PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Demographic and clinical characteristics of patients with delirium: analysis of a nationwide Japanese medical database
AUTHORS	Ueda, Naoya; Igarashi, Masakazu; Okuyama, Kotoba; Sano, Hideki; Takahashi, Kanae; P. Qureshi, Zaina; Tokita, Shigeru; Ogawa, Asao; Okumura, Yasuyuki; Okuda, Shoki

VERSION 1 – REVIEW

REVIEWER	Sahathevan, R Ballarat Health Services
REVIEW RETURNED	04-Mar-2022

GENERAL COMMENTS	Thank you for asking me to review this manuscript. The authors have sought to determine demographic and causative factors for delirium in a cohort of hospitalised patients across Japan. Analyses are based on the data provided by Medical Data Vision, which is described as an administrative database of >30 million patients. MDV is a private commercial entity. My initial comments/questions would include: 1. Why is MSD interested in the analyses of delirium in a cohort of Japanese patients? 2. Is there any link between MSD and MDV? 3. Are the authors connected to MDV? 3. I suggest that the declaration of competing interests include a statement about current medications produced by MSD that are triggers or treatments of delirium. 4. Is there a reason that the authors have not included clinicians who might have been able to provide input into the approach to their analyses and discussion? The rationale, introduction and methodology of the study are acceptable. However: 1.The authors should provide an explanation regarding MDV in the introduction. 2.I would encourage the authors to make a distinction between risk factors and triggers of delirium. This will have an impact on the variables collected and how they are analysed. 3.The classification of PIMs needs to be relooked. There is considerable overlap between the medication classes. The authors should look at the anticholinergic effects of certain medications like H1 and H2 antagonists and understand that the increased risk of delirium with use of these medications is mitigated by their anti-cholinergic effect. The potential of drug interactions must be explored, especially between anti-cholinergics and benzodiazepines.

	4. Is there a better classification of disease states that the authors might be able to provide? For instance, what is meant by circulatory disease? The description of results is fairly straightforward. As stated, classification of risk and trigger factors of delirium should be clarified. The use of descriptive statistics is sensible given the limitation of the source data and interpretation of risk etc. The discussion needs to be the strangest part of a paper like this. There are a few changes I would recommend. 1. The authors conclude in the first paragraph that the lower prevalence of delirium in their analyses is due to the algorithm used and because of poor identification of delirium by doctors. While this is probably true, I feel the more likely issue is poor coding of disease. The authors have mentioned poor coding in the limitations of their study but I feel that this point must be discussed in more depth. 2. Similarly, the conclusion in the second paragraph of their discussion is also incorrect. The authors must address the nature of the data they have used and limitations of the retrospective evaluation. 3. The third paragraph regarding medication effect on delirium should be reviewed. The drug classes used must be clarified to reflect the impact of anti-cholinergic effect of many medications, drug interactions and the potential role of anti-psychotics in worsening delirium 4. The 4th paragraph of the discussion is the most problematic for me. The authors have referenced the CPG used in Japan recommending the use of haloperidol and other anti-psychotics in treating delirium. I suggest a review of other treatment guidelines and mention of the paradox of increased risk of delirium in patients prescribed anti-psychotics. There are more recent reviews and research on the futility of antipsychotic use in the treatment of delirium which should be included. Most geriatricians would not recommend the use of olanzapine due to the significant anti-cholinergic effect. I feel that the manuscript is not suitable for publication in it's current form. I recommend revisions as outlined above.

REVIEWER	FANG, CHENG-CHUNG National Taiwan University Hospital, Emergency Medicine
REVIEW RETURNED	10-Mar-2022

GENERAL COMMENTS	This study 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 claims database in Japan. The authors concluded the prescription rate of injectable haloperidol and potentially inappropriate medications (PIMs) was high in the patients with delirium. Comments: 1. This is a retrospective, cross-sectional, observational study using an administrative database, which covers approximately 24% of all acute care hospitals in Japan. However, the authors did not describe the characteristics of the hospitals in this study. What are the sizes, facility levels, and geographic distributions of these

	hospitals? Can the hospitals represent the whole country? This article entitled “analysis of a nationwide Japanese medical database” should prove the database can represent the whole country's situation without sampling bias. 2. The study results provide descriptive statistics of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. However, there was no comparative analysis to demonstrate the importance of the PIMs or other factors associated with delirium. The high portion of patients with delirium prescribed PIMs may be a common scenario in elderly patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments

The authors have sought to determine demographic and causative factors for delirium in a cohort of hospitalised patients across Japan. Analyses are based on the data provided by Medical Data Vision, which is described as an administrative database of >30 million patients. MDV is a private commercial entity.

Initial comments
My initial comments/questions would include:

Comment 1: Why is MSD interested in the analyses of delirium in a cohort of Japanese patients?
Response: We thank the reviewer for this question. Our company has developed a suvorexant (approved for insomnia treatment), and many studies conducted by Japanese researchers have reported its potential preventive effects on delirium in Japanese patients. Currently, the phase 3 clinical trial “Efficacy and safety of suvorexant (MK-4305) for reducing incidence of delirium in Japanese participants at high risk of delirium (MK-4305-085)” is ongoing in Japan (https://clinicaltrials.gov/ct2/show/NCT04571944). Therefore, we believe that assessing a nationwide cohort of Japanese patients with delirium is critical to understand the real-world clinical setting in Japan where a suvorexant may be used.

Comment 2: Is there any link between MSD and MDV?
Response: We thank the reviewer for this question. MSD K.K. (Merck Sharp & Dohme) is a Japanese subsidiary of Merck & Co., Inc., Rahway, NJ, USA. MDV Co., Ltd. (Medical Data Vision) is a private company that hosts the MDV database, one of the most-used commercially available databases, utilized by both academicians and pharmaceutical companies for pharmacoepidemiology research in Japan. There is no link between MSD K.K. and MDV Co., Ltd. In this study, we have used MDV data based on the contract between MSD K.K. and MDV Co., Ltd.

Comment 3: Are the authors connected to MDV?
Response: We thank the reviewer for this question. The authors are not connected to MDV Co., Ltd. MDV Co., Ltd. is a private company independent of MSD K.K. In this study, we have used MDV data based on the contract between MSD K.K. and MDV Co., Ltd.

Comment 4: I suggest that the declaration of competing interests include a statement about current medications produced by MSD that are triggers or treatments of delirium.

Response: We thank the reviewer for this suggestion. You have recommended that the declaration of competing interests include a statement on the current medications produced by MSD K.K. In reference to the guidelines prescribed by the ICMJE and BMJ Open, as it seems to be usual to specify associations with commercial entities such as organizations/companies, all authors have declared their association with MSD K.K. in the manuscript (several authors are employees of MSD K.K.). However, we would appreciate it if we could be excused from disclosing information in the manuscript about products that are currently under development at MSD K. K. From the Japanese regulatory perspective, i.e., the local fair competition rules, we would prefer not to disclose any information related to our company products in the manuscript, as it may bear the risk of pre-promotion or off-label use. However, if you and/or the Editor strongly recommend the addition of a statement on compounds being developed at MSD K.K., and if this may preclude the acceptance of this manuscript, we will be happy to discuss it. Thank you for your understanding.

Comment 5: Is there a reason that the authors have not included clinicians who might have been able to provide input into the approach to their analyses and discussion?
Response: We thank the reviewer for the question. Dr. Asao Ogawa is a clinician and delirium expert who has been involved in this study. He is also an author on this manuscript. His inputs from a clinical standpoint have been included in the manuscript.

The Rationale, Introduction and Methodology
The rationale, introduction and methodology of the study are acceptable. However:

Comment 1: The authors should provide an explanation regarding MDV in the introduction.
Response: We thank the reviewer for this suggestion. Based on reporting guidelines such as STROBE or ISPOR/ISPE, an explanation of the MDV database has been provided in the Methods section (Page 7, paragraph 1):
“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.”

We have now added more information about the MDV database in the Introduction section as follows (Page 6, paragraph 2):
“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.”

Comment 2: I would encourage the authors to make a distinction between risk factors and triggers of delirium. This will have an impact on the variables collected and how they are analyzed.
Response: We thank the reviewer for this suggestion. We have now made this distinction in the Methods section (Outcomes subsection) as follows (Page 8, paragraph 1):
“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]”

Comment 3: The classification of PIMs needs to be relooked. There is considerable overlap between the medication classes. The authors should look at the anticholinergic effects of certain medications like H1 and H2 antagonists and understand that the increased risk of delirium with use of these medications is mitigated by their anti-cholinergic effect. The potential of drug interactions must be explored, especially between anti-cholinergics and benzodiazepines.

Response: We thank the reviewer for the comment. In the present study, potentially inappropriate medications (PIMs) associated with delirium have been categorized based on the "Beers Criteria" (2019 American Geriatrics Society Beers Criteria®, J Am Geriatr Soc, 2019), the "Guidelines for medical treatment and its safety in the elderly from the Japan Geriatrics Society Working Group" (Kojima et al., Geriatr Gerontol Int, 2016), and the report from Noshiro et al. describing the relationship between the onset of delirium during hospitalization and the use of high-risk drugs to manage delirium (Noshiro et al., Med J Matsue City Hosp, 2018). In these guidelines and the report, the medication classes were categorized based on the primary effect of the drugs. We have now included a short description in the Discussion section regarding the anticholinergic effects of medications such as antihistamines and antidepressants, the role of antipsychotics in the worsening of delirium, and the potential risk of drug interactions in patients with delirium (Page 11, paragraph 3; Page 12, paragraph 1). Please also refer to our response to Comment 3 under the Discussion section that appears subsequently in this response letter.

Text added on Page 11, paragraph 3:
"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."
Text added on Page 12, paragraph 1:
"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]"

Comment 4: Is there a better classification of disease states that the authors might be able to provide? For instance, what is meant by circulatory disease?
Response: We thank the reviewer for the comment. For a comprehensive categorization, we classified diseases based on the International Classification of Diseases, 10th revision (ICD-10) categories. For example, the disease group "circulatory system diseases" contains all diseases designated under the ICD-codes I00–I99, such as hypertensive diseases (I10–I15), ischemic heart diseases (I20–I25), pulmonary heart diseases and diseases of pulmonary circulation (I26–I28), or cerebrovascular diseases (I60–I69). We have now added the ICD-10 codes in Table 1 and Supplemental Table 3. In addition, we have revised some category names in Table 1, Supplemental Table 3, Supplemental Table 5, and Results (Page 9, paragraph 2) to be consistent with the ICD-10 classification, as shown below. We would appreciate if the reviewer could allow us to retain this classification method.

Old classification	Revised classification
Circulatory disease	Circulatory system diseases
Gastrointestinal disorders	Digestive system diseases
Respiratory disease	Respiratory system diseases
Nervous system disorders	Nervous system diseases
Genitourinary diseases	Genitourinary system diseases
Musculoskeletal/connective tissue disease	Musculoskeletal system/connective tissue diseases
Blood disease	Blood diseases

Results

The description of results is fairly straightforward. As stated, classification of risk and trigger factors of delirium should be clarified. The use of descriptive statistics is sensible given the limitation of the source data and interpretation of risk etc.
Response: We thank the reviewer for this comment. As previously described, we have made this distinction in the Methods section (Outcomes subsection) as follows (Page 8, paragraph 1):
"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]"
We have now made the distinction between risk factors and the triggers of delirium in the Results subsections "Patient demographics and baseline characteristics" and "Clinical practice" (Page 9, paragraph 2; Page 9, paragraph 3, respectively) as follows:
"These outcomes were assessed as the risk (predisposing) factors of delirium."
"These factors were assessed as triggers (precipitating factors) of delirium."

Discussion
The discussion needs to be the strangest part of a paper like this. There are a few changes I would recommend.
Response: We thank the reviewer for the comment. We have revised the discussion per the guidance.

Comment 1: The authors conclude in the first paragraph that the lower prevalence of delirium in their analyses is due to the algorithm used and because of poor identification of delirium by doctors. While this is probably true, I feel the more likely issue is poor coding of disease. The authors have mentioned poor coding in the limitations of their study but I feel that this point must be discussed in more depth.
Response: We thank the reviewer for their comment and agree on poor coding of the disease. As mentioned in the 5th paragraph in the Discussion, in our study, the prevalence of delirium obtained based on the ICD-10-coded diagnosis was 0.2% among patients who were hospitalized for surgery or an emergency. The primary reason for poor coding record may be insufficient awareness about delirium in the Japanese clinical setting. Another possible reason is that many physicians may not proactively note the diagnostic code for delirium in medical records for obtaining reimbursement because, currently, there is no approved drug for delirium treatment or prevention in Japan (only tiapride has been approved for delirium after stroke, but it is rarely used). Therefore, in this study, we included antipsychotics prescription as an additional criterion to identify as many patients with delirium as possible. We have discussed the issue of poor coding of the disease in the last sentence of the first paragraph (Page 11, paragraph 1) as follows:
"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."

Comment 2: Similarly, the conclusion in the second paragraph of their discussion is also incorrect. The authors must address the nature of the data they have used and limitations of the retrospective evaluation.
Response: We thank the reviewer for their comment. We have now deleted several sentences and revised the last sentence in the second paragraph to focus on the characteristics of patients with delirium (Page 11, paragraph 2) as follows:
"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."

Comment 3: The third paragraph regarding medication effect on delirium should be reviewed. The drug classes used must be clarified to reflect the impact of anti-cholinergic effect of many medications, drug interactions and the potential role of anti-psychotics in worsening delirium.
Response: We thank the reviewer for their comment. We have now included a short discussion regarding the anticholinergic effect of medications and the role of antipsychotics in the worsening of delirium (Page 11, paragraph 3) as follows:
"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."
Text added on Page 12, paragraph 1:
"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]"

As the reviewer has pointed out, drug interactions are a concern when PIMs are prescribed to patients with polypharmacy. Moreover, polypharmacy with ≥3 drugs has been shown to increase the risk of delirium (Inouye et al, JAMA, 1996). This may be due to pharmacokinetic or pharmacodynamic drug interactions, or because patients using a large number of medications have a significant number of comorbidities. However, it is challenging for physicians to identify the detailed risks of drug-drug interactions, especially in patients with poor health conditions such as delirium (these patients are often prescribed multiple drugs). We searched for epidemiological research studies investigating drug-drug interactions between benzodiazepines and anticholinergic drugs; however, we could not find concrete evidence. Based on our findings, we have revised the Discussion section in the manuscript to include a sentence on drug interactions (Page 11, paragraph 3):
"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."

Comment 4: The 4th paragraph of the discussion is the most problematic for me. The authors have referenced the CPG used in Japan recommending the use of haloperidol and other anti-psychotics in treating delirium. I suggest a review of other treatment guidelines and mention of the paradox of increased risk of delirium in patients prescribed anti-psychotics. There are more recent reviews and research on the futility of antipsychotic use in the treatment of delirium which should be included. Most geriatricians would not recommend the use of olanzapine due to the significant anti-cholinergic effect.
Response: We thank the reviewer for their comment. We would like to supplement the description of the Japanese guidelines. As several recent guidelines have stated, nonpharmacological treatment is the first-line treatment for delirium in Japan as well. According to Japanese guidelines, antipsychotics are the mainstay of delirium treatment in the real-world clinical setting only when patients are severely agitated or distressed and present a substantial risk of harm to themselves and/or others. This description is aligned with the following description from the 2019 Beers Criteria® by the American Geriatrics Society: "Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others." We have added this explanation in the manuscript (Page 12, paragraph 1):

“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]”

Additionally, as suggested by you, we understand that some recent guidelines highlight concerns related to the use of antipsychotics in the treatment of delirium. We have discussed the concerns regarding the increased risk of delirium in patients who are prescribed antipsychotics in the context of other guidelines and some case reports as follows (Page 12, paragraph 1):
“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 managingspan style="font-family:'Times New Roman'; color:#4472c4"> 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.”

I feel that the manuscript is not suitable for publication in it's current form. I recommend revisions as outlined above.
Response: We thank the reviewer for their comments. We have now revised the manuscript accordingly.

Reviewer 2 comments

This study 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 claims database in Japan. The authors concluded the prescription rate of injectable haloperidol and potentially inappropriate medications (PIMs) was high in the patients with delirium.

Comment 1: This is a retrospective, cross-sectional, observational study using an administrative database, which covers approximately 24% of all acute care hospitals in Japan. However, the authors did not describe the characteristics of the hospitals in this study. What are the sizes, facility levels, and geographic distributions of these hospitals? Can the hospitals represent the whole country? This article entitled “analysis of a nationwide Japanese medical database” should prove the database can represent the whole country's situation without sampling bias.
Response: We thank the reviewer for their comment. The MDV database contains anonymized administrative data of more than 30 million patients from over 400 hospitals, covering approximately 24% of all acute care hospitals in Japan. The MDV database collects patient data from hospitals registered under the Diagnosis Procedures Combination program across Japan, regardless of the size and location of these hospitals.
With regard to the term “nationwide,” we have observed that several recently published real-world studies utilizing the MDV database incorporate this term in their titles. We have listed some examples for your reference:

1. Terasaka N, et al. Thrombotic and cardiovascular events and treatment patterns among patients hospitalized with COVID-19 in Japan: an analysis of a nationwide medical claims database. Cardiol Ther 2022;11:297–308.
2. Abe D, et al. Actual state of “triple therapy” for heart failure patients in eight regions of Japan: an analysis of a nationwide medical claims database. PLoS One 2021;16:e0249711.
3. Tsutsué S, et al. Nationwide claims database analysis of treatment patterns, costs and survival of Japanese patients with diffuse large B-cell lymphoma. PLoS One 2020;15:e0237509.
4. Suzuki M, et al. Prescription pattern of anti-Parkinson’s disease drugs in Japan based on a nationwide medical claims database. eNeurologicalSci 2020;20:100257.
5. Suzuki M, et al. Adherence to treatment guideline recommendations for Parkinson’s disease in Japan: a longitudinal analysis of a nationwide medical claims database between 2008 and 2016. PLoS One 2020;15:e0230213.

The main advantages of the MDV database are that it provides a large sample size and is representative of the population of acute care hospitals in Japan. In the present study, we have focused on patients hospitalized for elective surgery or an emergency. Therefore, we believe that the MDV database enables a comprehensive analysis of patients hospitalized for delirium.

Comment 2: The study results provide descriptive statistics of the clinical characteristics of patients with delirium and treatment patterns with antipsychotics in the Japanese acute care setting. However, there was no comparative analysis to demonstrate the importance of the PIMs or other factors associated with delirium. The high portion of patients with delirium prescribed PIMs may be a common scenario in elderly patients.
Response: We thank the reviewer for their comment. As the goal of our study was to understand the demographics and clinical characteristics of patients with delirium in Japan using descriptive analyses, comparative analyses were not performed. Thank you for your understanding.

VERSION 2 – REVIEW

REVIEWER	Sahathevan, R Ballarat Health Services
REVIEW RETURNED	01-Jul-2022

GENERAL COMMENTS	I have no further comments. Thank you for revising the manuscript.