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

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ABSTRACT

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 characterised. In this study, we assessed incremental medical costs of delirium in hospitalised elderly Japanese patients with cognitive impairment.

Design Retrospective, cross-sectional, observational study.

Setting Administrative data collected from acute care hospitals in Japan between April 2012 and September 2020.

Participants Hospitalised patients ≥65 years old with cognitive impairment were categorised into groups—with and without delirium. Delirium was identified using a delirium identification algorithm based on the International Classification of Diseases 10th Revision codes or antipsychotic prescriptions.

Outcome measures Total medical costs during hospitalisation were compared between the groups using a generalised linear model.

Results The study identified 297 600 hospitalised 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 hospitalisation was 979 907.7 (871 366.4) yen for patients with delirium and 816 137.0 (794 745.9) yen 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% CI: 1.09 to 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 hospitalisation 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 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 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.
⇒ The study identified over 290 000 Japanese patients with cognitive impairment, with and without delirium.
⇒ This study did not limit patients by baseline characteristics such as departments, surgical procedures and comorbidities, thus providing a more generalisable view of the economic impact of delirium.
⇒ The study demonstrates that delirium is associated with significantly higher medical costs during hospitalisation, suggesting that prevention strategies may be critical to reducing the economic burden imposed by delirium.
⇒ This study only assessed a single episode of delirium during hospitalisation, potentially underestimating incremental costs associated with delirium beyond those captured in this cohort and time frame.

INTRODUCTION

Delirium is an acute neuropsychiatric disorder characterised 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 hospitalised patients such as intensive care unit (ICU), postoperative and palliative care patients.[2 4] The incidence rate of delirium in the elderly ranges from 4% to 25% among hospitalised 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 non-pharmacological,[4] frequent rehospitalisation and a greater risk of admission to long-term care.[9] The presence of delirium has been shown to prolong hospital stays,[10–12] which 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 hospitalisation costs.[13]

Dementia is one of the leading risk factors for delirium and often coexists with delirium among elderly patients.[4 14 15] It has also been reported that patients with Alzheimer's disease 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 USA, comprising 2796 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 4285 hospitals in the USA.[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 hospitalised patients over 65 years old is increasing.[21] Furthermore, 2.9%–12.5% of the ageing 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 hospitalised 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 anonymised 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 1 April 2012 and 30 September 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 anonymised administrative hospital database.

Patient selection and characteristics

Patients were included if they were hospitalised for surgery or under an emergency, were ≥65 years of age at hospitalisation 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 hospitalisation (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 (online supplemental 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; online supplemental table S2), as recommended for the treatment of delirium by the Japanese Society of General Hospital Psychiatry.[26] Prescriptions made within 1 week of hospitalisation 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 hospitalisation were not evaluated, that is, only the first hospitalisation was evaluated if there was a record of multiple hospital admissions. The observation period was from the index date to the end of hospitalisation, defined as discharge, transfer to another hospital/nursing home or death.

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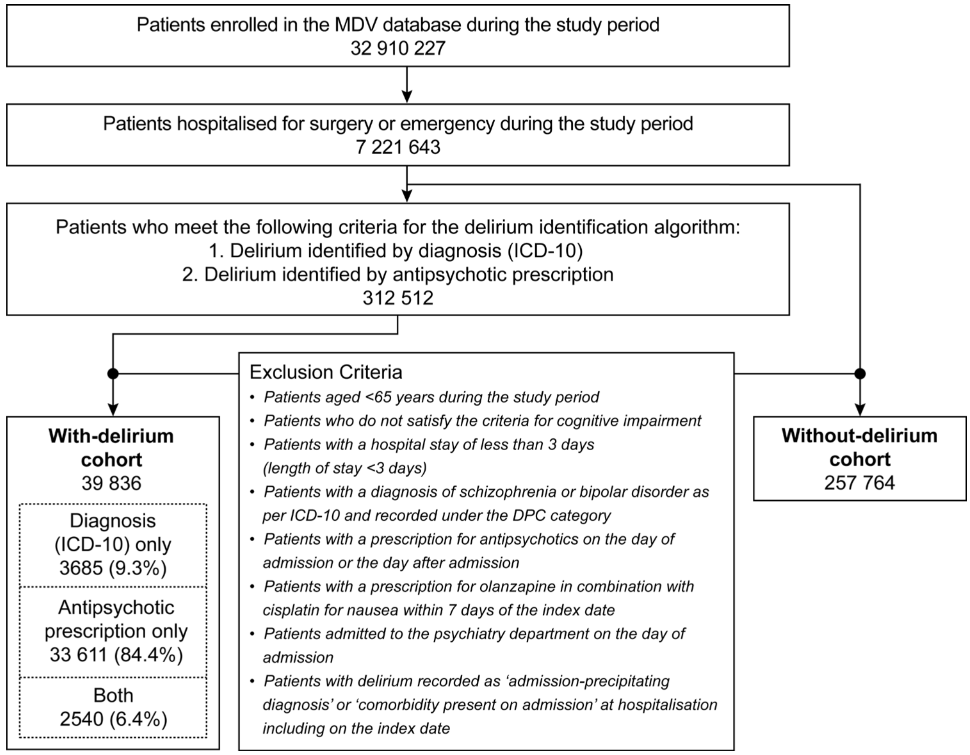

Figure 1 Patient selection flow chart. DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th Revision; MDV, Medical Data Vision.

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 hospitalisation; type of surgery including type and duration of anaesthesia; 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 hospitalisation including ICU stay and patient outcomes such as death.

Outcomes

Total medical costs during hospitalisation (from index date to discharge date) were assessed for patients with and without delirium. The total medical expenses include the following: (1) drug cost, including formulations for internal and external use, and potions; (2) 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; (3) surgical cost, including cost of surgery and anaesthesia; (4) treatment cost, including only treatment fee; (5) inspection cost, including pathological examination cost; (6) imaging cost, including image diagnosis; and (7) hospitalisation cost, including hospitalisation basic rate, specific hospital charge, diet therapy standard cost-sharing and life therapy standard cost-sharing.

Statistical analyses

In each group, outcome variables were summarised using standard descriptive statistics including mean, SD, median and 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 generalised 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 hospitalisation, type and duration of anaesthesia 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 VIF 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

Table 1 Patient demographics and characteristics

Number of patients	Number of patients with delirium 39 836	Number of patients without delirium 257 764
Age (years), n (%)		
Mean (SD)	84.6 (7.0)	84.1 (7.3)
65–74	3623 (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)	9206 (23.1)	78 154 (30.3)
Unknown	582 (1.5)	3215 (1.2)
Emergency hospitalisation, n (%)		
Yes	31 662 (79.5)	189 328 (73.5)
Inpatient department*, n (%)		
Internal medicine	10 699 (26.9)	72 910 (28.3)
Orthopaedics	4842 (12.2)	28 591 (11.1)
Gastroenterology	4462 (11.2)	25 993 (10.1)
Surgery	4139 (10.4)	19 011 (7.4)
Cardiology	3890 (9.8)	25 536 (9.9)
Neurosurgery	2946 (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 behavioural disorders	11 492 (28.8)	54 927 (21.3)
Surgery, n (%)		
Yes	17 994 (45.2)	116 178 (45.1)
Type of surgery/anaesthesia		
Surgery+no/local/light general anaesthesia	10 050 (25.2)	78 114 (30.3)
Surgery+general anaesthesia (<2 hours)	4522 (11.4)	25 203 (9.8)
Surgery+general anaesthesia (≥2 hours)	3422 (8.6)	12 861 (5.0)
Prescription of PIMs, n (%)		
Yes	18 370 (46.1)	108 326 (42.0)
Number of PIMs (drugs)		
1	2146 (5.4)	21 407 (8.3)
2	2319 (5.8)	20 086 (7.8)
3	2070 (5.2)	13 859 (5.4)
≥4	11 835 (29.7)	52 974 (20.6)
Duration of hospitalisation‡ (days)		
Mean (SD)	15.9 (11.6)	14.2 (13.4)

Continued

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Table 1 Continued

Number of patients	Number of patients with delirium 39 836	Number of patients without delirium 257 764
Median	14.0	12.0
(Q1, Q3)	(9.0, 20.0)	(7.0, 18.0)
Duration of ICU stay (days)		
Yes	5942 (14.9)	20 975 (8.1)
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)
Death, n (%)		
Yes	3574 (9.0)	23 121 (9.0)
No	36 262 (91.0)	234 633 (91.0)

*Top 6 of all selected departments are shown here.
†Top 6 of all selected comorbidities are shown here.
‡Duration of hospital stay (minimum, maximum): with delirium cohort (3 days, 495 days); without delirium cohort (3 days, 1357 days).
ADL, activities of daily living; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit; PIMs, potentially inappropriate medications; Q, quartile.

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 online supplemental 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% CI 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 V.9.4 (SAS Institute). For all statistical analyses, a two-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 hospitalised for either elective surgery or emergency during the study period were available in the MDV database.[23] Subsequently, 312 512

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
Hospitalisation 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	1115.2±926.6	896.3±1036.2

JPY, Japanese yen; N, number of patients.

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 to 821 273.9	1.09	1.09 to 1.10	<0.001
Patients without delirium	257 764	745 295.0 (1.0)	743 312.2 to 747 283.0			

*Geometric LS mean ratio, with delirium/without delirium.
GLM, generalised linear model; JPY, Japanese yen; LS, least squares; n, number of patients.

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, 3685 patients were identified by the ICD-10 criteria (F05) for delirium, 33 611 patients were identified by prescriptions of selected antipsychotics and 2540 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 4093 patients (10.3%, under the code F05.9; online supplemental table S2), followed by delirium superimposed on dementia in 1027 patients (2.6%, code F05.1; online supplemental 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 7489 patients (18.8%). The use of perospirone and olanzapine tablets was relatively uncommon (1.9% and 0.9%, respectively; online supplemental 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 (online supplemental 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).

Prognosis/hospitalisation

The median (IQR) duration of hospitalisation 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 hospitalised 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 online supplemental table S3).

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

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

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% CI: 1.09 to 1.10; p<0.001; table 3). When categorised 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 hospitalisation (p<0.001), PIM use (p<0.001) and surgery (p=0.006). The geometric LS mean ratios of the total medical

		n	Ratio with vs. without delirium	95% CI for ratio	p-value	Interaction p-value
	ALL		1.09	[1.09, 1.10]	p<0.001	
Age (years)	65–74	29 772	1.13	[1.09, 1.17]	p<0.001	0.003
	75–84	102 309	1.10	[1.09, 1.12]	p<0.001	
	≥85	142 072	1.09	[1.08, 1.10]	p<0.001	
Sex	Male	112 576	1.11	[1.10, 1.13]	p<0.001	p<0.001
	Female	161 577	1.08	[1.07, 1.10]	p<0.001	
ADL score (point)	0–59	192 370	1.08	[1.07, 1.09]	p<0.001	p<0.001
	60–100	81 783	1.15	[1.13, 1.17]	p<0.001	
Emergency hospitalisation	Yes	217 812	1.09	[1.08, 1.10]	p<0.001	p<0.001
	No	56 341	1.15	[1.12, 1.19]	p<0.001	
Number of PIM drugs	0	157 311	1.09	[1.08, 1.11]	p<0.001	p<0.001
	1	21 990	1.11	[1.08, 1.15]	p<0.001	
	2	20 868	1.14	[1.10, 1.17]	p<0.001	
	3	14 807	1.10	[1.07, 1.14]	p<0.001	
	≥4	59 177	1.08	[1.06, 1.09]	p<0.001	
ICU admission	Yes	21 134	1.10	[1.08, 1.13]	p<0.001	0.275
	No	253 019	1.10	[1.09, 1.10]	p<0.001	
Type of surgery	No surgery	161 236	1.10	[1.09, 1.11]	p<0.001	0.006
	Surgery + NA/LA/light GA	73 192	1.10	[1.08, 1.13]	p<0.001	
	Surgery + GA (<2 h)	25 461	1.08	[1.06, 1.11]	p<0.001	
	Surgery + GA (≥2 h)	14 264	1.05	[1.02, 1.08]	p<0.001	
Myocardial infarction	Yes	7950	1.12	[1.08, 1.16]	p<0.001	0.530
	No	266 203	1.10	[1.09, 1.11]	p<0.001	
Congestive heart failure	Yes	48 349	1.10	[1.08, 1.11]	p<0.001	p<0.001
	No	225 804	1.10	[1.09, 1.11]	p<0.001	
Peripheral vascular disease	Yes	8143	1.13	[1.09, 1.17]	p<0.001	0.509
	No	266 010	1.10	[1.09, 1.11]	p<0.001	
Cerebrovascular disease	Yes	58 803	1.07	[1.05, 1.08]	p<0.001	p<0.001
	No	215 350	1.10	[1.09, 1.11]	p<0.001	
Chronic pulmonary disease	Yes	16 569	1.11	[1.09, 1.14]	p<0.001	0.744
	No	257 584	1.10	[1.09, 1.11]	p<0.001	
Rheumatic disease	Yes	3709	1.08	[1.02, 1.14]	0.006	0.639
	No	270 444	1.10	[1.09, 1.11]	p<0.001	
Peptic ulcer disease	Yes	14 500	1.06	[1.03, 1.09]	p<0.001	0.013
	No	259 653	1.10	[1.09, 1.11]	p<0.001	
Mild liver disease	Yes	8598	1.07	[1.03, 1.11]	p<0.001	0.063
	No	265 555	1.10	[1.09, 1.11]	p<0.001	
Diabetes without chronic complication	Yes	36 882	1.10	[1.07, 1.12]	p<0.001	0.278
	No	237 271	1.10	[1.09, 1.11]	p<0.001	
Diabetes with chronic complication	Yes	8302	1.16	[1.11, 1.21]	p<0.001	0.033
	No	265 851	1.10	[1.09, 1.10]	p<0.001	
Hemiplegia or paraplegia	Yes	3759	1.06	[0.99, 1.13]	0.092	0.113
	No	270 394	1.10	[1.09, 1.11]	p<0.001	
Renal disease	Yes	16 789	1.13	[1.09, 1.16]	p<0.001	0.520
	No	257 364	1.10	[1.09, 1.10]	p<0.001	
Any malignancy	Yes	31 885	1.10	[1.08, 1.12]	p<0.001	0.204
	No	242 268	1.10	[1.09, 1.11]	p<0.001	
Moderate or severe liver disease	Yes	1224	1.10	[1.01, 1.20]	0.027	0.819
	No	272 929	1.10	[1.09, 1.11]	p<0.001	
Metastatic solid tumor	Yes	5026	1.11	[1.07, 1.16]	p<0.001	0.664
	No	269 127	1.10	[1.09, 1.11]	p<0.001	

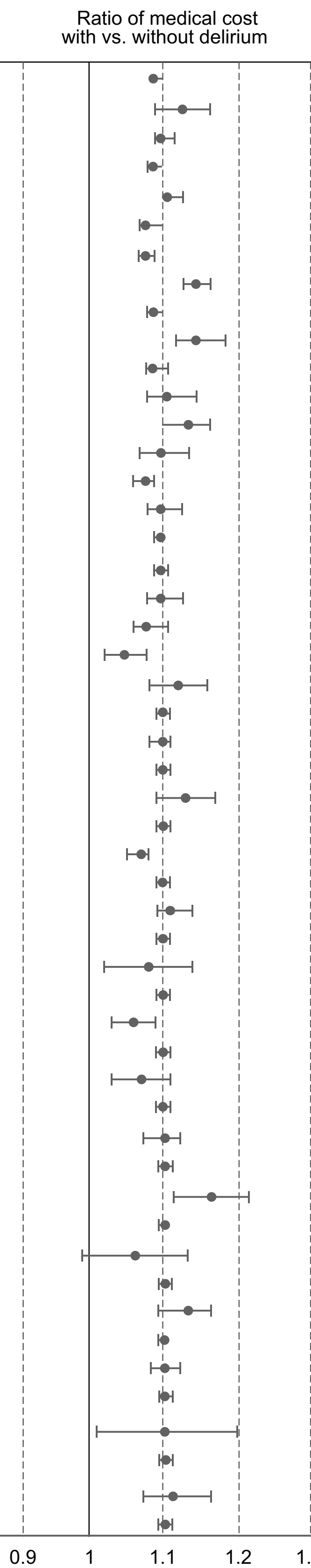

Figure 2 Adjusted medical cost categorised by patient characteristics and comorbidities. Since multiple imputation (MI) for missing values was not conducted for subgroup analyses due to time constraints, the total number of patients in each subgroup was not consistent with those in the main analysis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

costs from the univariate analysis were generally similar to those from the multivariable analysis, although only emergency hospitalisation was adjusted for in the multivariable analysis (online supplemental table S4).

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 hospitalisation 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 US$806–US$24 509.[35] A population-based retrospective study from 490 US hospitals reported an additional admission cost of US$2697 (23.7% increase) for patients with postoperative delirium after major urological 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 hospitalisation 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 twofold 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 utilisation of healthcare resources and consequent increase in treatment cost.

Previous studies have reported non-pharmacological interventions for the prevention of delirium in hospitalised elderly patients and patients with surgical treatments.[41–45] Multicomponent non-pharmacological interventions for delirium have been implemented worldwide to reduce the incidence of delirium.[46] In Japan, a systematic prevention programme 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 patients with delirium 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 programme,[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 (ie, 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 hospitalisation, not considering recurrences, rehospitalisation 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 hospitalised 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.

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

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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Data availability statement No data are available. The Medical Data Vision database analysed 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.

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