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Direct medical costs in the preceding, event and subsequent years of first severe hypoglycaemia requiring hospital transfer: A population-based cohort study

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Abstract

Aims

To estimate healthcare services use and the direct medical costs accrued by patients with diabetes mellitus (DM) in the year of first severe hypoglycaemia (SH), the years before and after event year.

Materials and Methods

We analyzed a population-based, retrospective cohort including all DM adults managed in primary care setting from the Hong Kong Hospital Authority between 2006-2013. DM patients who had first recorded SH during the observation period were identified, and matched to control group of patients without SH based on the propensity score method. Direct medical costs in the years before, during and after the first SH were determined by summing up the costs of health services utilized within respective year.

Results

After matching, a total of 22,694 DM patients was identified in first recorded SH group (n=11,347) and non-SH control group (n=11,347). Patients with first SH on average utilized 7.85 outpatient clinic visits, 1.89 emergency visits and 17.75 nights of hospitalization in the event year. Mean direct medical cost in the event year was US$11,751, more than twofold of that in the preceding year (US$4,846, p<0.001) and subsequent years (US$4,198-4,700, p<0.001), and 4.5

times of that in two years before the event (US$2,481, $p<0.001$). Incremental costs of SH versus matched control in the event year and preceding year were US$10,873 ($p<0.001$) and US$3,974 ($p<0.001$), respectively.

Conclusions

SH is associated with excessive hospitalization admission rates and direct medical costs in the event year and, in particular, in the year before as compared to patients without SH.

Manuscript Text

Introduction

Hypoglycaemia is one of the commonest acute complications associated with intensification of glucose-lowering therapies, often experienced by treated with insulin. Given that insulin use accounts for one-fourth of all diabetes mellitus (DM) treatment [1], the number of insulin-related DM complications is expected to rise further with the growing number of DM by 2045 [2]. Severe hypoglycaemia (SH) is defined as any hypoglycaemia episode requiring the emergency assistance from health service personnel, has been recorded as high as one in nine patients per year [3] among patients with type 1 and type 2 DM (T1DM and T2DM) treated with insulin. As well as this, the use of oral anti-diabetic drugs can also result in SH events [4]. Evidence from large prospective cohort studies showed that SH is associated with an accelerated cognitive decline in the elderly [5], an elevated risk of cardiovascular diseases [6-8], all-site cancer [9] and mortality [6, 7, 9, 10], with the need in emergency admissions and hospitalizations.

On a global scale, SH imposes substantial economic burden onto national healthcare services, driven by an increasing need in blood glucose monitoring, emergency services, hospitalization, and additional visits to doctors and allied health professionals [11]. A number of cost-of-illness and cost-consequence studies have reported the direct medical cost incurred per severe hypoglycaemic episode across clinical characteristics in developed countries, including the United States (US) [12-14], United Kingdom (UK) [15, 16], Denmark [17], Netherlands [18], Germany [7], Spain [19-21], South Korea [22].

Whilst the mean costs of SH episode could be estimated, there is a scarcity of information, so far, on the costs in the preceding and subsequent years. Population cohort data could be used to estimate the direct medical costs in the year of episode, preceding and subsequent years. Use of population cohort data could also help in quantifying the disease burden at a national level, enabling an estimate of direct medical costs of patients and their determinants, such as the number of comorbid conditions and the presence of DM-related complications [23, 24]. This research extends our knowledge in the area of comparative effectiveness and cost-effectiveness analysis of glucose-lowering therapies focusing on the reduction of hypoglycaemic episodes and their associated economic impacts.

The aim of the present study is to report the healthcare resource use and estimate direct medical costs in Hong Kong among patients with DM in the event year, preceding year and subsequent years of the first SH episode. We examined the influence of the socio-demographic factor (including gender and age) and the clinical characteristics (such as drug treatment regimen, duration of DM, type of DM, glycaemic control, mortality, presence of DM-related complications, and presence of comorbidities) on the direct medical costs of first SH, allowing for improved projections of healthcare expenditure incurred by DM patients suffering from SH.

Materials and Methods

Study design and patient sampling

The population-based retrospective cohort data on 206,238 patients with DM, defined by the International Classification of Primary Care, Second edition (ICPC-2) codes T89/T90, who visited at least one primary care general outpatient clinic or family medicine clinic under the Hong Kong Hospital Authority between August 1, 2008 and December 31, 2013, was extracted from Hospital Authority administrative database. From this broad cohort in primary care setting, adult DM patients with a recorded occurrence of SH episodes (identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 250.3, 250.8, 251.0, 251.1, 251.2, 270.3, 775.0, 775.6 and 962.3 [25]) between January 1, 2006 and December 31, 2013 were identified. The index date was defined as the date of first ever SH event occurred during the mentioned period, with median index with of August 19, 2010. To reduce the bias of observations with index dates that are near the start or the end of the data period, patients with index dates before January 1, 2007 or after December 31, 2012 were excluded. The median index date for SH group was December 10, 2010. The median index date in full cohort and SH groups were roughly the same.

A control group of DM patients who did not have any SH event in the observed period were matched one-to-one with the SH group using propensity score method. The patients were matched using their characteristics/covariates at index date of January 1, 2010 to ensure balanced follow-up durations and to allow for estimations of the healthcare resource uses and associated costs across the years.

Estimation of annual direct medical costs

The approach adopted for estimating the direct medical costs was similar to previous published studies [23, 24]. The annual direct medical costs were estimated by the frequency of the attended healthcare service used under Hospital Authority in a year multiplied by the unit cost of the corresponding types of the healthcare services. The frequencies of attended healthcare services including general outpatient clinic (GOPC), specialist outpatient clinics (SOPC), allied health professional, accident & emergency (A&E) department and overnight hospitalization with respect to the types of wards admitted (general ward, intensive care unit (ICU), cardiac care unit (CCU) and high dependency unit (HDU)) between 2006-2013 were retrieved from the Hospital Authority administrative database. The unit cost of types of services were referred to the price list for non-Hong Kong residents, published in the 2013 Government Gazette and Hospital Authority Ordinance [26] and listed in Supplementary Table 1.

The direct medical costs in the event year, denoted as year0, were estimated by aggregating the costs incurred from index date to 1 year after index date. The direct medical costs in the preceding year before event and two years before event (denoted as year-1 and year-2 respectively) were the aggregate of the costs incurred from 1 year before index date to index date, and from 2 years before index date to 1 year before index date respectively. The direct medical costs in the first, second, and third subsequent year (denoted year+1, year+2 and year+3, respectively) of the first SH event were the aggregates of the costs incurred in the respective years. Patients who died in the subsequent years of SH event were not accounted for the cost calculations at the years after the death year. Inclusion of death patients with zero costs would underestimate the direct medical costs in subsequent years.

Patient characteristics at index date

Patient characteristics at index date in SH and matched control groups included gender, age group, glycaemic control, duration of DM diagnosis, type of DM, presence of comorbidities, presence of DM-related complications, death within the year of first SH event occurrence, and DM drug regimen. DM-related complications and events of diseases were identified by the diagnosis codes of the ICD-9-CM and the ICPC-2. Lists of relevant diagnosis codes used in this study were provided in Supplementary Table 2. The DM drug regimen included lifestyle modification only, insulin use, oral antidiabetic drugs such as metformin, sulphonylurea, and other drug classes.

Statistical analysis

To assess the incremental effect of SH on direct medical costs, a group of control patients who had not ever been diagnosed with SH between August 1, 2008 and December 31, 2013 were matched by propensity score matching using the characteristics at index date in one-to-one basis. The use of propensity score matching is to summarize all patient's characteristics at index date to a single-index estimate, called propensity score. A propensity score was generated for each patient by fitting a logistic regression model of the presence of a recorded SH during the observation period by patient's characteristics. These characteristics included age, gender, duration of DM diagnosis, type of DM, Charlson Comorbidity index (CCI), treatment modality (insulin, metformin, sulphonylurea and other DM drug regimen), and existence of macrovascular and microvascular complications. SH patients were then matched to the control patients based on the similar propensity score, i.e. similar characteristics [27, 28]. The caliper criterium improved the quality of the nearest neighbor matching by specifying a maximum tolerance of the propensity score distance between SH patients and control [29]. The propensity score matching was performed by ‘psmatch2’ command in one-to-one basis without replacement and a calliper criteria of 0.001 in STATA [30].

Descriptive statistics including mean, standard deviation (SD), 95% confidence interval (CI) were used to present the baseline demographics and clinical characteristics between the SH group and matched control group. Differences in baseline characteristics between two groups were tested using independent t-test for continuous variables or Chi-square test for categorical variables. The balance of the characteristics between two groups after matching was also indicated by standardized mean difference.

Mean numbers of healthcare service utilization in the event year, years before and after the event year for each group were reported. Independent t-test was applied to test the mean number of healthcare service utilization between groups. Negative binomial regressions were performed to assess factors that associated with annual healthcare utilization at the event year of first SH.

In order to compare the direct medical costs before and after the index years, similar approach was adopted to estimate the costs of the preceding and subsequent years. Mean annual direct medical costs in different subgroups were presented and compared using independent t-test for two groups, or one-way analysis of variance for three groups or above. The association between annual direct medical costs in the event year and baseline covariates were further analyzed by fitting generalized linear model with gamma family and identity link.

All statistical analyses were performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA). All significance tests were two-tailed and P values < 0.05 were taken to indicate statistical significance.

Results

The detailed flowchart of subject sampling and the distribution of propensity score matching between the SH group and control group are shown in Supplementary Figure 1 and Supplementary Figure 2, respectively.

A total of 14,796 patients with a documented diagnosis of SH were identified. 11,347 patients remained in the cohort after excluding those who had events near the start or end date of the observation period. These patients were matched with a one-to-one ratio with the same number of control patients without any SH event. A total of 22,694 patients (11,347 patients in SH group and 11,347 in matched control group) were included in the analysis.

Sample characteristics

Baseline characteristics of patients in SH group and control group are shown in Supplementary Table 3. Though there were significant differences between the SH group and the control group for a number of characteristics, most of the standardized mean differences of the characteristics were less than 0.1, implying that a balance was achieved in most covariates between the two groups.

Healthcare service utilization

Figure 1 depicts the frequency of healthcare services attendance for SH and matched control groups from year-2 to year+3.

The mean GOPC visit in the SH group reached the highest in year-2 (5.36) and fell monotonically year by year and became the lowest in year+3 (3.58). A similar pattern was observed for GOPC visit in the control group. The mean GOPC visit in the control group was greater than the SH group in all years except in year-1 (for year-1: $p=0.517$; for other years: all $p<0.001$).

There was an initial increase in the mean SOPC visit in the SH group from year-2 (2.31) to year0 (3.30) and was followed by a subsequent monotonic decrease. The number of visits was the lowest in year+3 (2.25).

On the other hand, the mean visit to the A&E for patients in the SH group increased from 0.44 in year-2 and reached a peak in the index/event year (year0) (1.89) with a subsequent fall back. In general, the mean A&E visit was greater for the SH group than the control group in all years ($p<0.001$).

The mean utilization of allied health professionals' services was relatively low, with less than 0.3 for the SH group and less than 0.5 for the control group in all years.

Similarly, the mean hospital night stays in ICU, CCU and HDU for overnight hospitalization in the SH group was fairly low, with less than 0.13, 0.05 and 0.006 in all years, respectively. The average night stay in general ward troughed in year-2 (3. 04) and peaked at event year (17.58). On the other hand, the average night stay in general ward stayed similar throughout with a mean of around 6 nights. Overall, patients in the SH group had a far higher mean hospitalized nights than that for patients in the control group (17.75 vs 0.29, $p<0.001$) in event year.

As for healthcare services related to SH event, patients utilized overnight hospitalization the most in the event year (by staying in general ward), followed by the use of A&E services. In contrast, patients utilized A&E services the most from year+1 to year+3, followed by overnight hospitalization. In the event year, nearly all patients (98.6%) in SH group were admitted to a hospital, unlike those in the control group where only few (1.1%) were admitted.

In summary, the healthcare service of outpatient visits and overnight hospitalization of general ward, in particular, were mostly utilized by all patients, whereas A&E service and allied health professionals' services were utilized the least. Supplementary Table 4a-4e illustrates the factors associated with each healthcare service within event year for SH patients.

Costs

Figure 2 shows the annual average direct medical cost for SH patients and matched control from year-2 to year+3. In SH group, the mean cost of patients was the lowest in year-2, and reached the highest in event year, then dropped monotonically. The mean costs in year-1 and year+1 to year+3 were similar with a difference less than US$505. The mean cost in SH event year was US$11,751, which was more than twofold of year-1 and year+1 to year+3 and nearly 5 times of year-2. The mean cost related to SH was the greatest in event year which accounted for 42.1% of the cost, while the mean cost related to SH was similar in year+1 to year+3 and accounted for approximately 12-13% of the cost.

The annual direct medical cost of SH patients was much higher compared to that of patients in control group with its approximately five times greater in year-1, year+1, year+2 and year+3. The mean total cost of patients was more than tenfold of that of control group in event year. Incremental cost of SH versus matched control in the event year was US$10,873 (95% CI: US$ 10,502- US$11,244, p<0.001).

Comparison of annual direct medical cost by time and covariates

Table 1 presents the annual direct medical cost in the year of first SH event of each subgroup.

In our sample, males reported a significantly higher direct medical cost than females with the mean direct medical cost of male US$12,287 and that of female US$11,305 ($p=0.006$).

The minimum mean direct medical cost was US$8,329 for patients aged below 55 up to US$13,120 for patients aged 75 or above in the subgroup analysis as by age group. The mean costs between age groups were significantly different to each other ($p<0.001$).

Considering the direct medical cost by duration of DM ($p<0.001$), patients with DM for 1 to less than 5 years were recorded highest cost paid (US$14,345), and patients with DM for less than 1 year and for 5-10 years had close direct medical cost for around US$11,000.

In terms of the level of glycaemic control, patients with normal control (HbA1c<7%) were associated with significantly less direct medical cost (US$11,702) compared to those who had poor control (HbA1c≥7%) (US$12,578) ($p=0.039$).

For mortality status in the event year, patients who died (US$24,700) were recorded more than 2 times higher costs than that of patients who survived (US$9,552) ($p<0.001$).

For type of DM, the two types of patients got very close direct medical cost with difference approximately US$23 (T1DM: US$11,728 vs. T2DM: US$11,751, $p=0.991$).

For the number of existing co-morbid conditions (p<0.001), patients having CCI of 1 got the minimum direct medical cost (US$6,350) while patients with CCI equal to or greater than 4 got the maximum direct medical cost (US$12,416). Patients with CCI of 2 and 3 had similar average direct medical cost (US$7,596 and US$7,527 respectively).

The mean direct medical cost of patients having DM-related complications was US$15,218, approximately 50% higher than those without complications (US$10,082) (p<0.001).

Patients receiving different treatment modalities had different direct medical costs. Insulin users got the highest cost with mean US$13,643 while patients with lifestyle modification had the lowest cost with mean US$10,509 (p<0.001). The cost associated with attending GOPC (US$176 vs US$260, p<0.001) was significantly lower for patients having insulin than those with lifestyle modification, but was significantly higher in attending A&E service (US$271 vs US$141, p<0.001), allied health professional service (US$14 vs US$5, p<0.001), general ward (US$11,776 vs US9,321, p=0.001), ICU (US$758 vs US$199, p<0.001) and HDU (US$31 vs US6, p=0.021). Among the patients receiving oral anti-diabetic drug, patients prescribed with sulphonylurea was associated with the highest cost (US$12,063) but was insignificantly different to those on other drugs (US$10,015) (p=0.292).

Figure 3 displays the mean annual direct medical cost of SH patients by year and covariates. Regarding the cost by gender, the costs of males and females were similar in all years with males showing greater costs in year-1 and year0. For the cost by age group, SH patients of age greater than 75 years had the greatest cost in most years except year-2.

Concerning the cost by duration of DM, SH patients suffering from DM for 1 - < 5 years got the highest cost throughout all years except year-2. For glycaemic control, patients with normal or poor control were observed with similar cost in all years.

As to the cost by death group, SH patients who died within 1 year after year0 got higher costing from year-2 to year0 and had significantly greater increasing rate from year-1 to year0. In regard to cost by types of DM, SH patients suffering from T1DM had similar costing with those suffering from T2DM. With respect to the cost by CCI group, SH patients with CCI ≥ 4 got highest cost in most year except year-2. SH patients suffering from DM complication had higher costs than those with no DM complication in all years. For treatment modality, patients with insulin were observed with highest cost in all periods except year+2. To sum up, the cost of SH patients increased drastically from year-1 to year0 and dropped significantly from year0 to year+1 regardless of the covariate, so the shapes of the graphs and hence the trends were similar. Detailed results were shown in Supplementary Table 5a and Supplementary Table 5b for the direct medical costs of the patients in the years preceding and in the subsequent years of first SH by the covariates at index date, respectively.

Table 2 presents the effect of baseline covariates on direct medical costs in the event year by fitting a generalized linear model with gamma family and identity link. Male patients costed

US$1,043 more than female patients (p=0.004). Patients who suffered from DM for 1 year to less than 5 years spent US1,697 than those patients suffered from DM for less than 1 year (p=0.038). For glycaemic control, patients who had poor control costed US$1,459 than those who had good control (p<0.001). Patients who died within the event year would increase the cost by US$14,235 (p<0.001). For CCI, patients scored 2, 3 and 4 or above paid US$2,604 (p=0.024), US$2,985 (p=0.009) and US$4,993 (p<0.001) more by comparing to the patients scored 1 respectively. Any history of DM-related complications would increase the medical cost by US$3,239 (p<0.001), but the use of metformin would save US$1,742 (p=0.001).

Discussion

This study used population-based retrospective cohort data to describe the pattern of health service utilization and associated direct medical costs of DM patients in the event year, preceding years, and subsequent years of SH. The focus of the study is to estimate its economic impact and increased use of healthcare services associated with the occurrence of SH.

Healthcare utilization in event year of SH was higher than those in the preceding and subsequent years. Inpatient hospitalization costs were main driver in medical expenditure across the years. Our further analysis of healthcare service utilizations found that patients with history of DM-related complications and an increasing number of comorbidities were associated with greater hospitalization admission rates in the event year. Correspondingly, the increase in the direct medical costs were associated with poor glycaemic control [31], treatment intensification [32], incidence of DM-related complications [24, 33] and all-cause mortality [23]. The annual direct medical costs grew by 95.3% from $2,481 in two years preceding the SH to $4,846 in year preceding the SH. Such excessive growth in annual direct medical costs might be an additional valuable information to be utilized in risk assessment models for occurrence of first SH.

In contrast, healthcare services utilization in those without SH was lower, especially with a zero utilization of HDU and CCU in hospital stay during the study period. The major driver of total direct medical costs for matched controls was outpatient visits with a small proportion observed in emergency visits and allied health professionals in particular. Direct medical costs in the year of SH patients were approximately ten-fold higher than those without SH, primarily attributed to the additional length of hospital stays and emergency visits.

The type of DM and insulin use are highly inter-dependent, and have been identified as important covariates for direct medical costs in the SH event year. Although differences in cost per SH episode between patients with T1DM and T2DM exist across countries, our results were consistent with some published data. Using the Local Impact of Hypoglycaemia Tool for financial impact assessment, average direct medical cost of severe episodes for patients with T1DM was found to higher than those for patients with T2DM in a Spanish population [17, 21]. The results were similar to that for T2DM patients in Denmark [17], but less than that for T2DM patients in UK [16].

Comparing those with and without metformin, the direct medical costs at the SH event year for those with metformin were lower than those without metformin. Based on the local treatment regimen [34], a high proportion (23.3%) of patients only received lifestyle intervention. For those with HbA1c ≥7%, they were given oral anti-diabetes drugs, for instance metformin, as a monotherapy, when there was inadequate glycaemic control [34] despite lifestyle intervention.

In line with previous cost analyses [23, 24, 33], current analysis demonstrated that patients with poor glycaemic control, a history of DM-related complications and an increased number of comorbidities were associated with a high annual direct medical cost in SH event year. Given that a huge impact of SH occurrence, targeting those covariates were of importance in minimizing healthcare utilization and avoiding expensive direct medical cost in the event year, in both clinical and health economic perspectives.

Limitations

Although this study utilized a large retrospective cohort data, several limitations should be acknowledged. First, incidence of SH was identified by the first occurrence of SH captured by the retrospective database. Our study did not include records of SH occurred beyond the observation period, and records of SH requiring third-person assistance without transferring to hospital incurring subsequent emergency attendance and/or hospitalization. Moreover, SH recurrence, defined as having a patient with repeated SH records detected by ICD-9-CM diagnosis codes, could not identified in our retrospective database. Patients carried repeated SH records due to the follow-up SH episodes in outpatient clinics and hospitals. In addition, recognized risk factors including mild or moderate hypoglycaemia (causing non-specific symptoms such as tiredness, dizziness, and palpitation, etc.), insulin sensitivity, physical activity, dietary pattern, alcohol consumption, were neither coded in ICD-9-CM diagnosis coding nor routinely recorded in our retrospective database. Finally, current cost analysis estimated public healthcare resource utilization and associated annual direct medical costs attributable to DM patients is from the perspective of Hospital Authority, which is known to be the largest public healthcare provider in Hong Kong. Outpatient visits and hospitalization utilized in private healthcare providers, patients' out-of-pocket costs, and indirect costs measured by productivity losses were not measurable from our retrospective cohort data.

Conclusions

SH is associated with excessive hospitalization admission rates and associated with direct medical costs predominately in the first event year and significantly in the year before, comparative to the matched control patients without SH. The population-based cohort data highlighted that the increased rates of emergency visits and hospitalizations in the year before the first event could potentially be regarded as the occurrence of SH.

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Conflict of interest

Authors do not have any conflicts of interest.

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Legends to Figures

Figure 1. Mean annual healthcare resource use (and 95% confidence interval) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia and matched controls

Figure 2. Mean annual direct medical cost (US$, and 95% confidence interval) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia and matched controls

Figure 3. Mean annual direct medical cost (US$) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia by patient covariates (from left to right, up to down): 1. Gender; 2. Age group; 3. Duration of diabetes; 4. Glycaemic control; 5. Death within first year of severe hypoglycaemia; 6. Types of diabetes; 7. Charlson comorbidity index; 8. History of diabetes-related complication; and 9. Treatment modality

Tables

Table 1. Direct medical costs of the patients in the year of first severe hypoglycaemia by the covariates at index date

	N	Mean (US$)	SD	95% CI	P-value
Overall	11347	11751	18997	(11,401.71, 12,100.87)	
Gender					0.006*
Male	5157	12287	19419	(11,757.16, 12,817.42)	
Female	6190	11305	18628	(10,840.59, 11,768.90)	
Age					<0.001*
< 55 years	1192	8329	18554	(7,275.14, 9,383.82)	
55 - < 65 years	1527	9906	23133	(8,744.90, 11,067.30)	
65 - < 75 years	2628	11250	19348	(10,510.11, 11,990.27)	
≥ 75 years	6000	13120	17578	(12,675.30, 13,565.05)	
Duration of diabetes					<0.001*
< 1 years	1731	11512	20299	(10,554.74, 12,468.58)	
1 - < 5 years	3437	14345	21101	(13,639.18, 15,050.56)	
5 - < 10 years	2539	10951	19018	(10,210.59, 11,690.77)	
≥ 10 years	3640	9975	15707	(9,464.34, 10,485.19)	
Glycaemic control					0.039*
Normal (HbA1c<7%)	4054	11702	17094	(11,175.66, 12,228.36)	
Poor (HbA1c≥7%)	4000	12578	20807	(11,932.90, 13,222.88)	
Dead within the event year					<0.001*
Yes	1640	24770	23738	(23,620.56, 25,920.04)	
No	9707	9552	17124	(9,211.03, 9,892.43)	
Type of Diabetes					0.991
Insulin dependent (Type 1 diabetes)	92	11728	15543	(8,509.57, 14,947.41)	
Non-insulin dependent (Type 2 diabetes)	11255	11751	19024	(11,399.99, 12,102.97)	
Charlson Comorbidity Index					<0.001*
1	133	6350	17881	(3,282.85, 9,416.88)	
2	414	7596	20538	(5,611.41, 9,579.70)	
3	969	7527	17988	(6,392.78, 8,660.76)	
4 or above	9831	12416	18957	(12,040.99, 12,790.54)	
History of diabetes-related complications					<0.001*
Yes	3688	15218	21541	(14,522.25, 15,913.16)	
No	7659	10082	17399	(9,692.41, 10,471.85)	
Treatment modality					<0.001*‡
Lifestyle modification	2646	10509	17543	(9,840.19, 11,177.65)	
Insulin	638	13643	20513	(12,048.37, 15,237.84)	
Oral anti-diabetic drug	8460	11934	19136	(11,526.50, 12,342.15)	
Metformin	6248	11046	18592	(10,584.45, 11,506.64)	0.006*§
Sulphonylurea	7263	12063	19338	(11,618.68, 12,508.31)	
Others†	100	10015	14993	(7,040.45, 12,990.45)	

HbA1c = Hemoglobin A1c; SD = Standard Deviation; CI = Confidence Interval;

Notes:
*Significant difference at 0.05 level by independent t-test or one-way analysis of variance, as appropriate.
† Other anti-diabetic drugs included DPP4, TZD, GLP1, Meglitinide and Alpha-glucosidase inhibitors.

‡ Statistical test on the equality of direct medical costs across three treatment modalities: "Lifestyle modification", "Insulin" and "Oral anti-diabetic drug".

§ Statistical test on the equality of direct medical costs across three oral anti-diabetic drugs: "Metformin", "Sulphonylurea" and "Other anti-diabetic drug".

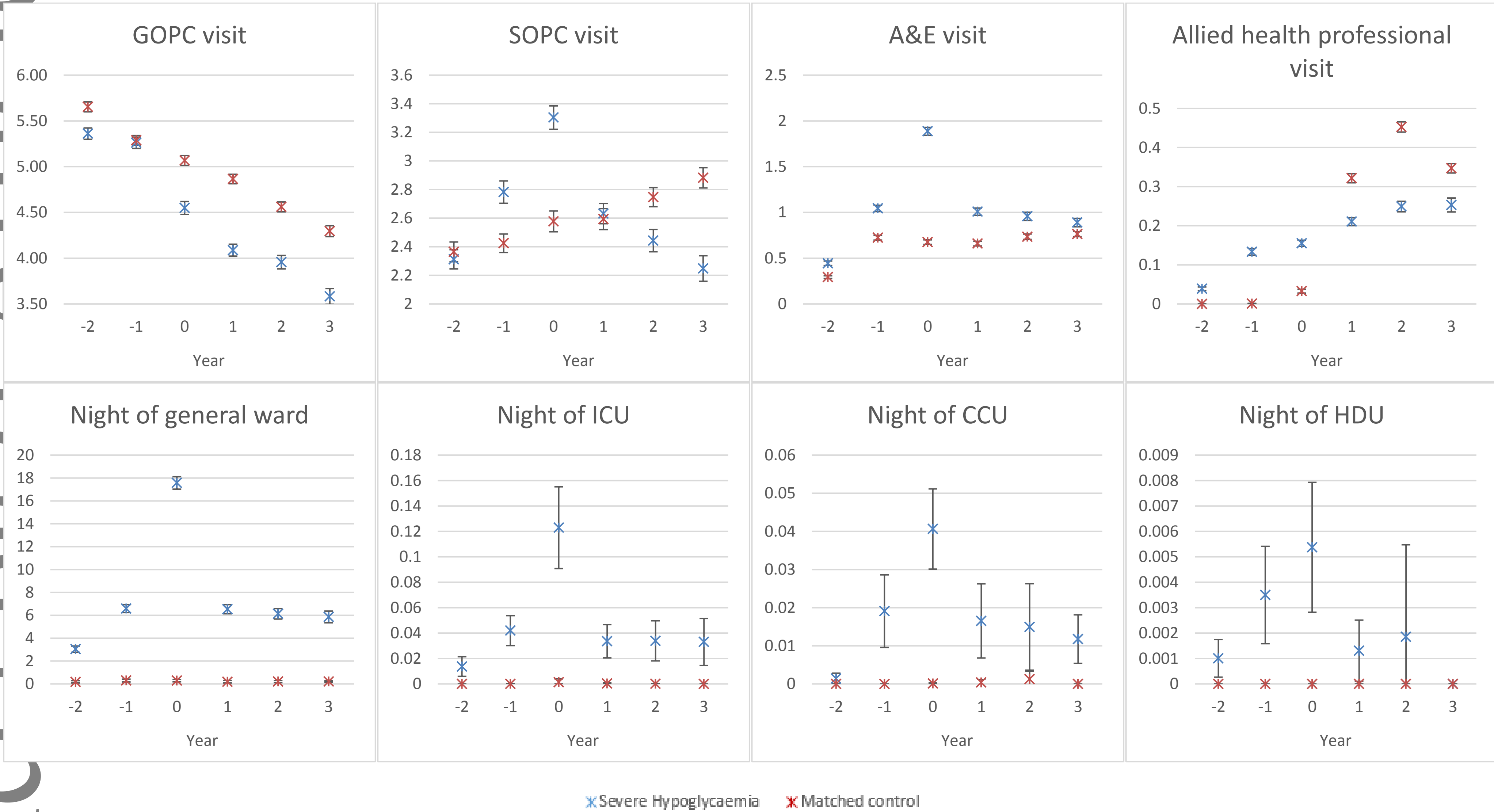
Table 2. Effect of baseline covariates on annual direct medical cost for patients with severe hypoglycaemia event within index year (Generalized linear model with gamma family and identity link function)

Covariate	Coefficient	95% CI	P-value
Constant	3,208.58	(-916.79, 7,333.94)	0.127
Age in years (“<55” as reference)			
55 - < 65	-679.57	(-2,333.97, 974.82)	0.421
65 - < 75	-670.91	(-2,507.42, 1,165.60)	0.474
≥ 75	115.81	(-1,676.82, 1,908.45)	0.899
Male (vs Female)	1,042.59	(324.00, 1,761.19)	0.004*
Duration of diabetes in years (“<1” as reference)			
1 - < 5	1,696.73	(92.60, 3,300.86)	0.038*
5 - < 10	173.47	(-1,350.58, 1,697.52)	0.823
≥ 10	-274.97	(-1,794.82, 1,244.88)	0.723
Glycaemic control (“Normal (HbA1c<7%)” as reference)			
Poor (HbA1c≥7%)	1,458.70	(760.93, 2,156.48)	<0.001*
Dead within 1 year after diagnosis of hypoglycaemia	14,235.28	(12,022.25, 16,448.31)	<0.001*
Type 2 diabetes (vs Type 1 diabetes)	820.04	(-2,695.18, 4,335.27)	0.648
Charlson Comorbidity Index (“1” as reference)			
2	2,603.91	(342.75, 4,865.06)	0.024*
3	2,985.00	(747.12, 5,222.88)	0.009*
4 or above	4,993.42	(2,640.51, 7,346.32)	<0.001*
History of any diabetes-related complications	3,238.81	(2,330.12, 4,147.50)	<0.001*
Treatment modality			
Lifestyle modification	-1,483.63	(-3,464.84, 497.59)	0.142
Use of Insulin	-327.44	(-1,845.06, 1,190.19)	0.672
Use of Oral anti-diabetic drug			
Use of Metformin	-1,742.26	(-2,735.89, -748.63)	0.001*
Use of Sulphonylurea	-348.09	(-1,360.81, 664.63)	0.501
Use of Other anti-diabetic drug†	-1,598.10	(-3,899.31, 703.12)	0.173

HbA1c = Hemoglobin A1c; CI = Confidence Interval;

Notes:
* Statistically significant with p-value <0.05.
† Other anti-diabetic drugs included DPP4, TZD, GLP1, Meglitinide and Alpha-glucosidase inhibitors.

Figure 1. Mean annual healthcare resource use (and 95% confidence interval) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia and matched controls



GOPC = general outpatient clinic; SOPC = specialist outpatient clinic; A&E = accident & emergency department; ICU = intensive care unit; CCU = cardiac care unit; HDU = high dependency unit

Figure 2. Mean annual direct medical cost (US$, and 95% confidence interval) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia and matched controls

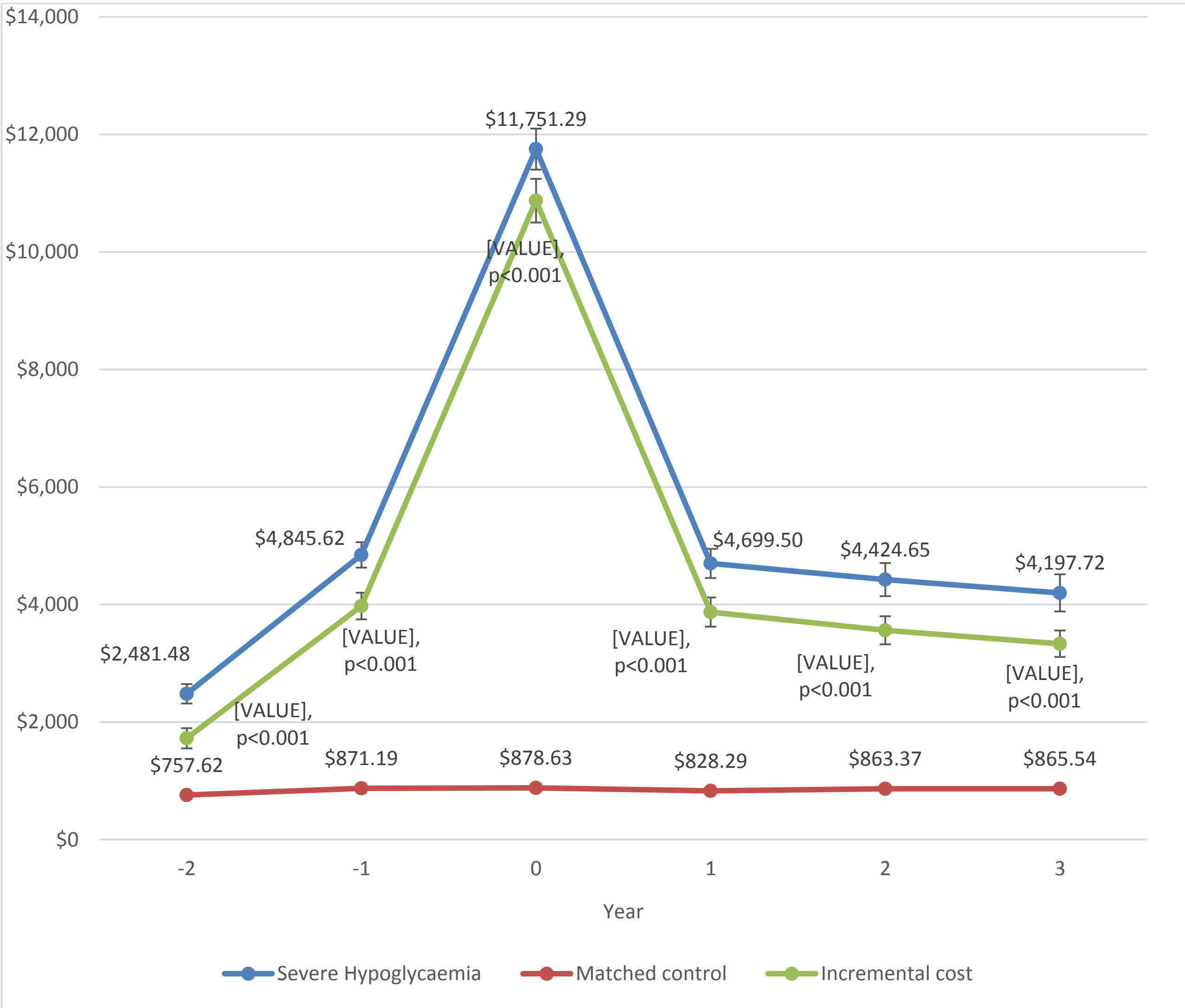


Figure 3. Mean annual direct medical cost (US$) in the preceding years, event year, and subsequent years of patients with first severe hypoglycaemia by patient covariates (from left to right, up to down): 1. Gender; 2. Age group; 3. Duration of diabetes; 4. Glycaemic control; 5. Death within first year of severe hypoglycaemia; 6. Types of diabetes; 7. Charlson comorbidity index; 8. History of diabetes-related complication; and 9. Treatment modality