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# Retrospective analysis of medical costs and resource utilization for severe hypoglycemic events in patients with type 2 diabetes in Japan

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## ABSTRACT

**Aims/Introduction:** The present study aimed to describe hospital utilization and examine actual medical costs for severe hypoglycemic events in patients with type 2 diabetes mellitus in Japan.

**Materials and Methods:** Medical resource utilization associated with severe hypoglycemia was evaluated using a receipt database of acute-care hospitals in Japan. Patients with type 2 diabetes treated with antihyperglycemic agents were included. Severe hypoglycemic events were identified and divided into two groups: with or without hospitalization. Total and attributable medical costs per event were calculated based on the actual medical treatment after severe hypoglycemic events. Attributable costs were estimated from the receipt codes directly associated with the treatment of severe hypoglycemia.

**Results:** In the hospitalized patients, the median length of hospital stay was 11 days, and the median total and attributable medical costs were ¥402,081 and ¥302,341, respectively. The majority of the hospitalized patients underwent a radiographic examination and general blood tests. Apart from the hospitalization costs, the costs associated with diagnosis accounted for 29.6% of the total medical costs. In the outpatients, 60.6% visited hospitals only once for the severe hypoglycemic event, whereas 11.4% visited hospitals daily for a week after the severe hypoglycemic event. The mean number of hospital visits of the outpatient after a severe hypoglycemic event was 2.7 ± 2.6 days. The median total and attributable medical costs were ¥265,432 and ¥4,628, respectively.

**Conclusions:** Significant medical resources are used for the treatment of severe hypoglycemic events of patients with type 2 diabetes in Japan.

## INTRODUCTION

Hypoglycemia occurs quite often in patients with type 2 diabetes mellitus and is mostly associated with the use of glucose-lowering drugs[1–3]. In most hypoglycemic episodes, patients restore plasma glucose levels by oral consumption of carbohydrates; however, severe hypoglycemia that is defined as a hypoglycemic event requiring assistance from others has a significant risk of leading to serious events, injuries, coma and death[2,4,5].

Many severe hypoglycemic events (SHEs) require hospital treatment, where substantial medical resources are utilized, such as ambulance use, emergency department use and hospital admission. An economic analysis of SHEs in the USA showed that SHEs requiring treatment by a healthcare provider cost $1,161 per episode compared with $77 per episode for SHEs not requiring treatment by a healthcare provider[6]. Another economic analysis estimated that the average treatment costs per SHE in patients with type 2 diabetes mellitus receiving insulin ranged from €533 to €691 per episode in European countries, including Germany, Spain and the UK[7]. A study in the UK estimated the mean cost of SHEs to be approximately £377 per episode. Extrapolating this estimation, the entire annual cost of SHEs in the UK would be more than £13 million[8].

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In Japan, an economic burden analysis based on a literature review estimated that the medical cost per SHE was ¥18,659, and the overall medical cost of SHEs in Japan per year was ¥16.3 billion[9]. However, the actual medical resource utilization after SHEs in the clinical setting remains unknown.

Previously, we carried out a retrospective database analysis in which we evaluated the incidence rate of and factors associated with severe hypoglycemia in patients with type 2 diabetes mellitus in Japan[10]. As part of that study, we investigated healthcare resource utilization for the treatment of SHEs[10]. The current analysis aimed to describe the actual medical costs and hospital stays or visits resulting from SHEs in Japan.

## METHODS

### Study Population

As reported previously,[10] we carried out a retrospective observational study of type 2 diabetes mellitus patients who were prescribed antihyperglycemic agents from April 2008 through September 2014 using a medical database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan). The data were obtained from Diagnosis Procedure Combination (DPC) hospitals throughout Japan using anonymous information from health insurance claims, administrative data and laboratory values stored in hospital electronic records since January 2003[11,12]. The treated type 2 diabetes mellitus patients were defined as those who were: (i) diagnosed with diabetes mellitus (International Statistical Classification of Diseases and Related Health Problems, 10th Revision: E11 or E14), but had no history of type 1 diabetes or other secondary diabetes diagnoses; (ii) prescribed with any antihyperglycemic agents; and (iii) visited the hospitals on a regular basis for >6 months. In the definition of severe hypoglycemia, we included hypoglycemic coma, hypoglycemic seizure and hospital admission or emergency department visit for hypoglycemia. The study conformed to the provisions of the Declaration of Helsinki and its late amendments, and the research protocol has been approved by the ethics committee.

Severe hypoglycemic episodes were divided into two groups: (i) SHEs with hospitalization; and (ii) SHEs without hospitalization (outpatient only), and the medical costs and hospital utilization of the total patients and the respective groups were analyzed. For the sensitivity analysis, SHEs with hospitalization were divided into two groups according to the main reason for hospitalization: (i) severe hypoglycemia; and (ii) reasons other than severe hypoglycemia. Given the expectation that patients with severe comorbidities would require higher medical costs, patients were stratified based on the presence of comorbidities, including kidney disease requiring dialysis, macrovascular disease and cancer. Comorbidities were defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (Table S1).

### Medical Cost Calculation

In Japan, the entire population is covered by public health insurance, and all the listed medical services are covered by the national health insurance system. When patients receive medical services, the health insurance covers at least 70% of the medical costs, with the patients paying for the remaining cost. Medical service fees are centrally determined and listed in the national health insurance price list published by the Ministry of Health, Labor and Welfare. Medical costs are calculated based on the fee-for-service basis, whereas per diem payment is basically applied for hospitalization in DPC hospitals.

DPC/Per Diem Payment System (PDPS) codes, which are a variation of the Diagnosis-Related Group/Per Diem Payment System, were introduced on a trial basis in 1998[13]. Hospitals chose whether to receive payment through DPC/PDPS or to remain under fee-for-service. More than half of all acute-care hospital beds are paid for by DPC/PDPS, and all the hospitals included in the present study participated in DPC/PDPS[14,15].

Given that the present study aimed to investigate the details about the types of treatment after an SHE, the medical costs of SHEs were calculated on each treatment item provided based on fee-for-service basis, instead of calculation by the DPC payment of per diem payment basis. Both health insurance coverage and copayment were included. All of the receipt data were extracted from the Medical Data Vision database and classified into the following seven categories based on receipt category code: (i) drug costs; (ii) dispensary fee; (iii) treatment costs; (iv) surgical costs; (v) inspection and testing costs; (vi) diagnostic imaging costs; and (vii) hospitalization costs (Table S2). Drug costs were further classified into three categories: (i) standard care for SHEs; (ii) chemotherapy; and (iii) others (Table 3). The standard care for SHEs is administration of intravenous glucose and/or glucagon. Costs directly related to SHEs were estimated from the receipt code associated with the treatment of SHEs. The associated treatments were determined based on the practice guideline for the treatment of diabetes in Japan[16] and a previous article[9]. In addition to the standard of care, we also included standard laboratory tests (for outpatients and inpatients), electrocardiogram (for inpatients) and radiographic examinations (for inpatients) that were carried out for >70% of the patients with SHEs in the present study (Table S3).

Hospital utilization was assessed by length of stay for hospitalized patients and by the number of hospital visits during the 1 week after a SHE for outpatients. Hospital visits on the day of the SHE were also included.

### Statistical Analysis

Patient characteristics, medical costs and length of hospital stay were summarized with standard descriptive statistics, including mean, standard deviation, median/interquartile range for continuous variables and frequency/percent for categorical variables. Fisher's exact test and the Wilcoxon rank-sum test were used to compare two groups in terms of categorical and continuous variables. The significance level was set at two-sided *P*-value of <0.05 for the comparison. All analyses were carried out using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA).

## RESULTS

### Baseline patient characteristics

Figure 1 shows the process used to identify patients included in the study. Among the 1,228 patients analyzed, 1,096 patients were hospitalized and 132 patients were treated as outpatients. Among the 1,096 hospitalized patients, 816 (74.5%) were hospitalized with severe hypoglycemia as the main reason for admission according to DPC receipt data (Figure 1). The average age of the included patients was 74.4 ± 10.5 years, and 58.6% were men (Table 1). Compared with the outpatients, the hospitalized patients were older (average age 74.8 years vs 71.1 years, $P < 0.001$; Table 1) and were more likely to have cancer (23.6% [259/1,096] vs 12.9% [17/132], $P = 0.004$; Table 1). In the overall cohort, 2.9% required dialysis, 22.5% had cancer and 55.7% had macrovascular disease. The remaining 32.6% of patients did not have any of the pre-specified comorbidities in this study described above. Regarding patient demographics, there was no significant difference between the hospitalized patients whose main reason for hospitalization was a SHE compared with those hospitalized for other reasons (Table 1. columns C and D).

### Total Medical Costs and Hospital Resource Use for SHEs Without Hospitalization (Outpatients)

The total medical costs for the outpatients treated for severe hypoglycemia ($n = 132$) per episode were ¥36,109 ± 31,438 on average (median ¥26,413; Table 2 and Figure S1c). The median attributable costs per episode were ¥4,628 (average ¥4,821 ± 2,411; Table 3), which accounted for 23.0% of the total medical costs.

The number of hospital visits of the outpatients in the 1 week after the SHE including the day of the SHE was 2.7 ± 2.6 days on average (median 1 day; Table 1; Figure S1a). After the event, 60.6% of patients did not visit a hospital in the subsequent week, whereas 11.4% of patients visited the hospital every day in the subsequent 7 days (Figure S1a).

We then evaluated the impact of comorbidities on medical cost and resource utilization. The average total medical cost of the outpatients with comorbidities were higher than that of the patient without comorbidities (¥41,511 vs ¥29,001, $P = 0.049$; Table S4).

As shown in Table 2 and Figure 2, we examined the details of medical costs. Inspection and testing fees (¥9,606) accounted for 26.6% of the total medical cost (¥36,109), followed by drug costs (¥8,685, 24.1%) and other costs including doctors' fees (¥7,407, 20.5%). Glucagon and/or intravenous glucose (oral glucose administration was not included) was administered to 79.5% of the patients, the cost (¥223) of which accounted for 2.6% of drug cost and 0.6% of the total medical costs. The percentage of patients who incurred drug costs, inspection and testing costs, and

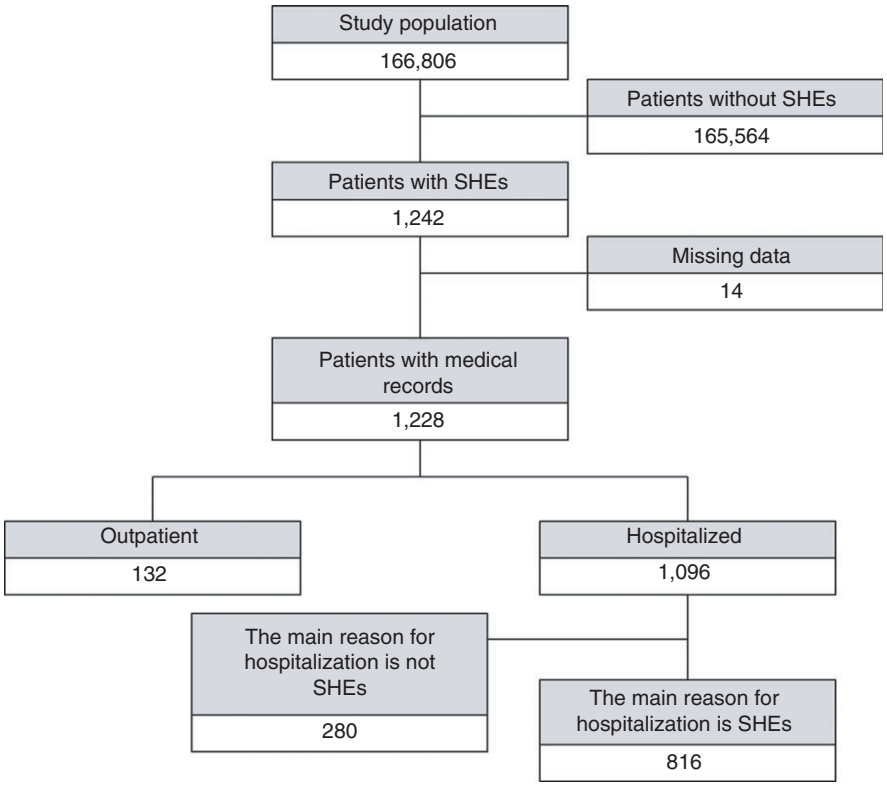


**Figure 1** | Flow chart showing patient composition for cost analysis. SHE, severe hypoglycemic event; Study population, eligible type 2 diabetes mellitus patients treated with antihyperglycemic agents; The main reason for hospitalization, the main reason for hospitalization recorded in the code: A006020-2 data in Diagnosis Procedure Combination receipt data.

**Table 1** | Patient characteristics of the study population

| | Outpatients | Inpatient† (total) | Inpatients | | Total | *P*-Value | |
|---|---|---|---|---|---|---|---|
| | | | Inpatient‡ (hypoglycemia) | Inpatient§ (others) | | A vs B | C vs D |
| No. patients | 132 | 1,096 | 816 | 280 | 1,228 | | |
| Sex | | | | | | | |
| Male | 79 (59.8%) | 641 (58.5%) | 470 (57.6%) | 171 (61.1%) | 720 (58.6%) | 0.780¶ | 0.326¶ |
| Female | 53 (40.2%) | 455 (41.5%) | 346 (42.4%) | 109 (38.9%) | 508 (41.4%) | | |
| Age (years) | | | | | | | |
| Mean (±SD) | 71.1 ± 12.2 | 74.8 ± 10.2 | 74.71 ± 10.0 | 75.1 ± 11 | 74.4 ± 10.5 | <0.001†† | 0.271†† |
| Comorbidities | | | | | | | |
| Without dialysis (A) | 127 (96.2%) | 1,065 (97.2%) | 792 (97.1%) | 273 (97.5%) | 1,192 (97.1%) | 0.580¶ | 0.836¶ |
| With dialysis (A) | 5 (3.8%) | 31 (2.8%) | 24 (2.9%) | 7 (2.5%) | 36 (2.9%) | | |
| Without cancer (B) | 115 (87.1%) | 837 (76.4%) | 635 (77.8%) | 202 (72.1%) | 952 (77.5%) | 0.004¶ | 0.061¶ |
| With cancer (B) | 17 (12.9%) | 259 (23.6%) | 181 (22.2%) | 78 (27.9%) | 276 (22.5%) | | |
| Without macrovascular disease (C) | 68 (51.5%) | 476 (43.4%) | 345 (42.3%) | 131 (46.8%) | 544 (44.3%) | 0.079¶ | 0.209¶ |
| With macrovascular disease (C) | 64 (48.5%) | 620 (56.6%) | 471 (57.7%) | 149 (53.2%) | 684 (55.7%) | | |
| Without any comorbidities above | 57 (43.2%) | 343 (31.3%) | 254 (31.1%) | 89 (31.8%) | 400 (32.6%) | | |
| With (A) only | 1 (0.8%) | 7 (0.6%) | 6 (0.7%) | 1 (0.4%) | 8 (0.7%) | | |
| With (B) only | 10 (7.6%) | 125 (11.4%) | 85 (10.4%) | 40 (14.3%) | 135 (11.0%) | | |
| With (C) only | 54 (40.9%) | 467 (42.6%) | 360 (44.1%) | 107 (38.2%) | 521 (42.4%) | | |
| With (A) + (B) | 0 (0.0%) | 1 (0.1%) | 0 (0.0%) | 1 (0.4%) | 1 (0.1%) | | |
| With (A) + (C) | 3 (2.3%) | 20 (1.8%) | 15 (1.8%) | 5 (1.8%) | 23 (1.9%) | | |
| With (B) + (C) | 6 (4.5%) | 130 (11.9%) | 93 (11.4%) | 37 (13.2%) | 136 (11.1%) | | |
| With (A) + (B) + (C) | 1 (0.8%) | 3 (0.3%) | 3 (0.4%) | 0 (0.0%) | 4 (0.3%) | | |
| Hospital visits/inpatient length of stay (days) | | | | | | | |
| Average | 2.7 | 18.4 | 16.5 | 24.0 | 16.7 | – | <0.001†† |
| SD | 2.6 | 25.8 | 22.5 | 33.1 | 24.9 | | |
| Minimum | 1 | 1 | 1 | 1 | 1 | | |
| Median | 1 | 11 | 9 | 15 | 9 | | |
| Maximum | 8 | 350 | 218 | 350 | 350 | | |

†All the hospitalized patients. ‡Patients whose main reason for hospitalization was severe hypoglycemic events (SHEs). §Patients whose main reason for hospitalization was not SHEs. Hospital visits/inpatient length of stay, inpatient length of stay if patients were hospitalized and days of hospital visit during 1 week after the SHEs if patients were not hospitalized. Hospital visits on the day of SHEs were included. ¶Fisher's exact test. ††Wilcoxon rank sum test. A, outpatients; B, inpatients; C, inpatients (hypoglycemia); D, inpatients (others); SD, standard deviation.

**Table 2** | Medical costs per severe hypoglycemic event

| | Drug cost (¥) | | Dispensary fee (¥) | Treatment (¥) | Surgery | Inspection and testing (¥) | Diagnostic imaging (¥) | Hospitalization cost (¥) | Total (¥) |
|---|---|---|---|---|---|---|---|---|---|
| | Glucagon + glucose | Total (¥) | | | | | | | |
| A Outpatient ($n$ = 132) | | | | | | | | | |
| Average | 223 | 8,685 | 223 | 3,305 | 680 | 9,606 | 6,291 | 0 | 36,109 |
| SD | 294 | 16,541 | 294 | 16,844 | 7,292 | 6,388 | 8,581 | 0 | 31,438 |
| 1st quantile | 98 | 341 | 98 | 0 | 0 | 5,330 | 0 | 0 | 12,730 |
| Median | 196 | 615 | 196 | 0 | 0 | 8,765 | 0 | 0 | 26,413 |
| 3rd quantile | 291 | 8,890 | 291 | 0 | 0 | 11,965 | 15,800 | 0 | 52,744 |
| No. patients (%) | 105 (79.5%) | 128 (97.0%) | 105 (79.5%) | 26 (19.7%) | 2 (1.5%) | 127 (96.2%) | 61 (46.2%) | 0 (0.0%) | 132 (100.0%) |
| B inpatient† ($n$ = 1,096) | | | | | | | | | |
| Average | 824 | 50,437 | 824 | 17,112 | 32,802 | 46,387 | 22,317 | 407,643 | 639,375 |
| SD | 1,872 | 102,300 | 1,872 | 67,989 | 268,070 | 51,654 | 26,219 | 462,086 | 791,199 |
| 1st quantile | 128 | 4,121 | 128 | 0 | 0 | 15,150 | 3,200 | 131,675 | 195,050 |
| Median | 323 | 19,589 | 323 | 81 | 0 | 29,455 | 18,600 | 288,480 | 402,081 |
| 3rd quantile | 750 | 51,848 | 750 | 4,928 | 0 | 58,460 | 29,985 | 497,675 | 730,520 |
| No. patients (%) | 903 (82.4%) | 1,094 (99.8%) | 903 (82.4%) | 558 (50.9%) | 111 (10.1%) | 1,095 (99.9%) | 978 (89.2%) | 1,096 (100.0%) | 1,096 (100.0%) |
| C Inpatient‡ (hypoglycemia) ($n$ = 816) | | | | | | | | | |
| Average | 725 | 43,885 | 725 | 13,713 | 18,941 | 41,664 | 20,394 | 364,669 | 558,550 |
| SD | 1,257 | 96,626 | 1,257 | 57,747 | 214,134 | 46,856 | 25,435 | 398,241 | 688,832 |
| 1st quantile | 131 | 3,145 | 131 | 0 | 0 | 14,425 | 2,870 | 119,210 | 176,311 |
| Median | 332 | 15,498 | 332 | 0 | 0 | 25,235 | 17,900 | 249,910 | 348,277 |
| 3rd quantile | 736 | 44,289 | 736 | 2,741 | 0 | 49,765 | 26,950 | 463,345 | 651,783 |
| No. patients (%) | 690 (84.6%) | 814 (99.8%) | 690 (84.6%) | 375 (46.0%) | 63 (7.7%) | 816 (100.0%) | 717 (87.9%) | 816 (100.0%) | 816 (100.0%) |
| D Inpatient§ (others) ($n$ = 280) | | | | | | | | | |
| Average | 1,112 | 69,530 | 1,112 | 27,020 | 73,196 | 60,151 | 27,923 | 532,882 | 874,922 |
| SD | 3,004 | 115,363 | 3,004 | 90,931 | 381,960 | 61,669 | 27,674 | 594,642 | 998,011 |
| 1st quantile | 81 | 10,523 | 81 | 0 | 0 | 20,890 | 7,520 | 222,780 | 323,981 |
| Median | 313 | 32,994 | 313 | 2,050 | 0 | 44,953 | 21,250 | 395,130 | 571,171 |
| 3rd quantile | 792 | 75,722 | 792 | 13,383 | 0 | 74,000 | 37,585 | 608,360 | 973,143 |
| No. patients (%) | 213 (76.1%) | 280 (100.0%) | 213 (76.1%) | 183 (65.4%) | 48 (17.1%) | 279 (99.6%) | 261 (93.2%) | 280 (100.0%) | 280 (100.0%) |
| $P$-value* | | | | | | | | | |
| A vs B | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P = 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| C vs D | $P = 0.489$ | $P < 0.001$ | $P = 0.489$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |

†All the hospitalized patients. ‡Patients whose main reason for hospitalization was severe hypoglycemic events. §Patients whose main reason for hospitalization was not severe hypoglycemic events. *$P$-value was calculated by Wilcoxon rank-sum test. Glucagon + glucose, costs for drugs whose generic name is glucose or glucagon; SD, standard deviation;

**Table 3** | Attributable medical costs for severe hypoglycemic events

| | *n* | Direct costs (¥) | | | Percentage of direct costs/total costs |
|---|---|---|---|---|---|
| | | Mean ± SD | Median | IQR | |
| A Outpatient | 132 | 4,821 ± 2,411 | 4,628 | 3,025–6,488 | 23.0 |
| B Inpatient[†] | 1,096 | 430,531 ± 481,180 | 302,341 | 142,085–529,162 | 73.2 |
| C Inpatient[‡](hypoglycemia) | 816 | 385,149 ± 417,636 | 265,432 | 130,691–482,703 | 74.2 |
| D Inpatient[§](others) | 280 | 562,788 ± 612,881 | 414,906 | 238,417–640,264 | 70.4 |
| *P*-value* | | | | | |
| A vs B | | $P < 0.001$[§] | | | |
| C vs D | | $P < 0.001$[§] | | | |

[†]All the hospitalized patients. [‡]Patients whose main reason for hospitalization was severe hypoglycemic events. [§]Patients whose main reason for hospitalization was not severe hypoglycemic events. **P* value was calculated by Wilcoxon rank-sum test. A, outpatients; B, inpatients; C, inpatients (hypoglycemia); D, inpatients (others); IQR, interquartile range; SD, standard deviation.

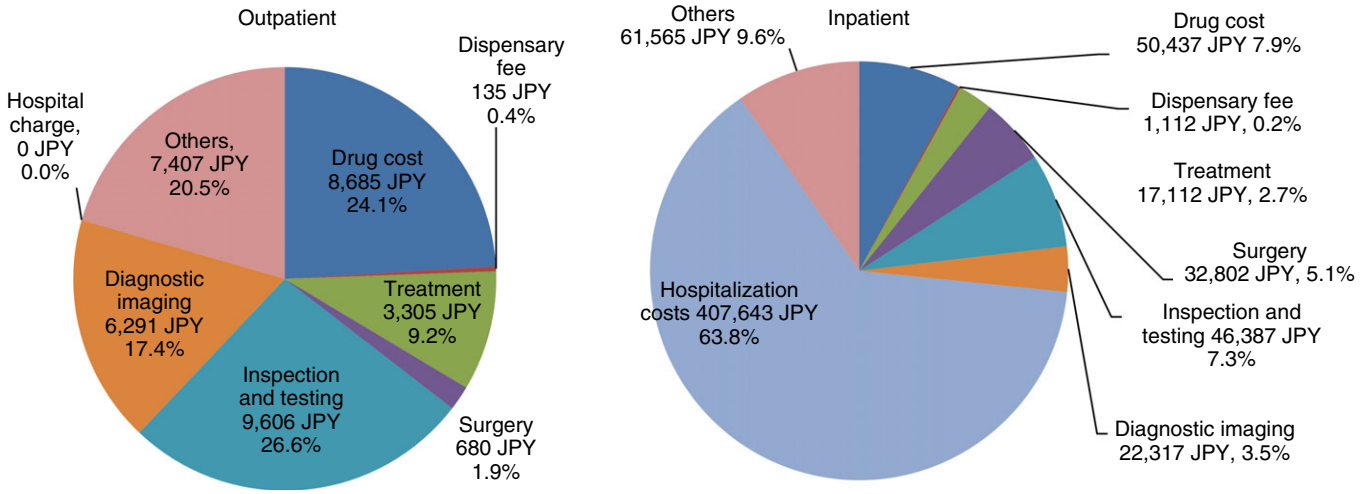


**Figure 2** | Composition of the medical costs. Medical cost is classified according to the receipt category code. Drug costs, 21 (internal use), 22 (portion), 23 (external use), 31 (injection, subcutaneous/intramuscular), 32 (injection, intravenous) and 33 (injection, others); dispensary fee, 24 (dispensing), 25 (prescription), 26 (narcotic/poisonous drug addiction), 27 (basic fee on receiving prescription), 28 (others) and 39 (medication cost reduction); treatment, 40 (treatment); surgery, 50 (operation) and 54 (anesthesia); inspection and testing, 60 (examination/pathological examination); diagnostic imaging, 70 (image diagnosis); hospitalization cost, 90 (hospitalization basic rate) and 92 (specific hospitalization cost and others); others, 11 (fee charged for a patient's first visit), 12 (fee charged for a patient's revisit), 13 (medical administration), 14 (Home treatment) and 80 (others). JPY, Japanese yen.

diagnostic imaging costs were 97.0%, 96.2% and 46.2%, respectively (Table 2). Diagnostic imaging included radiography in 46.2% and computed tomography in 32.6% of the outpatients (Table 4).

### Total Medical Costs and Hospital Resource Use for SHEs Requiring Hospitalization

As shown in Table 2 and Figure S1d, the mean total medical cost for the inpatients per episode was ¥639,375 ± 791,199, and median cost was ¥402,081. The mean and median lengths of hospital stay in the inpatients were 18.4 ± 25.8 days and 11 days, respectively (Table 1, column B; Figure S1b). The median attributable costs per episode were ¥302,341 (average ¥430,531 ± 481,180; Table 3), which accounted for 73.2% of the total medical costs. The total and attributable medical costs for the patients primarily hospitalized for SHE were significantly lower as compared with the patients hospitalized for other reasons (Tables 2,3). The lengths of hospital stay for patients admitted for SHEs were shorter than those admitted for other main reasons (median length of hospitalization 9 vs 15 days, $P < 0.001$; Table 1).

Subsequently, we examined the impact of comorbidities on the medical cost and the length of hospital stay. There was no significant difference in the medical cost or the length of hospital stay between inpatients with ($n = 753$) or without any comorbidities ($n = 343$; Table S4).

**Table 4** | Details of diagnostic imaging costs

| Type of diagnosis | No. patients | Total cost (¥) | Average cost per patient (¥) |
|---|---|---|---|
| Outpatient ($n$ = 132) | | | |
| X-ray diagnosis (E00) | 61 (46.2%) | 234,740 | 3,848 |
| Nuclear medicine diagnosis (E10) | 0 (0.0%) | 0 | 0 |
| Computer tomography diagnosis (E20) | 43 (32.6%) | 591,840 | 13,764 |
| Others | 12 (9.1%) | 3,869 | 322 |
| Inpatient ($n$ = 1,096) | | | |
| X-ray diagnosis (E00) | 978 (89.2%) | 7,387,630 | 7,554 |
| Nuclear medicine diagnosis (E10) | 9 (0.8%) | 281,250 | 31,250 |
| Computer tomography diagnosis (E20) | 697 (63.6%) | 15,686,160 | 22,505 |
| Others | 324 (29.6%) | 1104915.1 | 3,410 |

Types of diagnosis were defined by the receipt codes (E00, E10 and E20). Others are defined as the receipt code including E except E00, E10 and E20. Average cost per patient is total cost divided by the number of patients. Total cost is the total cost used for the total patients.

Regarding the distribution of the medical costs of each category, hospitalization costs accounted for the highest percentage of the overall cost (¥407,643, 63.8%), followed by other costs including doctors' fees (¥61,565, 9.6%), drug costs (¥50,437, 7.9%), and inspection and testing costs (¥46,387, 7.3%; Table 2; Figure 2). A similar tendency was observed in the patients whose main reasons for hospitalization were SHEs. Glucagon and/or intravenous glucose was administered to 82.4% of the patients (Table 2), the cost (¥824) of which accounted for 1.6% of the drug cost (average ¥50,437) and 0.1% of the total medical costs (average ¥639,375). The percentage of patients who incurred drug costs, inspection and testing costs, and diagnostic imaging costs were 99.8%, 99.9 and 89.2%, respectively (Table 2). Diagnostic imaging was carried out using radiography in 89.2% and using computed tomography in 63.6% of patients (Table 4).

## DISCUSSION

In the present study, we evaluated the medical resource utilization for SHEs, including a detailed breakdown of medical costs, frequency of hospital visits and lengths of hospital stays in Japan. Most of the total medical costs for SHEs were derived from direct medical costs in hospitalized patients. In contrast, direct medical costs for SHEs in outpatients were 23.0%, suggesting that other medical treatment was carried out for outpatients. Mano[9] previously reported that the medical costs of SHEs calculated based on the epidemiological data, table of points of remuneration for diagnosis and treatment, and the costs for SHE with or without hospitalization were approximately ¥181,101 or ¥6,677. We speculated that one of the main reasons for the increase of the costs attributable to SHEs in the current study was due to the inclusion of unexpected additional medical costs, such as inspection, and testing and diagnostic imaging costs. In addition, the length of hospital stay was assumed from the DPC tables in the previous study, which was considerably shorter (7.84 days on average) than that in the present study (18.4 days on average), thus causing the differences in hospitalization cost calculation.

In France, the mean medical cost for SHEs was $2,100 per episode, and the mean length of hospital stay was 6.6 days[17]. In Germany, type 2 diabetes mellitus patients with SHEs were admitted for 9.5 days on average[1,18]. The Diabetes Audit and Research in Tayside Scotland-Department of Medicine and the Medicines Monitoring Unit database analysis showed that the mean length of hospital stay after a SHE was 4.4 days at a cost of £959 per hospitalization[1,7]. In the present study, SHEs with hospitalization cost ¥639,375, and required hospital admission for 18.4 days on average, which is slightly more expensive and longer compared with those in European countries. According to Organization for Economic Cooperation and Development Health statistics, the mean length of all-cause hospital stay in 2014 was 5.6 days in France, 9.0 days in Germany and 6.9 days in the UK[19], in Japan it was 31.9 days according to the 2014 Patient Survey[20].

Another important aspect of the present study is the detailed description of medical treatment after SHEs. The standard treatment for severe hypoglycemia (glucose and glucagon) did not account for the greatest portion of the medical costs. Inspection and testing, and diagnostic imaging costs accounted for a considerable proportion of the medical costs. Given that physicians need to examine possibilities of other medical conditions, such as brain and macrovascular disorders, because of the similarities in symptoms between these conditions and those of SHEs, it therefore is reasonable that various tests, such as computed tomography, were carried out after SHEs. This result implies that the economic burden of SHEs could be underestimated if those testing costs are not included in the analysis.

To analyze sensitivity, we classified the patients according to their main reason for hospitalization based on the DPC receipt data. Patients whose main reason for admission was an SHE incurred lower total medical costs and shorter hospital stays compared with patients admitted for other reasons. Therefore, we reviewed other reasons for hospitalization. We found that some patients were hospitalized with serious conditions, such

as cardiovascular disease, neoplasms, injuries and pneumonia, suggesting that some of these serious conditions might have resulted in concomitant malnutrition and subsequent SHEs. Medical resource use was likely to increase as a result of these underlying serious conditions. It is also speculated that SHEs might have caused some of the serious conditions that required additional medical treatment that increased the medical cost, such as fall-related fractures.

The present study had some limitations. First, it was carried out using a hospital-based composite database, hence medical treatments and diagnosis cannot be captured if patients visited other hospitals. Second, the data might not represent the general population of patients with type 2 diabetes mellitus in Japan, as the patients in the present study had visited DPC hospitals >6 months before SHEs. There is a tendency that patients in the present study showed a similar prevalence of diabetic complications, such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, and had more medical history of comorbidities, particularly macrovascular diseases, compared with previous studies[21–23]. In addition, patients in the present study were younger, and the number of male patients was higher than that in the national patient survey[20]. The proportion of patients hospitalized after SHEs was higher in the present study compared with that in previous studies[8,17,18,24], supporting the possibility that more severe patients were included in the present study. Finally, the costs related to emergency transportation and other indirect costs were not captured. Namba *et al.*[25] estimated that approximately 20,000 patients were transported to hospitals by ambulance per year in Japan; therefore, it is expected that in Japan a significant number of patients were transported to hospitals by ambulance. Considering that outpatient visits for SHEs could have been underestimated and that ambulance costs were not included, further studies are required to clarify the overall direct costs of SHEs in Japan.

According to the estimates of the National Medical Care Expenditure by the Ministry of Health, Labor and Welfare in 2015, the total medical expenditures were ¥42.36 trillion, and the treatment of diabetes accounted for ¥1.12 trillion. Hence, the economic burden of diabetes is a critical issue in Japan. Furthermore, elderly patients are known to be more vulnerable to hypoglycemia[26]. The aging of the Japanese population is considered to be faster than that in other nations, and Japanese patients with diabetes are also older compared with those in other countries. The Joint Committee of the Japan Diabetes Society and the Japan Geriatrics Society issued the treatment guidelines for elderly patients at the 59th Annual Meeting of the Japan Diabetes Society[26]. In the guidelines, it is specified that treatment goals and medications are to be determined based on patient demographics, such as age, comorbidities, cognitive function and activities of daily living, to avoid hypoglycemia.

The findings of the present study showed that the direct costs of SHEs are high in Japan, as a significant amount of medical resources were required for diagnosis and testing, treatment of related symptoms and after-effects, as well as the treatment of SHEs. As the patients with type 2 diabetes mellitus age, an increasing number of patients become susceptible to hypoglycemia. Personalized management of diabetes conforming to the established guideline is required to reduce hypoglycemia, and consequently, the economic burden of diabetes.

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## DISCLOSURE

YI, TK, MA and ST are employed by MSD K.K., Tokyo, Japan, and own stock or stock options in Merck & Co., Inc., Kenilworth, NJ, USA. EO is an employee of AC Medical Inc., which was contracted by MSD K.K., Tokyo, Japan, to carry out the statistical analysis.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Definition of comorbid conditions.
**Table S2** | Medical costs.
**Table S3** | Costs directly associated with severe hypoglycemic events.
**Table S4** | Medical costs of severe hypoglycemic events for patients with comorbidities.
**Figure S1** | Histograms of hospital visits/inpatient length of stay and medical costs.