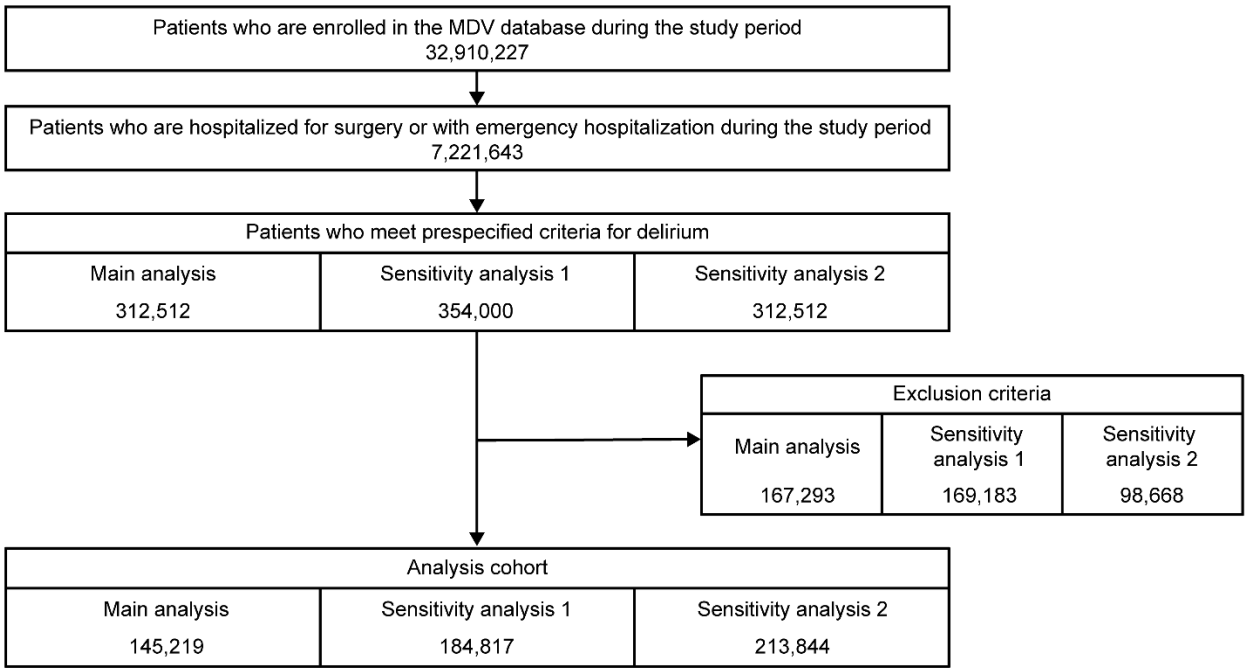
Characteristics			Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
	Surgery + general anesthesia (≥2 hours)		36,379	(19.7)	34,636	(16.2)
Duration of hospitalization	Mean (SD), days		19.5 (18.9)		14.9 (11.7)	
	≤1 week		22,368	(12.1)	44,771	(20.9)
	>1 week to ≤2 weeks		60,821	(32.9)	81,671	(38.2)
	>2 weeks to ≤3 weeks		48,981	(26.5)	50,271	(23.5)
	>3 weeks to ≤4 weeks		26,094	(14.1)	22,322	(10.4)
	>4 weeks to ≤12 weeks		24,247	(13.1)	14,092	(6.6)
	>12 weeks		2,306	(1.2)	717	(0.3)
Use of ICU	Yes		42,565	(23.0)	47,127	(22.0)
Duration, days	Mean (SD)		3.8 (3.7)		3.3 (3.0)	
	1 day		14,765	(8.0)	17,264	(8.1)
	2 days		7,146	(3.9)	8,810	(4.1)
	3 days		5,101	(2.8)	6,174	(2.9)
	4 days		3,723	(2.0)	4,281	(2.0)
	5 days		2,665	(1.4)	2,913	(1.4)
	6 days		1,970	(1.1)	2,119	(1.0)
	≥7 days		7,195	(3.9)	5,566	(2.6)
Antipsychotics used for delirium						
Antipsychotic use for delirium	Yes		176,416	(95.5)	203,970	(95.4)
Type of drug formulation	Haloperidol	INJ	107,433	(58.1)	128,456	(60.1)
		TAB	3,030	(1.6)	2,861	(1.3)
		FGR	311	(0.2)	308	(0.1)
		SOL	26	(0.0)	22	(0.0)
	Risperidone	SOL	45,913	(24.8)	50,360	(23.5)
		ODT	10,987	(5.9)	11,442	(5.4)
		TAB	7,314	(4.0)	7,493	(3.5)
		FGR	445	(0.2)	415	(0.2)
		INJ	9	(0.0)	7	(0.0)
	Quetiapine	TAB	28,040	(15.2)	30,390	(14.2)
		FGR	1,126	(0.6)	1,006	(0.5)
		SRT	26	(0.0)	34	(0.0)
	Olanzapine	TAB	4,055	(2.2)	3,569	(1.7)
		ODT	1,678	(0.9)	1,569	(0.7)
		FGR	270	(0.1)	248	(0.1)
		INJ	27	(0.0)	16	(0.0)
	Perospirone	TAB	3,280	(1.8)	3,334	(1.6)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Duration of prescription, days	Mean (SD)	5.7 (10.1)		5.3 (7.9)	
Patient outcomes					
Transfer to other hospitals/nursing homes	Yes	43,028	(23.3)	47,980	(22.4)
	Transfer to other hospitals or clinics	29,407	(15.9)	32,083	(15.0)
	Admission to long-term care health facilities	3,146	(1.7)	3,614	(1.7)
	Admission to facilities covered by public aid providing long-term care to the elderly	3,909	(2.1)	4,485	(2.1)
	Admission to social welfare facilities or fee-based homes for the elderly, etc.	6,555	(3.5)	7,783	(3.6)
	Nursing home	11	(0.0)	15	(0.0)
Death	Yes	25,377	(13.7)	21,567	(10.1)
	No	159,397	(86.2)	192,239	(89.9)

*Low degree of independence in daily life for the elderly with dementia

ADL, activities of daily living; FGR, fine granule; ICD-10, International Classification of Diseases, 10th revision; ICU, intensive care unit; INJ, injectable; ODT, orally disintegrating tablet; PIM, potentially inappropriate medication; SD, standard deviation; SOL, solution; SRT, sustained-release tablet; TAB, tablet.

Supplemental Figure 1 Patient selection flowchart for the sensitivity analysis.



MDV, Medical Data Vision.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7 and 8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	9 and 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	15 to 18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12 and 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12 and 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title:

Demographic and clinical characteristics of patients with delirium: analysis of a nationwide Japanese medical database

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ABSTRACT

Objectives: Delirium commonly occurs during hospitalization and is associated with increased mortality, especially in elderly patients. This study aimed to determine the demographic and clinical characteristics of patients with delirium in the Japanese real-world clinical setting using a nationwide database comprising claims and discharge abstract data.

Design: This was an observational, cross-sectional, retrospective study in hospitalized patients with an incident delirium identified by a diagnosis based on International Classification of Diseases, 10th revision codes or initiating antipsychotics recommended for delirium treatment in Japan during their hospitalization.

Setting: Patients from the Medical Data Vision database including more than 400 acute care hospitals in Japan were evaluated from admission to discharge.

Participants: Of the 32,910,227 patients who were included in the database between April 2012 and September 2020, 145,219 patients met the criteria for delirium.

Primary and secondary outcome measures: Demographic and baseline characteristics, comorbidities, clinical profiles, and pharmacological treatments were evaluated in patients with delirium.

Results: The mean (standard deviation [SD]) patient age was 76.5 (13.8) years. More than half of the patients (n=82,159; 56.6%) were male. The most frequent comorbidities were circulatory system diseases, observed in 81,954 (56.4%) patients. Potentially inappropriate medications (PIMs) with risk of delirium including benzodiazepines and opioids were prescribed to 76,798 (52.9%) patients. Approximately three-fourths of these patients (56,949; 74.2%) were prescribed ≥4 PIMs. The most prescribed treatment for delirium was injectable haloperidol (n=82,490; 56.8%). Mean (SD) length of hospitalization was 16.0 (12.1) days.

Conclusions: The study results provide comprehensive details of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. In this patient population, the prescription rate of injectable haloperidol and PIMs was high, suggesting the need for improved understanding among healthcare providers about the appropriate management of delirium, which may benefit patients.

ARTICLE SUMMARY - Strengths and limitations of this study

- This was the first nationwide study that comprehensively assessed the clinical characteristics of patients with delirium in the real-world setting of acute care hospitals in Japan.
- Analysis of the nationwide claims and discharge abstract database, using an algorithm adapted to the Japanese clinical setting, enabled identification of a large sample of patients with delirium in acute care hospitals in Japan.
- As data were identified from the Medical Data Vision database, which is designed to capture claims and discharge abstracts in Japan and is not for research use, misclassification of the International Classification of Diseases, 10th revision codes may occur, given that no quality check is performed.

KEYWORDS: Acute care hospitals, Antipsychotics, Delirium, Medical record database, Real-world evidence

INTRODUCTION

Delirium is an acute condition characterized by fluctuating disturbances in attention, awareness, and cognition.[1] It frequently occurs in hospitalized elderly patients in an acute care setting, especially those in intensive care units (ICUs), and in postoperative care settings.[2,3] The prevalence of delirium is reported as 10%–31% among hospitalized patients within 24 hours of admission.[4] Among elderly patients, the prevalence is reported as 15%–53% after surgery [5,6] and 80% in those admitted to the ICU.[5] Previous studies have shown that delirium is associated with prolonged hospital stay and institutionalization [2,7] and increased mortality in nonsurgical and surgical patients in general wards, emergency departments, and ICUs.[7,8] Furthermore, long-term cognitive and functional decline is associated with delirium, often lasting up to a year following hospital discharge.[7,9] Consequently, delirium increases economic burden by raising healthcare expenditure and imposing costs related to loss of well-being.[3]

Despite its high prevalence and poor prognosis, delirium remains unrecognized in a substantial proportion of old patients. In a prospective clinical epidemiological study, even nursing personnel was unable to recognize delirium in up to two-thirds of the hospitalized elderly patients.[10] Recent evidence suggests that antipsychotics and multicomponent interventions can notably reduce the incidence of delirium and improve clinical outcomes,[11-13] emphasizing the need for early intervention and prevention in the hospitalized or postoperative elderly population that is at risk of delirium.[14]

Antipsychotics are widely used for the treatment of delirium, although no standard clinical pathway for the management of delirium has been established. The Japanese Ministry of Health, Labour and Welfare (MHLW) issued a notification in 2011, permitting the reimbursement of off-label oral and injectable haloperidol, oral perospirone, quetiapine, and risperidone for the treatment of delirium, psychomotor agitation, and irritability associated with organic diseases.[15] In addition, the Japanese Society of General Hospital Psychiatry recommended the use of several antipsychotics in a pharmacotherapy algorithm for delirium.[16] However, few studies have quantitatively investigated the use of antipsychotics for the treatment of patients with delirium in real-world clinical practice in Japan.[17,18]

A limited number of studies have examined the characteristics of patients experiencing delirium based on a medical database.[17-25] This is because identification of delirium through a medical database is quite challenging, given the inconsistent and poor documentation of records.[26] Moreover, the identification of delirium requires bedside cognitive assessments and application of validated diagnostic tools such as the Confusion Assessment Method (CAM) [27] or the Diagnostic and Statistical Manual of Mental Disorders criteria.[1] Therefore, delirium is not routinely evaluated in acute care hospitals,[26,28] and the information on delirium diagnosis rarely gets recorded in healthcare utilization databases (e.g., claims data or hospital clinical data repository).

Although several medical database studies in the USA [19] and Japan [24] have used International Classification of Diseases, 9th revision (ICD-9) or ICD, 10th revision (ICD-10) codes to identify patients with a diagnosis of delirium, only around 2% of patients with

delirium (postoperative in Japan) could be identified. On the other hand, several medical database studies have employed antipsychotic use to identify patients with delirium.[21,23,25] However, either of these criteria, when used exclusively, may be inadequate in obtaining a comprehensive and true picture of delirium patients in the real-world clinical setting in Japan.

To date, few studies have investigated the overall profile of patients with delirium in the real-world clinical setting in Japan. The present study aimed to assess the demographic characteristics, comorbidities, clinical profiles, and treatments in patients with delirium during hospitalization from a nationwide administrative database of acute care hospitals in Japan, the Medical Data Vision (MDV) database. In this study, delirium was defined using the algorithms that were recommended in the recently published claims-based database studies with slight modifications.[22,24]

METHODS

Study design

This was a retrospective, cross-sectional, observational study using a nationwide administrative database (MDV Co., Ltd., Tokyo, Japan), with data collected from April 1, 2012, to September 30, 2020. The MDV database contains anonymized administrative data of more than 30 million patients from over 400 hospitals, which cover approximately 24% of all acute care hospitals in Japan. The MDV database includes claims data and discharge abstract data collected from inpatient and outpatient visits.

Study ethics

This study utilized de-identified data from the MDV database and ethics approval was not required, in line with the Ethical Guidelines for Epidemiological Research from the MHLW, Japan. Therefore, no ethics or institution review board approval was obtained.

Patient selection

In this study, patients admitted to general wards and ICUs were included. Patients meeting the prespecified delirium identification algorithm criteria who were hospitalized for surgery or an emergency and those who were discharged, transferred to other hospitals, or died after hospitalization during the study period were included in the analyzed data set.

The delirium identification algorithm in this study was based on that recently reported by Kim et al.[22] Kim et al. proposed an algorithm that defines delirium based on ICD diagnosis codes or antipsychotic use and has a modestly better profile (30% sensitivity; 97% specificity) than existing algorithms such as either ICD diagnosis codes alone or antipsychotic use alone. In this study, patients were identified and included as the study participants based on the following criteria: a confirmed diagnosis of delirium during hospitalization, coded as F05 per ICD-10 (criterion 1) or prescription of at least one antipsychotic agent (haloperidol, olanzapine, perospirone, quetiapine, or risperidone) between the index date (admission date) and the next 7 days (criterion 2). The algorithm was modified to adjust with the clinical setting in Japan. Patients with a minimum stay of 3 days, including at least 2 antipsychotic-free days, were included in the study.[23] This “two-day washout” period after hospitalization allowed the exclusion of patients who already had a prescription of the selected antipsychotic because of pre-existing conditions. Patients who were hospitalized for less than 3 days; who had schizophrenia spectrum disorder (F20-29 codes per ICD-10), bipolar disorder (F30-31 codes per ICD-10), or delirium (F05 code per ICD-10) as “admission-precipitating diagnosis” or “comorbidities present on admission”; who were prescribed antipsychotics on the hospitalization date or the next day; and who were prescribed olanzapine in combination with cisplatin for nausea within 1 week from the index date were excluded from the analyses.

Patients hospitalized multiple times were evaluated only at the first hospitalization when the inclusion criteria were met. Repeated episodes of delirium in the same patient were not tracked or included in the analysis. The observation period was from the index date (date of hospitalization) to the end of hospitalization, defined as discharge, hospital transfer, or death of the patient.

Outcomes

The following demographic and baseline characteristics, clinical profiles, and comorbidities of patients with delirium were assessed from the MDV database: patients' baseline characteristics (sex, age, activities of daily living score calculated using the Barthel Index [29] cognitive impairment [assessed as "present" if the patient was previously diagnosed with dementia or prescribed anti-dementia medications or had a low degree of independence]), inpatient departments, comorbidities, type of clinical practice (delirium-associated PIM use [identified based on the Beers Criteria,[30] the Guidelines for medical treatment and its safety in the elderly from the Japan Geriatrics Society Working Group,[31] and the report from Noshiro et al.,[32]] type of surgery [sites or duration of anesthesia], duration of hospitalization and ICU stay), hospitalization information (type of hospitalization [surgery or emergency hospitalization], number of beds), prescription pattern for each antipsychotic, and patient outcomes (transfer to other hospitals/nursing homes, death). Among the outcomes, age, ADL, cognitive impairment, and comorbidities were assessed as the risk (predisposing) factors of delirium. Surgery information, hospitalization information (surgery or emergency), and PIM use were assessed as triggers (precipitating factors) of delirium.[8]

Statistical analysis

The aim of this study was descriptive; therefore, no sample size calculations were performed. Data were summarized as mean (standard deviation [SD]) or number and frequency (%). All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis

As many assumptions were made while creating the delirium identification algorithm, two sensitivity analyses were conducted for patients selected in the main analyses to confirm how different assumptions on the analyzed populations might have influenced the outcomes. As some patients could have undergone surgery several days after their admission and the criteria used to identify patients to be included in the main analysis do not allow their inclusion, patients who had a prescription of any of the "selected" antipsychotics between the 3rd day of hospitalization and the day of discharge (or transfer or death) were included in the sensitivity analysis 1 (SA1). Furthermore, as some patients may undergo surgery immediately after the emergency admission and have delirium on the next day and the criteria set for the main analysis do not allow their inclusion, patients who had a prescription of the specified antipsychotics between the 2nd and 8th day of hospitalization were included in the sensitivity analysis 2 (SA2).

Patient and public involvement

Patients were not involved in any phase of this retrospective study, and data were collected from de-identified administrative claims database.

RESULTS

Identification of patients with delirium

Of the 32,910,227 patients who were included in the MDV database during the study period, 145,219 were identified as having delirium (Figure 1). Among patients who were hospitalized for surgery or an emergency (n=7,221,643), 2.0% were identified as having delirium. Overall, 9,898 (6.8%) patients who met the delirium identification algorithm criteria were diagnosed with delirium based on ICD-10 codes and did not receive any of the selected antipsychotic treatments during their hospitalization; 128,095 (88.2%) patients were identified because they had been prescribed any of the selected antipsychotics, and 7,226 (5.0%) patients who met the delirium identification algorithm criteria had both a diagnosis of delirium and an antipsychotic prescription (Figure 1). Most (n=14,801; 86.4%) of the 17,124 patients with an ICD-10 coded diagnosis had "delirium" (code F05.9), followed by "nocturnal delirium" (code F05.9), "delirium superimposed on dementia" (code F05.1), and "delirium not superimposed on dementia" (code F05.0; Supplemental Table 1).

Patient demographics and baseline characteristics

Mean (SD) patient age was 76.5 (13.8) years, and approximately 65% of patients were ≥75 years of age; more than 50% (n=82,159) of patients were male. Approximately half (n=76,422; 52.6%) of the patients with delirium were categorized as "dependent (need someone's help)" based on the Barthel Index score (Table 1). Cognitive impairment was noted in 40,376 (27.8%) patients (Table 1; Supplemental Table 2). Circulatory system diseases were the most common comorbidity, observed in 81,954 (56.4%) patients, followed by endocrine, nutritional, and metabolic diseases (n=59,955; 41.3%) and digestive system diseases (n=59,691; 41.1%; Table 1; Supplemental Table 3). These outcomes were assessed as the risk (predisposing) factors of delirium.

Clinical practice

Around half (n=85,492; 58.9%) of the patients with delirium underwent any surgery, of whom approximately one-third (n=28,557) were anesthetized for more than 2 hours (Table 2). There was a wide distribution of surgical sites, with the abdomen being the most common site (n=38,898; 26.8%; Supplemental Table 4). Mean (SD) duration of hospitalization was 16.0 (12.1) days; 55,709 (38.4%) patients were hospitalized for 1–2 weeks (Table 2). Overall, 33,718 (23.2%) patients were admitted to the ICU for a mean (SD) of 3.4 (3.1) days, of whom 4,379 (3.0%) spent at least 7 days in the ICU (Table 2). PIMs were prescribed to 76,798 (52.9%) patients, including benzodiazepines in 31,324 (21.6%) patients and opioids in 29,268 (20.2%) patients. Approximately three-fourths (n=56,949; 74.2%) of these patients were prescribed ≥4 PIMs. Multiple classes of PIMs were used by 38.6% of patients to whom PIMs were prescribed (Table 2). These factors were assessed as triggers (precipitating factors) of delirium.

Treatment for delirium

Injectable haloperidol was the most prescribed antipsychotic (n=82,490; 56.8%) for the treatment of delirium, followed by risperidone solution (n=34,282; 23.6%), quetiapine tablet (n=19,830; 13.7%), risperidone orodispersible tablet (n=7,645; 5.3%), and risperidone tablet (n=4,958; 3.4%; Table 3). The mean (SD) duration of these antipsychotic prescriptions was 5.4 (8.1) days (Table 3).

Hospitalizations and patient outcome

Assessment of patients with delirium by hospital department showed that the departments where at least 5% of patients experienced delirium were surgery (n=28,656; 19.7%), internal medicine (n=28,232; 19.4%), gastroenterology (n=15,445; 10.6%), cardiology (n=12,337; 8.5%), orthopedics (n=11,302; 7.8%), and neurosurgery (n=8,144; 5.6%; Table 1; Supplemental Table 4). In general, 52,766 (36.3%) patients with delirium were hospitalized for planned elective surgery, whereas 59,727 (41.1%) patients were hospitalized due to an emergency (without subsequent surgery) and 32,726 (22.5%) patients were hospitalized due to an emergency and underwent surgery (Supplemental Table 4). A total of 15,556 (10.7%) patients died while in hospital, and 22,081 (15.2%) were transferred to other hospitals or clinics (Table 4).

Sensitivity analysis

The results of the sensitivity analyses identified 184,817 patients with delirium in SA1 and 213,844 in SA2 (Supplemental Figure 1). Patients' mean (SD) age was 76.1 (13.8) years in SA1 and 76.3 (14.1) years in SA2. A total of 96,591 (52.3%) patients in SA1 and 113,005 (52.8%) patients in SA2 were classified as dependent (Supplemental Table 5).

The proportion of patients prescribed one or more antipsychotics to treat their delirium was 95.5% in SA1 and 95.4% in SA2. The proportion of injectable haloperidol prescriptions was 58.1% in SA1 and 60.1% in SA2, while the proportion of prescriptions for risperidone solution was 24.8% in SA1 and 23.5% in SA2 and that for risperidone tablets was 4.0% in SA1 and 3.5% in SA2 (Supplemental Table 5).

DISCUSSION

The present study was the first nationwide database study that assessed the clinical characteristics of patients with delirium in acute care hospitals in Japan. To identify patients with delirium from the hospital database, the study used the delirium identification algorithm which consists of diagnoses based on ICD-10 codes and prescriptions of antipsychotics frequently used in the treatment of delirium.[22] The prevalence of delirium obtained in our study was 2.0% among patients who were hospitalized for surgery or an emergency, which was lower than the incidence of new delirium per admission (3%–29%) reported in a systematic review of the literature.[4] The low prevalence of delirium might be due to the sensitivity of the algorithm used in our study. A potential explanation is that physicians are not aware of delirium, thereby leading to its inappropriate management. Another possible explanation is that physicians do not proactively record a diagnosis of delirium in claims because there is no approved drug for delirium treatment or prevention in Japan, except for tiapride that is approved for the management of delirium after stroke.

In our study, about half of the patients (n=85,492; 58.9%) underwent surgery during their hospital stay, and delirium was also identified among nonsurgical patients in general medical wards such as internal medicine, gastroenterology, and cardiology. A systematic literature review reported the prevalence of delirium among patients admitted to general medical and geriatric wards as 18%–35%.[8] Our findings revealed the occurrence of delirium in broad clinical departments in Japanese acute care hospitals, suggesting the need for physicians and nurses in these departments to understand the diagnosis and management of patients with delirium.

Drug classes such as benzodiazepines, opioids, and H2 blockers were selected as PIMs, which are reported to be associated with the onset of delirium in guidelines [30,31] and several studies.[32-36] In our study, more than half (52.9%) of the patients were prescribed a PIM of any type; approximately one-fifth of patients were prescribed either benzodiazepines or opioids (21.6% and 20.2%, respectively). Benzodiazepines and opioids are associated with an increased risk of delirium in medical and surgical patients.[34] In a single center study in Canada, the risk was more than doubled within 28 days of hospitalization in patients with cancer who were receiving benzodiazepines (>2 mg/day) and opioids (>90 mg/day).[37] It should be noted that Japan is one of the countries with a high rate of consumption of benzodiazepine-type sedative hypnotics.[38] In addition, opioids are necessary to control severe pain, and pain is also known to be associated with a risk of delirium.[16] suggesting the importance of delirium control in combination with pain control. PIMs also include several drugs with anticholinergic activities, such as antihistamines and antidepressants.[30] Use of anticholinergic drugs is associated with an increased risk of delirium.[39,40] Thus, physicians should avoid unnecessarily prescribing drugs with anticholinergic effects considering the risk of delirium onset. Furthermore, at least 4 PIMs were prescribed in 74.2% of patients with delirium in the present study. Polypharmacy with ≥3 drugs is reported to increase the risk of delirium by 2.9 times in elderly patients during hospitalization.[41] As drug interactions are a concern regarding PIMs in patients with polypharmacy, potential drug interactions in addition to the number of PIMs used should be carefully considered especially in patients with polypharmacy. The frequent use of PIMs that increase the risk of delirium in the real world, particularly in elderly patients, reaffirms the need for a better understanding of the benefit-risk profile of such medications.

In our study, injectable haloperidol was the most frequently prescribed (56.8%) antipsychotic, followed by risperidone solution (23.6%) and quetiapine tablets (13.7%) in patients with

delirium. The outcomes are similar to those from a recent database study in Japan, where haloperidol infusion was the most frequently used treatment in postoperative patients with delirium.[17] These results are also consistent with those of a questionnaire-based cross-sectional study in which more than two-thirds of Japanese experts recommended intravenous haloperidol as the initial drug (if an intravenous line was placed during hospitalization) and atypical oral antipsychotics such as risperidone or quetiapine as initial oral drugs for hyperactive delirium.[42] Risperidone solution and olanzapine orodispersible tablets could be useful for patients who have difficulties in taking medicines.[16] In our study, a relatively high proportion of patients were prescribed risperidone solution (23.6%); however, only 0.6% were prescribed olanzapine orodispersible tablets. The low proportion of olanzapine prescription could be due to the long half-life of olanzapine and its contraindication in patients with diabetes in Japan.[16] Overall, our findings suggest that injectable haloperidol is the major treatment modality for delirium in an acute care setting likely because it can be used as needed for the treatment of delirium in such a setting. Unlike psychiatrists, the majority of physicians who treat patients with delirium are likely to be unfamiliar with use of atypical antipsychotics. However, in a broader clinical context, the risk of death in the elderly was reported to be 2.26-fold higher with haloperidol versus olanzapine,[43] and the likelihood of overall survival was 1.73-fold higher with placebo in a randomized control trial.[44] Moreover, the incidence of adverse events, particularly extrapyramidal symptoms, is reportedly higher with haloperidol versus risperidone, although their efficacy is reportedly similar.[45,46] While antipsychotics are frequently used for treating delirium in real-world clinical settings, physicians should note that nonpharmacological treatment is the first-line therapy for delirium and that antipsychotic use should be considered only if the nonpharmacological treatment is ineffective and patients are at risk of injuring themselves and others. For example, the NICE delirium guidelines state that short-term haloperidol may be given when an individual with delirium is distressed or considered to be at risk to themselves or others, and if verbal and nonverbal de-escalation methods have not shown effect.[47] The Beers Criteria by the American Geriatrics Society recommend that PIMs including antipsychotics be avoided in older adults at high risk of delirium owing to the risk of inducing or worsening the condition.[30] Moreover, olanzapine has anticholinergic effects, and its use in managing delirium is controversial because some case reports have shown that its use may be associated with delirium onset.[48,49] Therefore, it is important for healthcare providers to understand the appropriate nonpharmacological management of delirium.

The greatest strength of this study is the large size of the MDV database, which enabled the identification of a large number of patients with delirium. The use of our algorithm optimized for the Japanese clinical setting led to an increased number of patients being retrieved from hospital databases, thus highlighting the utility of this algorithm in real-world scenarios. More importantly, outcomes of the sensitivity analyses, which considered different treatment time frames in determining index, were consistent with those of the main analysis reinforcing the robustness of our study results. The prevalence of delirium obtained by identifying patients using an ICD-coded diagnosis was only 0.2% among patients who were hospitalized for surgery or an emergency in our study, which is similar to that reported in previous studies in Japan.[18,24] However, this low prevalence may not be a true reflection of the occurrence of delirium in the real world, as observed in a prospective study that compared the sensitivity and specificity of various delirium identification algorithms.[22] According to Sakakibara et al., delirium is recorded on the claims receipt only for patients with severe delirium requiring more medical resources, but not for those with mild-to-moderate delirium.[24] Our results confirm that the majority of Japanese patients with delirium can be identified from a Japanese claims database based on prescription of an antipsychotic during their hospital stay; 88.2% of

patients with delirium were identified based on an antipsychotic prescription. A recent study employing a Japanese national inpatient database used the daily nursing necessity score (dangerous behavior or misunderstanding of nursing instructions) as the criterion of delirium, but reported a prevalence of delirium of approximately 1% (n=21,182) among 2,070,000 postoperative patients.[17] The results of the present study show the feasibility of using administrative databases for identifying patients with delirium in an acute care hospital setting in Japan.

This study has several limitations. First, the data were extracted from the MDV database, which is designed primarily for insurance purposes and not for research; therefore, no quality checks for data are performed and there is a likelihood of misclassification of ICD-10 coding. Second, as the data of patients transferred to other hospitals were not registered in this database, patients who were moved to or hospitalized in a different hospital after the index hospitalization could not be identified. This could have led to multiple hospitalizations of the same high-risk patients, with multiple episodes of delirium at different times being identified as separate events and possibly increasing the number of identified cases. Third, the number of prescribed antipsychotics may be inflated because some patients with psychotic disorders may have been included from the database during analysis although the present study excluded patients with schizophrenia or bipolar disease. Lastly, the sensitivity and specificity of the modified delirium identification algorithm used in this study have not yet been validated in Japan. The recent addition of a medical fee for the care of high-risk patients with delirium in the medical reimbursement revision of 2020 in Japan may increase the accuracy of identification of patients with delirium from the medical database. For future research, the delirium identification algorithm used in our study needs to be validated.

In conclusion, the results of the present study provide comprehensive details of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. The results reinforce the need to consider the risk of delirium in hospitals, especially in high-risk patients, and provide useful information for healthcare professionals to understand the clinical profile of patients who are likely to experience delirium when hospitalized. The study reveals two important findings in this patient population: 1) the high prescription rate of injectable haloperidol and 2) the frequent use of PIMs in patients with delirium. Thus, there is a need for improved understanding among healthcare providers about appropriate management of delirium in an acute care setting, which may benefit patients.

COMPETING INTERESTS

NU, MI, KO, HS, KT, ST, and SO are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. ZPQ is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. AO and YO have received funding from MSD K.K., Tokyo, Japan for research consulting.

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AUTHOR CONTRIBUTIONS

SO, HS, KT, ZPQ, ST, AO, and YO conceptualized the study. NU, MI, KO, and SO conducted the study designing and data analysis planning. HS, KT, ZPQ, and ST contributed to the study designing. KT, AO, and YO provided advice on study design and contributed to the interpretation of the findings from the viewpoint of the clinical scientist, the physician and the epidemiologist, respectively. All authors contributed to interpretation of data and approved the final version of the manuscript. NU and SO are guarantors and accept full responsibility for the work.

DATA SHARING STATEMENT

The Medical Data Vision database analyzed in this study is not publicly accessible, and the data cannot be shared with external researchers according to the contract with Medical Data Vision Co., Ltd.

Table 1 Patient demographic and baseline characteristics.

		Number of patients N (%)	
Number of patients		145,219	
Age (years)	Mean (SD)	76.5 (13.8)	
	≤64	22,168	(15.3)
	65–74	28,371	(19.5)
	75–84	49,739	(34.3)
	≥85	44,941	(30.9)
Sex	Male	82,159	(56.6)
	Female	63,060	(43.4)
ADL score (point)*	Dependent group (0–59)	76,422	(52.6)
	Independent group (60–100)	66,381	(45.7)
	Unknown	2,416	(1.7)
Cognitive impairment†	Yes	40,376	(27.8)
	No	104,843	(72.2)
Inpatient department	Surgery	28,656	(19.7)
	Internal Medicine	28,232	(19.4)
	Gastroenterology	15,445	(10.6)
	Cardiology	12,337	(8.5)
	Orthopedics	11,302	(7.8)
	Neurosurgery	8,144	(5.6)
	Urology	7,031	(4.8)
	Cardiovascular Surgery	6,042	(4.2)
	Respiratory Medicine	5,506	(3.8)
	Gastrointestinal Surgery	4,093	(2.8)
	Emergency Medicine	3,414	(2.4)

	Neurology	3,008	(2.1)
	Others	11,573	(8.0)
Comorbidities	Circulatory system diseases (I00-I99)	81,954	(56.4)
(ICD-10 major category)‡	Endocrine, nutritional, and metabolic diseases (E00-E90)	59,955	(41.3)
	Digestive system diseases (K00-K93)	59,691	(41.1)
	Malignant neoplasms (C00-C97)	41,710	(28.7)
	Respiratory system diseases (J00-J99)	36,958	(25.4)

*Barthel Index will be used for evaluation.

†Cognitive Impairment was assessed as "present" if the patient was previously diagnosed with dementia or prescribed anti-dementia drugs or had a low degree of independence.

‡Top 5 major ICD-10 categories are presented.

ADL, activity of daily living; ICD-10, International Classification of Diseases, 10th revision; SD, standard deviation.

Table 2 Clinical practice.

		Number of patients N (%)	
Number of patients		145,219	
Prescription of PIM	Yes (any type of PIM)	76,798	(52.9)
	Antidepressants	299	(0.2)
	Anticholinergic drugs	163	(0.1)
	Benzodiazepines	31,324	(21.6)
	Non-benzodiazepines	10,582	(7.3)
	Corticosteroids	16,879	(11.6)
	H1-receptor antagonists	10,283	(7.1)
	H2-receptor antagonists	17,360	(12.0)
	Opioids	29,268	(20.2)
	Number of PIMs (drugs)	76,798	(100.0)
	1	5,268	(6.9)
	2	7,232	(9.4)
	3	7,349	(9.6)
	≥4	56,949	(74.2)
	Number of PIMs (classes)	76,798	(100.0)
	1	47,128	(61.4)
	2	21,637	(28.2)
	3	6,561	(8.5)
	≥4	1,472	(1.9)
Surgery	Yes	85,492	(58.9)
	Anesthesia type/duration:	85,492	(100.0)
	Surgery + no anesthesia/local anesthesia/light general anesthesia	35,048	(41.0)

	Surgery + general anesthesia (<2 hours)	21,887	(25.6)
	Surgery + general anesthesia (≥2 hours)	28,557	(33.4)
Duration of hospitalization (days)	Mean (SD)	16.0 (12.1)	
	≤1 week	22,542	(15.5)
	>1 week to ≤2 weeks	55,709	(38.4)
	>2 weeks to ≤3 weeks	38,342	(26.4)
	>3 weeks to ≤4 weeks	17,004	(11.7)
	4> weeks to ≤12 weeks	11,046	(7.6)
	>12 weeks	576	(0.4)
Use of ICU	Yes	33,718	(23.2)
Duration of ICU (days)	Mean (SD)	3.4 (3.1)	
	1 day	12,218	(8.4)
	2 days	5,970	(4.1)
	3 days	4,247	(2.9)
	4 days	3,104	(2.1)
	5 days	2,192	(1.5)
	6 days	1,608	(1.1)
	≥7 days	4,379	(3.0)

ICU, intensive care unit; PIM, potentially inappropriate medication; SD, standard deviation.

Table 3 Antipsychotics used for treating delirium.

			Number of patients N (%)	
Number of patients			145,219	
Antipsychotics used for delirium	Yes		135,321	(93.2)
Type of drug formulation	Haloperidol	INJ	82,490	(56.8)
		TAB	1,913	(1.3)
		FGR	192	(0.1)
		SOL	13	(0.0)
	Risperidone	SOL	34,282	(23.6)
		ODT	7,645	(5.3)
		TAB	4,958	(3.4)
		FGR	257	(0.2)
		INJ	6	(0.0)
	Quetiapine	TAB	19,830	(13.7)
		FGR	652	(0.4)
		SRT	20	(0.0)
	Olanzapine	TAB	2,262	(1.6)
		ODT	915	(0.6)
		FGR	156	(0.1)
		INJ	11	(0.0)
	Perospirone	TAB	2,210	(1.5)
Duration of prescription (days)	Mean (SD)		5.4 (8.1)	

FGR, fine granule; INJ, injectable; ODT, orodispersable tablet; SD, standard deviation; SOL, solution; SRT, sustained-release tablet; TAB, tablet.

Table 4 Patient outcome – Transfer to other hospitals/nursing homes and death.

		Number of patients N (%)	
Number of patients		145,219	
Transfer to other hospitals/nursing homes	Yes	32,651	(22.5)
	Transfer to other hospitals or clinics	22,081	(15.2)
	Admission to social welfare facilities or fee-based homes for the elderly, etc.	5,070	(3.5)
	Admission to facilities covered by public aid providing long-term care to the elderly	3,017	(2.1)
	Admission to long-term care health facilities	2,472	(1.7)
	Nursing home	11	(0.0)
Death	Yes	15,556	(10.7)
	No	129,637	(89.3)

FIGURE LEGENDS

Figure 1 Patient selection flowchart.

DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th revision; MDV, Medical Data Vision.

Supplemental Figure 1 Patient selection flowchart for the sensitivity analysis.

MDV, Medical Data Vision.

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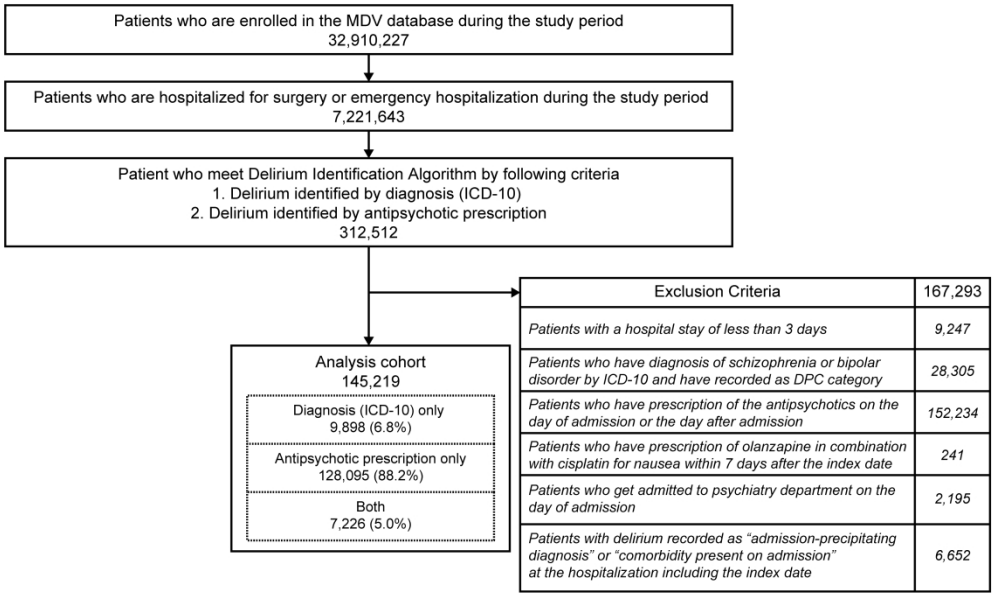


Figure 1 Patient selection flowchart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th revision; MDV, Medical Data Vision.

Supplemental Table 1 ICD-10 codes for delirium diagnosis.

		Number of patients N (%)	
Number of delirium patients identified by diagnosis (ICD-10)	Total	17,124	(11.8)
	Delirium not superimposed on dementia (F05.0)	977	(0.7)
	Delirium superimposed on dementia (F05.1)	1,447	(1.0)
	Other delirium (F05.8)	37	(0.0)
	Subacute infection psychosis	0	(0.0)
	Subacute organic reaction	0	(0.0)
	Subacute organic psychiatric syndrome	0	(0.0)
	Subacute cerebral syndrome	5	(0.0)
	Acute infectious psychosis	1	(0.0)
	Acute organic reaction	3	(0.0)
	Acute organic psychiatric syndrome	2	(0.0)
	Acute confusional state	14	(0.0)
	Acute brain syndrome	11	(0.0)
	Nonalcoholic acute confusional state	1	(0.0)
	Delirium, unspecified (F05.9)	14,801	(10.2)
	Delirium	11,828	(8.1)
	Nocturnal delirium	2,494	(1.7)
	Senile nocturnal delirium	498	(0.3)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 2 Definition of cognitive impairment.

		Number of patients N (%)	
Number of patients		145,219	
Cognitive impairment	Yes	40,376	(27.8)
	Diagnosis of dementia (ICD-10)	21,498	(14.8)
	Prescription of anti-dementia drugs	12,032	(8.3)
	Low degree of independence in daily life for the elderly with dementia	25,537	(17.6)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 3 Comorbidities (diseases present in ≥3% of patients with delirium in each category).

Category	Disease	ICD-10	Number of patients N (%)
Number of patients			145,219
Circulatory system diseases		I00-I99	81,954 (56.4)
	Essential (primary) hypertension	I10	47,887 (33.0)
	Heart failure	I50	23,214 (16.0)
	Atrial fibrillation and flutter	I48	12,774 (8.8)
	Angina pectoris	I20	11,296 (7.8)
	Sequelae of cerebrovascular disease	I69	8,759 (6.0)
	Cerebral infarction	I63	6,577 (4.5)
	Aortic aneurysm and dissection	I71	4,432 (3.1)
Endocrine, nutritional, and metabolic diseases		E00-E90	59,955 (41.3)
	Type 2 diabetes mellitus	E11	23,809 (16.4)
	Disorders of lipoprotein metabolism and other lipidemia	E78	17,530 (12.1)
	Volume depletion	E86	13,698 (9.4)
	Other disorders of fluid, electrolyte, and acid-base balance	E87	4,896 (3.4)
	Unspecified diabetes mellitus	E14	4,364 (3.0)
Digestive system diseases		K00-K93	59,691 (41.1)
	Gastroesophageal reflux disease	K21	13,242 (9.1)
	Other functional intestinal disorders	K59	10,515 (7.2)
	Gastric ulcer	K25	9,864 (6.8)
	Cholelithiasis	K80	8,230 (5.7)

	Paralytic ileus and intestinal obstruction without hernia	K56	5,276	(3.6)
	Gastritis and duodenitis	K29	5,025	(3.5)
	Other diseases of the biliary tract	K83	4,850	(3.3)
Malignant neoplasms		C00-C97	41,710	(28.7)
	Malignant neoplasm of stomach	C16	7,644	(5.3)
	Malignant neoplasm of colon	C18	7,163	(4.9)
	Secondary malignant neoplasm of respiratory and digestive organs	C78	5,631	(3.9)
	Malignant neoplasm of bronchus and lung	C34	4,433	(3.1)
Respiratory system diseases		J00-J99	36,958	(25.4)
	Respiratory failure, not elsewhere classified	J96	14,385	(9.9)
	Pneumonia, organism unspecified	J18	7,004	(4.8)
	Pneumonitis due to solids and liquids	J69	6,991	(4.8)
Nervous system diseases		G00-G99	28,557	(19.7)
	Alzheimer disease	G30	9,659	(6.7)
	Sleep disorders	G47	9,351	(6.4)
Genitourinary system diseases		N00-N99	25,617	(17.6)
	Chronic kidney disease	N18	8,208	(5.7)
	Benign prostatic hyperplasia	N40	5,360	(3.7)
Mental and behavioral disorders		F00-F99	20,047	(13.8)
	Unspecified dementia	F03	8,934	(6.2)
Musculoskeletal system/connective tissue diseases		M00-M99	17,523	(12.1)

Injury		S00-T35	15,866	(10.9)
	Fracture of femur	S72	6,427	(4.4)
Blood diseases		D50-D89	13,458	(9.3)
	Iron deficiency anemia	D50	6,881	(4.7)
Infectious disease (excluding parasitic disease)	-	A00-A49 / B90-99	12,442	(8.6)
Skin/subcutaneous tissue disease	-	L00-L99	4,094	(2.8)
Eye disease	-	H00-H59	1,565	(1.1)
Poisoning	-	T36-T65	806	(0.6)
Ear disease	-	H60-H95	624	(0.4)
Others			39,232	(27.0)
	Somnolence, stupor, and coma	R40	6,943	(4.8)

ICD-10, International Classification of Diseases, 10th revision.

Supplemental Table 4 Hospitalization information.

		Number of patients N (%)	
Number of patients		145,219	
Type of hospitalization	Hospitalization with elective surgery	52,766	(36.3)
	Emergency hospitalization without surgery	59,727	(41.1)
	Emergency hospitalization with surgery	32,726	(22.5)
Number of beds	0–199 beds	6,760	(4.7)
	200–499 beds	79,995	(55.1)
	≥500 beds	58,464	(40.3)
Inpatient department	Surgery	28,656	(19.7)
	Internal Medicine	28,232	(19.4)
	Gastroenterology	15,445	(10.6)
	Cardiology	12,337	(8.5)
	Orthopedics	11,302	(7.8)
	Neurosurgery	8,144	(5.6)
	Urology	7,031	(4.8)
	Cardiovascular Surgery	6,042	(4.2)
	Respiratory Medicine	5,506	(3.8)
	Gastrointestinal Surgery	4,093	(2.8)
	Emergency Medicine	3,414	(2.4)
	Neurology	3,008	(2.1)
	Pulmonary Surgery	1,734	(1.2)
	Obstetrics & Gynecology	1,528	(1.1)
	Otolaryngology	1,416	(1.0)
	Nephrology	1,252	(0.9)
	Hematology	729	(0.5)

	Endocrinology, Metabolism & Diabetology	706	(0.5)
	Reconstructive Surgery	625	(0.4)
	Ophthalmology	606	(0.4)
	Others	2,977	(2.1)
	Unknown	436	(0.3)
Surgery	Yes	85,492	(58.9)
	Surgery sites:		
	Abdomen	38,898	(26.8)
	Heart and blood vessels	15,240	(10.5)
	Musculoskeletal system, extremities, and trunk	10,424	(7.2)
	Thoracic	6,061	(4.2)
	Urinary system and adrenal glands	4,893	(3.4)
	Nervous system and cranial	3,708	(2.6)
	Skin or subcutaneous tissue	3,076	(2.1)
	Genital	2,557	(1.8)
	Ear, nose, and throat	1,113	(0.8)
	Face, mouth, and neck	738	(0.5)
	Eyes	606	(0.4)

Supplemental Table 5 Sensitivity analyses: Delirium identification algorithm, patient characteristics, clinical practice, delirium treatment with antipsychotics, and patient outcomes.

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Number of subjects		184,817		213,844	
Delirium identification algorithm					
Patients meeting criteria	Diagnosis (ICD-10) only	8,401	(4.5)	9,874	(4.6)
	Antipsychotic prescription only	167,756	(90.8)	193,507	(90.5)
	Both	8,660	(4.7)	10,463	(4.9)
Patient demographic and baseline characteristics					
Age (years)	Mean (SD)	76.1 (13.8)		76.3 (14.1)	
	≤64	29,659	(16.0)	34,204	(16.0)
	65–74	37,770	(20.4)	41,091	(19.2)
	75–84	62,820	(34.0)	71,825	(33.6)
	≥85	54,568	(29.5)	66,724	(31.2)
Sex	Male	105,167	(56.9)	120,696	(56.4)
	Female	79,650	(43.1)	93,148	(43.6)
ADL score (point)	Dependent group (0–59)	96,591	(52.3)	113,005	(52.8)
	Independent group (60–100)	85,101	(46.0)	97,296	(45.5)
	Unknown	3,125	(1.7)	3,543	(1.7)
Cognitive impairment	Yes	49,445	(26.8)	60,930	(28.5)
	Diagnosis of dementia (ICD-10)	26,470	(14.3)	33,014	(15.4)
	Prescription of anti-dementia drugs	15,214	(8.2)	18,685	(8.7)
	Low degree of independence*	30,820	(16.7)	38,575	(18.0)
Inpatient department	Surgery	36,983	(20.0)	38,799	(18.1)
	Internal Medicine	33,955	(18.4)	40,868	(19.1)
	Gastroenterology	20,135	(10.9)	26,557	(12.4)
	Cardiology	14,845	(8.0)	19,516	(9.1)
	Orthopedics	14,769	(8.0)	15,886	(7.4)
	Neurosurgery	10,039	(5.4)	12,943	(6.1)
	Urology	8,619	(4.7)	10,501	(4.9)
	Cardiovascular Surgery	7,953	(4.3)	7,405	(3.5)
	Respiratory Medicine	7,056	(3.8)	7,484	(3.5)
	Gastrointestinal Surgery	5,427	(2.9)	4,905	(2.3)
	Emergency Medicine	4,047	(2.2)	5,245	(2.5)
	Neurology	3,598	(1.9)	4,648	(2.2)
	Pulmonary Surgery	2,134	(1.2)	2,297	(1.1)
	Obstetrics & Gynecology	2,034	(1.1)	2,274	(1.1)
	Otolaryngology	2,033	(1.1)	2,047	(1.0)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
	Nephrology	1,728	(0.9)	1,755	(0.8)
	General Medicine	1,272	(0.7)	1,574	(0.7)
	Hematology	1,024	(0.6)	974	(0.5)
	Endocrinology, Metabolism & Diabetology	859	(0.5)	1,037	(0.5)
	Reconstructive Surgery	905	(0.5)	958	(0.4)
	Ophthalmology	720	(0.4)	1,040	(0.5)
	Others	4,093	(2.2)	4,550	(2.1)
	Unknown	589	(0.3)	581	(0.3)
Comorbidities	Circulatory system diseases	103,602	(56.1)	119,306	(55.8)
	Endocrine, nutritional, and metabolic diseases	77,200	(41.8)	86,310	(40.4)
	Digestive system diseases	76,319	(41.3)	88,300	(41.3)
	Malignant neoplasms	56,282	(30.5)	58,680	(27.4)
	Others	51,859	(28.1)	57,420	(26.9)
	Respiratory system diseases	47,586	(25.7)	52,118	(24.4)
	Nervous system diseases	36,193	(19.6)	42,476	(19.9)
	Genitourinary system diseases	32,942	(17.8)	36,993	(17.3)
	Mental and behavioral disorders	24,824	(13.4)	30,773	(14.4)
	Musculoskeletal system/connective tissue diseases	22,601	(12.2)	24,732	(11.6)
	Injury	20,340	(11.0)	23,901	(11.2)
	Blood diseases	18,251	(9.9)	19,041	(8.9)
	Infectious disease (excluding parasitic disease)	16,392	(8.9)	17,308	(8.1)
	Skin/subcutaneous tissue disease	5,688	(3.1)	5,836	(2.7)
	Eye disease	1,960	(1.1)	2,445	(1.1)
	Poisoning	876	(0.5)	1,399	(0.7)
	Ear disease	793	(0.4)	927	(0.4)
Hospitalization information					
Type of hospitalization	Hospitalization for elective surgery	52,647	(28.5)	64,141	(30.0)
	Emergency hospitalization without surgery	71,805	(38.9)	88,286	(41.3)
	Emergency hospitalization with surgery	44,391	(24.0)	48,568	(22.7)
	Unknown	15,974	(8.6)	12,849	(6.0)
Number of beds	0–199	8,992	(4.9)	9,895	(4.6)
	200–499	101,596	(55.0)	117,555	(55.0)
	≥500	74,229	(40.2)	86,394	(40.4)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Clinical practice					
Prescription of PIM	Yes	94,998	(51.4)	69,827	(32.7)
	Antidepressants	371	(0.2)	254	(0.1)
	Anticholinergic drugs	194	(0.1)	137	(0.1)
	Benzodiazepines	38,988	(21.1)	28,269	(13.2)
	Non-benzodiazepines	12,954	(7.0)	8,780	(4.1)
	Corticosteroids	21,746	(11.8)	13,734	(6.4)
	H1-receptor antagonists	12,388	(6.7)	6,959	(3.3)
	H2-receptor antagonists	21,028	(11.4)	15,246	(7.1)
	Opioids	35,588	(19.3)	19,253	(9.0)
Prescription of PIM (number of PIM drugs)	1	5,640	(3.1)	4,728	(2.2)
	2	7,794	(4.2)	6,064	(2.8)
	3	7,985	(4.3)	6,451	(3.0)
	≥4	73,579	(39.8)	52,584	(24.6)
Prescription of PIM (number of PIM classes)	1	58,500	(31.7)	51,123	(23.9)
	2	26,719	(14.5)	15,136	(7.1)
	3	8,011	(4.3)	3,089	(1.4)
	≥4	1,768	(1.0)	479	(0.2)
Surgery	Yes	113,012	(61.1)	125,558	(58.7)
	Surgery sites:				
	Skin or subcutaneous tissue	4,477	(2.4)	4,672	(2.2)
	Musculoskeletal system, extremities, and trunk	13,859	(7.5)	14,564	(6.8)
	Nervous system and cranial	4,825	(2.6)	5,695	(2.7)
	Eyes	704	(0.4)	1,060	(0.5)
	Ear, nose, and throat	1,895	(1.0)	1,570	(0.7)
	Face, mouth, and neck	874	(0.5)	1,192	(0.6)
	Thoracic	7,613	(4.1)	9,017	(4.2)
	Heart and blood vessels	21,172	(11.5)	21,846	(10.2)
	Abdomen	51,061	(27.6)	57,020	(26.7)
	Urinary system and adrenal gland	6,173	(3.3)	7,365	(3.4)
	Genital	2,964	(1.6)	3,933	(1.8)
	Anesthesia type/duration:				
	Surgery + no/local/light general anesthesia	49,357	(26.7)	58,743	(27.5)
	Surgery + general anesthesia (<2 hours)	27,276	(14.8)	32,179	(15.0)

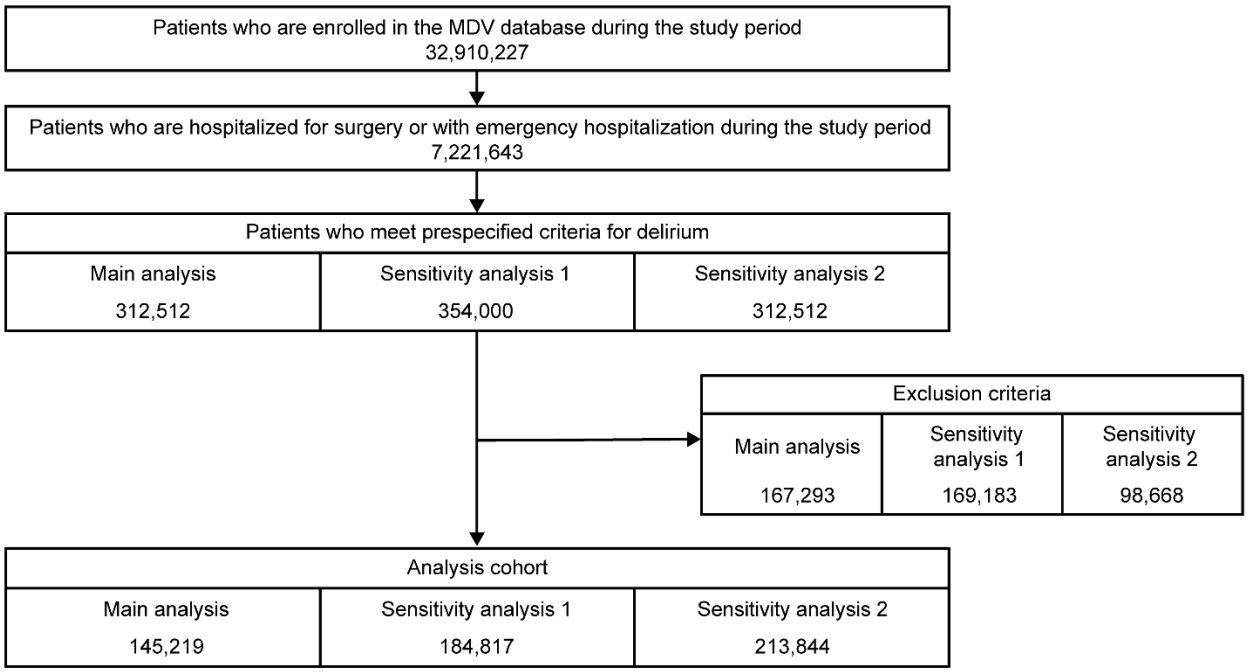
Characteristics			Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
	Surgery + general anesthesia (≥2 hours)		36,379	(19.7)	34,636	(16.2)
Duration of hospitalization	Mean (SD), days		19.5 (18.9)		14.9 (11.7)	
	≤1 week		22,368	(12.1)	44,771	(20.9)
	>1 week to ≤2 weeks		60,821	(32.9)	81,671	(38.2)
	>2 weeks to ≤3 weeks		48,981	(26.5)	50,271	(23.5)
	>3 weeks to ≤4 weeks		26,094	(14.1)	22,322	(10.4)
	>4 weeks to ≤12 weeks		24,247	(13.1)	14,092	(6.6)
	>12 weeks		2,306	(1.2)	717	(0.3)
Use of ICU	Yes		42,565	(23.0)	47,127	(22.0)
Duration, days	Mean (SD)		3.8 (3.7)		3.3 (3.0)	
	1 day		14,765	(8.0)	17,264	(8.1)
	2 days		7,146	(3.9)	8,810	(4.1)
	3 days		5,101	(2.8)	6,174	(2.9)
	4 days		3,723	(2.0)	4,281	(2.0)
	5 days		2,665	(1.4)	2,913	(1.4)
	6 days		1,970	(1.1)	2,119	(1.0)
	≥7 days		7,195	(3.9)	5,566	(2.6)
Antipsychotics used for delirium						
Antipsychotic use for delirium	Yes		176,416	(95.5)	203,970	(95.4)
Type of drug formulation	Haloperidol	INJ	107,433	(58.1)	128,456	(60.1)
		TAB	3,030	(1.6)	2,861	(1.3)
		FGR	311	(0.2)	308	(0.1)
		SOL	26	(0.0)	22	(0.0)
	Risperidone	SOL	45,913	(24.8)	50,360	(23.5)
		ODT	10,987	(5.9)	11,442	(5.4)
		TAB	7,314	(4.0)	7,493	(3.5)
		FGR	445	(0.2)	415	(0.2)
		INJ	9	(0.0)	7	(0.0)
	Quetiapine	TAB	28,040	(15.2)	30,390	(14.2)
		FGR	1,126	(0.6)	1,006	(0.5)
		SRT	26	(0.0)	34	(0.0)
	Olanzapine	TAB	4,055	(2.2)	3,569	(1.7)
		ODT	1,678	(0.9)	1,569	(0.7)
		FGR	270	(0.1)	248	(0.1)
		INJ	27	(0.0)	16	(0.0)
	Perospirone	TAB	3,280	(1.8)	3,334	(1.6)

Characteristics		Sensitivity analysis 1 N (%)		Sensitivity analysis 2 N (%)	
Duration of prescription, days	Mean (SD)	5.7 (10.1)		5.3 (7.9)	
Patient outcomes					
Transfer to other hospitals/nursing homes	Yes	43,028	(23.3)	47,980	(22.4)
	Transfer to other hospitals or clinics	29,407	(15.9)	32,083	(15.0)
	Admission to long-term care health facilities	3,146	(1.7)	3,614	(1.7)
	Admission to facilities covered by public aid providing long-term care to the elderly	3,909	(2.1)	4,485	(2.1)
	Admission to social welfare facilities or fee-based homes for the elderly, etc.	6,555	(3.5)	7,783	(3.6)
	Nursing home	11	(0.0)	15	(0.0)
Death	Yes	25,377	(13.7)	21,567	(10.1)
	No	159,397	(86.2)	192,239	(89.9)

*Low degree of independence in daily life for the elderly with dementia

ADL, activities of daily living; FGR, fine granule; ICD-10, International Classification of Diseases, 10th revision; ICU, intensive care unit; INJ, injectable; ODT, orally disintegrating tablet; PIM, potentially inappropriate medication; SD, standard deviation; SOL, solution; SRT, sustained-release tablet; TAB, tablet.

Supplemental Figure 1 Patient selection flowchart for the sensitivity analysis.



MDV, Medical Data Vision.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7 and 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	9 and 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	15 to 18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12 and 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.