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ORIGINAL RESEARCH

A Retrospective Cohort Study of Patients with Type 2 Diabetes in China: Associations of Hypoglycemia with Health Care Resource Utilization and Associated Costs

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ABSTRACT

Introduction: This study aimed to examine the associations of hypoglycemia with health care resource utilization (HCRU) and health care costs among patients with type 2 diabetes mellitus (T2DM) in China.

Methods: This retrospective cohort study was conducted with 23,680 T2DM patients >18 years old who visited the Second Affiliated Hospital of Nanchang University between 1 January 2011 and 31 December 2015. Univariate descriptive statistics were used to relate the HCRU and associated costs to patient characteristics, and regression analysis was used to examine the association between hypoglycemia and HCRU, controlling for other confounding factors.

Results: In the T2DM patients with or without insulin treatment, when compared with non-hypoglycemic patients, hypoglycemia was

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associated with more medical visits (all T2DM patients 19.48 vs. 10.46, insulin users 23.45 vs. 14.12) and higher diabetes-related medical costs (all T2DM patients ¥5187.54 vs. ¥3525.00, insulin users ¥6948.84 vs. ¥3401.15) and medication costs (T2DM patients ¥1349.40 vs. ¥641.92, insulin users: ¥1363.87 vs. ¥853.96). Controlling for age, gender, and Charlson comorbidity index (CCI) score, hypoglycemia and insulin intake were associated with greater health care resource utilization. As compared to nonhypoglycemic patients, hypoglycemic T2DM patients and those on insulin therapy performed more outpatient visits (proportions of hypoglycemic vs nonhypoglycemic T2DM patients performing 3+ visits: 72.69% vs. 65.49%; proportions of hypoglycemic vs nonhypoglycemic patients on insulin therapy performing 3+ visits: 78.26% vs. 71.73%) and were hospitalized more often (proportions of hypoglycemic vs nonhypoglycemic T2DM patients with 3+ admissions 75.90% vs. 50.24%; proportions of hypoglycemic vs nonhypoglycemic patients on insulin therapy with 3+ admissions: 83.19% vs. 58.51%).

Conclusion: Hypoglycemia in diabetes patients was associated with increased healthcare resource utilization and health-related expenditure, especially for patients on insulin treatment. Insulin treatment regimens should be more individualized and account for hypoglycemia risk.

Keywords: Diabetes; Healthcare cost; Healthcare utilization; Hypoglycemia

INTRODUCTION

Diabetes is currently one of the biggest public health issues worldwide. The World Health Organization states that the prevalence of diabetes has risen continuously from a total of 108 million (4.7%) globally in 1980 to around four times that number (8.5%) in 2014. China, which has the world's largest population and is undergoing sustained economic growth, is currently facing a serious diabetes epidemic: nearly 12% (114 million) of Chinese adults are diabetic (Dr. Margaret Chan at the 47th Meeting of the National Academy of Medicine, 2016). Adults living with diabetes suffer from a long-term economic burden and are at high risk of blindness, kidney failure, lower limb amputation, and several other long-term consequences that impact significantly on their quality of life [1].

Most (80–90%) cases of diabetes mellitus are of type 2 (T2DM), which is a progressive disease that affects glucose regulation [2, 3]. In recent years, the main goal of T2DM treatment has been to achieve good glycemic control [3] through a combination of diet, physical activity, and—if necessary—medication. Insulin therapy is an effective medication for achieving a common target of T2DM treatment: a glycated hemoglobin (HbA1c) level of below 7% [4, 5]. However, insulin therapy is a risk factor for iatrogenic hypoglycemia [6–9]. Diabetes-related hypoglycemia can cause complications such as pronounced effects on the cardiovascular (CV) system, atherosclerosis, patient depression, and even death [9–14]. Hypoglycemia can also significantly affect the quality of life of elderly patients due to their increased potential for dysrhythmias, accidents, falls, and neurological symptoms [15, 16]. All of these substantially influence healthcare utilization by and the burden of healthcare costs for diabetic patients [15, 17].

International studies have indicated that even though hypoglycemia prevalence varies markedly from country to country, the prevalence of hypoglycemia in each country is generally underestimated [17, 18]. In some recent Chinese studies it was found that the level of monitoring of glucose control outcomes varies among regions, but that the usage of insulin therapy is commonly high and is continuously increasing [19–22].

Given the increasing rate of hypoglycemia, the objective of this study of a subgroup of insulin users was to examine health care resource utilization (HCRU) by and health-related costs for Chinese T2DM patients with or without hypoglycemia.

METHODS

Data Sources

This retrospective cohort study was conducted with 23,680 patients with type 2 diabetes who were selected from 1,477,727 patients who were over 18 years old and visited the Second Affiliated Hospital of Nanchang University (SAHNU) between 1 January 2011 and 31 December 2015. All of the patients in this study were required to be alive and to visit the SAHNU at least once a year during the 4-year period. At visits to the SAHNU, patients were required to provide venous blood after fasting for >8 h overnight. Serum was separated from the venous blood and stored at − 80 °C before inspection. The electronic medical records from the Second Affiliated Hospital of Nanchang University database were processed using the da Vinci S® system (provided by HEBTA, Pearland, TX, USA). The records included admission, diagnosis, medication, testing, surgical, nursing, and cost data as well as images, and the database contained all of the clinical data for the hospital. We calculated the HCRU associated with diabetes complications in both the hypoglycemic and nonhypoglycemic cohorts.

Variables

Type 2 diabetes mellitus was identified in this study based on the ICD-10 codes E11, E11.901, and E11.902. The date of first recorded T2DM diagnosis was defined as the index date. Pre-index-date patient information was used to derive baseline data on demographic and illness characteristics. Hypoglycemia after the index date was identified based on the ICD-10 codes E16.01, E16.001, E16.101, and E16.201, or a laboratory-measured glucose level of ≤ 3.9 mmol/L. Post-index-date diabetes-specific HCRU variables included number of medical visits and hospitalization. Post-index-date health care costs included medical costs and prescription drug costs.

Statistical Methods

Univariate descriptive statistics were used to describe the patient diabetes-specific HCRU and associated costs. Continuous data were reported as mean values and standard deviations (SD), and categorical data were reported as percentages. T2DM patients and patients on insulin therapy with or without hypoglycemia were compared in terms of the number of visits to a physician, the percentage of patients who performed 3+ outpatient visits, the percentage of patients who underwent 3+ hospitalizations, and associated medical costs.

Binary logistic regression analysis was used to estimate the likelihood of an outpatient visit and the likelihood of hospitalization in the diabetes patients, and then groups of patients were compared based on an independent variable: either age group (19–64 years old, 65–-74 years old, or ≥ 75 years old), gender, Charlson comorbidity index (CCI) score (0–4, 5–10, or 11–14), hypoglycemic/nonhypoglycemic, and insulin use.

To further probe the relationship between HCRU and hypoglycemia, two multiple regression analyses controlling for baseline characteristics were conducted: a linear regression analysis of the number of outpatient visits and a Poisson regression analysis of number of hospitalizations. All statistical data were analyzed using the SPSS19.0 software package.

COMPLIANCE WITH ETHICS GUIDELINES

This article is based on previously conducted studies of de-identified medical records and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Among 23,680 patients with type 2 diabetes mellitus, 3.29% reported hypoglycemia (54.87% male, mean age 69.02 years old). Among the insulin users (n = 8187), 4.21% suffered from

Table 1 Baseline demographics and illness characteristics of the patients

Characteristic	Type 2 diabetes mellitus patients		Patients on insulin therapy	
	Hypoglycemic	Nonhypoglycemic	Hypoglycemic	Nonhypoglycemic
Number of patients (%)	780 (3.29)	22,900 (96.70)	345 (4.21)	7842 (95.78)
Age in years, mean (SD)	69.02 (11.55)	64.01 (12.81)	69.11 (11.73)	63.14 (13.16)
Gender (male %)	482 (54.87)	12,458 (54.40)	198 (57.39)	4386 (55.92)
CCI score, mean (SD)	4.62 (1.86)	3.66 (1.66)	4.77 (1.93)	3.83 (1.81)

SD standard deviation, *CCI* Charlson comorbidity Index

hypoglycemia (57.39% male, mean age 69.11 years old) (Table 1). As shown in Table 2, the CCI scores for T2DM patients and for patients on insulin therapy were higher when the patients were hypoglycemic than when they were not (4.62 vs. 3.66 and 4.77 vs. 3.83).

In T2DM patients, as compared with patients who did not report hypoglycemia, the patients with hypoglycemia had a higher number of medical visits (19.48 vs. 10.46) (Table 2), as well as higher diabetes-related medical costs (¥5187.54 per visit vs. ¥3525.00 per visit) and prescription drug costs (¥1349.40 per visit vs. ¥641.92 per visit). As shown in Table 2, among the patients who received insulin therapy, the patients with hypoglycemia had a higher number of medical visits (23.45 vs. 14.12). Among T2DM patients, the proportion with 3+ outpatient visits was 72.69% for the hypoglycemic group vs. 65.49% for the nonhypoglycemic group, while the corresponding proportions with 3+ hospitalizations were 75.90% and 50.24%, respectively. In a similar manner, among the patients taking insulin, the proportion with a mean number of outpatient visits of 3+ was 78.26% for hypoglycemic patients vs. 71.73% for nonhypoglycemic patients, while the corresponding proportions with 3+ admissions were 83.19% and 58.51%, respectively.

Table 3 shows effects of various patient characteristics on the likelihood of outpatient visits and hospital admissions. Compared with males, females had a lower risk of outpatient visits [OR 0.79 (0.73–0.84)] but a higher hospitalization risk [OR 1.15 (1.08–1.22)]. Patients aged 65–74 years and patients older than 74 years showed an increased frequency of hospitalization compared to those aged less than 65 years [OR 1.80 (1.64–1.98) and 2.73 (2.43–3.06), respectively]. Patients aged 65–74 years had a lower risk of outpatient visits than patients younger than 65 years old [OR 0.90 (0.82–0.98)] and patients older than 74 years [OR 0.82 (0.74–0.91)]. When the 65–74 year-old group was used as the reference, the risk for patients older than 74 was 1.51 times that for the reference group. Sicker T2DM patients had a higher hospitalization risk than healthier ones, as the OR for a CCI score of 5–10 vs. 0–4 was 3.03 (2.72–3.37) and the OR for a CCI score of 11–14 vs. 0–4 was 8.31 (2.63–26.28). The risk of outpatient visits [OR 1.50 (1.36–1.66)] or hospitalization [OR 6.40 (4.52–9.05)] was higher in hypoglycemic patients than in nonhypoglycemic patients. Patients on insulin were at a higher risk of walk-in visits than those who were not on insulin [OR 1.11 (1.04–1.18)].

Table 4 presents the results of multivariable linear regression analysis for outpatient visits and Poisson regression for hospitalization. CCI [regression coefficient: 4.37 (3.98–4.76)], hypoglycemia [regression coefficient: 19.07 (17.60–20.54)], and insulin use [regression coefficient: 5.52 (4.63–6.41)] were positively correlated with the number of outpatient visits. The number of hospitalizations was positively associated with gender, CCI, hypoglycemia, and insulin use [regression coefficients of 0.08 (0.05–0.12), 0.17 (0.15–0.19), 0.75 (0.70–0.79), and 0.17 (0.14–0.20), respectively]. Nevertheless, when the 19–64 year-old group was selected as the reference, the regression coefficient of the 65–74 year-old group was − 0.19 [− 0.22 to − 0.15] and that of the over 74 year-old group was 0.20 (0.16–0.23), meaning that the

Table 2 Dependence of HCRU and associated costs on patient characteristics

Characteristic	Type 2 diabetes mellitus patients		Patients on insulin therapy	
	Hypoglycemic	Nonhypoglycemic	Hypoglycemic	Nonhypoglycemic
Number of visits to the physician, mean (SD)	19.48 (33.79)	10.46 (19.15)	23.45 (35.95)	14.12 (24.16)
Number of outpatient visits[a]				
None, *N* (%)	118 (15.13)	4218 (17.90)	40 (11.59)	1251 (15.95)
1–2, *N* (%)	95 (12.18)	3897 (16.60)	35 (10.14)	966 (12.32)
3+ , *N* (%)	567 (72.69)	15,565 (65.49)	270 (78.26)	5625 (71.73)
Number of times patient was hospitalized[a]				
None, *N* (%)	3 (0.38)	4300 (18.76)	2 (0.58)	1348 (17.19)
1–2, *N* (%)	185 (23.72)	7284 (31.00)	56 (16.23)	1906 (24.31)
3+ , *N* (%)	592 (75.90)	12,096 (50.24)	287 (83.19)	4588 (58.51)
Costs (CNY)[b]				
Medical cost per visit, mean (SD)	5817.54 (18,156.07)	3525.00 (6832.26)	6948.84 (14,325.21)	3401.15 (6483.15)
Prescription drug cost per visit, mean (SD)	1349.40 (34,574.53)	641.92 (27,294.43)	1363.87 (37,434.04)	853.96 (34,037.53)
Inpatient cost per admission, mean (SD)	27,437.44 (37,902.24)	10,153.36 (18,671.26)	40,140.41 (42,615.87)	13,529.81 (21,940.84)
Outpatient cost per visit, mean (SD)	11,761.44 (32,801.13)	4608.88 (14,584.99)	14,296.82 (33,739.50)	6865.97 (19,358.07)
Outpatient reimbursement per person, mean (SD)	7605.88 (24,349.99)	3086.11 (11,152.56)	9569.48 (25,095.73)	4734.81 (14,353.15)

HCRU health care resource use

[a] Values shown are the number and percentage of hypoglycemic T2DM patients / nonhypoglycemic T2DM patients / hypoglycemic patients on insulin therapy / nonhypoglycemic patients on insulin therapy (depending on the column considered) who performed the specified number of outpatient visits or were hospitalized the specified number of times

[b] Exchange rate: USD 1 = CNY 6.40

frequency of hospitalization was lowest in the 65–74 year-old group and highest in patients older than 74 years.

DISCUSSION

To the best of our knowledge, our study is one of the first to use electronic medical records from a hospital to examine diabetes management in China. Hypoglycemia is commonly drug-induced in T2DM patients, while the most common cause of severe hypoglycemia is insufficient food intake [10]. Among the T2DM patients on insulin in our study, those who reported hypoglycemia performed more visits to the physician, were admitted to hospital more, and presented a greater economic burden

Table 3 Results of the binary logistic regression analysis of the effects of various patient characteristics on the likelihood of outpatient visits and hospital admissions

Variable	Outpatient[a]		Inpatient[a]	
	OR	95% CI	OR	95% CI
Age (count; 19–64 group used as reference)				
19–64 (18,285)	–	–	–	–
65–74 (10,620)	0.90	0.82–0.98	1.80	1.64–1.98
≥ 75 (8818)	0.82	0.74–0.91	2.73	2.43–3.06
Age (count; 65–74 group used as reference)				
19–64 (18,285)	1.12	1.01–1.23	0.55	0.50–0.61
65–74 (10,620)	–	–	–	–
≥ 75 (8818)	0.92	0.82–1.02	1.51	1.33–1.73
Gender[b]	0.88	0.83–0.93	1.15	1.08–1.22
CCI score				
0–4 (26,363)	–	–	–	–
5–10 (12,355)	1.05	0.97–1.15	3.03	2.72–3.37
11–14 (124)	0.94	0.55–1.59	8.31	2.62–26.28
Hypoglycemia[b]	1.50	1.36–1.66	6.40	4.52–9.05
Insulin[b]	1.11	1.04–1.18	1.02	0.96–1.09

[a] The dependent variable is a binary variable: whether the patient was an outpatient or whether they required hospitalization

[b] Independent variable: 0 = female/no; 1 = male/yes

(especially in terms of diabetes drugs) than those who did not report hypoglycemia. These findings are consistent with previous research showing that hypoglycemia significantly influences productivity and health care resource utilization and negatively affects patient quality of life [10, 17]. Studies show that patients who suffer from hypoglycemia tend to interrupt the therapy regimen (i.e., perform more medical visits) and are associated with higher diabetes-related costs [15, 23]. Among these costs, those associated with treating complications and drugs were the highest [24]. Whether or not the hypoglycemia is severe, the economic burden of a hypoglycemic patient is higher than that of a nonhypoglycemic patient [25–28].

In our study, we found that a confounder, age, influenced hospitalization frequency: older patients were at a higher risk of hospitalization than 19–64 year-old patients. Patients older than 74 years presented a lower frequency of hospitalization. However, this effect may relate to the association between age and the incidence of hypoglycemia and related complications. Elderly patients are more likely to develop complications of hypoglycemia due to decreasing physiological function [10]. The elderly are more prone to hypoglycemia than other age groups, but they also find it more difficult to spot their own symptoms of hypoglycemia [29, 30]. To avoid severe complications, the target blood glucose level among the elderly could be adjusted to give a moderate regimen with a target HbA1c level that is above 7% [31].

Self-monitoring and family support are important for T2DM patients, as they make it more likely that hypoglycemia will be identified promptly, and glycemic status could be monitored dynamically to ensure that blood glucose levels remain optimal [32, 33]. Adherence to the treatment regimen also influences the frequency of hypoglycemia, while adherence to diabetes treatment has generally been found to be poor [34, 35]. Efforts have been made to reduce the healthcare costs associated with hypoglycemia and to increase knowledge of hypoglycemia in patients and their families [36]. In addition to alleviating the hypoglycemia itself, hypoglycemic patients should be shifted to a more appropriate insulin therapy option in order to reduce side effects, improve the outcome, and to initially mitigate the burden on the patient [6, 37–41].

There are some limitations of this study. First, the retrospective design of the study meant that we could not pinpoint the causality in the relationship of T2DM-related hypoglycemia to HCRU and costs. Second, there may have been a selection bias, since we only obtained medical records from one hospital, and those records lacked data on discharge status and length of hospital stay, which are two important HCRU factors. Third, the hypoglycemia cases considered in this study were those of severe hypoglycemia, which requires medical attention. Cases of asymptomatic

Table 4 Factors associated with HCRU in T2DM patients

Factor[a]	Outpatient visits[b]		Hospitalization[c]	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Age (years)				
19–64	–	–	–	–
65–74	− 0.30	− 0.31 to − 0.29	− 0.19	− 0.22 to − 0.15
≥ 75	0.31	0.30–0.32	0.20	0.16–0.23
Gender	0.20	− 0.64 to 1.04	0.08	0.05–0.12
CCI	4.37	3.98–4.76	0.17	0.15–0.19
Hypoglycemia	19.07	17.60–20.54	0.75	0.70–0.79
Insulin	5.52	4.63–6.41	0.17	0.14–0.20

CI confidence interval

[a] The dependent variable is a continuous variable: the number of outpatient visits or hospitalizations

[b] Using linear regression for outpatient visits, 0 = female/no; 1 = male/yes for independent variables

[c] Using Poisson regression for hospitalization, 0 = male/yes; 1 = female/no for independent variables

hypoglycemia were not included in the hypoglycemia group, meaning that the prevalence and therefore social cost of hypoglycemia may have been underestimated in this study. Lastly, this study is a single-institute study, so the results may not be representative of the Chinese health system nationally; our findings cannot therefore be generalized to primary health institutions or other areas in China.

CONCLUSION

Insulin use and hypoglycemia in T2DM patients are associated with an increased likelihood of medical visits as well as greater healthcare resource utilization by and health-related expenditure on the patient. To ease the disease burden on and the economic burden of the patient, the insulin treatment regimen needs to be individualized, taking into account the patient's status.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available due to the confidentiality provision of SAHNU, but are available from the corresponding author on reasonable request.

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