BMJ Open

Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062141
Article Type:	Original research
Date Submitted by the Author:	17-Feb-2022
Complete List of Authors:	Igarashi, Masakazu; MSD KK Okuyama, Kotoba; MSD KK Ueda, Naoya; MSD KK Sano, Hideki; MSD KK Takahashi, Kanae; MSD KK P. Qureshi, Zaina; Merck & Co Inc Tokita, Shigeru; MSD KK Ogawa, Asao; National Cancer Center Japan Okumura, Yasuyuki; Ippan Shadan Hojin Rinsho Ekigaku Kenkyu Suishin Kiko Okuda, Shoki; MSD KK
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Old age psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan

Authors: Masakazu Igarashi[1], Kotoba Okuyama[1], Naoya Ueda[1], Hideki Sano[1], Kanae Takahashi[2], Zaina P. Qureshi[3], Shigeru Tokita[1], Asao Ogawa[4], Yasuyuki Okumura[5], Shoki Okuda[1]

Affiliations:

[1]Medical Affairs, MSD K.K., Tokyo, Japan

[2]Japan Development, MSD K.K., Tokyo, Japan

[3]Center for Observational and Real-world Evidence (CORE), Merck & Co., Inc., Kenilworth, NJ, USA

[4]Division of Psycho-Oncology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan

[5]Initiative for Clinical Epidemiological Research, Tokyo, Japan

Corresponding author:

Shoki Okuda, PhD

Address: MSD K.K., Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku

Tokyo 102-8667, Japan

Email: shoki.okuda@merck.com

Telephone: +81-3-6272-0136

Word count: 3063/4000 words

Number of figures: 2

Number of tables: 3

Number of supplementary figures: 2

Number of supplementary tables: 3

Number of references: 52

ABSTRACT (Current: 293/300 words)

Objectives: Delirium is a neuropsychiatric disorder that commonly occurs in elderly patients with cognitive impairment. The economic burden of delirium in Japan has not been well characterized. In this study, we assessed incremental medical costs of delirium in hospitalized elderly Japanese patients with cognitive impairment.

Methods: This retrospective, cross-sectional, observational study used administrative data from acute care hospitals in Japan between April 2012 and September 2020. Hospitalized patients ≥65 years old with cognitive impairment were categorized into groups – with and without delirium. Delirium was identified using a delirium identification algorithm based on the International Classification of Diseases 10th Revision (ICD-10) codes and antipsychotic prescriptions. Total medical costs were compared between the groups using a generalized linear model.

Results: The study identified 297,600 hospitalized patients ≥65 years of age with cognitive impairment: 39,836 had delirium and 257,764 did not. Patient characteristics such as age, sex, inpatient department, and comorbidities were similar between groups. Mean (SD) unadjusted total medical cost during hospitalization was JPY 979,907.7 (871,366.4) for patients with delirium and JPY 816,137.0 (794,745.9) for patients without delirium. Adjusted total medical cost was significantly greater for patients with delirium compared with those without delirium (cost ratio = 1.09, 95% confidence interval: [1.09, 1.10]; p<0.001). Subgroup analyses revealed significantly higher total medical costs for patients with delirium compared with those without delirium in most subgroups except patients with hemiplegia or paraplegia.

Conclusions: Medical costs during hospitalization were significantly higher for patients with delirium compared with those without, in elderly Japanese patients with cognitive impairment, regardless of patient subgroups such as age, sex, intensive care unit (ICU) admission, and most comorbidities. These findings suggest that delirium prevention strategies are critical to reducing the economic burden as well as psychological/physiological burden in cognitively impaired elderly patients in Japan.

ARTICLE SUMMARY - Strengths and limitations of the study

1. This study is the first in Japan to assess medical costs associated with delirium using a large nationwide database consisting of claims and discharge abstract data.
2. The study identified over 290,000 Japanese patients with cognitive impairment, with and without delirium.
3. This study did not limit patients by baseline characteristics such as departments, surgical procedures, and comorbidities, thus providing a more generalizable view of the economic impact of delirium.
4. The study demonstrates that delirium is associated with significantly higher medical costs, suggesting that prevention strategies may be critical to reducing the economic burden imposed by delirium.
5. This study only assessed a single episode of delirium during hospitalization, potentially underestimating incremental costs associated with delirium beyond those captured in this cohort and timeframe.

KEYWORDS: Cognitive impairment, Delirium, Hospitalization, Incremental medical cost, Medical record database

INTRODUCTION

Delirium is an acute neuropsychiatric disorder characterized by inattention and cognitive decline.[1-3] Delirium is often observed in the elderly and in patients with cognitive impairment including dementia,[4] and is commonly observed in hospitalized patients such as intensive care unit (ICU), postoperative, and palliative care patients.[2, 4] The incidence rate of delirium in the elderly ranges from 10% to 42% among hospitalized patients,[5] from 15% to 53% among postoperative patients,[1] and is 80% among patients in the ICU.[1]

Patients with delirium often require additional resource use, which increases the burden on healthcare workers such as nurses.[6-8] As a result, delirium poses a substantial burden on the healthcare system at large, as ongoing care requires additional medical resources. The presence of delirium may result in the administration of additional treatments, both pharmacological and nonpharmacological,[4] frequent rehospitalizations, and a greater risk of admission to long-term care.[9] The presence of delirium has been shown to prolong hospital stays,[10-12] that may potentially increase treatment costs and resource use. In fact, delirium following transcatheter and surgical aortic valve replacement resulted in a longer hospital stay and, consequently, an increase in hospitalization costs.[13]

Dementia is one of the leading risk factors for delirium and often co-exists with delirium among elderly patients.[4, 14, 15] It has also been reported that Alzheimer's disease patients with delirium have a poorer trajectory of cognitive decline in the long term, than those without delirium,[16, 17] and there has been evidence to show incremental medical cost of delirium in elderly patients with cognitive impairment in several populations.[18,19] For instance, Fick et al reported incremental medical cost in a community-dwelling population with dementia from southeastern US, comprising 2,796 individuals over a period of 3 years.[18] Boone et al reported additional medical costs for patients with postoperative neurocognitive disorders including delirium and dementia across 4,285 hospitals in the US.[19] However, there is currently no published literature investigating the economic burden of delirium in Japan using a large-scale medical record database. Japan has the highest elderly population in the world, with almost 30% of the population aged 65 years and above.[20] In addition, the number of the hospitalized patients over 65 years old is increasing.[21] Furthermore, 2.9%–12.5% of the aging population in Japan is estimated to

have dementia, which is increasing annually.[22] Therefore, it is important to understand the economic burden of delirium in elderly patients with dementia in Japan. This study aimed to estimate the economic burden of delirium in hospitalized elderly patients with cognitive impairment in the Japanese population by means of a nationwide administrative database of acute care hospitals.

METHODS

Study design and data source

This was a retrospective, cross-sectional, observational study evaluating medical costs of cognitively impaired elderly patients with and without delirium, using a nationwide administrative database (Medical Data Vision [MDV]; Medical Data Vision Co., Ltd., Tokyo, Japan).[23] The MDV database comprises anonymized administrative data of over 30 million patients from over 400 acute care hospitals, which covers approximately 24% of all acute care hospitals in Japan and contains claims and discharge abstract data acquired from inpatient and outpatient visits.[23] The data used in the present study were collected between April 1, 2012, and September 30, 2020.

Patient characteristics were obtained from the discharge abstract data called *Form 1*. Data on treatments, procedures, and prescriptions based on the Anatomical Therapeutic Chemical (ATC) classification system codes were obtained from the medical practice information field called *Act Data*. Disease diagnosis information based on the International Classification of Diseases 10th revision (ICD-10) was obtained from the *Disease Data* field. Hospital scale information was obtained from the *Patient Data* field.

Study ethics

This study utilized anonymized/de-identified data and therefore ethical review was not required, per the Ethical Guidelines for Epidemiological Research of the Japanese Ministry of Health, Labour and Welfare. Thus, no ethical or institutional review board approval was sought for this study.

Patient and public involvement

This retrospective study did not involve patients in any phase, and the data presented here were obtained from an anonymized administrative hospital database.

Patient selection and characteristics

Patients were included if they were hospitalized for surgery or under an emergency, were ≥65 years of age at hospitalization, and had cognitive impairment. Cognitive impairment was

defined as a diagnosis of dementia, prescription of anti-dementia medication, or presence of a low degree of independence in daily life (Table S1).

Patients with delirium were identified if they met the criteria for the delirium identification algorithm based on the algorithm previously proposed by Kim et al.[24], which was modified to reflect with the clinical setting in Japan. Delirium was defined as having either a diagnosis of delirium (ICD-10 code, F05) or a prescription of at least one of five antipsychotic drugs (ATC code, N05A: quetiapine, haloperidol, perospirone, risperidone, or olanzapine; Table S2), as recommended for the treatment of delirium by the Japanese Society of General Hospital Psychiatry.[25] Prescriptions made within 1 week of hospitalization were included. Patients were required to have a minimum hospital stay of 3 days with at least 2 days free from antipsychotic treatment after admission. This "2-day washout" period was set to exclude patients who were prescribed antipsychotics for pre-existing conditions. Patients with other psychiatric conditions such as schizophrenia (ICD-10 codes F20-29) and bipolar disorder (ICD-10 codes F30-31) were excluded. Patients who had delirium recorded as "admission precipitating diagnosis" or "comorbidities present on admission" on the index date or the day after, were also excluded (Figure 1). Patients prescribed olanzapine combined with cisplatin for nausea within 7 days from the index date were excluded.

Repeated episodes of hospitalization were not evaluated, i.e., only the first hospitalization was evaluated if there was a record of multiple hospitalizations. The observation period was from the index date to the end of hospitalization, defined as discharge, transfer to another hospital/nursing home, or death.

The following information was collected from the administrative database for the groups with and without delirium: patient characteristics such as sex, age, and activities of daily living (ADL) score (based on the Barthel Index [26]); comorbidities based on ICD-10 codes; inpatient departments; presence or absence of hospitalization; type of surgery including type and duration of anesthesia; numbers and classes of potentially inappropriate medications (PIMs; benzodiazepines, non-benzodiazepines, opioids, corticosteroids, H1-receptor antagonists, H2-receptor antagonists, antidepressants, and anticholinergic drugs) that are thought to increase the risk of delirium, as identified based on the Beers criteria,[27] the guidelines for medical treatment and its safety in the elderly from the Japan Geriatrics

Society Working Group,[28] and the report by Noshiro et al.,[29]; duration of hospitalization including ICU stay; and patient outcomes such as death.

Outcomes

Total medical cost during hospitalization (from index date to discharge date) were assessed for patients with and without delirium. The total medical expenses include the following: i) drug cost, including formulations for internal and external use, and potions; ii) dispensary fee, including pharmacy charge and compounding fee such as for dispensing, prescription, narcotic/poisonous drug addiction, basic fee on receiving prescription, and medication cost reduction; iii) surgical cost, including cost of surgery and anesthesia; iv) treatment cost, including only treatment fee; v) inspection cost, including pathological examination cost; vi) imaging cost, including image diagnosis; and vii) hospitalization cost, including hospitalization basic rate, specific hospital charge, diet therapy standard cost-sharing, and life therapy standard cost-sharing.

Statistical analyses

In each group, outcome variables were summarized using standard descriptive statistics including mean, standard deviation (SD), median, and interquartile range (IQR) for continuous variables, and the number and percentage of patients for categorical variables. Total medical expenses were adjusted for patient characteristics and other confounders using a generalized linear model (GLM). Predefined covariates such as age, sex, ADL, presence or absence of 16 comorbidities (except dementia) based on Charlson comorbidities, presence or absence of emergency hospitalization, type and duration of anesthesia during surgery, number of PIMs, and ICU admission were included as covariates.

Multicollinearity was evaluated before the GLM analysis. Since there was no covariate with a variance inflation factor of >10, all covariates were included in the final model. For the GLM-adjusted total medical cost, missing values for the response variable and covariates were imputed (except in the subgroup analysis) by means of the multiple imputation method using the full conditional specification approach. Imputations were performed 100 times; the response variable was also included in the imputation model to reduce bias. To impute missing values, Bayesian regression models such as linear, discriminant function, and logistic models were adopted for response variable and covariates, depending on the nature of the

data.[30, 31] To address the non-normality and heteroscedasticity of the total medical cost, the quasi-likelihood method (QLM) was used with a logarithmic link function,[32, 33] and a dispersion parameter was introduced in the GLM. QLM allows for the variance function to be proportional to a power (exponent) of the mean (see Supplementary Information for more details). The least squares (LS) mean for total medical cost in each group, ratio between the two groups, and its 95% confidence interval was calculated.

Subgroup analyses based on patient characteristics, comorbidities, and other covariates were performed using a similar GLM to investigate how total medical cost varied among the different subgroups. Statistical p-value for the comparison between two groups in each subgroup was computed using a similar GLM used for the primary analysis, excluding the corresponding subgroup variable. Interaction for p-values were computed in a similar manner but with the addition of an interaction term between the subgroup variable and the indicative variable of delirium (with or without delirium) to the primary analysis model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). For all statistical analyses, a 2-sided p-value of <0.05 was considered statistically significant. No corrections for multiple comparisons were performed.

RESULTS

Patient attrition

A total of 7,221,643 patients hospitalized for either elective surgery or emergency during the study period were available in the MDV database.[23] Subsequently, 312,512 patients were identified by the delirium identification algorithm. The final cohort of patients ≥65 years of age and with cognitive impairment comprised 39,836 patients with delirium and 257,764 patients without delirium (Figure 1). In the group of patients with delirium, 3,685 patients were identified by the ICD-10 criteria (F05) for delirium, 33,611 patients were identified by prescriptions of selected antipsychotics, and 2,540 patients were identified by both the ICD-10 criteria and prescriptions of antipsychotics.

Among the patients with delirium identified by the delirium identification algorithm (n=39,836), the most common diagnosis based on the ICD-10 criteria was *delirium* in 4,093 patients (10.3%, under the code F05.9; Table S2), followed by *delirium superimposed on dementia* in 1,027 patients (DSD; 2.6%, code F05.1; Table S2). For the prescribed antipsychotics used for the delirium identification algorithm, the most common medication was haloperidol injection in 17,188 patients (43.1%), followed by risperidone solution in 12,081 patients (30.3%) and quetiapine tablet in 7,489 patients (18.8%). The use of perospirone and olanzapine tablets was relatively uncommon (1.9% and 0.9%, respectively; Table S2).

Baseline characteristics

Patient demographics were comparable between the two groups (Table 1), with a male population of 45.4% in the group with delirium and 40.1% in the group without delirium. Overall, 54.5% of patients with delirium and 51.4% of patients without delirium were aged ≥85 years. Moreover, 75.4% of patients with delirium and 68.4% of patients without delirium were dependent (ADL score 0-59). The proportion of patients with dementia diagnosed by the ICD-10 criteria was 53.6% in the group with delirium and 43.7% in the group without delirium. Additionally, 30.0% of patients with delirium were prescribed anti-dementia medications compared with 25.6% of patients without delirium (Table S1). More than 20% of patients across both groups had been prescribed ≥4 PIMs (with delirium group: 29.7%, without delirium group: 20.6%) (Table 1).

Table 1: Patient demographics and characteristics

		Number of patients with delirium		Number of patients without delirium	
Number of patients		39,836		257,764	
Age (years), n (%)	Mean (SD)	84.6 (7.0)		84.1 (7.3)	
	65-74	3,623	(9.1)	28,597	(11.1)
	75-84	14,491	(36.4)	96,685	(37.5)
	≥85	21,722	(54.5)	132,482	(51.4)
Sex, n (%)	Male	18,104	(45.4)	103,313	(40.1)
	Female	21,732	(54.6)	154,451	(59.9)
ADL score (point), n (%)	Dependent group (0-59)	30,048	(75.4)	176,395	(68.4)
	Independent group (60-100)	9,206	(23.1)	78,154	(30.3)
	Unknown	582	(1.5)	3,215	(1.2)
Emergency hospitalization, n (%)	Yes	31,662	(79.5)	189,328	(73.5)
Inpatient department§, n (%)	Internal medicine	10,699	(26.9)	72,910	(28.3)
	Orthopedics	4,842	(12.2)	28,591	(11.1)
	Gastroenterology	4,462	(11.2)	25,993	(10.1)
	Surgery	4,139	(10.4)	19,011	(7.4)
	Cardiology	3,890	(9.8)	25,536	(9.9)
	Neurosurgery	2,946	(7.4)	23,876	(9.3)
Comorbidities*, n (%) (ICD-10 major category)	Circulatory disease	25,456	(63.9)	162,440	(63.0)
	Endocrine, nutritional, and metabolic diseases	17,047	(42.8)	110,282	(42.8)
	Gastrointestinal disorders	14,120	(35.4)	83,928	(32.6)
	Nervous system disorders	14,016	(35.2)	85,399	(33.1)
	Respiratory disease	12,325	(30.9)	74,019	(28.7)
	Mental and behavioral disorders	11,492	(28.8)	54,927	(21.3)
Surgery, n (%)	Yes	17,994	(45.2)	116,178	(45.1)
	Type of surgery/anesthesia				
	Surgery + no/local/light general anesthesia	10,050	(25.2)	78,114	(30.3)
	Surgery + general anesthesia (<2 hours)	4,522	(11.4)	25,203	(9.8)
	Surgery + general anesthesia (≥2 hours)	3,422	(8.6)	12,861	(5.0)
Prescription of PIMs, n (%)	Yes	18,370	(46.1)	108,326	(42.0)
	Number of PIMs (drugs)				
	1	2,146	(5.4)	21,407	(8.3)
	2	2,319	(5.8)	20,086	(7.8)
	3	2,070	(5.2)	13,859	(5.4)
	≥4	11,835	(29.7)	52,974	(20.6)
Duration of hospitalization† (days)	Mean (SD)	15.9 (11.6)		14.2 (13.4)	
	Median [Q1, Q3]	14.0 [9.0, 20.0]		12.0 [7.0, 18.0]	
Duration of ICU stay (days)	Yes	5,942	(14.9)	20,975	(8.1)
	Mean (SD)	3.2 (2.9)		2.9 (2.9)	
	Median [Q1, Q3]	2.0 [1.0, 4.0]		2.0 [1.0, 4.0]	
Death, n (%)	Yes	3,574	(9.0)	23,121	(9.0)
	No	36,262	(91.0)	234,633	(91.0)

*[†]Duration of hospital stay (minimum, maximum): with delirium cohort (3, 495) days; without delirium cohort (3, 1,357) days; [§]Top 6 of all selected departments are shown here; *Top 6 of all selected comorbidities are shown here.*

ADL, activities of daily living; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit; PIM, potentially inappropriate medication; Q, quartile; SD, standard deviation.

Prognosis/hospitalization

The median (IQR) duration of hospitalization was 14 (9.0, 20.0) days for patients with delirium and 12 (7.0, 18.0) days for patients without delirium. Only 16.1% of patients with delirium were hospitalized for ≤1 week compared with 27.1% of patients without delirium. Median (IQR) duration of ICU stay was 2 (1.0, 4.0) days in both groups; 14.9% of the patients with delirium and 8.1% of the patients without delirium were admitted to the ICU for at least 1 day (Table 1 and Table S3).

Unadjusted medical costs in elderly patients with cognitive impairment with and without delirium

The mean (SD) total medical cost per patient was JPY 979,907.7 (871,366.4) in the group with delirium and JPY 816,137.0 (794,745.9) in the group without delirium (Table 2). In both groups, the largest contributor to the total medical cost was hospitalization, followed by surgery (Table 2). When categorized by patient characteristics, a similar pattern was observed; hospitalization costs and surgical costs were the major contributors to total medical cost (Figure S1) in both groups. The subgroup of patients who underwent surgery and longer anesthesia (≥2 hours) incurred the highest total cost across subgroups (Figure S1). When characterized by patient comorbidities, across most subgroups, hospitalization cost emerged as the greatest contributor to total cost, followed by surgery. However, for patients with peripheral vascular disease, surgical cost was higher than hospitalization cost (Figure S2).

Table 2: Unadjusted medical costs in patients with cognitive impairment with and without delirium

	Patient cohort with delirium Mean ± SD [JPY] per patient	Patient cohort without delirium Mean ± SD [JPY] per patient
N	39,836	257,764
Total	979,907.7 ± 871,366.4	816,137.0 ± 794,745.9
Hospitalization cost	528,760.0 ± 351,385.0	445,497.1 ± 347,548.9

Surgical cost	277,683.9 ± 576,399.4	231,177.1 ± 511,700.1
Inspection cost	66,846.6 ± 90,615.6	54,202.6 ± 49,425.2
Drug cost	53,420.9 ± 159,390.4	41,097.3 ± 182,713.4
Imaging cost	35,129.7 ± 31,289.1	29,423.4 ± 29,107.7
Treatment cost	16,951.5 ± 72,122.6	13,843.1 ± 84,341.6
Dispensary cost	1,115.2 ± 926.6	896.3 ± 1,036.2

JPY, Japanese Yen; N, number of patients; SD, standard deviation.

Adjusted medical costs in elderly patients with cognitive impairment with and without delirium

The adjusted total medical cost per patient was significantly greater in patients with delirium compared with patients without delirium (cost ratio = 1.09, 95% confidence interval: [1.09, 1.10]; p<0.001; Table 3). When categorized by patient characteristics and comorbidities, patients with delirium incurred significantly higher costs compared with those without delirium, in most of the subgroups except patients with hemiplegia or paraplegia (Figure 2). Specifically, the increases in cost between those with delirium versus without delirium ranged from 5% to 16% across subgroups (Figure 2). The greatest increase in cost was observed among patients having diabetes with chronic complications (cost ratio=1.16), patients who were independent (ADL score 60-100; cost ratio=1.15), and patients who had prescriptions of two PIMs (cost ratio=1.14). When the effect of each subgroup on adjusted cost ratio was assessed, significant interaction effects (Figure 2) were observed for subgroups based on patient characteristics such as age (p=0.003), sex (p<0.001), ADL (p<0.001), emergency hospitalization (p<0.001), PIM use (p<0.001), and surgery (p=0.006).

Table 3: Difference in the GLM-adjusted total medical cost

	N	LS mean (JPY) (SE)	95% CI	Difference vs without delirium	95% CI for difference	p-value
Patients with delirium	39,836	815,721.2 (1.0)	(810,206.1, 821,273.9)	1.09	(1.09, 1.10)	p<0.001
Patients without delirium	257,764	745,295.0 (1.0)	(743,312.2, 747,283.0)			

CI, confidence interval; GLM, generalized linear model; JPY, Japanese Yen; LS, least squares; N, number of patients; SE, standard error of the mean.

DISCUSSION

This study is the largest medical cost analysis of delirium in Japan to date, aimed at evaluating elderly patients with cognitive impairment in acute care hospitals. There was a 9% increase in total medical cost during hospitalization in the patient group with delirium compared with the patient group without delirium. The total medical cost was consistently higher in the patient group with delirium than in the patient group without delirium, irrespective of patient characteristics, type of surgery, and comorbidities (except patients with hemiplegia or paraplegia). There have been various reports of increased medical costs for patients with delirium. According to a systematic review, the additional cost of delirium is estimated to be in the range of USD 806 to 24,509.[34] A population-based retrospective study from 490 US hospitals reported an additional admission cost of USD 2,697 (23.7% increase) for postoperative delirium patients after major urologic cancer surgeries.[35] Thus, the additional cost of delirium varies depending on the study duration and the target population, as well as the specific healthcare system in each country. Although the present study did not follow the medical cost of post-discharge period, additional medical cost during hospitalization was observed in the patient group with delirium compared with the patient group without delirium, implying that the actual difference in medical costs for longer duration could be much larger. A study by Leslie et al, with a longer observation period, reported that the incremental healthcare costs due to delirium up to 1 year after discharge were nearly 2-fold higher for patients with delirium compared with patients without delirium.[36] It has been previously reported that patients experiencing delirium have poorer prognosis even after hospital discharge,[37-39] indicating prolonged utilization of healthcare resources and consequent increase in treatment cost.

Previous studies have reported nonpharmacological interventions for the prevention of delirium in hospitalized elderly patients and patients with surgical treatments.[40-44] Multicomponent nonpharmacological interventions for delirium have been implemented worldwide to reduce the incidence of delirium.[45] In Japan, a systematic prevention program reportedly decreased the incidence of delirium and improved clinical outcomes such as length of stay and incidence of falls.[46] Pharmacological approaches to prevent delirium have also been studied.[47, 48] Effective delirium prevention strategies may contribute to reducing the incremental medical cost reported in the present study, as it has previously been reported that

the prevention of delirium by multicomponent, targeted interventions decreased long-term nursing home costs.[49]. However, this must be further explored in larger, dedicated studies.[50]

In the present study, we identified over 39,000 cognitively impaired elderly patients with delirium from a nationwide administrative database (MDV database [23]) using a delirium identification algorithm. The diagnosis of delirium by the ICD-10 criteria alone identified 9.3% of all patients identified by our algorithm. By contrast, 84.4% of delirium patients were identified based on the prescription of antipsychotics. This result is consistent with the finding of a previous report (Ueda N et al., unpublished observation) from our research group as well as another study in Japan.[51]

Certain limitations to our study should be noted. The sensitivity and specificity of our modified delirium identification algorithm have not been validated in Japan.[51] This requires that the algorithm be evaluated against the bedside assessment by an expert,[24] which is usually feasible for single institutions but not for large-scale medical databases with more than 400 acute care hospitals, such as the one used in this study. Moreover, data on hypoactive delirium were not captured, because the included antipsychotics are used to treat hyperactive delirium. Data were limited to acute care hospitals and clinics registered under the Diagnosis Procedure Combination (DPC) program,[52] thereby under-representing cases. This study reports the costs pertaining to only one delirium-related hospitalization, not considering recurrences, rehospitalizations, or outpatient and rehabilitation costs. Finally, this study was not designed to investigate the causal link between the increase in cost and delirium.

In conclusion, this study demonstrated significantly higher medical costs associated with delirium among hospitalized elderly patients with cognitive impairment in Japan. The difference in medical cost was consistent regardless of patient characteristics and clinical settings, such as age, sex, ICU admission, and most comorbidities, suggesting the economic burden of delirium is not attributed to specific patient characteristics and clinical settings. These findings suggest that delirium prevention strategies are important for reducing the economic burden of delirium for the cognitively impaired elderly in Japan.

ACKNOWLEDGMENTS

The authors thank Shinya Miura, Hideaki Ogawa, and Shinichiro Suzuki of CMIC Co., Ltd. for medical writing of the protocol and data analysis, and Hirokazu Kikuchi of CMIC Co., Ltd. for statistical modeling and data analysis support, which was funded by and performed under the guidance and approval of MSD K.K., Tokyo, Japan. The authors also thank Machiko Abe of MSD K.K., Tokyo, Japan, and Rezaul Karim Khandker and Geoffrey Johnson of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, for advising on statistical analyses for cost comparisons. Editorial support, in the form of medical writing, assembling tables and creating high-resolution images based on authors' detailed directions, collating author comments, copyediting, fact-checking, and referencing, was provided by Annirudha Chillar, MD, PhD, and Varsha Sreenivasan, PhD, of Cactus Life Sciences (part of Cactus Communications) and funded by MSD K.K., Tokyo, Japan.

COMPETING INTERESTS

KO, NU, 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 Merck & Co. stock and/or stock options. MI was an employee of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA at the time of the study. ZPQ is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own Merck & Co. stock and/or stock options. AO and YO have received funding from MSD K.K., Tokyo, Japan, for research consulting.

FUNDING

This work was supported by MSD K.K., Tokyo, Japan. The funder of the study was involved in the development of the study design, data analysis, data interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. All authors had full access to the study results.

DATA AVAILABILITY

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

AUTHOR CONTRIBUTIONS

SO, HS, KT, ZPQ, ST, AO, and YO conceptualized the study. MI, NU, KO, and SO planned the study designing and data analysis. KO and YO designed the statistical analysis. HS, KT, ZPQ, and ST contributed to the study design. 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. MI and SO are guarantors and accept full responsibility for the work.

REFERENCES

1. Fricchione GL, Nejad SH, Esses JA, et al. Postoperative delirium. *Am J Psychiatry* 2008;165:803–12.
2. Hshieh, TT, Inouye SK, Oh ES. Delirium in the elderly. *Clin Geriatr Med* 2020;36:183–99.
3. Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: Advances in diagnosis and treatment. *JAMA* 2017;318:1161–74.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35:350–64.
6. Inouye SK, Marcantonio ER, Metzger ED. Doing damage in delirium: The hazards of antipsychotic treatment in elderly persons. *Lancet Psychiatry* 2014;1:312–15.
7. Mc Donnell S,Timmins F. A quantitative exploration of the subjective burden experienced by nurses when caring for patients with delirium. *J Clin Nurs* 2012;21:2488–98.
8. Schmitt EM, Gallagher J, Albuquerque A, et al. Perspectives on the delirium experience and its burden: Common themes among older patients, Their Family Caregivers, and Nurses. *Gerontologist* 2019;59:327–37.
9. Fick DM, Hodo DM, Lawrence F, et al. Recognizing delirium superimposed on dementia: assessing nurses' knowledge using case vignettes. *J Gerontol Nurs* 2007;33:40–47.
10. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–62.
11. Thomason JW, Shintani A, Peterson JF, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care* 2005;9:R375–81.
12. van den Boogaard M, Schoonhoven L, van der Hoeven JG, et al. Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. *Int J Nurs Stud* 2012;49:p775–83.
13. Potter BJ, Thompson C, Green P, et al. Incremental cost and length of stay associated with postprocedure delirium in transcatheter and surgical aortic valve replacement patients in the United States. *Catheter Cardiovasc Interv* 2019;93:1132–36.
14. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. *Lancet Neurol* 2015;14:823–32.
15. Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157-65.
16. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009;72:1570–75.

17. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med* 2012;172:1324–31.
18. Fick DM, Kolanowski AM, Waller JL, et al. Delirium superimposed on dementia in a community-dwelling managed care population: a 3-year retrospective study of occurrence, costs, and utilization. *J Gerontol A Biol Sci Med Sci* 2005;60:748–53.
19. Boone MD, Sites B, von Recklinghausen FM, et al. Economic burden of postoperative neurocognitive disorders among US Medicare patients. *JAMA Netw Open* 2020;3:e208931.
20. Statistics Bureau, Ministry of Internal Affairs and Communications. Population Estimates by Age (Five-Year Groups) and Sex, 2021. Available: https://www.stat.go.jp/english/data/jinsui/tsuki/index.html [Accessed Feb 2, 2022].
21. Summary of patient survey, Ministry of Health and Welfare (Japanese), 2017. Available: https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/index.html [Accessed Feb 2, 2022].
22. Okamura H, Ishii S, Ishii T, et al. Prevalence of dementia in Japan: A systematic review. *Dement Geriatr Cogn Disord* 2013;36:111–18.
23. Medical Data Vision (MDV) Database, 2021. Available: https://www.mdv.co.jp/mdv_database/english/ [Accessed Feb 2, 2022].
24. Kim DH, Lee J, Kim CA, et al. Evaluation of algorithms to identify delirium in administrative claims and drug utilization database. *Pharmacoepidemiol Drug Saf* 2017;26:945–53.
25. Clinical guideline for the treatment of delirium, 2nd edition (Japanese Society of General Hospital Psychiatry Practice Guidelines 1). Tokyo, Japan: Seiwa Shoten Publishers 2015:85–111.
26. Mahoney FI, Barthel DW. Functional evaluation: The Barthel index. *Md State Med J* 1965;14:61–65.
27. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67:674–94.
28. Kojima T, Mizukami K, Tomita N, et al. Screening tool for older persons' appropriate prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly". *Geriatr Gerontol Int* 2016;16:983–1001.
29. Noshiro Y, Imai T, Sakai M, et al. Relationship between the onset of delirium during hospitalization and the use of high-risk drugs for delirium. *The Medical Journal of Matsue City Hospital* 2018;1:33–5.
30. Brand JPL. Development, implementation and evaluation of multiple imputation strategies for the statistical analysis of incomplete data sets, 1999. Available:

https://repub.eur.nl/pub/19790/990408_BRAND,%20Jacob%20Pieter%20Laurens.pdf [Accessed Feb 2, 2022].

31. van Buuren, S., Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219-42.
32. Barber J, Thompson S. Multiple regression of cost data: Use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.
33. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Serv Outcomes Res Methodol* 2000;1:185–202.
34. Kinchin I, Mitchell E, Agar M, et al. The economic cost of delirium: A systematic review and quality assessment. *Alzheimers Dement* 2021;17:1026–41.
35. Ha A, Krasnow RE, Mossanen M, et al. A contemporary population-based analysis of the incidence, cost, and outcomes of postoperative delirium following major urologic cancer surgeries. *Urol Oncol* 2018;36:341:e15–22.
36. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;168:27–32.
37. Buurman BM, Hoogerduijn JG, de Haan RJ, et al. Geriatric conditions in acutely hospitalized older patients: Prevalence and one-year survival and functional decline. *PLoS One* 2011;6:e26951.
38. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med* 2005;165:1657–62.
39. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: An independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;58:643–49.
40. Burry LD, Cheng W, Williamson DR, et al. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. *Intensive Care Med* 2021;47:943–60.
41. Inouye, SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669–76.
42. Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: A randomized trial. *J Am Geriatr Soc* 2001;49:516–22.
43. Tabet N, Hudson S, Sweeney V, et al. An educational intervention can prevent delirium on acute medical wards. *Age Ageing* 2005;34:152–56.
44. Vidán MT, Sánchez E, Alonso M, et al. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc* 2009;57:2029–36.
45. Hshieh TT, Yang T, Gartaganis SL, et al. Hospital elder life program: Systematic review and meta-analysis of effectiveness. *Am J Geriatr Psychiatry* 2018;26:1015–33.

46. Ogawa, A, Okumura Y, Fujisawa D, et al. Quality of care in hospitalized cancer patients before and after implementation of a systematic prevention program for delirium: The DELTA exploratory trial. *Support Care Cancer* 2019:27:557–65.
47. Wu, YC, Tseng PT, Tu YK, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: A Network meta-analysis. *JAMA Psychiatry* 2019;76:526–35.
48. Xu S, Cui Y, Shen J, et al. Suvorexant for the prevention of delirium: A meta-analysis. *Medicine (Baltimore)* 2020;99:e21043.
49. Leslie DL, Zhang Y, Bogardus ST, et al. Consequences of preventing delirium in hospitalized older adults on nursing home costs. *J Am Geriatr Soc* 2005:53:405–09.
50. Rubin FH, Neal K, Fenlon K, et al. Sustainability and scalability of the hospital elder life program at a community hospital. *J Am Geriatr Soc* 2011;59:359–65.
51. Sakakibara Y, Ochibe T, Amari S, et al. Study on the risk factors for postoperative delirium using the national health insurance claims database in Japan. *Japanese Journal of Pharmaceutical Health Care and Sciences* 2019;45:195–207.
52. Matsuda S, Fujimori K, Kuwabara K, et al. Diagnosis Procedure Combination as an infrastructure for the clinical study. *Asian Pacific Journal of Disease Management* 2011;5:81–7.

FIGURE LEGENDS

Figure 1. Patient selection flowchart.

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

Figure 2. Adjusted medical cost categorized by patient characteristics and comorbidities.

Footnote: ADL, activities of daily living; CI, confidence interval; GA, general anesthesia; ICU, intensive care unit; LA, light anesthesia; n, number of patients; NoA, no anesthesia; PIM, potentially inappropriate medication. Since multiple imputation (MI) for missing values was not conducted for subgroup analyses due to time constraints, the total number of patients in each subgroup was not consistent with those in the main analysis where missing values were imputed using MI.

SUPPLEMENTARY FIGURE AND TABLE LEGENDS

Figure S1. Mean medical cost categorized by patient characteristics

Footnote: ICU, intensive care unit; PIM, potentially inappropriate medication.

Figure S2. Medical cost categorized by comorbidities

Table S1. Definition of cognitive impairment

Footnote: ICD-10, International Classification of Diseases, 10th Revision; n, number of patients.

Table S2. Identification of patients with delirium

Footnote: FGR, fine granule; ICD-10, International Classification of Diseases, 10th Revision; INJ, injectable; N, number of patients; ODT, oral disintegrating tablet; SOL, solution; SRT, sustained release tablet; TAB, tablet.

Table S3. Clinical practice

Footnote: ICU, intensive care unit; n, number of patients; PIM, potentially inappropriate medication; SD, standard deviation.

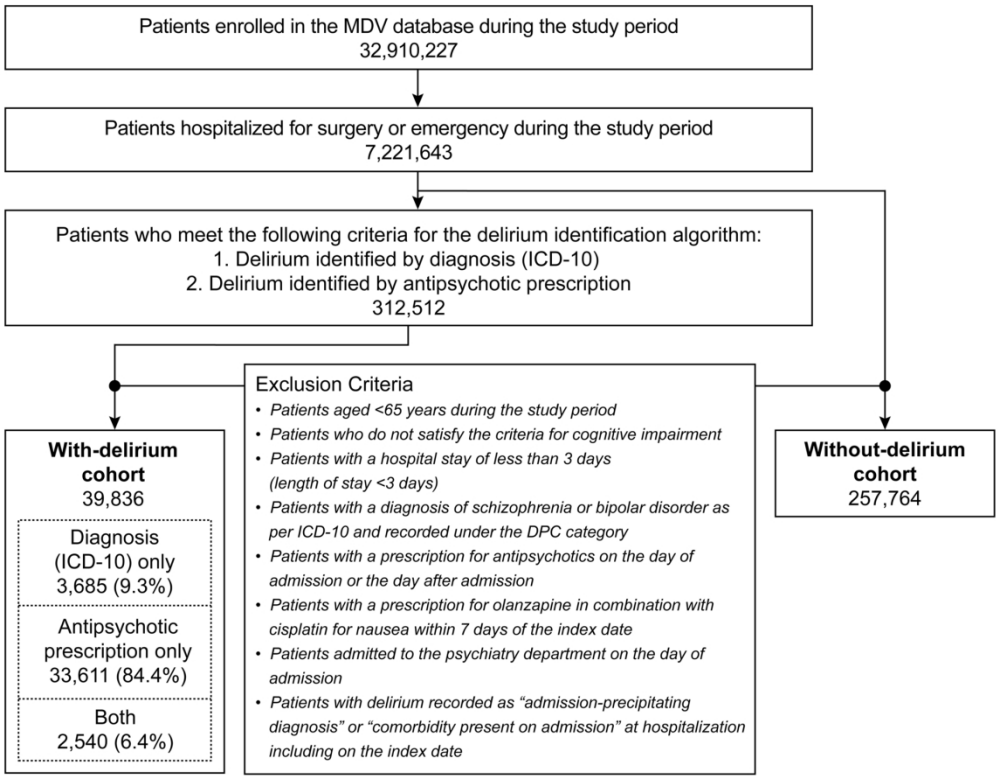


Figure 1. Patient selection flowchart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th Revision; MDV, Medical Data Vision.

173x138mm (300 x 300 DPI)

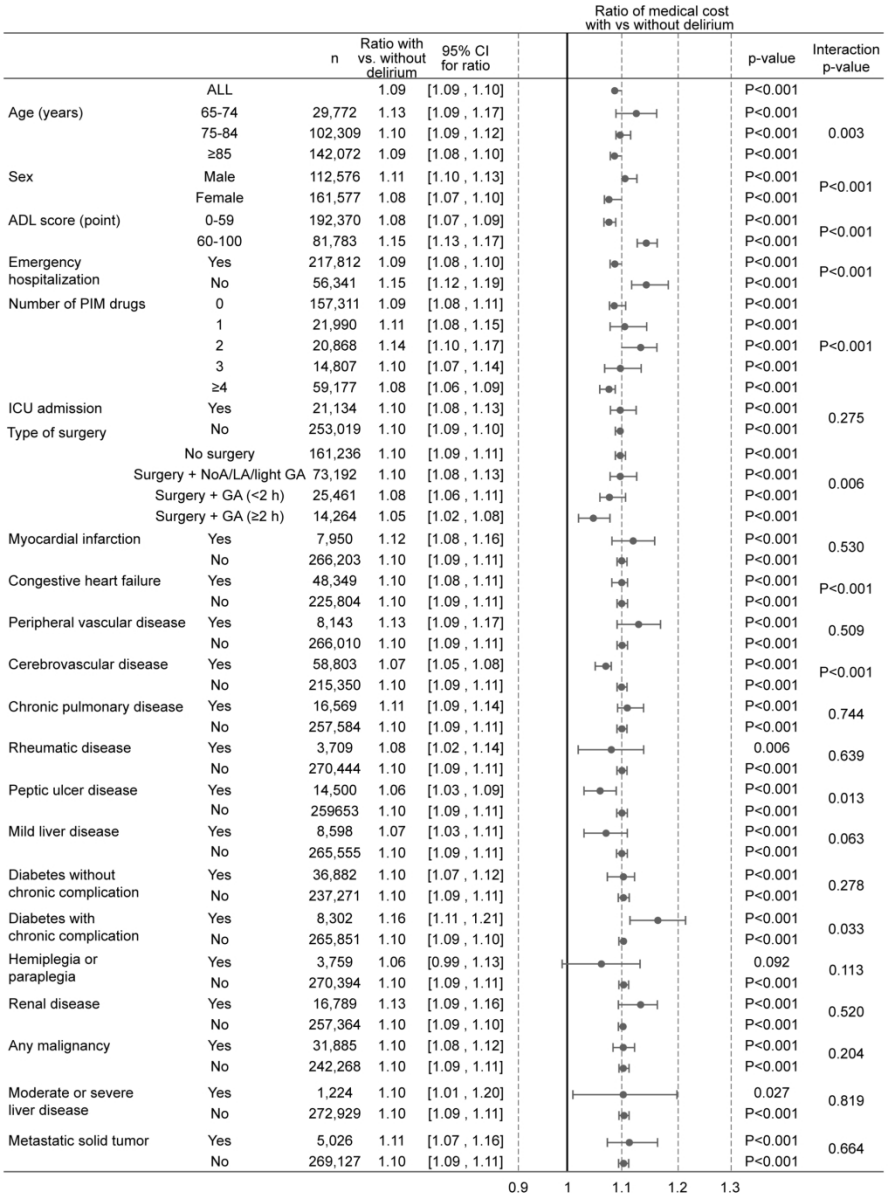


Figure 2. Adjusted medical cost categorized by patient characteristics and comorbidities. ADL, activities of daily living; CI, confidence interval; GA, general anesthesia; ICU, intensive care unit; LA, light anesthesia; n, number of patients; NoA, no anesthesia; PIM, potentially inappropriate medication. Since multiple imputation (MI) for missing values was not conducted for subgroup analyses due to time constraints, the total number of patients in each subgroup was not consistent with those in the main analysis where missing values were imputed using MI.

173x234mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Generalized linear model – exponent calculation

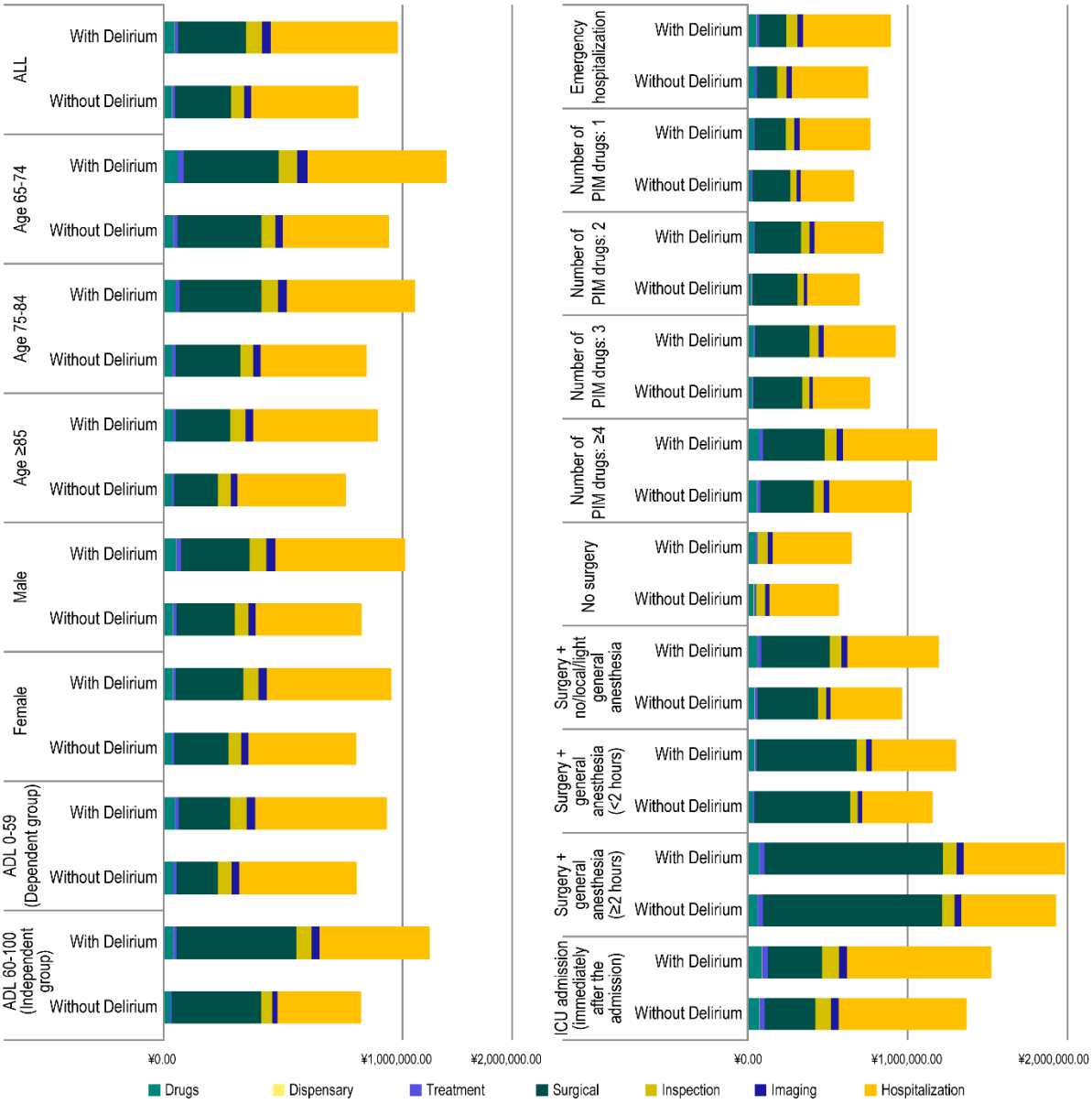
In the quasi-likelihood method (QLM), the variance function is proportional to a power (exponent) of the mean. To determine the initial value of the exponent, the sample means and variances for every combination of the categorized covariates included in the final model were calculated. A double logarithmic function was fit to the data, and the slope of the regression line was determined.[1] The initial value of the exponent was determined as 3.15, which was subsequently used as the exponent in the variance function.[1] A residual plot was generated to evaluate the model fit.[2] Because no specific trend in residuals was observed, the initial value of the exponent, 3.15, was retained. The least squares (LS) mean, difference ratio, and 95% confidence intervals for the total medical cost in the two groups were calculated.

REFERENCES

1. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Serv Outcomes Res Methodol* 2000;1:185–202.
2. Barber J, Thompson S. Multiple regression of cost data: Use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1: Mean medical cost categorized by patient characteristics



ICU, intensive care unit; PIM, potentially inappropriate medication.

Figure S2: Medical cost categorized by comorbidities

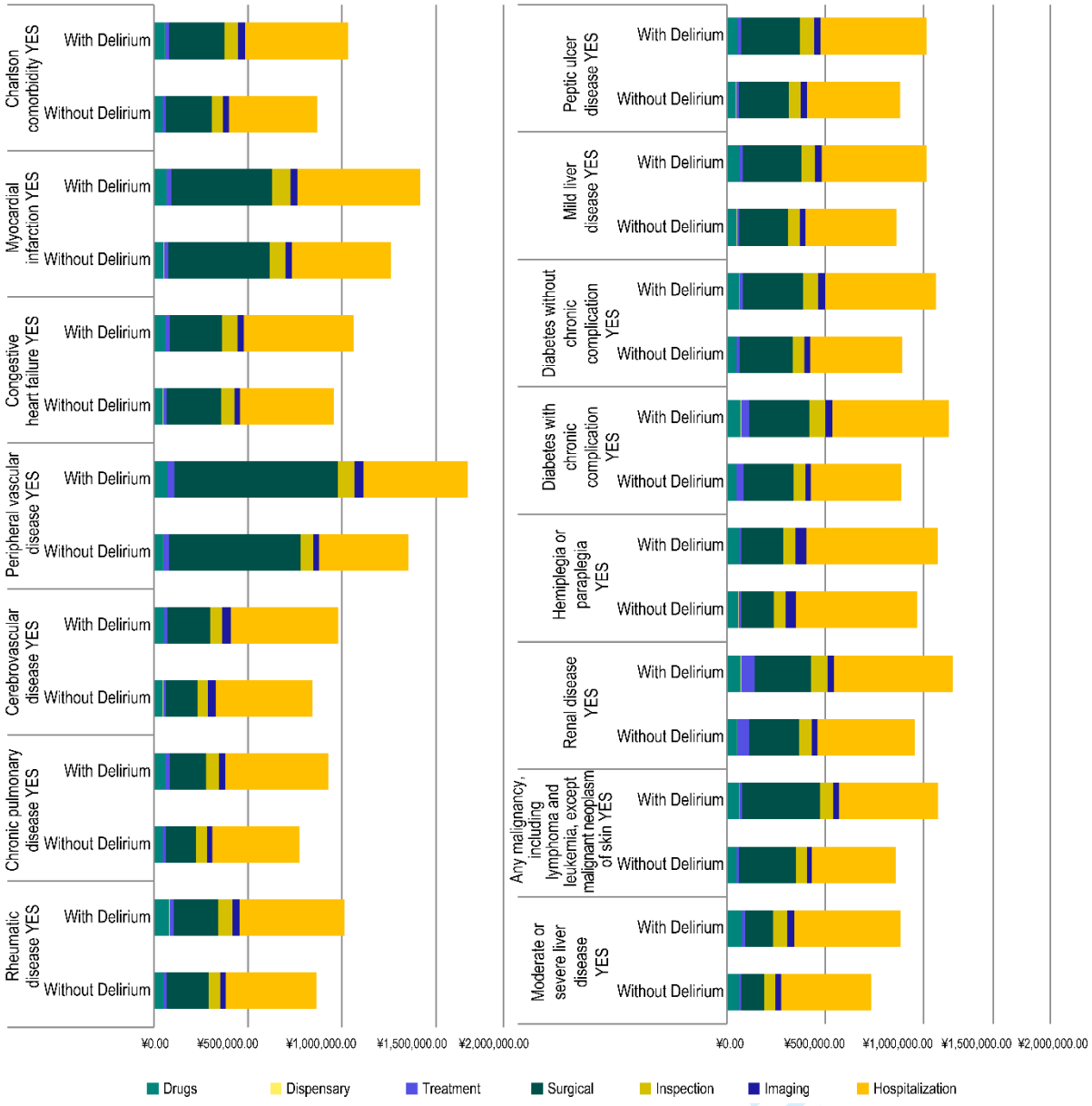


Table S1: Definition of cognitive impairment

		Number of patients with delirium		Number of patients without delirium	
		n	%	n	%
Cognitive impairment	Yes	39,836	(100.0)	257,764	(100.0)
	Diagnosis of dementia (ICD-10)	21,341	(53.6)	112,687	(43.7)
	Prescription of anti-dementia drugs	11,963	(30.0)	66,069	(25.6)
	Low degree of independence in daily life	25,154	(63.1)	169,760	(65.9)

ICD-10, International Classification of Diseases, 10th Revision; n, number of patients.

Table S2: Identification of patients with delirium

			Number of patients with delirium		Number of patients without delirium	
Number of patients			39,836		257,764	
Patients identified by delirium identification algorithm, n (%)	Diagnosis of delirium only (ICD-10)		3,685	(9.3)	0	(0.0)
	Prescription of antipsychotics only		33,611	(84.4)	0	(0.0)
	Both		2,540	(6.4)	0	(0.0)
Diagnosis of delirium (ICD-10), n (%)	Yes (delirium not induced by alcohol and other psychoactive substances, F05)		6,225	(15.6)	0	(0.0)
	Delirium not superimposed on dementia (F05.0)		130	(0.3)	0	(0.0)
	Delirium superimposed on dementia (F05.1)		1,027	(2.6)	0	(0.0)
	Other delirium (F05.8)		8	(0.0)	0	(0.0)
	Subacute cerebral syndrome		4	(0.0)	0	(0.0)
	Acute confusional state		2	(0.0)	0	(0.0)
	Acute brain syndrome		2	(0.0)	0	(0.0)
	Delirium, unspecified (F05.9)		5,100	(12.8)	0	(0.0)
	Delirium		4,093	(10.3)	0	(0.0)
	Nocturnal delirium		813	(2.0)	0	(0.0)
	Senile nocturnal delirium		199	(0.5)	0	(0.0)
Prescription of antipsychotics, n (%)	Yes		36,151	(90.7)	0	(0.0)
	Haloperidol	INJ	17,188	(43.1)	0	(0.0)
		TAB	490	(1.2)	0	(0.0)
		FGR	41	(0.1)	0	(0.0)
		SOL	2	(0.0)	0	(0.0)
	Risperidone	SOL	12,081	(30.3)	0	(0.0)
		ODT	2,727	(6.8)	0	(0.0)
		TAB	1,762	(4.4)	0	(0.0)
		FGR	75	(0.2)	0	(0.0)
		INJ	1	(0.0)	0	(0.0)
	Quetiapine	TAB	7,489	(18.8)	0	(0.0)
		FGR	278	(0.7)	0	(0.0)
		SRT	0	(0.0)	0	(0.0)
	Olanzapine	TAB	378	(0.9)	0	(0.0)
		ODT	224	(0.6)	0	(0.0)
		FGR	36	(0.1)	0	(0.0)
		INJ	1	(0.0)	0	(0.0)
	Perospirone	TAB	767	(1.9)	0	(0.0)

FGR, fine granule; ICD-10, International Classification of Diseases, 10th Revision; INJ, injectable; N, number of patients; ODT, oral disintegrating tablet; SOL, solution; SRT, sustained release tablet; TAB, tablet.

Table S3: Clinical practice

		Number of patients with delirium		Number of patients without delirium	
Number of patients		39,836		257,764	
Prescription of PIM, n (%)	Yes	18,370	(46.1)	108,326	(42.0)
	PIM class				
	Benzodiazepines	7,666	(19.2)	45,166	(17.5)
	Opioids	5,183	(13.0)	26,293	(10.2)
	Corticosteroids	3,933	(9.9)	28,048	(10.9)
	H2-receptor antagonists	3,925	(9.9)	24,036	(9.3)
	Non-benzodiazepines	2,606	(6.5)	12,624	(4.9)
	H1-receptor antagonists	2,488	(6.2)	11,214	(4.4)
	Antidepressants	72	(0.2)	578	(0.2)
	Anticholinergic drugs	62	(0.2)	459	(0.2)
Duration of hospitalization (days)	Mean (SD)	15.9 (11.6)		14.2 (13.4)	
	Median	14.0		12.0	
	[Q1, Q3]	[9.0, 20.0]		[7.0, 18.0]	
	[Min, Max]	[3, 495]		[3, 1357]	
	≤ 1 week	6,429	(16.1)	69,819	(27.1)
	1 week < - ≤ 2 weeks	14,771	(37.1)	88,409	(34.3)
	2 weeks < - ≤ 3 weeks	10,600	(26.6)	55,885	(21.7)
	3 weeks < - ≤ 4 weeks	4,860	(12.2)	26,227	(10.2)
	4 weeks < - ≤ 12 weeks	3,049	(7.7)	16,523	(6.4)
	>12 weeks	127	(0.3)	901	(0.3)
Use of ICU (days)	Yes	5,942	(14.9)	20,975	(8.1)
Duration of ICU stay (days)	Mean (SD)	3.2 (2.9)		2.9 (2.9)	
	Median	2.0		2.0	
	[Q1, Q3]	[1.0, 4.0]		[1.0, 4.0]	
	1 day	2,038	(5.1)	8,692	(3.4)
	2 days	1,232	(3.1)	4,204	(1.6)
	3 days	829	(2.1)	2,773	(1.1)
	4 days	535	(1.3)	1,649	(0.6)
	5 days	389	(1.0)	1,042	(0.4)
	6 days	277	(0.7)	691	(0.3)
	≥7 days	642	(1.6)	1,924	(0.8)

ICU, intensive care unit; n, number of patients; PIM, potentially inappropriate medication; SD, standard deviation.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	NA
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	NA
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	NA
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	8-9
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	10-11, 22-23
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11, 24-25
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	11-12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13-14
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

BMJ Open

Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062141.R1
Article Type:	Original research
Date Submitted by the Author:	05-Oct-2022
Complete List of Authors:	Igarashi, Masakazu; MSD KK Okuyama, Kotoba; MSD KK Ueda, Naoya; MSD KK Sano, Hideki; MSD KK Takahashi, Kanae; MSD KK P. Qureshi, Zaina; Merck & Co Inc Tokita, Shigeru; MSD KK Ogawa, Asao; National Cancer Center Japan Okumura, Yasuyuki; Ippan Shadan Hojin Rinsho Ekigaku Kenkyu Suishin Kiko Okuda, Shoki; MSD KK
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Geriatric medicine
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Dementia < NEUROLOGY, Old age psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan

Authors: Masakazu Igarashi[1], Kotoba Okuyama[1], Naoya Ueda[1], Hideki Sano[1], Kanae Takahashi[2], Zaina P. Qureshi[3], Shigeru Tokita[1], Asao Ogawa[4], Yasuyuki Okumura[5], Shoki Okuda[1]

Affiliations:

[1]Medical Affairs, MSD K.K., Tokyo, Japan

[2]Japan Development, MSD K.K., Tokyo, Japan

[3]Center for Observational and Real-world Evidence (CORE), Merck & Co., Inc., Rahway, NJ, USA

[4]Division of Psycho-Oncology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan

[5]Initiative for Clinical Epidemiological Research, Tokyo, Japan

Corresponding author:

Shoki Okuda, PhD

Address: MSD K.K., Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan

Email: shoki.okuda@merck.com

Telephone: +81-3-6272-0136

Word count: 3246/4000 words

Number of figures: 2

Number of tables: 3

Number of supplementary figures: 2

Number of supplementary tables: 4

Number of references: 54

ABSTRACT (Current: 296/300 words)

Objectives: Delirium is a neuropsychiatric disorder that commonly occurs in elderly patients with cognitive impairment. The economic burden of delirium in Japan has not been well characterized. In this study, we assessed incremental medical costs of delirium in hospitalized elderly Japanese patients with cognitive impairment.

Methods: This retrospective, cross-sectional, observational study used administrative data from acute care hospitals in Japan between April 2012 and September 2020. Hospitalized patients ≥65 years old with cognitive impairment were categorized into groups – with and without delirium. Delirium was identified using a delirium identification algorithm based on the International Classification of Diseases 10th Revision (ICD-10) codes and antipsychotic prescriptions. Total medical costs during hospitalization were compared between the groups using a generalized linear model.

Results: The study identified 297,600 hospitalized patients ≥65 years of age with cognitive impairment: 39,836 had delirium and 257,764 did not. Patient characteristics such as age, sex, inpatient department, and comorbidities were similar between groups. Mean (SD) unadjusted total medical cost during hospitalization was JPY 979,907.7 (871,366.4) for patients with delirium and JPY 816,137.0 (794,745.9) for patients without delirium. Adjusted total medical cost was significantly greater for patients with delirium compared with those without delirium (cost ratio = 1.09, 95% confidence interval: [1.09, 1.10]; p<0.001). Subgroup analyses revealed significantly higher total medical costs for patients with delirium compared with those without delirium in most subgroups except patients with hemiplegia or paraplegia.

Conclusions: Medical costs during hospitalization were significantly higher for patients with delirium compared with those without delirium, in elderly Japanese patients with cognitive impairment, regardless of patient subgroups such as age, sex, intensive care unit (ICU) admission, and most comorbidities. These findings suggest that delirium prevention strategies are critical to reducing the economic burden as well as psychological/physiological burden in cognitively impaired elderly patients in Japan.

ARTICLE SUMMARY - Strengths and limitations of the study

1. This study is the first in Japan to assess medical costs associated with delirium using a large nationwide database consisting of claims and discharge abstract data.
2. The study identified over 290,000 Japanese patients with cognitive impairment, with and without delirium.
3. This study did not limit patients by baseline characteristics such as departments, surgical procedures, and comorbidities, thus providing a more generalizable view of the economic impact of delirium.
4. The study demonstrates that delirium is associated with significantly higher medical costs during hospitalization, suggesting that prevention strategies may be critical to reducing the economic burden imposed by delirium.
5. This study only assessed a single episode of delirium during hospitalization, potentially underestimating incremental costs associated with delirium beyond those captured in this cohort and timeframe.

KEYWORDS: Cognitive impairment, Delirium, Hospitalization, Incremental medical cost, Medical record database

INTRODUCTION

Delirium is an acute neuropsychiatric disorder characterized by inattention and cognitive decline.[1-3] Delirium is often observed in the elderly and in patients with cognitive impairment including dementia,[4] and is commonly observed in hospitalized patients such as intensive care unit (ICU), postoperative, and palliative care patients.[2, 4] The incidence rate of delirium in the elderly ranges from 10% to 42% among hospitalized patients,[5] from 15% to 53% among postoperative patients,[1] and is 80% among patients in the ICU.[1]

Patients with delirium often require additional resource use, which increases the burden on healthcare workers such as nurses.[6-8] As a result, delirium poses a substantial burden on the healthcare system at large, as ongoing care requires additional medical resources. The presence of delirium may result in the administration of additional treatments, both pharmacological and nonpharmacological,[4] frequent rehospitalizations, and a greater risk of admission to long-term care.[9] The presence of delirium has been shown to prolong hospital stays,[10-12] that may potentially increase treatment costs and resource use. In fact, delirium following transcatheter and surgical aortic valve replacement resulted in a longer hospital stay and, consequently, an increase in hospitalization costs.[13]

Dementia is one of the leading risk factors for delirium and often co-exists with delirium among elderly patients.[4, 14, 15] It has also been reported that Alzheimer's disease patients with delirium have a poorer trajectory of cognitive decline in the long term, than those without delirium,[16, 17] and there has been evidence to show incremental medical cost of delirium in elderly patients with cognitive impairment in several populations.[18, 19] For instance, Fick et al reported incremental medical cost in a community-dwelling population with dementia from southeastern US, comprising 2,796 individuals over a period of 3 years.[18] Boone et al reported additional medical costs for patients with postoperative neurocognitive disorders including delirium and dementia across 4,285 hospitals in the US.[19] However, there is currently no published literature investigating the economic burden of delirium in Japan using a large-scale medical record database. Japan has the highest elderly population in the world, with almost 30% of the population aged 65 years and above.[20] In addition, the number of the hospitalized patients over 65 years old is increasing.[21] Furthermore, 2.9%–12.5% of the aging population in Japan is estimated to

have dementia, which is increasing annually.[22] Therefore, it is important to understand the economic burden of delirium in elderly patients with dementia in Japan. This study aimed to estimate the economic burden of delirium in hospitalized elderly patients with cognitive impairment in the Japanese population by means of a nationwide administrative database of acute care hospitals.

METHODS

Study design and data source

This was a retrospective, cross-sectional, observational study evaluating medical costs of cognitively impaired elderly patients with and without delirium, using a nationwide administrative database (Medical Data Vision [MDV]; Medical Data Vision Co., Ltd., Tokyo, Japan).[23] The MDV database comprises anonymized administrative data of over 30 million patients from over 400 acute care hospitals, which covers approximately 24% of all acute care hospitals in Japan and contains claims and discharge abstract data acquired from inpatient and outpatient visits.[23] The data used in the present study were collected between April 1, 2012, and September 30, 2020.

Patient characteristics were obtained from the discharge abstract data called *Form 1*. Data on treatments, procedures, and prescriptions based on the Anatomical Therapeutic Chemical (ATC) classification system codes were obtained from the medical practice information field called *Act Data*. Disease diagnosis information based on the International Classification of Diseases 10th revision (ICD-10) was obtained from the *Disease Data* field. Hospital scale information was obtained from the *Patient Data* field.

Patient and public involvement

This retrospective study did not involve patients in any phase, and the data presented here were obtained from an anonymized administrative hospital database.

Patient selection and characteristics

Patients were included if they were hospitalized for surgery or under an emergency, were ≥65 years of age at hospitalization, and had cognitive impairment. Cognitive impairment was defined as the presence of at least a diagnosis of dementia (ICD-10 codes F00–F03, F067, F107, G238), one prescription of an anti-dementia medication during hospitalization (donepezil, galantamine, memantine, or rivastigmine), or a low rank (I–IV and M) on the Dementia Scale - an observer-rated scale used to assess the degree of independence in activities of daily living (ADL) related to dementia (Table S1).[24]

Patients with delirium were identified if they met the criteria for the delirium identification algorithm based on the algorithm previously proposed by Kim et al.[25], which was modified to reflect with the clinical setting in Japan. Delirium was defined as having either a diagnosis of delirium (ICD-10 code, F05) or a prescription of at least one of five antipsychotic drugs (ATC code, N05A: quetiapine, haloperidol, perospirone, risperidone, or olanzapine; Table S2), as recommended for the treatment of delirium by the Japanese Society of General Hospital Psychiatry.[26] Prescriptions made within 1 week of hospitalization were included. Patients were required to have a minimum hospital stay of 3 days with at least 2 days free from antipsychotic treatment after admission. This "2-day washout" period was set to exclude patients who were prescribed antipsychotics for pre-existing conditions. Patients with other psychiatric conditions such as schizophrenia (ICD-10 codes F20-29) and bipolar disorder (ICD-10 codes F30-31) were excluded. Patients who had delirium recorded as "admission precipitating diagnosis" or "comorbidities present on admission" on the index date or the day after, were also excluded (Figure 1). Patients prescribed olanzapine combined with cisplatin for nausea within 7 days from the index date were excluded.

Repeated episodes of hospitalization were not evaluated, i.e., only the first hospitalization was evaluated if there was a record of multiple hospitalizations. The observation period was from the index date to the end of hospitalization, defined as discharge, transfer to another hospital/nursing home, or death.

The following information was collected from the administrative database for the groups with and without delirium: patient characteristics such as sex, age, and ADL score (based on the Barthel Index [27]); comorbidities based on ICD-10 codes; inpatient departments; presence or absence of hospitalization; type of surgery including type and duration of anesthesia; numbers and classes of potentially inappropriate medications (PIMs; benzodiazepines, non-benzodiazepines, opioids, corticosteroids, H1-receptor antagonists, H2-receptor antagonists, antidepressants, and anticholinergic drugs) that are thought to increase the risk of delirium, as identified based on the Beers criteria,[28] the guidelines for medical treatment and its safety in the elderly from the Japan Geriatrics Society Working Group,[29] and the report by Noshiro et al.[30]; duration of hospitalization including ICU stay; and patient outcomes such as death.

Outcomes

Total medical cost during hospitalization (from index date to discharge date) were assessed for patients with and without delirium. The total medical expenses include the following: i) drug cost, including formulations for internal and external use, and potions; ii) dispensary fee, including pharmacy charge and compounding fee such as for dispensing, prescription, narcotic/poisonous drug addiction, basic fee on receiving prescription, and medication cost reduction; iii) surgical cost, including cost of surgery and anesthesia; iv) treatment cost, including only treatment fee; v) inspection cost, including pathological examination cost; vi) imaging cost, including image diagnosis; and vii) hospitalization cost, including hospitalization basic rate, specific hospital charge, diet therapy standard cost-sharing, and life therapy standard cost-sharing.

Statistical analyses

In each group, outcome variables were summarized using standard descriptive statistics including mean, standard deviation (SD), median, and interquartile range (IQR) for continuous variables, and the number and percentage of patients for categorical variables. Total medical expenses were adjusted for patient characteristics and other confounders using a generalized linear model (GLM). Predefined covariates such as age, sex, ADL, presence or absence of 15 comorbidities (excluding dementia and AIDS/HIV from the 17 Charlson comorbidities; AIDS/HIV was excluded due to the lack of sufficient sample size during the study period), presence or absence of emergency hospitalization, type and duration of anesthesia during surgery, number of PIMs, and ICU admission were included as covariates. Univariate analysis was performed with each covariate listed above.

Multicollinearity was evaluated using pairwise correlation coefficients and variance inflation factors (VIFs) for the multivariable linear regression framework were calculated prior to a quasi-likelihood analysis. Since there was no covariate with a variance inflation factor of >10, all covariates were included in the final model. For the GLM-adjusted total medical cost, missing values for the response variable and covariates were imputed (except in the subgroup analysis) by means of the multiple imputation method using the full conditional specification approach. Imputations were performed 100 times; the response variable was also included in the imputation model to reduce bias. To impute missing values, Bayesian regression models such as linear, discriminant function, and logistic models were adopted for

response variable and covariates, depending on the nature of the data.[31, 32] To address the non-normality and heteroscedasticity of the total medical cost, the quasi-likelihood method (QLM) was used with a logarithmic link function,[33, 34] and a dispersion parameter was introduced in the GLM. QLM allows for the variance function to be proportional to a power (exponent) of the mean (see Supplementary Information for more details). The geometric least squares (LS) mean for total medical cost in each group, the geometric LS mean ratio between the two groups, and its 95% confidence interval were calculated.

Subgroup analyses based on patient characteristics, comorbidities, and other covariates were performed using a similar GLM to investigate how total medical cost varied among the different subgroups. Statistical p-value for the comparison between two groups in each subgroup was computed using a similar GLM used for the primary analysis, excluding the corresponding subgroup variable. Interaction for p-values were computed in a similar manner but with the addition of an interaction term between the subgroup variable and the indicative variable of delirium (with or without delirium) to the primary analysis model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). For all statistical analyses, a 2-sided p-value of <0.05 was considered statistically significant. No corrections for multiple comparisons were performed.

RESULTS

Patient attrition

A total of 7,221,643 patients hospitalized for either elective surgery or emergency during the study period were available in the MDV database.[23] Subsequently, 312,512 patients were identified by the delirium identification algorithm. The final cohort of patients ≥65 years of age and with cognitive impairment comprised 39,836 patients with delirium and 257,764 patients without delirium (Figure 1). In the group of patients with delirium, 3,685 patients were identified by the ICD-10 criteria (F05) for delirium, 33,611 patients were identified by prescriptions of selected antipsychotics, and 2,540 patients were identified by both the ICD-10 criteria and prescriptions of antipsychotics.

Among the patients with delirium identified by the delirium identification algorithm (n=39,836), the most common diagnosis based on the ICD-10 criteria was *delirium* in 4,093 patients (10.3%, under the code F05.9; Table S2), followed by *delirium superimposed on dementia* in 1,027 patients (DSD; 2.6%, code F05.1; Table S2). For the prescribed antipsychotics used for the delirium identification algorithm, the most common medication was haloperidol injection in 17,188 patients (43.1%), followed by risperidone solution in 12,081 patients (30.3%) and quetiapine tablet in 7,489 patients (18.8%). The use of perospirone and olanzapine tablets was relatively uncommon (1.9% and 0.9%, respectively; Table S2).

Baseline characteristics

Patient demographics were comparable between the two groups (Table 1), with a male population of 45.4% in the group with delirium and 40.1% in the group without delirium. Overall, 54.5% of patients with delirium and 51.4% of patients without delirium were aged ≥85 years. Moreover, 75.4% of patients with delirium and 68.4% of patients without delirium were dependent (ADL score 0-59). The proportion of patients with dementia diagnosed by the ICD-10 criteria was 53.6% in the group with delirium and 43.7% in the group without delirium. Additionally, 30.0% of patients with delirium were prescribed anti-dementia medications compared with 25.6% of patients without delirium (Table S1). More than 20% of patients across both groups had been prescribed ≥4 PIMs (with delirium group: 29.7%, without delirium group: 20.6%) (Table 1).

Table 1: Patient demographics and characteristics

		Number of patients with delirium		Number of patients without delirium	
Number of patients		39,836		257,764	
Age (years), n (%)	Mean (SD)	84.6 (7.0)		84.1 (7.3)	
	65-74	3,623	(9.1)	28,597	(11.1)
	75-84	14,491	(36.4)	96,685	(37.5)
	≥85	21,722	(54.5)	132,482	(51.4)
Sex, n (%)	Male	18,104	(45.4)	103,313	(40.1)
	Female	21,732	(54.6)	154,451	(59.9)
ADL score (point), n (%)	Dependent group (0-59)	30,048	(75.4)	176,395	(68.4)
	Independent group (60-100)	9,206	(23.1)	78,154	(30.3)
	Unknown	582	(1.5)	3,215	(1.2)
Emergency hospitalization, n (%)	Yes	31,662	(79.5)	189,328	(73.5)
Inpatient department§, n (%)	Internal medicine	10,699	(26.9)	72,910	(28.3)
	Orthopedics	4,842	(12.2)	28,591	(11.1)
	Gastroenterology	4,462	(11.2)	25,993	(10.1)
	Surgery	4,139	(10.4)	19,011	(7.4)
	Cardiology	3,890	(9.8)	25,536	(9.9)
	Neurosurgery	2,946	(7.4)	23,876	(9.3)
Comorbidities*, n (%) (ICD-10 major category)	Circulatory disease	25,456	(63.9)	162,440	(63.0)
	Endocrine, nutritional, and metabolic diseases	17,047	(42.8)	110,282	(42.8)
	Gastrointestinal disorders	14,120	(35.4)	83,928	(32.6)
	Nervous system disorders	14,016	(35.2)	85,399	(33.1)
	Respiratory disease	12,325	(30.9)	74,019	(28.7)
	Mental and behavioral disorders	11,492	(28.8)	54,927	(21.3)
Surgery, n (%)	Yes	17,994	(45.2)	116,178	(45.1)
	Type of surgery/anesthesia				
	Surgery + no/local/light general anesthesia	10,050	(25.2)	78,114	(30.3)
	Surgery + general anesthesia (<2 hours)	4,522	(11.4)	25,203	(9.8)
	Surgery + general anesthesia (≥2 hours)	3,422	(8.6)	12,861	(5.0)
Prescription of PIMs, n (%)	Yes	18,370	(46.1)	108,326	(42.0)
	Number of PIMs (drugs)				
	1	2,146	(5.4)	21,407	(8.3)
	2	2,319	(5.8)	20,086	(7.8)
	3	2,070	(5.2)	13,859	(5.4)
	≥4	11,835	(29.7)	52,974	(20.6)
Duration of hospitalization† (days)	Mean (SD)	15.9 (11.6)		14.2 (13.4)	
	Median [Q1, Q3]	14.0 [9.0, 20.0]		12.0 [7.0, 18.0]	
Duration of ICU stay (days)	Yes	5,942	(14.9)	20,975	(8.1)
	Mean (SD)	3.2 (2.9)		2.9 (2.9)	
	Median [Q1, Q3]	2.0 [1.0, 4.0]		2.0 [1.0, 4.0]	
Death, n (%)	Yes	3,574	(9.0)	23,121	(9.0)
	No	36,262	(91.0)	234,633	(91.0)

*[†]Duration of hospital stay (minimum, maximum): with delirium cohort (3, 495) days; without delirium cohort (3, 1,357) days; [§]Top 6 of all selected departments are shown here; *Top 6 of all selected comorbidities are shown here.*

ADL, activities of daily living; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit; PIM, potentially inappropriate medication; Q, quartile; SD, standard deviation.

Prognosis/hospitalization

The median (IQR) duration of hospitalization was 14 (9.0, 20.0) days for patients with delirium and 12 (7.0, 18.0) days for patients without delirium. Only 16.1% of patients with delirium were hospitalized for ≤1 week compared with 27.1% of patients without delirium. Median (IQR) duration of ICU stay was 2 (1.0, 4.0) days in both groups; 14.9% of the patients with delirium and 8.1% of the patients without delirium were admitted to the ICU for at least 1 day (Table 1 and Table S3).

Unadjusted medical costs in cognitively impaired elderly patients with and without delirium

The mean (SD) total medical cost per patient was JPY 979,907.7 (871,366.4) in the group with delirium and JPY 816,137.0 (794,745.9) in the group without delirium (Table 2). In both groups, the largest contributor to the total medical cost was hospitalization, followed by surgery (Table 2). When categorized by patient characteristics, a similar pattern was observed; hospitalization costs and surgical costs were the major contributors to total medical cost (Figure S1) in both groups. The subgroup of patients who underwent surgery and longer anesthesia (≥2 hours) incurred the highest total cost across subgroups (Figure S1). When characterized by patient comorbidities, across most subgroups, hospitalization cost emerged as the greatest contributor to total cost, followed by surgery. However, for patients with peripheral vascular disease, surgical cost was higher than hospitalization cost (Figure S2).

Table 2: Unadjusted medical costs in patients with cognitive impairment with and without delirium

	Patient cohort with delirium Mean ± SD [JPY] per patient	**Patient cohort without delirium Mean ± SD [JPY] per patient**
N	39,836	257,764
Total	979,907.7 ± 871,366.4	816,137.0 ± 794,745.9
Hospitalization cost	528,760.0 ± 351,385.0	445,497.1 ± 347,548.9

Surgical cost	277,683.9 ± 576,399.4	231,177.1 ± 511,700.1
Inspection cost	66,846.6 ± 90,615.6	54,202.6 ± 49,425.2
Drug cost	53,420.9 ± 159,390.4	41,097.3 ± 182,713.4
Imaging cost	35,129.7 ± 31,289.1	29,423.4 ± 29,107.7
Treatment cost	16,951.5 ± 72,122.6	13,843.1 ± 84,341.6
Dispensary cost	1,115.2 ± 926.6	896.3 ± 1,036.2

JPY, Japanese Yen; N, number of patients; SD, standard deviation.

Adjusted medical costs in cognitively impaired elderly patients with and without delirium

The adjusted total medical cost per patient was significantly greater in patients with delirium compared with patients without delirium (cost ratio = 1.09, 95% confidence interval: [1.09, 1.10]; p<0.001; Table 3). When categorized by patient characteristics and comorbidities, patients with delirium incurred significantly higher costs compared with those without delirium, in most of the subgroups except patients with hemiplegia or paraplegia (Figure 2). Specifically, the increases in cost between those with delirium versus without delirium ranged from 5% to 16% across subgroups (Figure 2). The greatest increase in cost was observed among patients having diabetes with chronic complications (cost ratio=1.16), patients who were independent (ADL score 60-100; cost ratio=1.15), and patients who had prescriptions of two PIMs (cost ratio=1.14). When the effect of each subgroup on adjusted cost ratio was assessed, significant interaction effects (Figure 2) were observed for subgroups based on patient characteristics such as age (p=0.003), sex (p<0.001), ADL (p<0.001), emergency hospitalization (p<0.001), PIM use (p<0.001), and surgery (p=0.006). The geometric LS mean ratios of the total medical costs from the univariate analysis were generally similar to those from the multivariable analysis, although only emergency hospitalization was adjusted for in the multivariable analysis (Table S4).

Table 3: Difference in the GLM-adjusted total medical cost

	n	Geometric LS mean [JPY] (SE)	95% CI	Geometric LS mean ratio†	95% CI for ratio	p-value
Patients with delirium	39,836	815,721.2 (1.0)	[810,206.1, 821,273.9]	1.09	[1.09, 1.10]	p<0.001
Patients without delirium	257,764	745,295.0 (1.0)	[743,312.2, 747,283.0]			

†*Geometric LS mean ratio, with delirium/without delirium.*

CI, confidence interval; GLM, generalized linear model; JPY, Japanese Yen; LS, least squares; n, number of patients; SE, standard error of the mean.

DISCUSSION

This study is the largest medical cost analysis of delirium in Japan to date, aimed at evaluating elderly patients with cognitive impairment in acute care hospitals. There was a 9% increase in total medical cost during hospitalization in the patient group with delirium compared with the patient group without delirium. The total medical cost was consistently higher in the patient group with delirium than in the patient group without delirium, irrespective of patient characteristics, type of surgery, and comorbidities (except patients with hemiplegia or paraplegia). There have been various reports of increased medical costs for patients with delirium. According to a systematic review, the additional cost of delirium is estimated to be in the range of USD 806 to 24,509.[35] A population-based retrospective study from 490 US hospitals reported an additional admission cost of USD 2,697 (23.7% increase) for postoperative delirium patients after major urologic cancer surgeries.[36] Thus, the additional cost of delirium varies depending on the study duration and the target population, as well as the specific healthcare system in each country. Although the present study did not follow the medical cost of post-discharge period, additional medical cost during hospitalization was observed in the patient group with delirium compared with the patient group without delirium, implying that the actual difference in medical costs for longer duration could be much larger. A study by Leslie et al, with a longer observation period, reported that the incremental healthcare costs due to delirium up to 1 year after discharge were nearly 2-fold higher for patients with delirium compared with patients without delirium.[37] It has been previously reported that patients experiencing delirium have poorer prognosis even after hospital discharge,[38-40] indicating prolonged utilization of healthcare resources and consequent increase in treatment cost.

Previous studies have reported nonpharmacological interventions for the prevention of delirium in hospitalized elderly patients and patients with surgical treatments.[41-45] Multicomponent nonpharmacological interventions for delirium have been implemented worldwide to reduce the incidence of delirium.[46] In Japan, a systematic prevention program reportedly decreased the incidence of delirium and improved clinical outcomes such as length of stay and incidence of falls.[47] Pharmacological approaches to prevent delirium have also been studied.[48, 49] Effective delirium prevention strategies may contribute to reducing the

incremental medical cost reported in the present study, as it has previously been reported that the prevention of delirium by multicomponent, targeted interventions decreased long-term nursing home costs.[50]. However, this must be further explored in larger, dedicated studies.[51]

In the present study, we identified over 39,000 cognitively impaired elderly patients with delirium from a nationwide administrative database (MDV database [23]) using a delirium identification algorithm. The diagnosis of delirium by the ICD-10 criteria alone identified 9.3% of all patients identified by our algorithm. By contrast, 84.4% of delirium patients were identified based on the prescription of antipsychotics. This result is consistent with the finding of a previous report from our research group [52] as well as another study in Japan.[53]

Certain limitations to our study should be noted. The sensitivity and specificity of our modified delirium identification algorithm have not been validated in Japan.[53] This requires that the algorithm be evaluated against the bedside assessment by an expert,[25] which is usually feasible for single institutions but not for large-scale medical databases with more than 400 acute care hospitals, such as the one used in this study. Moreover, data on hypoactive delirium were not captured, because the included antipsychotics are used to treat hyperactive delirium. Data were limited to acute care hospitals and clinics registered under the Diagnosis Procedure Combination (DPC) program,[54] thereby under-representing cases. Additionally, because the MDV database does not provide hospital identification data, we could not include the variability across hospitals as a random effect in the GLM. However, the variability across sites was included in the variability of error in the model (i.e., we used a larger variability of error than that adjusted by the random effect). Therefore, the current results are considered adequately conservative. This study reports the costs pertaining to only one delirium-related hospitalization, not considering recurrences, rehospitalizations, or outpatient and rehabilitation costs. Finally, this study was not designed to investigate the causal link between the increase in cost and delirium.

In conclusion, this study demonstrated significantly higher medical costs associated with delirium among hospitalized elderly patients with cognitive impairment in Japan. The difference in medical cost was consistent regardless of patient characteristics and clinical

settings, such as age, sex, ICU admission, and most comorbidities, suggesting the economic burden of delirium is not attributed to specific patient characteristics and clinical settings. These findings suggest that delirium prevention strategies are important for reducing the economic burden of delirium for the cognitively impaired elderly in Japan.

ACKNOWLEDGMENTS

The authors thank Shinya Miura, Hideaki Ogawa, and Shinichiro Suzuki of CMIC Co., Ltd. for medical writing of the protocol and data analysis, and Hirokazu Kikuchi of CMIC Co., Ltd. for statistical modeling and data analysis support, which was funded by and performed under the guidance and approval of MSD K.K., Tokyo, Japan. The authors also thank Machiko Abe of MSD K.K., Tokyo, Japan, and Rezaul Karim Khandker and Geoffrey Johnson of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, for advising on statistical analyses for cost comparisons. Editorial support, in the form of medical writing, assembling tables and creating high-resolution images based on authors' detailed directions, collating author comments, copyediting, fact-checking, and referencing, was provided by Annirudha Chillar, MD, PhD, and Varsha Sreenivasan, PhD, of Cactus Life Sciences (part of Cactus Communications) and funded by MSD K.K., Tokyo, Japan.

COMPETING INTERESTS

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

FUNDING

This work was supported by MSD K.K., Tokyo, Japan. The funder of the study was involved in the development of the study design, data analysis, data interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. All authors had full access to the study results.

DATA AVAILABILITY

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

AUTHOR CONTRIBUTIONS

SO, HS, KT, ZPQ, ST, AO, and YO conceptualized the study. MI, NU, KO, and SO planned the study designing and data analysis. KO and YO designed the statistical analysis. HS, KT, ZPQ, and ST contributed to the study design. 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. MI and SO are guarantors and accept full responsibility for the work.

STUDY ETHICS

This study utilized anonymized/de-identified data and therefore ethical review was not required, per the Ethical Guidelines for Epidemiological Research of the Japanese Ministry of Health, Labour and Welfare. Thus, no ethical or institutional review board approval was sought for this study.

REFERENCES

1. Fricchione GL, Nejad SH, Esses JA, et al. Postoperative delirium. *Am J Psychiatry* 2008;165:803–12.
2. Hshieh, TT, Inouye SK, Oh ES. Delirium in the elderly. *Clin Geriatr Med* 2020;36:183–99.
3. Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017;318:1161–74.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35:350–64.
6. Inouye SK, Marcantonio ER, Metzger ED. Doing damage in delirium: The hazards of antipsychotic treatment in elderly persons. *Lancet Psychiatry* 2014;1:312–5.
7. Mc Donnell S,Timmins F. A quantitative exploration of the subjective burden experienced by nurses when caring for patients with delirium. *J Clin Nurs* 2012;21:2488–98.
8. Schmitt EM, Gallagher J, Albuquerque A, et al. Perspectives on the delirium experience and its burden: Common themes among older patients, Their Family Caregivers, and Nurses. *Gerontologist* 2019;59:327–37.
9. Fick DM, Hodo DM, Lawrence F, et al. Recognizing delirium superimposed on dementia: assessing nurses' knowledge using case vignettes. *J Gerontol Nurs* 2007;33:40–7.
10. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–62.
11. Thomason JW, Shintani A, Peterson JF, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care* 2005;9:R375–81.
12. van den Boogaard M, Schoonhoven L, van der Hoeven JG, et al. Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study. *Int J Nurs Stud* 2012;49:p775–83.
13. Potter BJ, Thompson C, Green P, et al. Incremental cost and length of stay associated with postprocedure delirium in transcatheter and surgical aortic valve replacement patients in the United States. *Catheter Cardiovasc Interv* 2019;93:1132–6.
14. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. *Lancet Neurol* 2015;14:823–32.
15. Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157–65.
16. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009;72:1570–5.

17. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med* 2012;172:1324–31.
18. Fick DM, Kolanowski AM, Waller JL, et al. Delirium superimposed on dementia in a community-dwelling managed care population: a 3-year retrospective study of occurrence, costs, and utilization. *J Gerontol A Biol Sci Med Sci* 2005;60:748–53.
19. Boone MD, Sites B, von Recklinghausen FM, et al. Economic burden of postoperative neurocognitive disorders among US Medicare patients. *JAMA Netw Open* 2020;3:e208931.
20. Statistics Bureau, Ministry of Internal Affairs and Communications. Population Estimates by Age (Five-Year Groups) and Sex, 2021. Available: https://www.stat.go.jp/english/data/jinsui/tsuki/index.html [Accessed Feb 2, 2022].
21. Summary of patient survey, Ministry of Health and Welfare (Japanese), 2017. Available: https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/index.html [Accessed Feb 2, 2022].
22. Okamura H, Ishii S, Ishii T, et al. Prevalence of dementia in Japan: a systematic review. *Dement Geriatr Cogn Disord* 2013;36:111–8.
23. Medical Data Vision (MDV) Database, 2021. Available: https://www.mdv.co.jp/mdv_database/english/ [Accessed Feb 2, 2022].
24. Sakata N, Okumura Y, Fushimi K, et al. Dementia and risk of 30-day readmission in older adults after discharge from acute care hospitals. *J Am Geriatr Soc* 2018;66:871–8.
25. Kim DH, Lee J, Kim CA, et al. Evaluation of algorithms to identify delirium in administrative claims and drug utilization database. *Pharmacoepidemiol Drug Saf* 2017;26:945–53.
26. Clinical guideline for the treatment of delirium, 2nd edition (Japanese Society of General Hospital Psychiatry Practice Guidelines 1). Tokyo, Japan: Seiwa Shoten Publishers 2015:85–111.
27. Mahoney FI, Barthel DW. Functional evaluation: The Barthel index. *Md State Med J* 1965;14:61–5.
28. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67:674–94.
29. Kojima T, Mizukami K, Tomita N, et al. Screening tool for older persons' appropriate prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly." *Geriatr Gerontol Int* 2016;16:983–1001.
30. Noshiro Y, Imai T, Sakai M, et al. Relationship between the onset of delirium during hospitalization and the use of high-risk drugs for delirium. *The Medical Journal of Matsue City Hospital* 2018;1:33–5.

31. Brand JPL. Development, implementation and evaluation of multiple imputation strategies for the statistical analysis of incomplete data sets, 1999. Available: https://repub.eur.nl/pub/19790/990408_BRAND,%20Jacob%20Pieter%20Laurens.pdf [Accessed Feb 2, 2022].
32. van Buuren, S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219–42.
33. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.
34. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Serv Outcomes Res Methodol* 2000;1:185–202.
35. Kinchin I, Mitchell E, Agar M, et al. The economic cost of delirium: a systematic review and quality assessment. *Alzheimers Dement* 2021;17:1026–41.
36. Ha A, Krasnow RE, Mossanen M, et al. A contemporary population-based analysis of the incidence, cost, and outcomes of postoperative delirium following major urologic cancer surgeries. *Urol Oncol* 2018;36:341:e15–22.
37. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;168:27–32.
38. Buurman BM, Hoogerduijn JG, de Haan RJ, et al. Geriatric conditions in acutely hospitalized older patients: Prevalence and one-year survival and functional decline. *PLoS One* 2011;6:e26951.
39. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med* 2005;165:1657–62.
40. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: An independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;58:643–9.
41. Burry LD, Cheng W, Williamson DR, et al. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. *Intensive Care Med* 2021;47:943–60.
42. Inouye, SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669–76.
43. Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: A randomized trial. *J Am Geriatr Soc* 2001;49:516–22.
44. Tabet N, Hudson S, Sweeney V, et al. An educational intervention can prevent delirium on acute medical wards. *Age Ageing* 2005;34:152–6.
45. Vidán MT, Sánchez E, Alonso M, et al. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc* 2009;57:2029–36.

46. Hshieh TT, Yang T, Gartaganis SL, et al. Hospital elder life program: systematic review and meta-analysis of effectiveness. *Am J Geriatr Psychiatry* 2018;26:1015–33.
47. Ogawa, A, Okumura Y, Fujisawa D, et al. Quality of care in hospitalized cancer patients before and after implementation of a systematic prevention program for delirium: the DELTA exploratory trial. *Support Care Cancer* 2019:27:557–65.
48. Wu, YC, Tseng PT, Tu YK, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. *JAMA Psychiatry* 2019;76:526–35.
49. Xu S, Cui Y, Shen J, et al. Suvorexant for the prevention of delirium: A meta-analysis. *Medicine (Baltimore)* 2020;99:e21043.
50. Leslie DL, Zhang Y, Bogardus ST, et al. Consequences of preventing delirium in hospitalized older adults on nursing home costs. *J Am Geriatr Soc* 2005:53:405–9.
51. Rubin FH, Neal K, Fenlon K, et al. Sustainability and scalability of the hospital elder life program at a community hospital. *J Am Geriatr Soc* 2011;59:359–65.
52. Ueda N, Igarashi M, Okuyama K, et al. Demographic and clinical characteristics of patients with delirium: analysis of a nationwide Japanese medical database. *BMJ Open* 2022;12:e060630.
53. Sakakibara Y, Ochibe T, Amari S, et al. Study on the risk factors for postoperative delirium using the national health insurance claims database in Japan. *Jpn J Pharm Health Care Sci* 2019;45:195–207.
54. Matsuda S, Fujimori K, Kuwabara K, et al. Diagnosis Procedure Combination as an infrastructure for the clinical study. *Asia Pac J Dis Manag* 2011;5:81–7.

FIGURE LEGENDS

Figure 1. Patient selection flowchart.

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

Figure 2. Adjusted medical cost categorized by patient characteristics and comorbidities.

Footnote: ADL, activities of daily living; CI, confidence interval; GA, general anesthesia; ICU, intensive care unit; LA, light anesthesia; n, number of patients; NoA, no anesthesia; PIM, potentially inappropriate medication. Since multiple imputation (MI) for missing values was not conducted for subgroup analyses due to time constraints, the total number of patients in each subgroup was not consistent with those in the main analysis where missing values were imputed using MI.

SUPPLEMENTARY FIGURE AND TABLE LEGENDS

Figure S1. Mean medical cost categorized by patient characteristics

Footnote: ICU, intensive care unit; PIM, potentially inappropriate medication.

Figure S2. Medical cost categorized by comorbidities

Table S1. Definition of cognitive impairment

Footnote: ICD-10, International Classification of Diseases, 10th Revision; n, number of patients.

Table S2. Identification of patients with delirium

Footnote: FGR, fine granule; ICD-10, International Classification of Diseases, 10th Revision; INJ, injectable; N, number of patients; ODT, oral disintegrating tablet; SOL, solution; SRT, sustained release tablet; TAB, tablet.

Table S3. Clinical practice

Footnote: ICU, intensive care unit; n, number of patients; PIM, potentially inappropriate medication; SD, standard deviation.

Table S4. Univariate and multivariable analyses for total medical cost

Footnote: ADL, activities of daily living; CI, confidence interval; ICU, intensive care unit; JPY, Japanese Yen; LS, least squares; n, number of patients; PIM, potentially inappropriate medication; Ref, reference; SE, standard error of the mean.

†15 comorbidities excluding dementia and AIDS/HIV from the 17 Charlson comorbidities were examined.

‡Patients with missing data for the corresponding variable are not included. The multiple imputation method was applied only in the multivariable analysis.

§Unit: JPY

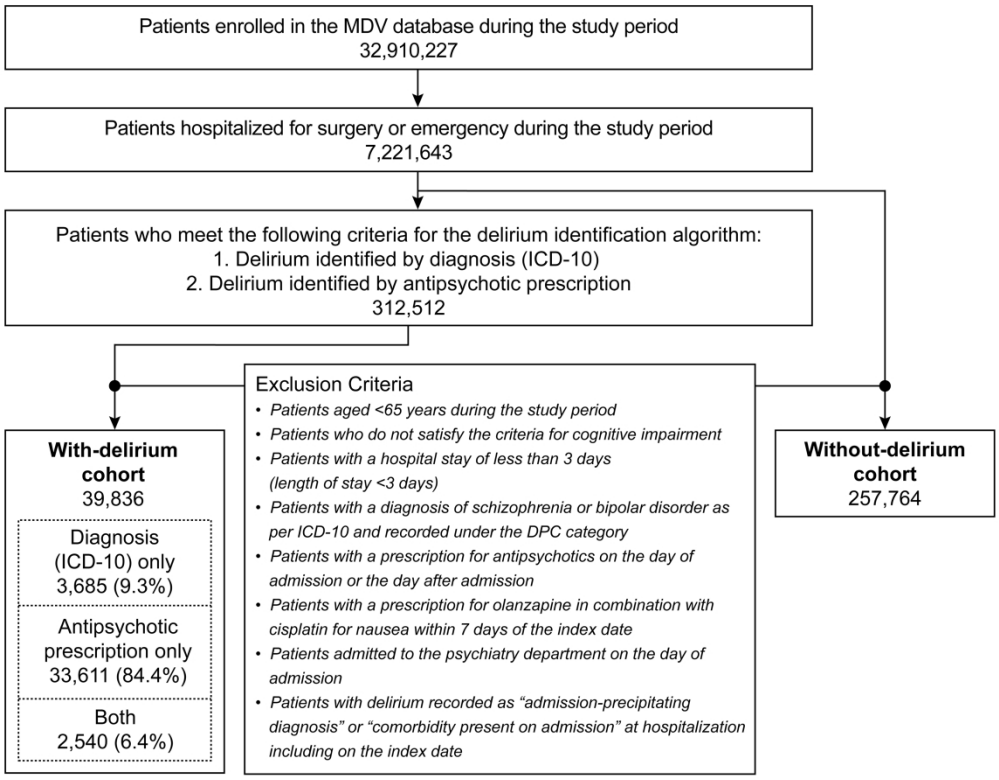


Figure 1. Patient selection flowchart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th Revision; MDV, Medical Data Vision.

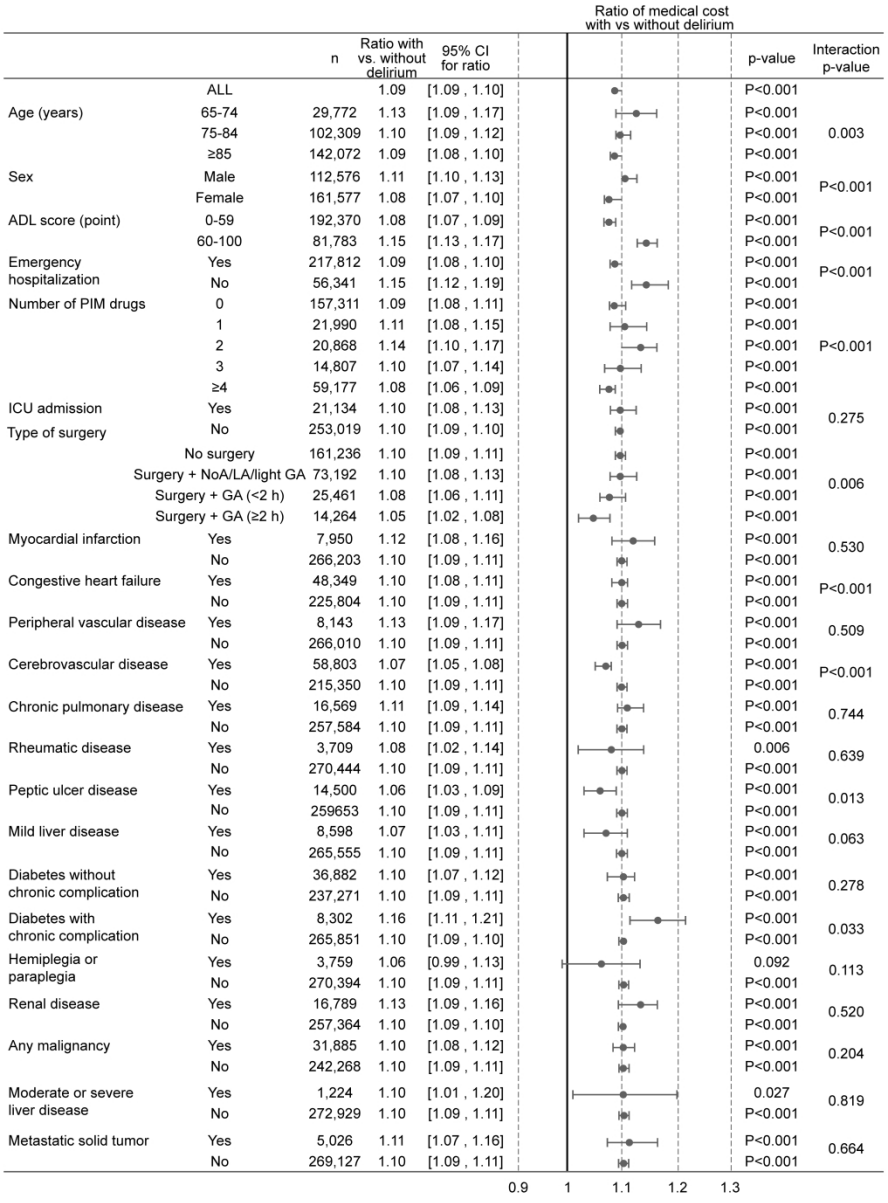


Figure 2. Adjusted medical cost categorized by patient characteristics and comorbidities. ADL, activities of daily living; CI, confidence interval; GA, general anesthesia; ICU, intensive care unit; LA, light anesthesia; n, number of patients; NoA, no anesthesia; PIM, potentially inappropriate medication. Since multiple imputation (MI) for missing values was not conducted for subgroup analyses due to time constraints, the total number of patients in each subgroup was not consistent with those in the main analysis where missing values were imputed using MI.

SUPPLEMENTARY INFORMATION

Generalized linear model – exponent calculation

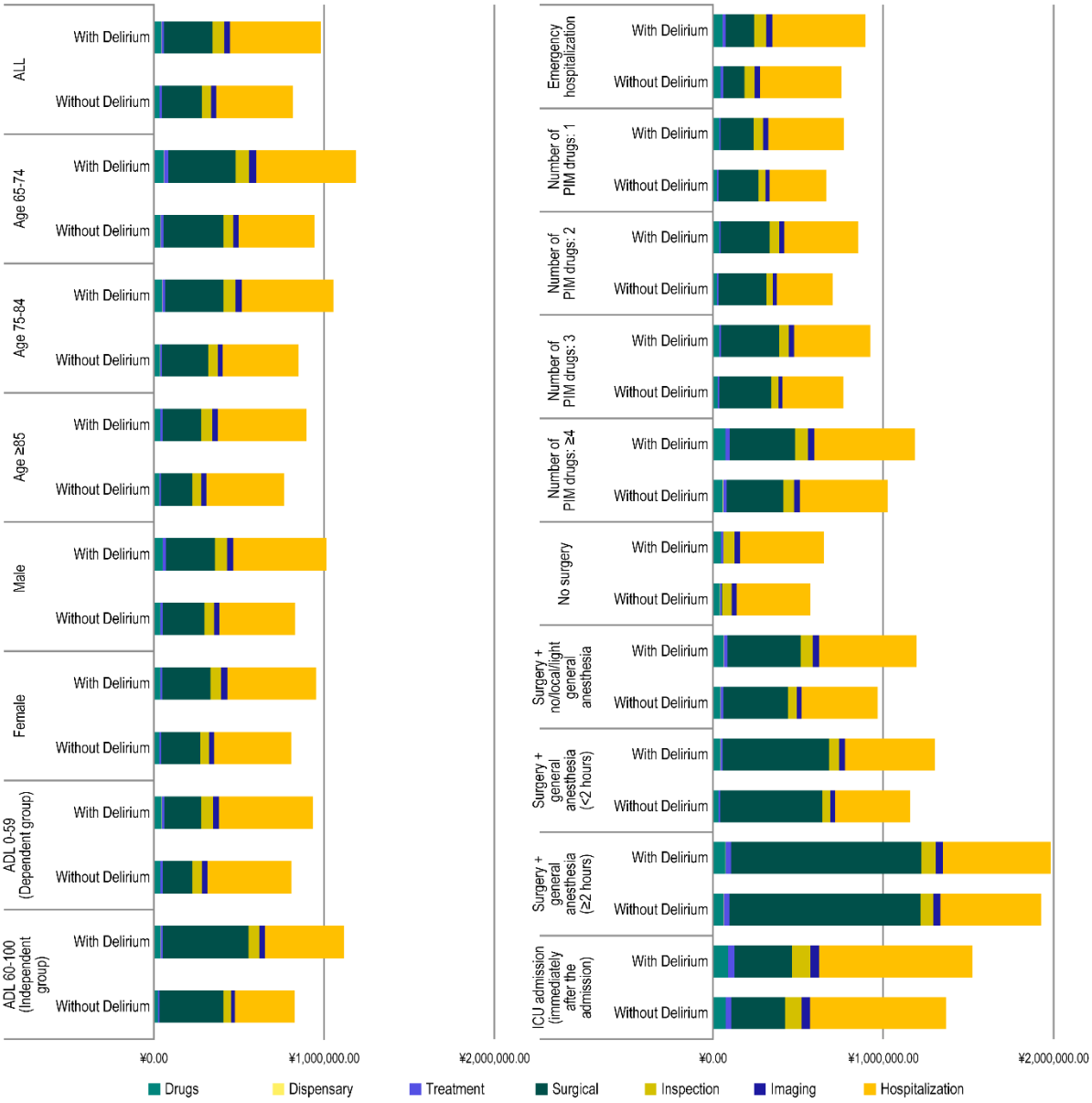
In the quasi-likelihood method (QLM), the variance function is proportional to a power (exponent) of the mean. To determine the initial value of the exponent, the sample means and variances for every combination of the categorized covariates included in the final model were calculated. A double logarithmic function was fit to the data, and the slope of the regression line was determined.[1] The initial value of the exponent was determined as 3.15, which was subsequently used as the exponent in the variance function.[1] A residual plot was generated to evaluate the model fit.[2] Because no specific trend in residuals was observed, the initial value of the exponent, 3.15, was retained. The geometric least squares (LS) mean, the geometric LS mean ratio, and 95% confidence intervals for the total medical cost in the two groups were calculated.

REFERENCES

1. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Serv Outcomes Res Methodol* 2000;1:185–202.
2. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1: Mean medical cost categorized by patient characteristics



ICU, intensive care unit; PIM, potentially inappropriate medication.

Figure S2: Medical cost categorized by comorbidities

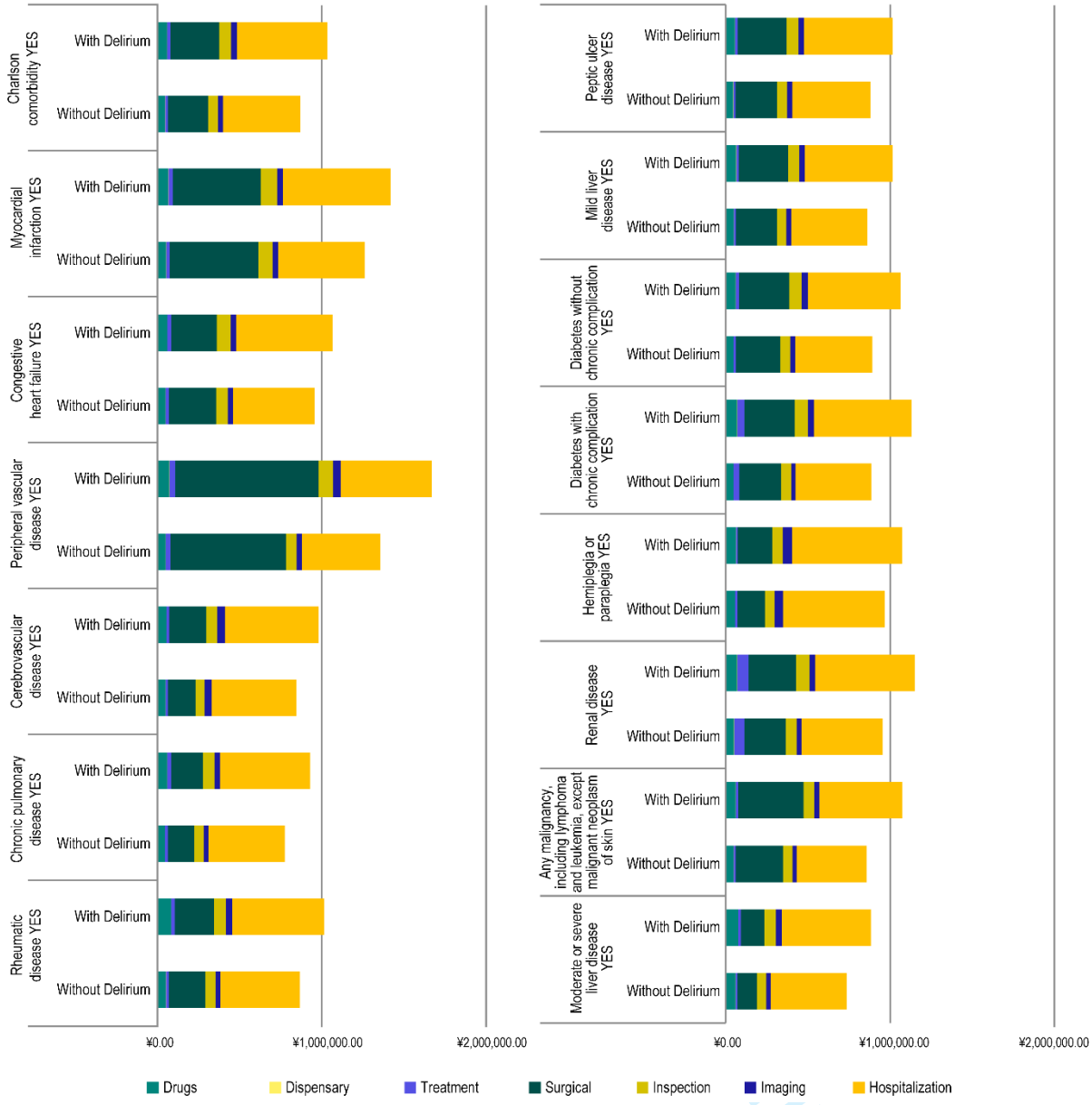


Table S1: Definition of cognitive impairment

		Number of patients with delirium		Number of patients without delirium	
		n	%	n	%
Cognitive impairment	Yes	39,836	(100.0)	257,764	(100.0)
	Diagnosis of dementia (ICD-10)	21,341	(53.6)	112,687	(43.7)
	Prescription of anti-dementia drugs	11,963	(30.0)	66,069	(25.6)
	Low degree of independence in activities of daily living related to dementia	25,154	(63.1)	169,760	(65.9)

ICD-10, International Classification of Diseases, 10th Revision; n, number of patients.

Table S2: Identification of patients with delirium

			Number of patients with delirium		Number of patients without delirium	
Number of patients			39,836		257,764	
Patients identified by delirium identification algorithm, n (%)	Diagnosis of delirium only (ICD-10)		3,685	(9.3)	0	(0.0)
	Prescription of antipsychotics only		33,611	(84.4)	0	(0.0)
	Both		2,540	(6.4)	0	(0.0)
Diagnosis of delirium (ICD-10), n (%)	Yes (delirium not induced by alcohol and other psychoactive substances, F05)		6,225	(15.6)	0	(0.0)
	Delirium not superimposed on dementia (F05.0)		130	(0.3)	0	(0.0)
	Delirium superimposed on dementia (F05.1)		1,027	(2.6)	0	(0.0)
	Other delirium (F05.8)		8	(0.0)	0	(0.0)
	Subacute cerebral syndrome		4	(0.0)	0	(0.0)
	Acute confusional state		2	(0.0)	0	(0.0)
	Acute brain syndrome		2	(0.0)	0	(0.0)
	Delirium, unspecified (F05.9)		5,100	(12.8)	0	(0.0)
	Delirium		4,093	(10.3)	0	(0.0)
	Nocturnal delirium		813	(2.0)	0	(0.0)
	Senile nocturnal delirium		199	(0.5)	0	(0.0)
Prescription of antipsychotics, n (%)	Yes		36,151	(90.7)	0	(0.0)
	Haloperidol	INJ	17,188	(43.1)	0	(0.0)
		TAB	490	(1.2)	0	(0.0)
		FGR	41	(0.1)	0	(0.0)
		SOL	2	(0.0)	0	(0.0)
	Risperidone	SOL	12,081	(30.3)	0	(0.0)
		ODT	2,727	(6.8)	0	(0.0)
		TAB	1,762	(4.4)	0	(0.0)
		FGR	75	(0.2)	0	(0.0)
		INJ	1	(0.0)	0	(0.0)
	Quetiapine	TAB	7,489	(18.8)	0	(0.0)
		FGR	278	(0.7)	0	(0.0)
		SRT	0	(0.0)	0	(0.0)
	Olanzapine	TAB	378	(0.9)	0	(0.0)
		ODT	224	(0.6)	0	(0.0)
		FGR	36	(0.1)	0	(0.0)
		INJ	1	(0.0)	0	(0.0)
	Perospirone	TAB	767	(1.9)	0	(0.0)

FGR, fine granule; ICD-10, International Classification of Diseases, 10th Revision; INJ, injectable; N, number of patients; ODT, oral disintegrating tablet; SOL, solution; SRT, sustained release tablet; TAB, tablet.

Table S3: Clinical practice

		Number of patients with delirium		Number of patients without delirium	
Number of patients		39,836		257,764	
Prescription of PIM, n (%)	Yes	18,370	(46.1)	108,326	(42.0)
	PIM class				
	Benzodiazepines	7,666	(19.2)	45,166	(17.5)
	Opioids	5,183	(13.0)	26,293	(10.2)
	Corticosteroids	3,933	(9.9)	28,048	(10.9)
	H2-receptor antagonists	3,925	(9.9)	24,036	(9.3)
	Non-benzodiazepines	2,606	(6.5)	12,624	(4.9)
	H1-receptor antagonists	2,488	(6.2)	11,214	(4.4)
	Antidepressants	72	(0.2)	578	(0.2)
	Anticholinergic drugs	62	(0.2)	459	(0.2)
Duration of hospitalization (days)	Mean (SD)	15.9 (11.6)		14.2 (13.4)	
	Median	14.0		12.0	
	[Q1, Q3]	[9.0, 20.0]		[7.0, 18.0]	
	[Min, Max]	[3, 495]		[3, 1357]	
	≤ 1 week	6,429	(16.1)	69,819	(27.1)
	1 week < - ≤ 2 weeks	14,771	(37.1)	88,409	(34.3)
	2 weeks < - ≤ 3 weeks	10,600	(26.6)	55,885	(21.7)
	3 weeks < - ≤ 4 weeks	4,860	(12.2)	26,227	(10.2)
	4 weeks < - ≤ 12 weeks	3,049	(7.7)	16,523	(6.4)
	>12 weeks	127	(0.3)	901	(0.3)
Use of ICU	Yes	5,942	(14.9)	20,975	(8.1)
Duration of ICU stay (days)	Mean (SD)	3.2 (2.9)		2.9 (2.9)	
	Median	2.0		2.0	
	[Q1, Q3]	[1.0, 4.0]		[1.0, 4.0]	
	1 day	2,038	(5.1)	8,692	(3.4)
	2 days	1,232	(3.1)	4,204	(1.6)
	3 days	829	(2.1)	2,773	(1.1)
	4 days	535	(1.3)	1,649	(0.6)
	5 days	389	(1.0)	1,042	(0.4)
	6 days	277	(0.7)	691	(0.3)
	≥7 days	642	(1.6)	1,924	(0.8)

ICU, intensive care unit; n, number of patients; PIM, potentially inappropriate medication; SD, standard deviation.

Table S4: Univariate and multivariable analyses for total medical cost

Categories	n‡	Univariate analysis: Geometric LS Mean§ [95% CI]	Univariate analysis: Geometric LS Mean Ratio [95% CI]	Univariate analysis: P-value	Multivariable analysis: Geometric LS Mean§ [95% CI]	Multivariable analysis: Geometric LS Mean Ratio [95% CI]	Multivariable analysis: P-value
Delirium							
Without	257,764	816,137.39 [813,142.03, 819,143.79]	Ref		745,294.95 [743,312.18, 747,283.02]	Ref	
With	39,836	979,907.90 [969,783.64, 990,137.85]	1.20 [1.19, 1.21]	p<0.001	815,721.23 [810,206.11, 821,273.88]	1.09 [1.09, 1.10]	p<0.001
Age (years)							
65-74	32,220	970,981.96 [960,264.35, 981,819.19]	Ref		791,810.64 [785,966.32, 797,698.42]	Ref	
75-84	111,176	875,684.51 [870,766.49, 880,630.30]	0.90 [0.89, 0.91]	p<0.001	759,844.50 [756,869.58, 762,831.11]	0.96 [0.95, 0.97]	p<0.001
≥85	154,204	783,162.50 [779,657.12, 786,683.63]	0.81 [0.80, 0.82]	p<0.001	742,836.46 [740,330.23, 745,351.18]	0.94 [0.93, 0.95]	p<0.001
Sex							
Male	121,417	856,423.75 [851,758.80, 861,114.26]	Ref		760,340.59 [757,466.10, 763,225.98]	Ref	
Female	176,183	825,403.68 [821,747.47, 829,076.15]	0.96 [0.96, 0.97]	p<0.001	750,235.54 [747,864.66, 752,613.94]	0.99 [0.98, 0.99]	p<0.001
ADL score (points)							
0-59	206,443	827,168.97 [823,776.86, 830,575.05]	Ref		782,325.73 [779,918.81, 784,740.08]	Ref	
60-100	87,360	858,426.56 [852,905.30, 863,983.56]	1.04 [1.03, 1.05]	p<0.001	692,121.10 [688,983.95, 695,272.52]	0.88 [0.88, 0.89]	p<0.001
Comorbidities†							
Myocardial infarction							
Yes	8,464	1,283,247.71 [1,250,209.84, 1,317,158.63]	Ref		858,222.93 [844,622.77, 872,042.08]	Ref	

Categories	n‡	Univariate analysis Geometric LS Mean§ [95% CI]	Univariate analysis Geometric LS Mean Ratio [95% CI]	Univariate analysis P-value	Multivariable analysis Geometric LS Mean§ [95% CI]	Multivariable analysis Geometric LS Mean Ratio [95% CI]	Multivariable analysis P-value
No	289,136	825,030.17 [822,176.08, 827,894.16]	0.64 [0.63, 0.66]	p<0.001	751,501.99 [749,592.23, 753,416.62]	0.88 [0.86, 0.89]	p<0.001
Congestive heart failure							
Yes	51,355	971,424.84 [962,803.22, 980,123.68]	Ref		880,345.55 [875,051.97, 885,671.14]	Ref	
No	246,245	810,245.79 [807,278.03, 813,224.46]	0.83 [0.83, 0.84]	p<0.001	730,461.61 [728,508.10, 732,420.35]	0.83 [0.82, 0.84]	p<0.001
Peripheral vascular disease							
Yes	8,850	1,411,778.68 [1,374,850.80, 1,449,698.41]	Ref		974,908.71 [959,465.71, 990,600.27]	Ref	
No	288,750	820,506.76 [817,721.02, 823,302.00]	0.58 [0.57, 0.60]	p<0.001	748,457.71 [746,561.13, 750,359.11]	0.77 [0.76, 0.78]	p<0.001
Cerebrovascular disease							
Yes	62,901	859,792.08 [853,239.47, 866,395.01]	Ref		832,895.13 [828,462.74, 837,351.23]	Ref	
No	234,699	832,234.89 [829,005.98, 835,476.38]	0.97 [0.96, 0.98]	p<0.001	734,578.88 [732,566.05, 736,597.24]	0.88 [0.88, 0.89]	p<0.001
Chronic pulmonary disease							
Yes	17,563	797,779.79 [786,809.06, 808,903.50]	Ref		781,634.02 [774,427.35, 788,907.75]	Ref	
No	280,037	840,585.61 [837,587.48, 843,594.47]	1.05 [1.04, 1.07]	p<0.001	752,656.84 [750,723.74, 754,594.92]	0.96 [0.95, 0.97]	p<0.001
Rheumatic disease							
Yes	4,017	885,481.30 [858,673.54, 913,125.99]	Ref		787,870.87 [772,432.04, 803,618.27]	Ref	
No	293,583	837,410.51 [834,498.94, 840,332.25]	0.95 [0.92, 0.98]	p<0.001	753,889.45 [751,985.70, 755,798.02]	0.96 [0.94, 0.98]	p<0.001
Peptic ulcer disease							

Categories	n‡	Univariate analysis Geometric LS Mean§ [95% CI]	Univariate analysis Geometric LS Mean Ratio [95% CI]	Univariate analysis P-value	Multivariable analysis Geometric LS Mean§ [95% CI]	Multivariable analysis Geometric LS Mean Ratio [95% CI]	Multivariable analysis P-value
Yes	15,858	898,974.79 [885,049.60, 913,119.07]	Ref		769,874.99 [762,026.48, 777,804.34]	Ref	
No	281,742	834,630.71 [831,673.42, 837,598.52]	0.93 [0.91, 0.94]	p<0.001	753,478.83 [751,542.42, 755,420.23]	0.98 [0.97, 0.99]	p<0.001
Mild liver disease							
Yes	9,482	883,934.28 [866,433.60, 901,788.44]	Ref		787,281.56 [776,793.81, 797,910.91]	Ref	
No	288,118	836,549.62 [833,614.25, 839,495.33]	0.95 [0.93, 0.97]	p<0.001	753,275.38 [751,357.62, 755,198.05]	0.96 [0.94, 0.97]	p<0.001
Diabetes without chronic complication							
Yes	40,046	914,169.39 [905,205.75, 923,221.79]	Ref		794,680.73 [789,536.56, 799,858.41]	Ref	
No	257,554	826,225.36 [823,201.28, 829,260.54]	0.90 [0.89, 0.91]	p<0.001	748,257.02 [746,268.72, 750,250.62]	0.94 [0.94, 0.95]	p<0.001
Diabetes with chronic complication							
Yes	8,959	915,347.36 [896,366.30, 934,730.35]	Ref		783,602.75 [773,012.63, 794,337.96]	Ref	
No	288,641	835,660.47 [832,737.34, 838,593.86]	0.91 [0.89, 0.93]	p<0.001	753,449.92 [751,534.01, 755,370.71]	0.96 [0.95, 0.97]	p<0.001
Hemiplegia or paraplegia							
Yes	3,955	976,219.29 [944,738.52, 1,008,749.07]	Ref		873,678.85 [854,561.54, 893,223.84]	Ref	
No	293,645	836,198.54 [833,292.41, 839,114.80]	0.86 [0.83, 0.89]	p<0.001	752,855.32 [750,954.84, 754,760.61]	0.86 [0.84, 0.88]	p<0.001
Renal disease							
Yes	18,117	981,851.58 [967,029.48, 996,900.86]	Ref		829,892.85 [821,699.57, 838,167.82]	Ref	

Categories	n‡	Univariate analysis Geometric LS Mean§ [95% CI]	Univariate analysis Geometric LS Mean Ratio [95% CI]	Univariate analysis P-value	Multivariable analysis Geometric LS Mean§ [95% CI]	Multivariable analysis Geometric LS Mean Ratio [95% CI]	Multivariable analysis P-value
No	279,483	828,738.49 [825,830.94, 831,656.27]	0.84 [0.83, 0.86]	p<0.001	749,684.48 [747,756.51, 751,617.42]	0.90 [0.89, 0.91]	p<0.001
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin							
Yes	34,770	894,940.92 [885,556.43, 904,424.87]	Ref		756,333.75 [750,844.57, 761,863.06]	Ref	
No	262,830	830,534.45 [827,488.96, 833,591.14]	0.93 [0.92, 0.94]	p<0.001	754,076.15 [752,060.81, 756,096.88]	1.00 [0.99, 1.00]	0.450
Moderate or severe liver disease							
Yes	1,293	759,638.71 [722,861.93, 798,286.57]	Ref		763,512.80 [737,776.84, 790,146.51]	Ref	
No	296,307	838,401.58 [835,498.51, 841,314.73]	1.10 [1.05, 1.16]	p<0.001	754,300.54 [752,402.34, 756,203.54]	0.99 [0.95, 1.02]	0.488
Metastatic solid tumor							
Yes	5,601	844,997.61 [823,846.20, 866,692.06]	Ref		799,764.56 [786,066.03, 813,701.82]	Ref	
No	291,999	837,926.28 [835,003.64, 840,859.16]	0.99 [0.97, 1.02]	0.520	753,493.48 [751,586.47, 755,405.34]	0.94 [0.93, 0.96]	p<0.001
Emergency hospitalization							
Yes	220,990	774,165.90 [771,234.05, 777,108.89]	Ref		801,606.91 [798,857.56, 804,365.73]	Ref	
No	56,736	972,011.84 [963,755.28, 980,339.13]	1.26 [1.24, 1.27]	p<0.001	607,271.67 [602,729.33, 611,848.24]	0.76 [0.75, 0.76]	p<0.001
Number of PIM drugs							
0	170,904	799,179.22 [795,776.56, 802,596.43]	Ref		773,552.61 [771,014.71, 776,098.86]	Ref	
1	23,553	675,395.61 [668,382.66, 682,482.15]	0.85 [0.84, 0.85]	p<0.001	632,724.36 [627,952.83, 637,532.13]	0.82 [0.81, 0.82]	p<0.001

Categories	n‡	Univariate analysis Geometric LS Mean§ [95% CI]	Univariate analysis Geometric LS Mean Ratio [95% CI]	Univariate analysis P-value	Multivariable analysis Geometric LS Mean§ [95% CI]	Multivariable analysis Geometric LS Mean Ratio [95% CI]	Multivariable analysis P-value
2	22,405	717,867.17 [709,955.60, 725,866.90]	0.90 [0.89, 0.91]	p<0.001	609,627.10 [604,829.38, 614,462.89]	0.79 [0.78, 0.79]	p<0.001
3	15,929	786,527.42 [775,709.98, 797,495.71]	0.98 [0.97, 1.00]	0.031	651,387.10 [645,148.52, 657,686.00]	0.84 [0.83, 0.85]	p<0.001
≥4	64,809	1,053,920.10 [1,045,398.80, 1,062,510.86]	1.32 [1.31, 1.33]	p<0.001	839,977.97 [835,377.19, 844,604.09]	1.09 [1.08, 1.09]	p<0.001
ICU admission (Immediately after the admission)							
Yes	21,843	1,400,460.24 [1,377,051.74, 1,424,266.67]	Ref		1,200,167.33 [1,186,502.18, 1,213,989.87]	Ref	
No	275,757	793,510.74 [790,796.18, 796,234.61]	0.57 [0.56, 0.58]	p<0.001	727,493.58 [725,647.54, 729,344.32]	0.61 [0.60, 0.61]	p<0.001
Type of surgery							
No surgery	163,428	582,783.35 [581,113.35, 584,458.15]	Ref		521,053.69 [519,281.97, 522,831.45]	Ref	
Surgery + no/local/light general anesthesia	88,164	992,997.25 [987,747.24, 998,275.17]	1.70 [1.69, 1.71]	p<0.001	1,010,902.09 [1,005,260.17, 1,016,575.68]	1.94 [1.93, 1.95]	p<0.001
Surgery + general anesthesia (<2 hours)	29,725	1,178,860.92 [1,167,047.13, 1,190,794.29]	2.02 [2.00, 2.04]	p<0.001	1,349,139.14 [1,335,579.50, 1,362,836.45]	2.59 [2.56, 2.62]	p<0.001
Surgery + general anesthesia (≥2 hours)	16,283	1,939,178.48 [1,904,403.92, 1,974,588.02]	3.33 [3.27, 3.39]	p<0.001	2,179,481.16 [2,141,798.56, 2,217,826.74]	4.18 [4.11, 4.26]	p<0.001

ADL, activities of daily living; CI, confidence interval; ICU, intensive care unit; JPY, Japanese Yen; LS, least squares; n, number of patients; PIM, potentially inappropriate medication; Ref, reference category; SE, standard error of the mean.

†*15 comorbidities excluding dementia and AIDS/HIV from the 17 Charlson comorbidities were examined.*

‡*Patients with missing data for the corresponding variable are not included. The multiple imputation method was applied only in the multivariable analysis.*

§*Unit: JPY.*

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	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-8
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	6,8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6,10
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	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
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	10
		(b) Give reasons for non-participation at each stage	10
		(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	10
		(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	12-13
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	12-13
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*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	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
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	18

*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.