Progress of Diabetes Severity Associated With Severe Hypoglycemia in Taiwan

Edy Kornelius, MD; Yi-Sun Yang, MD; Shih-Chang Lo, MD; Chiung-Huei Peng, DDS, PhD; Yung-Rung Lai, PharmD; Jeng-Yuan Chiou, PhD; and Chien-Ning Huang, MD, PhD

ABSTRACT

OBJECTIVES: The association between the progression of diabetes severity and risk of severe hypoglycemia is unknown. This study aimed to evaluate the association between the progression of diabetes severity and severe hypoglycemia in patients with diabetes.

STUDY DESIGN: A 13-year population-based retrospective cohort study of patients with diabetes in Taiwan.

METHODS: Diabetes progression was evaluated by the adapted Diabetes Complications Severity Index (aDCSI) score from index date to end of follow-up. The progression of diabetes severity was divided into 3 categories: slow, moderate, and rapid increase in aDSCI score. We further compared those 3 categories and evaluated the risk of first hospitalization due to severe hypoglycemia.

RESULTS: A total of 330,831 patients with diabetes were recruited. The mean age of patients in this study was 56.8 years, and mean follow-up duration was 9.3 years. The mean initial aDCSI score was 0.7, whereas the mean aDCSI score at the event date or end date was 2.9. A rapid increase in aDCSI score was associated with higher risk of severe hypoglycemia compared with a slow increase (hazard ratio, 4.91; 95% CI, 4.65-5.18). The incidence densities of severe hypoglycemia (per 1000 person-years) for slow, moderate, and rapid increase in aDCSI score were 2.3, 2.5, and 11.4, respectively.

CONCLUSIONS: This study demonstrated that rapid progression of diabetes complications was associated with higher risk of severe hypoglycemia. It is imperative that treating physicians identify patients with acute worsening of diabetes severity and provide proper hypoglycemia education and prevention care.

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The treatment of diabetes involves striking a delicate balance between attaining good glycemic control and avoiding hypoglycemic events. When ideal glycemic control is achieved, a favorable outcome can be expected due to the decreased frequency of microvascular and cardiovascular complications.[1-3] However, overtreatment with insulin or oral antidiabetic drugs (eg, a sulfonylurea) can lead to severe hypoglycemia, which has negative consequences due to its association with increased cardiovascular events,[4] cardiac arrhythmia,[5] cognitive impairment,[6] stress,[7] and mortality.[8] Although mild hypoglycemia can be easily resolved by consuming carbohydrates, when hypoglycemia occurs rapidly or goes untreated, confusion, seizure, or irreversible cognitive impairment can occur.

Severe hypoglycemia, which is a diabetes emergency, is defined as having low blood glucose that requires the assistance of another person to treat. The frequency of severe hypoglycemia is common. It has been estimated that about 7% to 25% of patients with type 2 diabetes who use insulin experience at least 1 severe episode annually.[9] Nevertheless, the distribution of severe hypoglycemia in patients with diabetes is skewed, with a small proportion (5%) of patients accounting for the majority (54%) of severe hypoglycemic events.[10] Therefore, it is important to improve the methods by which patients with a high risk of hypoglycemia are identified and managed. Previous study findings have demonstrated several risk factors for severe hypoglycemia in patients with diabetes, including antidiabetic medication prescription,[11-13] previous hypoglycemia,[13,14] preexisting retinopathy,[13] depression,[13] vigorous exercise,[13] history of chronic kidney disease,[15] advanced age,[16] and hypoglycemia unawareness.[17]

Moreover, the timing and progression of diabetes severity might play an important role in the development of severe hypoglycemia. However, few studies in the literature address the association between progression of diabetes severity and risk of severe hypoglycemia. Therefore, we conducted a 13-year population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD) to evaluate the association between the progression of diabetes severity and severe hypoglycemia in patients with newly diagnosed

TAKEAWAY POINTS

- Rapid progression of diabetes complications was associated with higher risk of severe hypoglycemia.
- Being 45 years or older or having a prescription for insulin or sulfonylureas was associated with increased risk of severe hypoglycemia, whereas having a prescription for biguanides, α-glucosidase inhibitors, thiazolidinediones, or dipeptidyl peptidase-4 inhibitors was associated with a lower risk of hypoglycemia.
- Patients with metabolic complications had the highest risk of severe hypoglycemia.

diabetes. We hypothesized that a rapid progression of adapted Diabetes Complications Severity Index (aDCSI) score is associated with higher risk of severe hypoglycemia.

METHODS AND MATERIALS

Setting and Data Source

This observational retrospective cohort study was conducted using the Longitudinal Cohort of Diabetes Patients database, which was obtained from Taiwan's National Health Insurance (NHI) program. This program is a compulsory insurance system that is regulated by Taiwan's government, providing coverage for almost 99% of the population. For data protection and privacy reasons, the NHIRD releases only about 75% of data from the diabetic population for research purposes every year. This data set contains detailed information pertaining to patients' disease diagnoses, drug prescriptions, medical expenses, hospital admissions, and discharge diagnoses. A detailed description of patient recruitment and sampling procedures is available on the NHIRD website.[18] The information on disease diagnoses, drug prescriptions, and hospitalizations contained in the NHIRD is of high quality, and numerous studies have been published based on data obtained from this database.[19] The accuracy of diabetes diagnoses in this NHI claims database has been validated with a good positive predictive value.[20] All patients' data in the NHIRD are encrypted and scrambled before being released to the public for academic research. Data for this study were extracted and analyzed by 1 independent reviewer. This study was reviewed and approved by the Institutional Review Board of Chung Shan Medical University Hospital (Taichung, Taiwan).

Participants

Patients were enrolled in the study by random selection of 360,000 newly diagnosed patients with diabetes between 1999 and 2001. Diabetes was defined as either an inpatient hospitalization for diabetes diagnosed in accordance with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 250.x, at least 2 outpatient physician visits with *ICD-9-CM* code 250.x, or 1 outpatient physician visit with *ICD-9-CM* code 250.x plus a prescription for an oral antihyperglycemic agent within 365 consecutive days. All patients with diabetes diagnosed during this study period were included except those with gestational diabetes. Patients were tracked from January 1, 1999, to December 31, 2011, with a total follow-up duration of 13 years. Overall, 330,831 patients were included in the retrospective cohort analyses.

Progress of Diabetes Severity and aDCSI Score

The Diabetes Complications Severity Index (DCSI), which was developed by Young et al in 2008, measures the severity of diabetes-related complications and is used to predict the risk of diabetes-related hospitalizations, healthcare utilization,[21] and mortality. A DCSI score ranges from 0 to 13 according to the presence of 7 categories of diabetes complications: retinopathy, nephropathy, neuropathy, stroke, cardiovascular disease, peripheral vascular disease, and metabolic complications. Each diabetes complication category is scored on a range of 0 to 2, determined by the presence and severity of complications (0 = not present, 1 = some abnormality, 2 = severe abnormality), except for neuropathy, which is given a score of 0 or 1 (0 = not present, 1 = abnormal). For example, within the cardiovascular category, patients with angina pectoris would be given a score of 1, whereas patients with myocardial infarction would have a score of 2. When multiple complications within the same category exist, the highest score within that category should be used (score of 2). It should be noted that the presence of severe hypoglycemia was identified as a disease event, rather than a DCSI item (**eAppendix Figure** [eAppendices available at **ajmc.com**]).

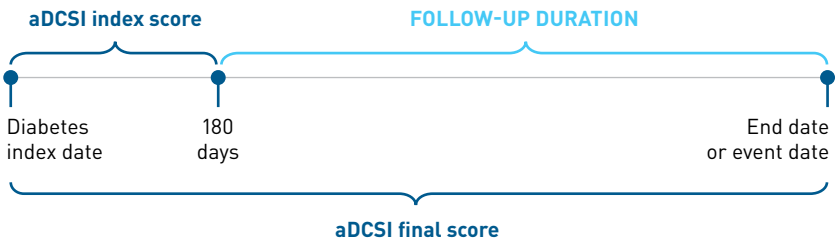
The patients' original DCSI scores were calculated using a combination of their diagnosis code (*ICD-9-CM* code) and laboratory data (within nephropathy category). However, a recently modified version of the DCSI developed by Chang et al, known as aDCSI, which omits laboratory data from the nephropathy category, was demonstrated to be as effective as the original DCSI for estimating diabetes severity and predicting hospitalizations.[22] The aDCSI was validated in a study that analyzed data from Taiwan's NHIRD, and the results showed that the performance of the aDCSI in predicting the risk of hospitalization was similar to that of the original DCSI found in the study by Young et al.[23]

Study Protocol

All patients with diabetes and their complications were identified from the index date, and the patients were followed until the event date (severe hypoglycemia) or the end date of the study (disenrollment, mortality, or December 31, 2011). An observation for each patient was stopped after the first episode of severe hypoglycemia. The highest aDCSI score occurring in the first 6 months after diagnosis of diabetes was used as the initial aDCSI score (**Figure**). When diabetes complications within the same category appeared multiple times during this study period, they were calculated only once. The progression of

diabetes severity was defined as the increase in aDCSI score per year, which was calculated by subtracting the initial aDCSI score from the total aDCSI score during this study period and dividing by the number of observation years. For instance, patient A had retinopathy at the initial diagnosis of diabetes and thus had a DCSI score of 1. In the fifth year, 1 additional diabetes complication developed (diabetic neuropathy with aDCSI score = 1) without the occurrence of severe hypoglycemia. In the seventh year, he experienced severe hypoglycemia, and during that time, he also had a first stroke (aDSCI score = 2), so his total aDCSI score was 4. Thus, the final score of progression of diabetes severity was 0.43 per year, which was obtained by subtracting the initial aDCSI score of 1 from the total aDCSI score of 4 and then dividing by 7, the number of observation years. We further classified the progression of diabetes severity into 3 categories (approximately 110,000 patients in each group): slow (increased scores of <0.1 per year), moderate (increased scores of 0.1-0.3 per year), or rapid increase in aDCSI score (increased scores of >0.3 per year). Thus, in this example, patient A should be categorized in the third group with an increase in aDCSI score of more than 0.3 per year.

FIGURE. Example of the Operational Definition of Eligibility[a]



aDCSI indicates adjusted Diabetes Complications Severity Index.

[a]The highest aDCSI score during the first 6 months since diagnosis of diabetes was used as the initial aDCSI score. The progression of diabetes severity was defined as the increase in aDCSI score per year, which was calculated by subtracting the initial aDCSI score from the total and final aDCSI score during this study period and then dividing this figure by the number of observation years.

Disease Variables

The date of diabetes diagnosis was defined as the index date. Patients were followed until the first event of severe hypoglycemia, which served as the event date, or the end date, which was designated as disenrollment; mortality; or December 31, 2011. Severe hypoglycemia was defined as a diagnosis of patients who required hospitalization or a visit to an emergency department (ED) for treatment with an *ICD-9-CM* code of 250.3, 251.0, 251.1, 251.2, or 962.3. Because of the possibility of ambiguity with *ICD-9-CM* code 250.3 (diabetes with other coma) between diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS) with hypoglycemic coma,[24] we manually identified and analyzed our data for patients who were diagnosed with *ICD-9-CM* code 250.3. However, none of the patients in our study population appeared to have DKA/HHS with hypoglycemic coma. Disease comorbidities that potentially increased the risk of severe hypoglycemia, such as hypertension (*ICD-9-CM* codes 401-405), coronary heart disease (*ICD-9-CM* codes 414, 429.2), chronic liver disease (*ICD-9-CM* code 571), chronic kidney disease (*ICD-9-CM* code 585), heart failure (*ICD-9-CM* code 428), cancer (*ICD-9-CM* codes 140-208), depression (*ICD-9-CM* codes 296.2, 296.3), chronic obstructive pulmonary disease (*ICD-9-CM* codes 490-492, 494, 496), and stroke (*ICD-9-CM* codes 430-437), were identified, as were prescriptions for antidiabetic drugs, such as biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, glinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin. Antidiabetic medication prescription was defined as a prescription with a drug exposure window of at least 180 days during this study period. A cutoff of 180 days was applied to avoid an irregular pattern of drug use, which might be related to patients' nonadherence or initial antidiabetic drug adverse effects. The primary end point of this study was the first hospitalization due to severe hypoglycemia.

Statistical Analysis

Hazard ratios (HRs) and 95% CIs for the Cox proportional hazards model were used to analyze the data and determine the risk of severe hypoglycemia. One-way analysis of variance was used to compare data among the 3 groups. The Kaplan-Meier method was used to estimate severe hypoglycemia cumulative incidences. A 2-sided *P* value <.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS Statistical Package, version 18 (SPSS; Chicago, Illinois).

RESULTS

Table 1 shows the baseline demographic characteristics of the patients in this study. A total of 330,831 patients were included in this cohort from January 1, 1999, through December 31, 2011. The mean age was 56.8 years, and mean follow-up duration was 9.3 years. The mean initial aDCSI score was 0.7, whereas the mean aDCSI score at the event date or end date was 2.9. Patients with rapid increase in aDSCI score per year generally were older, were more likely to be male, and had more disease comorbidities and complications and a shorter follow-up duration.

Table 2 shows that the risks of severe hypoglycemia were associated with progression in aDCSI score. Compared with the patients with diabetes with slow progression of diabetes severity (increase in aDCSI score of <0.1 per year), the HRs of patients with moderate progression (increase of 0.1-0.3) and rapid progression (increase of >0.3) increased in proportion to diabetic progression, with HRs of 1.08 (95% CI, 1.02-1.14) and 4.91 (95% CI, 4.65-5.18),

TABLE 1. Baseline Demographic Characteristics of Study Population (N = 330,831)

			Increase in aDCSI Score Per Year						
			Slow		Moderate		Rapid		
	n	%	n	%	n	%	n	%	*P*
Age, years			110,315		110,198		110,318		<.001*
<45	69,768	21.1	37,914	34.4	21,877	19.9	9977	9.0	
45-54	79,255	24.0	27,674	25.1	31,577	28.7	20,004	18.1	
55-64	75,119	22.7	20,022	18.1	28,226	25.6	26,871	24.4	
65-74	69,895	21.1	15,117	13.7	21,299	19.3	33,479	30.3	
75-84	31,309	9.5	7634	6.9	6589	6.0	17,086	15.5	
≥85	5485	1.7	1954	1.8	630	0.6	2901	2.6	
Mean ± SD	56.8 ± 15.1		51.6 ± 16.7		55.7 ± 13.1		63.1 ± 12.9		<.001*
Gender									<.001*
Female	161,551	48.8	53,825	48.8	56,499	51.3	51,227	46.4	
Male	169,280	51.2	56,490	51.2	53,699	48.7	59,091	53.6	
Comorbidities									
Hypertension	243,741	73.7	59,175	53.6	87,388	79.3	97,178	88.1	<.001*
Coronary heart disease	127,074	38.4	16,227	14.7	47,009	42.7	63,838	57.9	<.001*
Chronic liver disease	145,748	44.1	41,714	37.8	53,743	48.8	50,291	45.6	<.001*
Chronic kidney disease	39,407	11.9	2072	1.9	8390	7.6	28,945	26.2	<.001*
Heart failure	58,687	17.7	3841	3.5	14,335	13.0	40,511	36.7	<.001*
Cancer	63,315	19.1	17,094	15.5	19,881	18.0	26,340	23.9	<.001*
Major depressive disorder	14,192	4.3	3241	2.9	5040	4.6	5911	5.4	<.001*
COPD	145,429	44.0	35,214	31.9	49,405	44.8	60,810	55.1	<.001*
Stroke	105,050	31.8	10,240	9.3	29,190	26.5	65,620	59.5	<.001*
Antidiabetic drugs									
Biguanides	137,123	41.4	32,091	29.1	53,550	48.6	51,482	46.7	<.001*
Sulfonylureas	149,421	45.2	34,233	31.0	55,479	50.3	59,709	54.1	<.001*
α-glucosidase inhibitors	35,241	10.7	7184	6.5	14,488	13.1	13,569	12.3	<.001*
Thiazolidinediones	41,361	12.5	9471	8.6	17,606	16.0	14,284	12.9	<.001*
Glinides	21,121	6.4	3646	3.3	7695	7.0	9780	8.9	<.001*
DPP-4 inhibitors	17,346	5.2	4218	3.8	7921	7.2	5207	4.7	<.001*
Insulin and analogues	19,298	5.8	2964	2.7	6301	5.7	10,033	9.1	<.001*
Diabetes complications									
Retinopathy	76,960	23.3	5753	5.2	28,750	26.1	42,457	38.5	<.001*
Nephropathy	129,350	39.1	16,332	14.8	41,890	38.0	71,128	64.5	<.001*
Neuropathy	126,849	38.3	17,117	15.5	47,960	43.5	61,772	56.0	<.001*
Cerebrovascular	94,096	28.4	8294	7.5	23,682	21.5	62,120	56.3	<.001*
Cardiovascular	179,151	54.2	26,325	23.9	64,614	58.6	88,212	80.0	<.001*
Peripheral vascular disease	63,760	19.3	4691	4.3	18,678	16.9	40,391	36.6	<.001*
Metabolic	18,282	5.5	1755	1.6	3233	2.9	13,294	12.1	<.001*
aDCSI score, mean ± SD									
Onset	0.7 ± 1.1		0.7 ± 1.1		0.6 ± 1.0		0.7 ± 1.1		<.001*
End of follow-up (track duration)	2.9 ± 2.3		0.9 ± 1.2		2.7 ± 1.2		5.2 ± 1.9		<.001*
Track duration (years), mean ± SD	9.3 ± 3.2		9.3 ± 3.7		10.4 ± 1.6		8.2 ± 3.6		<.001*

aDCSI indicates adjusted Diabetes Complications Severity Index; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4.
*P <.05.

TABLE 2. Cox Proportional Hazards Model Between aDCSI Score and Severe Hypoglycemia

	Patients With Severe Hypoglycemia (n)	Observed Person-Years	Incidence Density (per 1000 person-years)	aHR[a]	95% CI
Increase in aDCSI score per year					
Slow	2360	1,024,212	2.3	1	
Moderate	2857	1,142,101	2.5	1.08*	1.02-1.14
Rapid	10,333	907,438	11.4	4.91*	4.65-5.18
Age, years					
<45	1576	724,046	2.2	1	
45-54	2320	804,097	2.9	1.24*	1.16-1.32
55-64	3796	728,390	5.2	2.21*	2.08-2.36
65-74	5245	595,012	8.8	3.90*	3.67-4.15
75-84	2325	200,463	11.6	5.67*	5.28-6.08
≥85	288	21,743	13.2	7.27*	6.38-8.28
Gender					
Female	8213	1,546,618	5.3	1	
Male	7337	1,527,133	4.8	0.91*	0.89-0.94
Comorbidities					
Hypertension	13,010	2,307,188	5.6	0.79*	0.75-0.83
Coronary heart disease	6890	1,207,297	5.7	0.75*	0.72-0.78
Chronic liver disease	5813	1,429,275	4.1	0.75*	0.73-0.77
Chronic kidney disease	3045	347,382	8.8	1.00	0.96-1.04
Heart failure	3893	501,383	7.8	0.87*	0.84-0.91
Cancer	2506	532,330	4.7	0.75*	0.71-0.78
Major depressive disorder	612	139,644	4.4	0.93	0.85-1.01
COPD	6570	1,359,643	4.8	0.68*	0.66-0.70
Stroke	6673	948,692	7.0	0.72*	0.70-0.75
Antidiabetic drugs					
Biguanides	8547	1,349,487	6.3	0.79*	0.76-0.83
Sulfonylureas	10,663	1,427,991	7.5	2.91*	2.78-3.04
α-glucosidase inhibitors	1895	363,132	5.2	0.78*	0.74-0.82
Thiazolidinediones	2047	428,608	4.8	0.79*	0.75-0.83
Glinides	1385	210,788	6.6	0.91*	0.86-0.97
DPP-4 inhibitors	235	185,420	1.3	0.21*	0.19-0.24
Insulin and analogues	1992	189,721	10.5	1.85*	1.76-1.95

aDCSI indicates adjusted Diabetes Complications Severity Index; aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4.
*P <.01.
[a]aHR was adjusted by all variables, including age, gender, comorbidities, and antidiabetic drugs.

respectively. The incidence densities of severe hypoglycemia (per 1000 person-years) for slow, moderate, and rapid increase in aDCSI score were 2.3, 2.5, and 11.4, respectively.

Table 3 shows the risk of severe hypoglycemia with different diabetes complications. Before adjustment for potential confounders, all diabetes complications were associated with higher risk of severe hypoglycemia. However, after adjustment for age, gender, and antidiabetic medication, patients with metabolic complications showed the highest risk of severe hypoglycemia (HR, 1.96; 95% CI, 1.87-2.06). Retinopathy (HR, 1.11; 95% CI, 1.07-1.15), nephropathy (HR, 1.33; 95% CI, 1.28-1.37), and stroke (HR, 1.21; 95% CI, 1.17-1.25) were also associated with severe hypoglycemia. Meanwhile, cardiovascular disease (HR, 0.90; 95% CI, 0.87-0.93) was associated with lower risk of severe hypoglycemia.

The eAppendix Figure shows the Kaplan-Meier curves of the cumulative incidence of severe hypoglycemia in the 3 groups of

TABLE 3. Cox Proportional Hazards Model of Diabetes Complication Subgroups With Severe Hypoglycemia

	Patients With Severe Hypoglycemia (n)	HR	95% CI	aHR[a]	95% CI
Diabetes complications					
Retinopathy	5199	1.45*	1.41-1.50	1.10*	1.07-1.14
Nephropathy	8272	1.79*	1.73-1.84	1.31*	1.26-1.35
Neuropathy	7430	1.32*	1.28-1.36	1.05*	1.02-1.09
Cerebrovascular disease	6298	1.89*	1.83-1.95	1.55*	1.45-1.67
Cardiovascular disease	9709	1.45*	1.41-1.50	1.07*	1.02-1.12
Peripheral vascular disease	4225	1.52*	1.46-1.57	1.10*	1.05-1.14
Metabolic disease	2149	2.99*	2.85-3.12	1.96*	1.87-2.05

aDCSI indicates adjusted Diabetes Complications Severity Index; aHR, adjusted hazard ratio; HR, hazard ratio.
*P <.01.
[a]aHR was adjusted by all variables, including age, gender, comorbidities, and antidiabetic drugs.

TABLE 4. Cox Proportional Hazard Model of Increase in aDCSI Score Per Year With Severe Hypoglycemia

	Increase in aDCSI Score Per Year (ref: slow)			
	Moderate		Rapid	
	aHR[a]	95% CI	aHR[a]	95% CI
Age, years				
<45	1.90**	1.63-2.23	13.76**	11.76-16.09
45-54	1.29**	1.12-1.49	7.47**	6.50-8.58
55-64	1.07	0.95-1.20	4.77**	4.26-5.33
65-74	0.90*	0.82-0.99	3.46**	3.15-3.81
75-84	0.60**	0.52-0.70	2.19**	1.92-2.50
≥85	0.52**	0.33-0.82	1.64**	1.16-2.30
Gender				
Female	1.11*	1.02-1.20	4.51**	4.18-4.87
Male	1.02	0.94-1.11	5.34**	4.94-5.78
Comorbidities				
Hypertension				
No	0.93	0.82-1.05	6.29**	5.63-7.02
Yes	1.04	0.97-1.11	4.29**	4.03-4.57
Coronary heart disease				
No	1.06	0.99-1.14	5.43**	5.09-5.79
Yes	1.02	0.90-1.15	3.89**	3.47-4.36
Chronic liver disease				
No	0.97	0.90-1.04	4.55**	4.26-4.86
Yes	1.33**	1.20-1.46	5.69**	5.17-6.27
Chronic kidney disease				
No	1.11**	1.04-1.17	4.97**	4.69-5.26
Yes	0.26**	0.21-0.33	1.23	0.99-1.50

(continued)

aDCSI score increase per year. The Kaplan-Meier curves showed that the risk of severe hypoglycemia seemed to emerge in the first year, and it can be seen that there was marked divergence of aDCSI score increase among the 3 groups over the 13-year follow-up period.

Table 4 shows various model adjustments that were performed to evaluate the risk of severe hypoglycemia according to the progression of diabetes complications. Despite adjustment for age, gender, disease comorbidities, and prescriptions for antidiabetic drugs, the progression of diabetes complications still had a significant effect on the risk of developing severe hypoglycemia.

DISCUSSION

This study found that progression of diabetes severity was associated with an increased incidence of severe hypoglycemia. To the best of our knowledge, this is the first study to examine the association between progression of diabetes severity and risk of severe hypoglycemia. An increase in aDCSI score per year was positively related to risk of severe hypoglycemia. Furthermore, we found that being older than 45 years or having a prescription for insulin or a sulfonylurea was associated with increased risk of severe hypoglycemia, whereas having a prescription for biguanides, α-glucosidase inhibitors, thiazolidinediones, or DPP-4 inhibitors was associated with a lower risk of hypoglycemia.

The progression of diabetes complications is difficult to quantify. The severity of diabetes complications increases with time after diabetes onset, and patients with diabetes often exhibit different patterns of progression and complications. Previous study findings have demonstrated that patients with older age,[16] previous hypoglycemia,[13,14] history of chronic kidney disease,[15] retinopathy,[13] and antidiabetic drug prescriptions[11-13] have a higher risk of hypoglycemia. In this study, we further explored the importance of timing and severity of these complications. We used increase in aDCSI score per year to measure the progression of diabetes complications. Compared with patients with slow progression of diabetes

complications, severe hypoglycemia occurred more frequently in patients with complications that progressed rapidly within a short period of time. Furthermore, we demonstrated that severe hypoglycemia risk increased in proportion to the progression of diabetes complications (Table 4).

Surprisingly, patients with metabolic complications, such as DKA or HHS, had the highest risk of developing severe hypoglycemia. In these patients, a high degree of glucose variability might contribute to the mechanism of severe hypoglycemia.[25,26] The potential mechanism of hypoglycemia might be characterized by deficient counterregulatory hormone release, especially in older patients, and a diminished autonomic response.[27]

Regarding antidiabetic medications, our findings showed that sulfonylurea prescription (HR, 2.50; 95% CI, 2.39-2.61) was associated with the highest risk of hypoglycemia, whereas DPP-4 inhibitor prescription was correlated with the lowest risk of hypoglycemia (HR, 0.22; 95% CI, 0.22-0.25). This finding was consistent with results reported in a previous study.[11-13]

Strengths and Limitations

This study has several strengths, most notably its large sample size and long-term follow-up. Our data are representative of Taiwan's general population. To minimize the risk of selection bias and overdiagnosis of severe hypoglycemia, we included only patients who required hospitalization or an ED visit with a primary diagnosis of hypoglycemia.

The potential limitations of this study should also be noted. First, because the NHIRD is primarily maintained for reimbursement purposes, there were no data on patients' personal information, such as smoking history, body weight, and body mass index; laboratory data, including glucose level, glycated hemoglobin, and lipid profile; and dosage of medications, such as insulin, which may each potentially influence the risk of hypoglycemia. Second, patients with self-reported severe hypoglycemia who did not have an ED visit or hospital admission were not included in this study. Third, the retrospective nature of the study itself may have potentially resulted in selection bias. Finally, this study included only

TABLE 4. *(Continued)* Cox Proportional Hazard Model of Increase in aDCSI Score Per Year With Severe Hypoglycemia

	Increase in aDCSI Score Per Year (ref: slow)			
	Moderate		Rapid	
	aHR[a]	95% CI	aHR[a]	95% CI
Heart failure				
No	1.12**	1.06-1.19	5.37**	5.07-5.70
Yes	0.43**	0.35-0.51	1.50**	1.28-1.77
Cancer				
No	1.10**	1.03-1.17	5.27**	4.96-5.59
Yes	0.93	0.80-1.07	3.31**	2.88-3.80
Major depressive disorder				
No	1.07*	1.01-1.13	4.93**	4.67-5.21
Yes	1.40*	1.01-1.94	4.23**	3.05-5.85
COPD				
No	1.03	0.96-1.11	5.23**	4.89-5.59
Yes	1.16**	1.05-1.28	4.43**	4.03-4.88
Stroke				
No	1.15**	1.07-1.22	5.94**	5.58-6.33
Yes	0.54**	0.48-0.61	1.89**	1.70-2.10
Antidiabetic drugs				
Biguanides				
No	0.96	0.89-1.05	5.15**	4.77-5.55
Yes	1.22**	1.12-1.32	4.73**	4.37-5.13
Sulfonylureas				
No	1.09	0.99-1.20	6.36**	5.82-6.96
Yes	1.02	0.95-1.09	4.07**	3.80-4.35
α-glucosidase inhibitors				
No	1.03	0.97-1.09	5.01**	4.73-5.31
Yes	1.64**	1.35-1.98	4.45**	3.68-5.38
Thiazolidinediones				
No	1.00	0.94-1.06	4.91**	4.64-5.20
Yes	1.93**	1.61-2.30	5.39**	4.50-6.45
Glinides				
No	1.04	0.98-1.11	4.91**	4.65-5.20
Yes	1.66**	1.29-2.13	4.94**	3.86-6.33
DPP-4 inhibitors				
No	1.04	0.98-1.10	4.84**	4.58-5.11
Yes	3.10**	1.75-5.50	4.34**	2.38-7.90
Insulin and analogues				
No	0.99	0.93-1.05	4.59**	4.34-4.86
Yes	1.19	0.99-1.42	3.91**	3.32-4.61

aDCSI indicates adjusted Diabetes Complications Severity Index; aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; ref, reference.
*P <.05; **P <.01.
[a]Adjusted for age, gender, comorbidities, and antidiabetic drugs.

Taiwanese patients, and thus the results might not be generalizable to other populations.

Because the data set used in the present study was derived from the whole population without applying a sampling procedure, potential selection bias related to sampling error was not a concern. Although disease diagnosis might have been misclassified, the likelihood of such an occurrence was low because miscategorized diagnoses influence reimbursement, which would not be tolerated by hospitals and clinics. Taiwan's NHI program also conducts stringent monitoring of claims and imposes strict penalties to avoid overdiagnosis and prevent financial irregularities.

CONCLUSIONS

The current guideline of the American Diabetes Association recommends frequent self-monitoring of blood glucose for patients receiving intensive insulin treatment (multiple-dose insulin or insulin pump) to monitor and prevent hypoglycemia. Patients should receive education to increase their awareness of certain situations that might increase the risk of hypoglycemia, such as vigorous exercise, fasting for medical tests or procedures, and during sleep.[27]

Finally, this study demonstrated that patients with rapid progression of diabetes complications had a higher risk of developing severe hypoglycemia. Therefore, it is important for treating physicians to slow the progression of diabetes complications and identify patients with increases in aDCSI score per year. At-risk patients should be given proper hypoglycemia education, prevention, and treatment. ■

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Author Affiliations: Division of Endocrinology and Metabolism, Department of Internal Medicine (EK, Y-SY, S-CL, C-NH), and Department of Pharmacy (Y-RL), Chung Shan Medical University Hospital, Taichung, Taiwan; School of Health Policy and Management (J-YC), Institute of Medicine of Chung Shan Medical University (EK, Y-SY, S-CL, C-NH), Taichung, Taiwan; Institute of Biotechnology, HungKuang University (C-HP), Taichung, Taiwan.

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Address Correspondence to: Chien-Ning Huang, MD, PhD, or Jeng-Yuan Chiou, PhD, Chung Shan Medical University Hospital, 110th, 1st Section, Jianguo North Rd, South District, Taichung, Taiwan. Email: tom@csmu.edu.tw.

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eAppendix Table. Adapted Diabetes Complications Severity Index[a]

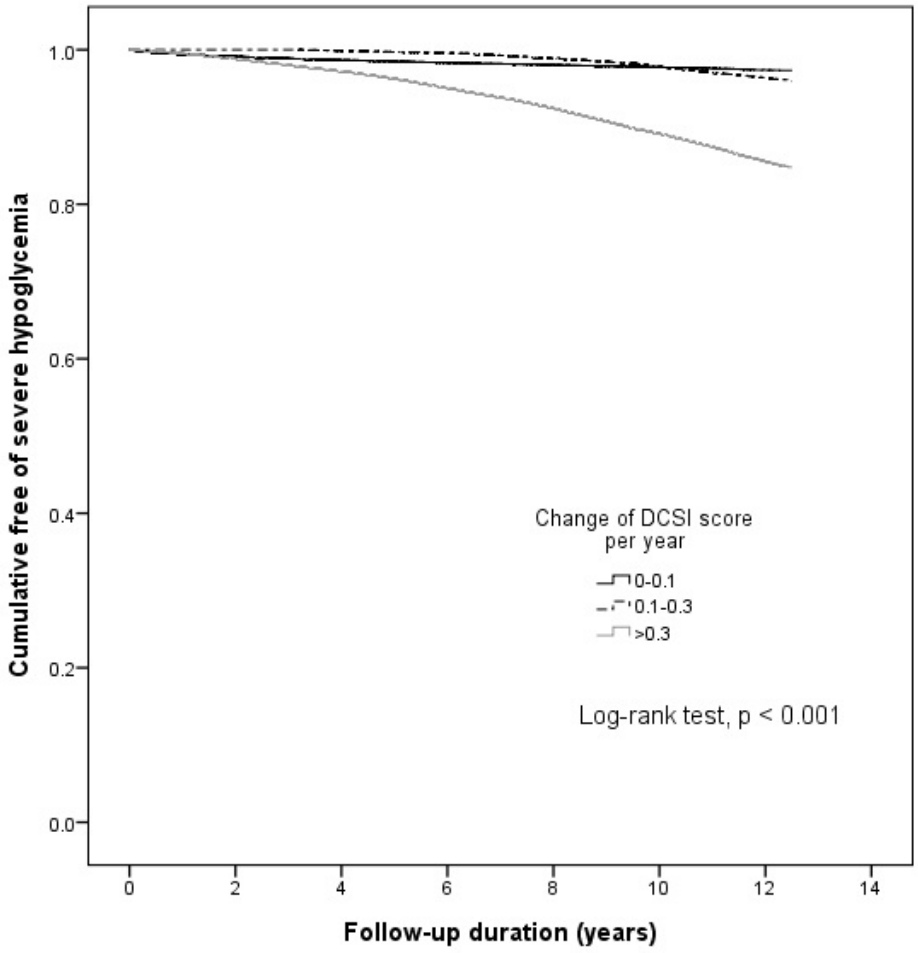
Complication and diagnosis	*ICD-9* code	aDCSI score	
		1	2
Retinopathy			
Diabetic ophthalmologic	250.5x	•	
Background retinopathy	362.01	•	
Other retinopathy	362.1	•	
Other retinopathy	362.83	•	
CSME	362.53	•	
Other retinal disorders	362.81, 362.82	•	
Proliferative retinopathy	362.02		••
Retinal detachment	361.xx		••
Blindness	369.xx, 00-.99		••
Vitreous hemorrhage	379.23		••
Nephropathy			
Diabetic nephropathy	250.4	•	
Acute glomerulonephritis	580	•	
Nephrotic syndrome	581	•	
Hypertension, nephrosis	581.81	•	
Chronic glomerulonephritis	582	•	
Nephritis/nephropathy	583	•	
Chronic renal failure	585		••
Renal failure NOS	586		••
Renal insufficiency	593.9		••
Neuropathy			
Diabetic neuropathy	356.9, 250.6	•	
Amyotrophy	358.1	•	
Cranial nerve palsy	951.0, 951.1, 951.3	•	
Mononeuropathy	354.0-355.9	•	
Charcot's arthropathy	713.5	•	
Polyneuropathy	357.2	•	
Cerebrovascular			
TIA	435	•	
Stroke	431, 433, 434, 436		••
Cardiovascular			
Atherosclerosis	440.xx	•	
Other IHD	411	•	
Angina pectoris	413	•	
Other chronic IHD	414	•	

Myocardial infarction	410		••
Ventricular fibrillation, arrest	427.1, 427.3		••
Atrial fibrillation, arrest	427.4, 427.5		••
Other ASCVD	429.2	•	
Old myocardial infarction	412		••
Heart failure	428		••
Atherosclerosis, severe	440.23, 440.24		••
Aortic aneurysm/dissection	441		••
Peripheral vascular disease			
Diabetic PVD	250.7	•	
Other aneurysm,	442.3	•	
PVD	443.81, 443.9	•	
Foot wound + complication	892.1	•	
Claudication, intermittent	443.9	•	
Embolism/thrombosis (LE)	444.22		••
Gangrene	785.4		••
Gas gangrene	0.4		••
Ulcer of lower limbs	707.1		••
Metabolic			
Ketoacidosis	250.1		••
Hyperosmolar	250.2		••

aDCSI indicates adapted Diabetes Complications Severity Index; ASCVD, atherosclerotic cardiovascular disease; CSME, cystoid macular edema/degeneration; DCSI, Diabetes Complications Severity Index; *ICD-9*, *International Classification of Diseases, Ninth Revision*; IHD, ischemic heart disease; LE, lower extremity; NOS, not otherwise specified; PVD, peripheral vascular disease; TIA, transient ischemic attack.

[a]Severity index was based on a scale ranging from 0 to 2 for each complication as follows: 0 =no abnormality, 1 = some abnormality, 2 = severe abnormality. Solid circle (•) indicates a count of 1 added to DCSI; double solid circle (••) indicates a count of 2 added to DCSI.

eAppendix Figure. Kaplan-Meier Analysis Among Patients With Diabetes With Different Category of Change in aDCSI Per Year and the Risk of Severe Hypoglycemia



aDCSI indicates adapted Diabetes Complications Severity Index.