Impact of patient characteristics and treatment procedures on hospitalization cost and length of stay in Japanese patients with influenza: A structural equation modelling approach

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Objectives: Little is known about the economic burden of influenza-related hospitalizations in Japan. This study sought to identify the factors that contribute to the total healthcare costs (THCs) associated with hospitalizations due to influenza in the Japanese population.

Study design: A retrospective cross-sectional database analysis study.

Methods: A structural equation modelling approach was used to analyse a nationwide Japanese hospital claims data. This study included inpatients with at least 1 confirmed diagnosis of influenza and with a hospital stay of at least 2 days, who were admitted between April 2014 and March 2015.

Results: A total of 5261 Japanese inpatients with a diagnosis of influenza were included in the final analysis. The elderly (≥65 years) and the young (≤15 years) comprised more than 85% of patients. The average length of stay (LOS) was 12.5 days, and the mean THC was 5402 US dollars (US$) per hospitalization. One additional hospital day increased the THC by 314 US$. Intensive care unit hospitalizations were linked to higher costs (+4957 US$) compared to regular hospitalizations. The biggest procedure-related cost drivers, which were also impacted by LOS, were blood transfusions (+6477 US$), tube feedings (+3501 US$) and dialysis (+2992 US$).

Conclusions: In Japan, the economic burden due to influenza-related hospitalizations for both children and the elderly is considerable and is further impacted by associated comorbidities, diagnostic tests and procedures that prolong the LOS.

Keywords: economic burden, healthcare costs, hospitalizations, Influenza, Japan, structural equation modelling

1 | INTRODUCTION

Influenza is a contagious respiratory illness caused by a highly infectious viral pathogen. The illness ranges from mild to severe and can lead to numerous complications such as superimposed infections, exacerbation of cardiovascular conditions and asthma. Most of the fatal cases occur in the elderly over 65 years old1 and in high-risk populations including children younger than 2 years old,2 pregnant women,3 healthcare workers4 and patients with associated comorbidities such as asthma, chronic lung disease, kidney disorders and blood disorders.5,6

Annual epidemics of influenza result in approximately 250 000 to 500 000 deaths worldwide.7 Cases of influenza also have a substantial...
socioeconomic impact in terms of medical care, healthcare utilization (eg increase in consultations, hospitalizations and length of stay [LOS]) and work absenteeism. In Europe, influenza is responsible for approximately 10% of sickness-related workplace absence. As influenza is an epidemic disease, it may disturb the healthcare services by acute overload during the epidemic.

Elderly patients comprise the group with the highest burden of influenza-related complications. Patients aged ≥85 years are 6 times more likely to be hospitalized and 16 times more likely to die compared with patients aged 65-69 years.10,11

The costs associated with influenza and its complications can be substantial. In the United States, a study based on the 2003 population estimated that the annual burden of influenza was 3.1 million hospital days and 31.4 million outpatient visits. From a societal perspective, the total economic burden of influenza (direct costs and indirect costs, including loss of earnings and loss of life) has been estimated to be 87.1 billion US$ annually, with direct costs accounting for more than 10 billion US$, of which 40% is spent on the treatment of patients older than 65 years of age.12

In the United States, the mean total cost of hospitalization for influenza-related illness for children was 13 159 US$ (39 792 US$ for patients admitted to an intensive care unit [ICU] and 7030 US$ for patients cared for exclusively on the wards). High-risk patients had a higher mean total cost than low-risk patients (15 269 vs 9107 US$, respectively).13

In Japan, it is estimated that 5%-10% of the population develops influenza annually, resulting in approximately 1000 to 2000 deaths from influenza alone and an additional 5000 deaths due to complications such as pneumonia.14 Approximately 20% to 25% of elderly Japanese patients with influenza develop pneumonia, 5% of whom die.14 From 1988 to 1991, 14.0% of all admissions to paediatric hospitals during the winter season in Japan were due to influenza viral infections, while respiratory syncytial virus accounted for 17.5% of admissions.15 Despite these statistics, there is limited information available about the extent of the disease burden due to influenza-related illness in Japan. Therefore, the aim of this study was to identify factors that impact hospitalization costs for patients with influenza in Japan utilizing a Japanese administrative database.

2 METHODS

2.1 Patient selection

We utilized a commercially available hospital claims database from Medical Data Vision Co., Ltd (MDV, Tokyo, Japan). This is an administrative database including approximately 4 400 000 patients, which represents approximately 3% of the total Japanese population.16 The MDV database has been used to investigate a wide range of conditions in Japan such as rheumatoid arthritis,17,18 schizophrenia,19 infectious diseases,20 multiple sclerosis21 and hypertension.22 We considered the inpatient claims from patients who were admitted between 1 April 2014 and 31 March 2015 with at least 1 confirmed diagnosis of influenza [International Classification of Diseases 10th Revision (ICD-10) codes: J10.1, J11.1 and J11.8] and a minimum hospital stay of 2 days (defined by at least 1 night was spent in the hospital).

2.2 Hospitalization cost calculation

Total healthcare costs (THCs) comprised all costs of healthcare services incurred during each hospitalization. These included basic management fees, examination, procedures and medication. Both Diagnosis Procedure Combination cost (DPC cost, which is a case-mix reimbursement cost) and total actual health care cost were calculated. All costs were converted from Japanese yen to US$ based on the average exchange rate during April 2014-March 2015 (Financial Market Department, Bank of Japan; 1 US$ = 109.33 yen).23

2.3 Statistical analysis

Descriptive analyses were performed on baseline characteristics as well as resource use, LOS and THC. As LOS is usually an important driver of the total hospitalization costs,24,25 we considered a structural equation modelling (SEM) approach to assess the relationship between the patients’ characteristics, procedures, LOS and hospitalization costs by considering LOS as an intermediate effect. Indeed, SEM is a flexible multivariate statistical framework that can be used to model complex relationships between variables.26 The SEM framework allows evaluating relationships among variables by combining the strengths of factor analysis and multiple regression in a single model that can be tested statistically.27 More specifically, in this study, a path analysis was conducted, which is a special case of the SEM framework that allows an exploration of the causal links (direct and indirect effects) between exogenous variables and 1 or more endogenous variables. In this framework, the total effects of a covariate on the main dependent variable can be decomposed into 2 categories of effects: (i) the indirect effects, consisting of the effect of the covariate on 1 or more intermediary endogenous variables, which in turn translates into an effect on the main variable; and (ii) the direct effect, which is the remaining effect of the covariate on the main variable while controlling for their indirect effects.28 In our case, the main endogenous variable of interest in the analysis was the total hospitalization cost expressed in Japanese yen, while we assumed that independent variables would have both a direct effect on total hospitalization costs and indirect effects through the LOS. Figure 1 depicts the underlying path diagram showing the relationship between each variable. We also conducted subgroup analyses of the children (≤15 years), the elderly (≥65 years) populations and the infants and toddlers (children ≤2 years old), 3 groups that are particularly susceptible to influenza complications and hospitalization. Statistical analyses were performed using STATA 15.0.29

3 RESULTS

A total of 5261 Japanese inpatients with influenza were included in the final analysis. We excluded 15 rehospitalized admissions due to the limited number of patients (Figure 2).
Table 1 shows patient baseline characteristics for all patients and each subgroup. The elderly (≥65 years) and children (≤15 years) were 61.8% and 26.1% of the patients, respectively. Overall, the average length of hospital stay was 12.5 days, and the mean THC was 5402 US$. 4.5% of the patients were admitted to an ICU, and 4.7% of the patients died in the hospital. The most prominent comorbidities were diabetes (14.9%), congestive heart failure (13.1%) and pneumonia (13.1%). A computerized tomography (CT) scan was used as a diagnostic aid in 49.9% of patients, 44.0% of patients received oxygen therapy, approximately 5.5% of patients received a blood transfusion during their hospitalization, 5.6% received tube feeding and 4.1% required mechanical ventilation.

The results of the SEM method are reported in Table 2. Results of the SEM analysis showed that hospitalizations where influenza was the primary diagnosis were 1994 US$ less costly than those with another medical diagnosis. One additional hospital day increased the THC by 314 US$. Not surprisingly, ICU stays were significantly more costly (+4957 US$) than regular stays. Among comorbidities, ischaemic heart disease, malignant neoplasm and Parkinson’s disease significantly increased the THC by 851 US$, 1462 US$ and 1626 US$, respectively.

Overall, patients who were transferred from other hospitals incurred higher total costs; however, the opposite was found for toddlers under the age of 2. Patients who were referred from nursing
| Characteristics N (%) | Total N (%) | Children (≤15 y) N (%) | Adults (16-64 y) N (%) | Elderly (≥65 y and older) N (%) | Subgroup: Infants and toddlers (≤2 y) N (%) |
|-----------------------|-------------|------------------------|------------------------|---------------------------------|--------------------------------------------|
| Number of patients    | 5261        | 1375 (26)              | 637 (12)               | 3249 (62)                       | 654 (12)                                   |
| Demographics          |             |                        |                        |                                 |                                            |
| Gender                |             |                        |                        |                                 |                                            |
| Female                | 2559 (49)   | 567 (41)               | 303 (47)               | 1689 (52)                       | 276 (42)                                   |
| Age                   |             |                        |                        |                                 |                                            |
| Mean ± SD (median [Q1; Q3]) | 57.5 ± 34.9  | 4.0 ± 3.8              | 45.6 ± 14.6            | 82.5 ± 8.0                      | 0.8 ± 0.8                                  |
| Hospitalization features |           |                        |                        |                                 |                                            |
| Influenza as diagnosis incurring most resources | 1867 (35) | 884 (64) | 130 (20) | 853 (26) | 436 (67) |
| Influenza as primary medical diagnosis | 2343 (44) | 924 (67) | 169 (26) | 1250 (38) | 445 (68) |
| Nature of hospitalization |             |                        |                        |                                 |                                            |
| Regular               | 3033 (58)   | 1196 (87)              | 385 (61)               | 1452 (45)                       | 566 (87)                                   |
| Emergency             | 1990 (38)   | 161 (12)               | 205 (32)               | 1250 (38)                       | 79 (12)                                    |
| ICU                   | 238 (4)     | 18 (1)                 | 47 (7)                 | 173 (5)                         | 9 (1)                                      |
| Origin of patient before hospitalization |           |                        |                        |                                 |                                            |
| Hospitalized from home | 4708 (89)  | 1355 (98)              | 612 (94)               | 2714 (84)                       | 643 (98)                                   |
| Transfer              | 91 (2)      | 10 (1)                 | 8 (1)                  | 73 (2)                          | 6 (1)                                      |
| Nursing home or welfare facilities | 436 (8) | 0 (0) | 11 (2) | 425 (13) | 0 (0) |
| Missing               | 26 (1)      | 10 (1)                 | 6 (1)                  | 10 (1)                          | 5 (1)                                      |
| Destination/outcome after discharge |           |                        |                        |                                 |                                            |
| Home                  | 4208 (80)   | 1357 (99)              | 595 (93)               | 2256 (70)                       | 647 (99)                                   |
| Transfer              | 349 (7)     | 5 (0)                  | 18 (3)                 | 326 (10)                        | 2 (0)                                      |
| Long-term care facilities | 414 (8)   | 0 (0)                  | 12 (2)                 | 402 (12)                        | 0 (0)                                      |
| Death                 | 248 (5)     | 1 (0)                  | 8 (1)                  | 239 (7)                         | 1 (0)                                      |
| Missing               | 42 (0)      | 12 (1)                 | 4 (1)                  | 26 (1)                          | 4 (1)                                      |
| Associated conditions |             |                        |                        |                                 |                                            |
| Congestive heart failure | 690 (13)   | 9 (1)                  | 41 (6)                 | 640 (80)                        | 7 (1)                                      |
| Atrial fibrillation   | 305 (6)     | 0 (0)                  | 8 (1)                  | 297 (9)                         | 0 (0)                                      |
| Acute respiratory failure | 535 (10)   | 67 (5)                 | 40 (6)                 | 428 (13)                        | 29 (4)                                     |
| Acute renal failure   | 65 (1)      | 3 (0)                  | 14 (2)                 | 48 (1)                          | 1 (0)                                      |
| Pneumonia             | 689 (13)    | 114 (8)                | 43 (7)                 | 532 (16)                        | 59 (9)                                     |
| Asthma                | 562 (11)    | 265 (19)               | 59 (9)                 | 238 (7)                         | 121 (10)                                   |
| COPD                  | 285 (5)     | 1 (0)                  | 21 (3)                 | 263 (8)                         | 0 (0)                                      |
| Chronic renal failure | 196 (4)     | 1 (0)                  | 26 (4)                 | 169 (5)                         | 1 (0)                                      |
| Diabetes mellitus     | 785 (15)    | 0 (0)                  | 97 (15)                | 688 (21)                        | 0 (0)                                      |
| Disease involving the immune mechanism | 11 (0) | 3 (0) | 4 (1) | 4 (0) | 0 (0) |
| Parkinson's disease    | 82 (2)      | 2 (0)                  | 3 (0)                  | 77 (2)                          | 0 (0)                                      |
| Ischaemic heart disease | 405 (8)   | 1 (0)                  | 33 (5)                 | 371 (11)                        | 0 (0)                                      |
| Malignant neoplasm (cancer) | 503 (10)   | 7 (1)                  | 78 (12)                | 418 (13)                        | 1 (0)                                      |

(Continues)
home or welfare facilities are less costly than those who were hospitalized from home.

The majority of additional procedures were significantly associated with higher THC both directly and due to an increase in the LOS. Among surgeries and interventions, the largest cost drivers were blood transfusions (+6477 US$), tube feedings (+3501 US$) and dialysis (+2992 US$). Bronchoscopy and echocardiography were the imaging procedures that increased the THC most significantly (+3482 and +1511 US$, respectively). Overall, the effects on DPC costs compared with total costs were similar (Data S1).

Subgroup analyses of children (≤15 years) (Table 3), the elderly (≥65 years) (Table 4) and the infants and toddlers (≤2 years old) (Table 5) showed similar results, although the magnitude of the effect was higher in children for most of the surgeries and interventions.
### TABLE 2  Direct, indirect and total effects of the factors on THC using a structure equation model

| Variable                                | Direct effect (USD$) | Indirect effect (USD$) | Total effects (USD$) |
|-----------------------------------------|----------------------|------------------------|----------------------|
|                                         | Coeff. 95% CI        | Coeff. 95% CI          | Coeff. 95% CI        |
|                                         | →THC                 | →LOS→THC               | →THC + (→LOS→THC)    |
| LOS (day)                               | 314  297  330        | 314  297  330          |                      |
| Gender (reference: male)                |                      |                        |                      |
| Female                                  | −176  −307  −45      | 259  94  424           | 82  −125  291        |
| Age (reference: 16-64 y)                |                      |                        |                      |
| ≤15 y                                   | 457  196  719        | −484  −753  −216       | −26  −429  375       |
| 16-64 y                                 | Reference            | Reference              | Reference            |
| 65 y and older                          | −473  −764  −182     | 854  580  1127         | 381  −33  795        |
| Hospitalization characteristics         |                      |                        |                      |
| Influenza as primary medical diagnosis  | −415  −543  −287     | −1579  −1767  −1390    | −1994  −2195  −1793  |
| Nature of hospitalization               |                      |                        |                      |
| Regular                                 |                      |                        |                      |
| Emergency                               | 459  326  593        | −261  −462  −61        | 197  −33  429        |
| ICU                                     | 4760  3915  5623     | 188  −384  762         | 4957  3832  6083     |
| Patient origin                          |                      |                        |                      |
| From home                               |                      |                        |                      |
| Transfer                                | −330  −906  246      | 763  −120  1647        | 433  −423  1290      |
| Nursing home or welfare facilities      | −685  −898  −472     | 209  −151  569         | −476  −853  −98      |
| Associated conditions                   |                      |                        |                      |
| Congestive heart failure                | −139  −446  167      | 218  −108  544         | 78  −347  505        |
| Atrial fibrillation                     | −246  −651  157      | 28  −407  464          | −218  −758  322      |
| Acute respiratory failure               | −64  −315  186       | −314  −639  10         | −379  −769  11       |
| Acute renal failure                     | 1001  −713  2716     | −881  −1777  13        | 119  −1849  2088     |
| Pneumonia                               | −405  −597  −213     | −41  −306  223         | −446  −748  −144     |
| Asthma                                  | −177  −406  52       | 97  −148  343          | −79  −428  269       |
| COPD                                    | −330  −590  −71      | 288  −143  720         | −42  −500  414       |
| Chronic renal failure                   | −1042  −1728  −357   | 141  −495  779         | −900  −1782  −19     |
| Diabetes mellitus                       | 141  −114  398       | 110  −161  383         | 252  −111  617       |
| Disease involving the immune mechanism  | 1499  −2046  5046    | −1379  −2709  −49      | 120  −4389  4630     |
| Parkinson’s disease                     | −128  −533  277      | 1755  799  2710        | 1626  680  2573      |
| Ischaemic heart disease                 | 516  99  934         | 334  −50  720          | 851  339  1363       |
| Malignant neoplasm (cancer)             | 464  124  804        | 997  597  1397         | 1462  904  2019      |
DISCUSSION

Using an administrative database of hospitalized Japanese patients with influenza, we found that influenza-related hospitalizations mostly consisted of elderly and young patients, confirming that these 2 age groups are at high risk of influenza complications.

4.1 Impact of comorbidities on THC

It is not surprising that healthcare costs significantly increase when influenza strikes in association with other medical disorders. Our data revealed that Parkinson’s disease had the highest impact on cost although it represented only 1.6% of the population, followed by cancer and ischaemic heart disease, which were 9.6% and 7.7% of the cases, respectively. The increased healthcare cost is most likely a reflection of the high incidence of influenza-related complications that occur with these comorbidities.

Despite the low incidence of neurologic disorders associated with influenza viral infection, patients have a high risk of developing complications. In addition, Parkinson’s disease has been reported to be a clinical manifestation of influenza, and parkinsonian-like symptoms such as tremors have also been described in severe influenza cases. Of note, influenza A is one of several viruses that have been implicated in the pathogenesis of Parkinson’s disease. Although a causal link has been difficult to establish in humans, a reduction in neuropsychiatric reactions in influenza patients treated with the antiviral oseltamivir suggests that the influenza virus may play a role in the pathogenesis of certain neurologic symptoms.

Cancer patients are susceptible to infections such as influenza because of either treatment-associated immunosuppression or the

**TABLE 2** (Continued)

| Variable | Direct effect (USD) | Indirect effect (USD) | Total effects (USD) |
|----------|---------------------|-----------------------|---------------------|
|          | →THC Coeff. 95% CI | →LOS→THC Coeff. 95% CI | →THC + (→LOS→THC) Coeff. 95% CI |
| Procedures (patients with at least 1 procedure charged) |
| Surgery and interventions |
| Blood transfusion | 3557 2846 4268 | 2919 2231 3608 | 6477 5379 7575 |
| Cardiac catheterization | 24 −242 292 | 1744 1388 2101 | 1769 1348 2191 |
| Dialysis | 2453 1109 3797 | 539 −483 1561 | 2992 1311 4673 |
| Mechanical ventilation | 2435 1618 3252 | −718 −1355 −80 | 1717 678 2756 |
| Oxygen therapy | 301 83 519 | 199 −68 468 | 501 149 853 |
| Tube feeding | 881 240 1522 | 2619 2028 3210 | 3501 2639 4362 |
| Tests/imaging |
| Biochemical testing | 56 −178 291 | −304 −619 9 | −248 −656 160 |
| Bronchoscopy/pulmonary function test | 2032 1045 3020 | 1449 717 2181 | 3482 2218 4746 |
| Chest X-ray | 282 114 450 | 109 −90 309 | 391 117 666 |
| Colour Doppler ultrasound/echocardiography | 538 338 739 | 972 690 1254 | 1511 1174 1848 |
| Computerized tomography | 19 −130 170 | 588 392 785 | 608 362 853 |
| Immunology test | −64 −261 132 | 420 218 622 | 355 31 680 |
| Oxygen saturation test | −67 −262 127 | 235 −2 474 | 168 −137 474 |
| Sputum test | −90 −242 60 | 529 358 700 | 438 207 669 |

Statistical significance at P-value < 0.05 in bold. Coeff., unstandardized coefficient; USD, US$; LOS, length of stay; THC, total healthcare cost; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

*Exchange rate: 1 USD = 109.33 Japanese yen.
These patients are also at high risk of developing influenza-related complications. A German study that included 203 patients who had influenza along with haematologic and solid tumours reported a high rate of pneumonia and bacterial or fungal superinfections. Influenza also appears to have a detrimental impact on the outcome of cancer treatment by delaying the initiation of anticancer therapy. Chronic heart disease is one of the highest predictors of influenza-related hospitalizations and complications. Epidemiologic studies have long reported an association between influenza epidemics and cardiovascular disease (CVD). For instance, acute myocardial infarctions (AMI) have their highest incidence in the winter months and are often preceded by an upper respiratory tract infection. In addition to the influenza-related increase in hospitalizations for CVD,

### Table 3 Direct, indirect and total effects of the factors on THC in children (≤15 y old) using a structure equation model

| Variable                              | Direct effect (USD) | Indirect effect (USD) | Total effects (USD) |
|---------------------------------------|---------------------|-----------------------|---------------------|
|                                       | Coeff. 95% CI       | Coeff. 95% CI         | Coeff. 95% CI       |
| LOS (day)                             | 549 485 612         |                       | 549 485 612         |
| Gender (reference: male)              |                     |                       |                     |
| Female                                | -44 -140 52         | 1 -240 243            | -42 -292 207        |
| Hospitalization characteristics       |                     |                       |                     |
| Influenza as primary medical diagnosis| 81 -37 199          | -980 -1295 -665       | -899 -1208 -589     |
| Nature of hospitalization             |                     |                       |                     |
| Regular                               | 336 230 443         | -73 -517 370          | 263 -165 692        |
| Emergency                             | 336 230 443         | -73 -517 370          | 263 -165 692        |
| ICU                                   | 2688 979 4398       | 140 -5917 6198        | 2829 -4505 10 164  |
| Patient origin                        |                     |                       |                     |
| From home                             | -203 -581 173       | -126 -731 478         | -330 -791 130      |
| Nursing home or welfare facilities    | Omitted             | Omitted               | Omitted             |
| Procedures (patients with at least 1 procedure charged) | | | |
| Surgery and interventions             |                     |                       |                     |
| Blood transfusion                     | 3865 37 7692        | 13 070 2433 23 707    | 16 935 3624 30 246 |
| Cardiac catheterization               | 764 -2491 4020      | 5278 -4391 14 948    | 6043 -5899 17 986  |
| Mechanical ventilation                | 848 -320 2018       | 2003 -1088 5094      | 2851 -973 6677     |
| Oxygen therapy                        | -104 -267 59        | 860 373 1347          | 756 259 1254       |
| Tube feeding                          | 914 -453 2282       | -2856 -7346 1634     | -1941 -7233 3350   |
| Tests/imaging                         |                     |                       |                     |
| Biochemical testing                   | 145 -37 329         | -348 -718 22         | -202 -552 147      |
| Bronchoscopy/pulmonary function test  | 755 -1534 3046      | -378 -2282 1526      | 377 -3249 4005     |
| Chest X-ray                           | -9 -137 117         | 306 22 589           | 296 16 576         |
| Colour Doppler ultrasound/echocardiography | 391 -116 899     | 2068 770 3366        | 2460 998 3922      |
| Computerized tomography               | 323 148 498         | 61 -314 436          | 384 -14 784        |
| Immunology test                       | 45 -80 171          | 40 -291 371          | 85 -249 420        |
| Oxygen saturation test                | 88 -25 202          | -179 -379 20         | -91 -302 120       |
| Sputum test                           | 1 -88 91            | 319 49 588           | 320 52 588         |

Statistical significance at P-value < 0.05 in bold. Coeff., unstandardized coefficient; USD, US$; LOS, length of stay; THC, total healthcare cost.

*Exchange rate: 1 USD = 109.33 Japanese yen.
| Variable                        | Direct effect (USD) | Indirect effect (USD) | Total effects (USD) |
|--------------------------------|---------------------|-----------------------|---------------------|
|                                | Coeff. 95% CI       | Coeff. 95% CI         | Coeff. 95% CI       |
| LOS (day)                      | 293 279 307         |                       | 293 279 307         |
| Gender (reference: male)       |                     |                       |                     |
| Female                         | -201 -385 -17       | 471 238 703           | 269 -28 567         |
| Hospitalization characteristics |                     |                       |                     |
| Influenza as primary medical diagnosis | -526 -690 -361 | -1920 -2160 -1680 | -2446 -2716 -2176 |
| Nature of hospitalization      |                     |                       |                     |
| Regular Reference              |                     |                       |                     |
| Emergency                      | 443 283 603         | -265 -556 673         | 177 -109 464        |
| ICU                            | 4943 3966 5920      | 58 -556 673           | 5002 3732 6272      |
| Patient origin                 |                     |                       |                     |
| From home                      |                     |                       |                     |
| Transfer                       | -332 -929 265       | 815 -179 1810         | 482 -515 1481       |
| Nursing home or welfare facilities | -662 -875 -448    | 124 -221 470          | -537 -922 -152      |
| Associated conditions          |                     |                       |                     |
| Congestive heart failure       | -216 -514 81        | 156 -171 484          | -60 -493 373        |
| Atrial fibrillation            | -198 -589 192       | 48 -368 465           | -150 -687 387       |
| Acute respiratory failure      | -33 -289 222        | -345 -712 22          | -379 -799 41        |
| Acute renal failure            | 1093 -958 3145      | -715 -1679 248        | 377 -1967 2723      |
| Pneumonia                      | -406 -645 -168      | -41 -358 274          | -448 -824 -72       |
| Asthma                         | -48 -518 422        | 26 -423 475           | -21 -699 656        |
| COPD                           | -316 -601 -30       | 287 -159 733          | -28 -542 484        |
| Chronic renal failure          | -1009 -1516 -502    | 58 -595 713           | -950 -1693 -207     |
| Diabetes mellitus              | 182 -82 448         | 73 -207 355           | 256 -132 645        |
| Disease involving the immune mechanism | 5115 -3837 14 067 | -874 -3519 1770       | 4240 -7000 15 481   |
| Parkinson’s disease            | 11 -386 409         | 1574 643 2505         | 1586 585 2586       |
| Ischaemic heart disease        | 271 -132 675        | 336 -53 726           | 608 82 1134         |
| Malignant neoplasm (cancer)    | 259 -83 603         | 723 333 1112          | 982 453 1512        |
| Procedures (patients with at least 1 procedure charged) | | | |
| Surgery and interventions      |                     |                       |                     |
| Blood transfusion              | 3354 2608 4099      | 2583 1936 3231        | 5938 4882 6993      |
| Cardiac catheterization        | 70 -196 338         | 1516 1171 1862        | 1587 1167 2008      |
| Dialysis                       | 2123 1232 3014      | 659 -524 1842         | 2782 1288 4276      |
| Mechanical ventilation         | 2519 1590 3448      | -630 -1316 55         | 1888 741 3035       |
| Oxygen therapy                 | 241 -53 536         | 150 -204 505          | 392 -86 870         |
| Tube feeding                   | 1014 366 1662       | 2563 1956 3169        | 3578 2691 4464      |
| Tests/imaging                  |                     |                       |                     |
| Biochemical testing            | 114 -357 586        | -460 -1313 392        | -345 -1318 627      |
| Bronchoscopy/pulmonary function test | 2222 1123 3322 | 1636 766 2506         | 3859 2407 5311      |
| Chest X-ray                    | 248 -124 621        | 733 249 1218          | 982 374 1590        |
| Colour Doppler ultrasound/ echocardiography | 553 338 768 | 753 455 1051          | 1306 947 1665       |
| Computerized tomography        | -20 -213 172        | 533 292 774           | 513 204 821         |
| Immunology test                | 37 -324 399         | 1166 711 1620         | 1203 619 1788       |
| Oxygen saturation test         | -51 -334 231        | 258 -83 600           | 207 -246 660        |
| Sputum test                    | -212 -431 6         | 474 241 708           | 262 -58 582         |

Statistical significance at P-value < 0.05 in bold. Coeff., unstandardized coefficient; USD, US$; LOS, length of stay; THC, total healthcare cost; COPD, chronic obstructive pulmonary disease.

*Exchange rate: 1 USD = 109.33 Japanese yen.*
influenza is also linked to both increases in AMI\(^43\) and AMI-related deaths.\(^{44,45}\) Influenza infection has also been associated with damage to the heart muscle leading to cardiomyopathy and myocarditis.\(^{46}\) Taken together, these observations are consistent with our findings that patients with heart disease comprised a significant share of influenza-related hospitalizations, and heart disease was an important driver of the increase in THC.

### 4.2 | Role of patient origin

It was found that patients who were referred from nursing home or welfare facilities incurred less cost than those who were hospitalized from home. One possible interpretation of this interesting finding is that institutions such as nursing homes or welfare facilities do monitor their clients well and send them to the hospital even in case of a
mild form of the disease. Elderly who live at home, on the other hand, might miss the right timing to seek medical advice.

4.3 Impact of procedures and ER and ICU admissions on THC

The most significant cost drivers among procedures were blood transfusions and tube feedings, which increased the THC by 380,000 Japanese yen (approximately 3450 US$).

Our findings of a high cost burden associated with ICU or ER admissions when compared with routine hospitalizations are consistent with other reports. In European countries, for instance, the daily cost of ICU admissions ranged from €1168 to €2025 (1240 to 2150 US$),47 while in the United States the estimated additional cost was 2190 US$ per day.48 These statistics underscore the importance of avoiding ICU or ER admissions whenever possible.

4.4 A role of vaccinations and antiviral treatment

The potential policy implication of our findings is that vaccination programmes should be promoted to avoid influenza-related hospitalizations. From 1977 to 1987, there was already a vaccination programme for Japanese schoolchildren that achieved between 50% and 85% annual coverage in children aged 3-15 years. It was shown that this vaccination programme was associated with a decrease in the overall number of influenza-related excess deaths and that excess deaths increased once the programme was discontinued.49 Furthermore, because the vaccination of schoolchildren can reduce influenza-related morbidity and mortality among non-immunized contacts as well as the elderly, it was estimated that the vaccination programme could also save 1000 elderly lives per year.50

For those patients still requiring hospitalization, medical treatment may be an option to reduce hospital LOS and healthcare costs. A recent study in the United States that included 1,557,437 cases of influenza from 4 influenza seasons found an overall 11% reduction in the risk of complications in oseltamivir-treated patients (an 81% reduction in those treated <2 days after the diagnosis).51 Antiviral treatment also decreased the risk of hospitalizations and emergency room visits by 29% and 24%, respectively. A recent cost-effectiveness analysis in the Japanese healthcare context, for instance, demonstrated that treatment with oseltamivir was highly cost-effective with an incremental cost-effectiveness ratio (ICER) of 398,571 Japanese yen (3645 US$) per quality-adjusted life year from a health insurance perspective.52 With the inclusion of productivity costs, the ICER for oseltamivir turned negative, meaning that medical treatment with oseltamivir was both cost-saving and more effective.51

4.5 Limitations

There are several limitations to our study. First, this analysis is based on a 1-year database. Thus, we could not capture the potential changes due to prescribing behaviour changes and the change of treatment guideline over time. Second, due to the limitations of the database, potentially useful information that might explain costs was lacking. For instance, we could not retrieve hospital ID numbers, which could have been used to identify heterogeneity between hospitals as well as patient characteristics such as region, social and professional status and clinical severity of their disease. Nevertheless, our analysis examined all available patient characteristics (such as age, gender and relevant comorbidities) that could be retrieved from the database. Third, bias may have resulted from the current DPC system that allows hospitals to choose the diagnosis that is incurring the most medical resource utilization as the main diagnosis. In general, patients with comorbidities will receive a higher reimbursement if hospitals choose comorbidities as the primary diagnosis. Finally, a major limitation of this study is that influenza-related hospitalizations can be difficult to identify because influenza is not always detected as the primary cause of the hospitalization, especially in severe cases.10 As a result, this study may underestimate the true burden of influenza as well as the cost of influenza-related hospitalizations because of the coding incentive. Only hospitalizations with influenza diagnosis, which are less costly, were included.10

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ETHICAL APPROVAL

The study was in line with the guidelines provided by Johnson & Johnson and was approved by the Janssen Approval Committee.

CONFLICT OF INTEREST

JM, KH and RS are affiliated with Janssen Pharmaceutical KK, a pharmaceutical company. SF and AJ are employees of Creativ-Ceutical, which received funding from Janssen Pharmaceutical KK to perform the study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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