

Subsequent mortality after hyperglycemic crisis episode in the non-elderly: a national population-based cohort study

Yuan Kao¹ · Chien-Chin Hsu^{1,2} · Shih-Feng Weng³ · Hung-Jung Lin^{1,2,4} · Jhi-Joung Wang³ · Shih-Bin Su^{5,6} · Chien-Cheng Huang^{1,5,7,8,9} · How-Ran Guo^{7,10}

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Abstract Hyperglycemic crisis episodes (HCEs)—diabetic ketoacidosis and the hyperosmolar hyperglycemic state—are the most serious acute metabolic complications of diabetes. We aimed to investigate the subsequent mortality after HCE in the non-elderly diabetic which is still unclear. This retrospective national population-based cohort study reviewed, in Taiwan's National Health Insurance Research Database, data from 23,079 non-elderly patients (≤ 65 years) with new-onset diabetes between 2000 and 2002: 7693 patients with HCE and 15,386 patients without HCE (1:2). Both groups were compared, and follow-up prognoses were done until 2011. One thousand eighty-five (14.1 %) patients with HCE and 725 (4.71 %) patients without HCE died ($P < 0.0001$) during follow-up. Incidence rate ratios (IRR) of mortality were 3.24 times higher in patients with HCE than in patients

without HCE ($P < 0.0001$). Individual analysis of diabetic ketoacidosis and hyperosmolar hyperglycemic state also showed the similar result with combination of both. After stratification by age, mortality was significant higher in the middle age (40–64 years) [IRR 3.29; 95 % confidence interval (CI) 2.98–3.64] and young adult (18–39 years) (IRR 3.91; 95 % CI 3.28–4.66), but not in the pediatric subgroup (< 18 years) (IRR 1.28; 95 % CI 0.21–7.64). The mortality risk was highest in the first month (IRR 54.43; 95 % CI 27.98–105.89), and still high after 8 years (IRR 2.05; 95 % CI 1.55–2.71). After adjusting for age, gender, and selected comorbidities, the mortality hazard ratio for patients with HCE was still four times higher than for patients without HCE. Moreover, older age, male gender, stroke, cancer, chronic obstructive pulmonary disease, congestive heart failure, and liver disease were independent mortality predictors. HCE significantly increases the subsequent mortality risk in the non-elderly with diabetes.

Yuan Kao and Chien-Chin Hsu have contributed equally to this work as first authors.

✉ Chien-Cheng Huang
chienchenghuang@yahoo.com.tw

✉ How-Ran Guo
hrguo@mail.ncku.edu.tw

¹ Department of Emergency Medicine, Chi-Mei Medical Center, 901 Zhonghua Road, Yongkang District, Tainan City 710, Taiwan

² Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan

³ Department of Medical Research, Chi-Mei Medical Center, Tainan, Taiwan

⁴ Department of Emergency Medicine, Taipei Medical University, Taipei, Taiwan

⁵ Department of Occupational Medicine, Chi-Mei Medical Center, Tainan, Taiwan

⁶ Department of Leisure, Recreation and Tourism Management, Southern Taiwan University of Science and Technology, Tainan, Taiwan

⁷ Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, No.1, Daxue Rd., East Dist., Tainan City 701, Taiwan

⁸ Department of Child Care and Education, Southern Taiwan University of Science and Technology, Tainan, Taiwan

⁹ Department of Geriatrics and Gerontology, Chi-Mei Medical Center, Tainan, Taiwan

¹⁰ Department of Occupational and Environmental Medicine, National Cheng Kung University Hospital, Tainan, Taiwan

Strategies for prevention and control of comorbidities are needed as soon as possible.

Keywords Diabetes · Hyperglycemic crisis · Middle age · Mortality · Non-elderly · Pediatric · Young adult

Introduction

Hyperglycemic crises—diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS)—are the two most serious acute metabolic complications of diabetes [1]. The basic underlying mechanism is the combination of absolute or relative insulin deficiency and an increase in counter regulatory hormones, viz., glucagon, catecholamines, cortisol, and growth hormone [1]. Despite recent improvements, the incidence and the cost of treating hyperglycemic crises are high and continue to rise. In the United States, the National Diabetes Surveillance Program of the Centers for Disease Control and Prevention estimated that from 1988 to 2009, the age-adjusted hospital discharge rate for DKA per 10,000 population consistently increased by 43.8 %, so the number of hospital discharges with DKA as the first-listed diagnosis increased from about 80,000 in 1988 to about 140,000 in 2009 [2]. DKA is responsible for more than 500,000 hospital days per year [3, 4] at an estimated annual direct medical expense and indirect cost of 2.4 billion USD [4, 5]. The incidence of and medical expenditure for HHS care are unknown because there are few population-based studies on the HHS, and because many patients with HHS have multiple comorbidities. The rate of hospital admissions for HHS was estimated more than a decade ago to be 1 % of all primary admissions for diabetes [6].

Because of improved awareness, prevention, and treatment guidelines, the age-adjusted death rate for hyperglycemic crises in 2009 was less than half the rate in 1980 (7.5 vs. 15.3 per 1000,000 population); however, hyperglycemic crises still caused 2417 deaths in 2009 in the United States [3]. The mortality rate for DKA is 1–9 %, for HHS is 5–45 % [1, 7, 8], and for overall hyperglycemic crises is 10.5 % [9]. Among the elderly (≥ 65 years old), the mortality rate was reported to be as high as 71 % [10]. Regardless of the observed decrease in the death rate in the United States, hyperglycemic crises remain a serious health problem, especially in developing and undeveloped countries [10]. The cause of death in patients with hyperglycemic crises is rarely ascribed to the metabolic complications of hyperglycemia or ketoacidosis; rather, it is usually related to the underlying precipitating illness [9, 11–13].

Almost all studies on hyperglycemic crises have focused on acute episodes [7–9, 11–14]. In 2013, Huang et al. [9] proposed predicting the hyperglycemic crisis death (PHD) score to help emergency and critical care. The PHD score

consists of six factors: Absent tachycardia, Hypotension, Anemia, Severe coma, Cancer history, and Infection (Mnemonic: AHA.SCI) which are used to predict 30-day mortality and manage, in the Emergency Department, adult patients with hyperglycemic crises. Poor compliance (i.e., uncontrolled diabetes) is the most common precipitating factor of hyperglycemic crises, which suggests that close follow-up and secondary prevention after an HCE are crucial [9]. The long-term effect of uncontrolled diabetes contributes to various complications, including death [1]. A study showed that geriatric patients (≥ 65 years) with diabetes had a higher mortality risk after HCE during the first 6 years of follow-up [15]. However, the subsequent mortality of the non-elderly (< 65 years) after HCE has never been clarified. To determine the subsequent mortality of non-elderly patients with HCE, we wanted to analyze a population-based cohort taken from Taiwan's National Health Insurance Research Database (NHIRD).

Methods

Data sources

The Taiwan NHI Program, a universal health care system that covers 99 % of the country's population of 23.3 million [16], has one of the largest and most complete population-based healthcare claims datasets in the world. The NHIRD contains encrypted patient identification numbers, ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes for applied clinical diagnoses and procedures, details of prescribed drugs, dates of admission and discharge, and basic sociodemographic information, including gender and date of birth. All the expenses of HCE therapy are covered by NHI (but not hospital room and board). Data used in this study came from two sub-datasets of the NHIRD. The HCE group data were obtained from the longitudinal cohort of diabetes patients (LHDB), which contains randomized selected data (120,000 patients/per year) from patients with newly diagnosed diabetes mellitus (DM). The definitions of DM in the LHDB are (a) Inpatient: at least one diagnosis of DM or a prescription for antidiabetes medication; (b) Ambulatory care: at least two diagnoses of DM or at least one diagnosis of DM with a prescription for antidiabetes medication. The comparison group (without HCE) data were obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), a sub-dataset of the NHIRD, which contains all claims data of one million (4.34 % of the total population) beneficiaries who were randomly selected in 2000. There are no significant differences in age, gender, or health care costs between the sample group and all NHI enrollees.

Design

In this longitudinal cohort study, we selected all non-elderly patients (<65 years) in the LHDB who had been diagnosed with HCE (ICD-9 code: DKA 250.1 or HHS 250.2) between January 1, 2000, and December 31, 2002. The comparisons (2 patients with a diagnosis of DM without HCE for every patient with HCE) were randomly selected from the LHID2000. The index date in the HCE group was the date that HCE was first diagnosed in the database; the index date in the comparison group corresponded with the index date of the HCE group. Data from patients who died between the DM diagnosis date and the HCE index date in both groups were deleted. The comparisons were matched with the patients with HCE by gender, age at which DM was diagnosed (± 30 days), duration between DM diagnosis date to HCE index date, and selected comorbidities by propensity score. Figure 1 shows the flowchart of this study.

We linked to the diagnostic codes through the inpatient and ambulatory care claims databases of the NHI. Our data collection included not only the patients' survival status, but also their date of death, demographics, and baseline comorbidities. Baseline comorbidities affecting mortality that may have presented before the index date were defined as follows: hypertension (HTN) (ICD-9 codes 401–405), renal disease (ICD-9 codes 582, 583, 585, 586, 588), coronary artery disease (CAD) (ICD-9 codes 410–414), stroke (ICD-9 codes 430–438), cancer (ICD-9 codes 140–208),

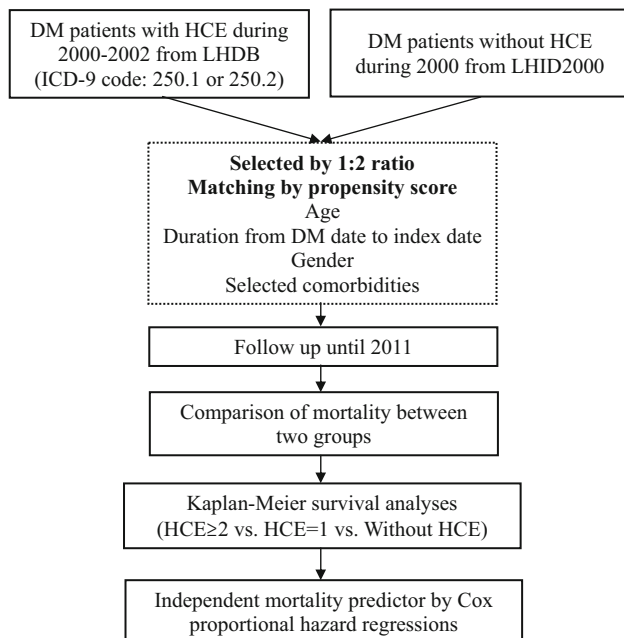


Fig. 1 Flowchart of this study. *DM* diabetes mellitus, *HCE* hyperglycemic crisis episode, *LHDB* longitudinal cohort of diabetes patients, *LHID2000* longitudinal health insurance database 2000

chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490–496, 500–505, 5064), congestive heart failure (CHF) (ICD-9 codes 428), and liver disease (ICD-9 codes 5712, 5714, 5715, 5716, 4560–4562, 5722–5728). We counted these comorbid conditions if they occurred either in the inpatient setting or in 3 or more ambulatory care claims coded before the index medical care date. Patients were followed from the index date to the date of death or December 31, 2011, the end of the database period. According to the law, enrollment NHI is mandatory for all citizens and other legal residents of Taiwan, and it must be withdrawn within 30 days after death. Therefore, those patients recorded as deceased in the inpatient claim or as withdrawing their NHI enrollment within 30 days after being discharged from their last hospitalization were presumed dead, and the discharge date was designated as the date of death. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) at Chi-Mei Medical Center. The IRB waived the need for informed consents (written and oral) from the patients because the dataset used in this study consists of nationwide, unidentifiable, secondary data released to the public for research purposes. This waiver does not adversely affect the rights and welfare of the patients.

Statistical analysis

The significance of the differences in baseline characteristics and comorbid variables between the two cohorts was evaluated using Student's *t* test for continuous variables and Pearson χ^2 tests for categorical variables. The risk of death between patients in the HCE and comparison groups was compared by estimating the incidence rate ratio (IRR) with Poisson regression. Kaplan–Meier analysis was used to calculate the cumulative survival rate between different age groups in the 2 cohorts, and the log-rank test was used to analyze the differences between the survival curves. Thereafter, separate Cox proportional hazard regressions were done to compute the risk of death between the HCE and comparison groups after adjusting for possible confounding factors. SAS for Windows 9.3.1 (SAS Institute, Inc, Cary, NC, USA) was used for all analyses. Significance was set at $P < 0.05$.

Results

Demographic data

Between 2000 and 2002, we recruited 7693 patients with HCE and 15,386 age-, gender-, and selected comorbidities-matched comparisons, after ineligible patients had been excluded. The mean age in the HCE group at the DM date

Table 1 Demographic characteristics and comorbidities for patients with HCE and without HCE

Characteristics	With HCE <i>n</i> = 7693	Without HCE <i>n</i> = 15,386	<i>P</i> value
Age at DM date (years) (mean ± SD)	45.60 ± 10.86	45.66 ± 10.86	0.6944
Age at index date (years) (mean ± SD)	48.92 ± 11.25	48.92 ± 11.21	0.9943
Age at index date			0.9530
Pediatric (0–17 years)	230 (1.52)	119 (1.57)	
Young adult (18–39 years)	2629 (17.37)	1312 (17.30)	
Middle age (40–64 years)	12,275 (81.11)	6155 (81.14)	
Duration from DM date to index date (years) (mean ± SD)	3.32 ± 3.37	3.26 ± 3.15	0.1771
Gender			0.0876
Male	4532 (58.91)	9244 (60.08)	
Female	3161 (41.09)	6142 (39.92)	
Baseline comorbidity			
HTN	2224 (28.91)	4360 (28.34)	0.3644
Renal disease	147 (1.91)	262 (1.70)	0.2589
CAD	532 (6.92)	993 (6.45)	0.1834
Stroke	295 (3.83)	558 (3.63)	0.4298
Cancer	194 (2.52)	364 (2.37)	0.4671
COPD	328 (4.26)	606 (3.94)	0.2376
CHF	74 (0.96)	137 (0.89)	0.5906
Liver disease	743 (9.66)	1392 (9.05)	0.1310
Area			0.4150
Northern	3653 (47.48)	7407 (48.14)	
Central	1271 (16.52)	2562 (16.65)	
Southern	2582 (33.56)	5088 (33.07)	
Eastern	187 (2.43)	329 (2.14)	
Monthly income (NTD)			
<15,840	3517 (45.72)	7017 (45.61)	0.7037
15,840–25,000	2516 (32.71)	5106 (33.19)	
>25,000	1660 (21.58)	3263 (21.21)	
Subgroups of HCE			
DKA	2378 (30.91)		
HHS	5315 (69.09)		

HCE hyperglycemic crisis episode, DM diabetes mellitus, SD standard deviation, HTN hypertension, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, CHF congestive heart failure, NTD new Taiwan dollars, DKA diabetic ketoacidosis, HHS hyperosmolar hyperglycemic state

was 45.60 ± 10.86 years and of the comparison group was 45.66 ± 10.86 years. We classified these patients into three age subgroups: 0–17 years old (pediatric), 18–39 years old (young adult), and 40–64 years old (middle age). Pearson χ^2 tests revealed no significant difference between to the distribution of the comorbidities of HTN, renal disease, CAD, stroke, cancer, COPD, CHF, and liver disease in patients with HCE and comparisons after matching (Table 1).

Incidence rates of mortality

Of the 23,079 patients recruited, 1810 (7.84 %) died during the follow-up period: 1085 of 7693 patients with HCE (14.1 %) and 725 of 15,386 comparisons (4.71 %)

(Table 2). The incidence rates of mortality were 21.59 (HCE group) and 6.61 (comparison group) per 1000 person-years (PY), which was significantly higher for the HCE group (IRR 3.24; 95 % CI 2.94–3.55) (Table 2).

The mortality risk was significantly higher in the HCE group during the entire follow-up period: first month after HCE (IRR 54.43; 95 % CI 27.98–105.89), 1–6 months after (IRR 4.85; 95 % CI 3.39–6.94), 6–12 months after (IRR 3.96; 95 % CI 2.78–5.64), 1–2 years after (IRR 3.66; 95 % CI 2.79–4.80), 2–4 years after (IRR 2.27; 95 % CI 1.84–2.81), 4–6 years after (IRR 1.72; 95 % CI 1.35–2.18), 6–8 years after (IRR 2.21; 95 % CI 1.70–2.86), and ≥ 8 years after (IRR 2.05; 95 % CI 1.55–2.71) (Table 2). Individual analysis of DKA (Table 3) and HHS (Table 4)

Table 2 Risk of death for patients with HCE and without HCE

Characteristics	With HCE				Without HCE				IRR (95 % CI)	P value
	n	Death	PY [#]	Rate*	n	Death	PY [#]	Rate*		
All	7693	1085	50,243.61	21.59	15,386	725	109,723.90	6.61	3.24 (2.94–3.55)	<0.0001
Age at index date										
Pediatric (0–17 years)	119	2	1158.67	1.73	230	3	2217.57	1.35	1.28 (0.21–7.64)	0.7895
Young adult (18–39 years)	3161	363	20,539.93	17.67	6142	192	42,981.22	4.47	3.91 (3.28–4.66)	<0.0001
Middle age (40–64 years)	6155	957	37,923.44	25.24	12,275	634	83,538.93	7.59	3.29 (2.98–3.64)	<0.0001
Gender										
Male	4532	722	29,703.67	24.31	9244	533	66,742.68	7.99	3.01 (2.69–3.37)	<0.0001
Female	3161	363	20,539.93	17.67	6142	192	42,981.22	4.47	3.91 (3.28–4.66)	<0.0001
Comorbidity										
HTN	2224	293	12,354.17	23.72	4360	244	27,915.02	8.74	2.67 (2.25–3.16)	<0.0001
Renal disease	147	25	638.49	39.15	262	34	1428.43	23.80	1.65 (0.98–2.76)	0.0589
CAD	532	82	2905.46	28.22	993	70	6568.45	10.66	2.58 (1.87–3.56)	<0.0001
Stroke	295	68	1292.03	52.63	558	51	3332.13	15.31	3.39 (2.35–4.88)	<0.0001
Cancer	194	91	696.64	130.63	364	83	1853.62	44.78	2.85 (2.11–3.85)	<0.0001
COPD	328	66	1903.55	34.67	606	51	4135.62	12.33	2.81 (1.95–4.05)	<0.0001
CHF	74	23	275.23	83.57	137	27	770.25	35.05	2.18 (1.23–3.85)	0.0075
Liver disease	743	212	3855.11	54.99	1392	138	9795.74	14.09	3.89 (3.13–4.81)	<0.0001
Follow-up period										
0–1 month	7693	250	624.39	400.39	15,386	9	1279.77	7.03	54.43 (27.98–105.89)	<0.0001
1–6 months	7414	100	3032.61	32.97	15,331	43	6327.78	6.80	4.85 (3.39–6.94)	<0.0001
6–12 months	7172	88	3509.27	25.08	15,042	47	7420.64	6.33	3.96 (2.78–5.64)	<0.0001
1–2 years	6875	141	6599.02	21.37	14,622	83	14,213.42	5.84	3.66 (2.79–4.80)	<0.0001
2–4 years	6327	174	11,766.48	14.79	13,791	169	25,952.85	6.51	2.27 (1.84–2.81)	<0.0001
4–6 years	5434	121	9918.55	12.20	12,129	158	22,230.75	7.11	1.72 (1.35–2.18)	<0.0001
6–8 years	4454	113	7871.58	14.36	10,068	116	17,819.11	6.51	2.21 (1.70–2.86)	<0.0001
≥8 year	3402	98	6921.70	14.16	7696	100	14,479.58	6.91	2.05 (1.55–2.71)	<0.0001

HCE hyperglycemic crisis episode, IRR incidence rate ratio, HTN hypertension, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, CHF congestive heart failure

* Rate Per 1000 person-years

PY person-years

was also performed, which showed significantly increased mortality, similar results with the combination of both.

Kaplan–Meier survival analyses and log-rank tests showed that patients in the HCE group (subclassified into HCE ≥ 2 and HCE = 1) had significantly ($P < 0.0001$) lower survival rates than did comparisons during the follow-up period (Fig. 2). Subsequent mortality in patients with HCE ≥ 2 was significantly higher than patients with HCE = 1 and patients without HCE (Fig. 2).

HCE age subgroups of middle age (IRR 3.29; 95 % CI 2.98–3.64) and young adult (IRR 3.91; 95 % CI 3.28–4.66) had a higher IRR than did their comparison group

counterparts, however, pediatric age subgroup did not (IRR 1.28; 95 % CI 0.21–7.64) (Table 2).

Male patients with HCE had a mortality rate of 24.31/1000 PY, whereas male comparisons had a death rate of only 7.99 per 1000 PY (IRR 3.01; 95 % CI 2.69–3.37) (Table 2). The difference between female patients with HCE and female comparisons was also significant (IRR 3.91; 95 % CI 3.28–4.66).

Patients with HCE comorbid with HTN (23.72/1000 PY), CAD (28.22/1000 PY), stroke (52.63/1000 PY), cancer (130.63/1000 PY), COPD (34.67/1000 PY), CHF (83.57/1000 PY), and those comorbid with a liver

Table 3 Risk of death for patients with DKA and without DKA

Characteristics	With DKA				Without DKA				IRR (95 % CI)	P value
	n	Death	PY [#]	Rate*	n	Death	PY [#]	Rate*		
All	5315	643	36,402.17	17.66	10,630	470	77,581.60	6.06	2.92 (2.59–3.28)	<0.0001
Age at index date (years)										
Pediatric (0–17 years)	124	2	1215.55	1.65	219	2	2148.64	0.93	1.77 (0.25–12.55)	0.5689
Young adult (18–39 years)	1116	71	9045.54	7.85	2191	46	18,514.77	2.48	3.16 (2.18–4.58)	<0.0001
Middle age (40–64 years)	4075	570	26,141.07	21.8	8220	422	56,918.18	7.41	2.94 (2.59–3.34)	<0.0001
Gender										
Male	3035	421	20,764.77	20.27	6290	337	46,213.73	7.29	2.78 (2.41–3.21)	<0.0001
Female	2280	222	15,637.39	14.20	4340	133	31,367.87	4.24	3.35 (2.70–4.15)	<0.0001
Comorbidity										
HTN	1326	152	7656.16	19.85	2747	154	17,825.08	8.64	2.30 (1.84–2.88)	<0.0001
Renal disease	79	7	370.86	18.88	148	20	793.11	25.22	0.75 (0.32–1.77)	0.5095
CAD	293	41	1647.46	24.89	617	42	4180.94	10.05	2.48 (1.61–3.81)	<0.0001
Stroke	128	26	622.56	41.76	347	34	2059.67	16.51	2.53 (1.52–4.22)	0.0004
Cancer	97	39	406.62	95.91	230	48	1238.8	38.75	2.48 (1.62–3.78)	<0.0001
COPD	220	35	1337.3	26.17	401	34	2805.84	12.12	2.16 (1.35–3.46)	0.0014
CHF	37	11	146.86	74.9	89	21	491.3	42.74	1.75 (0.84–3.63)	0.1317
Liver disease	456	105	2587.37	40.58	871	81	6301.35	12.85	3.16 (2.36–4.22)	<0.0001
Follow-up period										
0–1 month	5315	151	432.91	348.8	10,630	6	884.39	6.78	51.41 (22.74–116.25)	<0.0001
1–6 months	5151	45	2118.67	21.24	10,597	26	4379.2	5.94	3.58 (2.21–5.80)	<0.0001
6–12 months	5026	50	2469.40	20.25	10,429	33	5149.44	6.41	3.16 (2.04–4.90)	<0.0001
1–2 years	4845	77	4667.89	16.5	10,163	63	9884.06	6.37	2.59 (1.86–3.61)	<0.0001
2–4 years	4501	107	8440.82	12.68	9597	99	18,206.91	5.44	2.33 (1.77–3.06)	<0.0001
4–6 years	3932	73	7246.06	10.07	8558	108	15,763.81	6.85	1.47 (1.09–1.98)	0.0109
6–8 years	3291	75	5843.20	12.84	7190	71	12,780.91	5.56	2.27 (1.79–2.87)	<0.0001
≥8 year	2539	65	5183.21	12.54	5572	64	10,532.88	6.08	2.06 (1.46–2.91)	<0.0001

DKA diabetic ketoacidosis, *IRR* incidence rate ratio, *HTN* hypertension, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CHF* congestive heart failure

[#] *PY* person-years

* *Rate* Per 1000 person-years

disease (54.99/1000 PY) had a higher IRR for mortality than did comparisons comorbid with the same diseases (Table 2).

Risk factors for all-cause mortality in DM patients

Cox proportional hazard regressions were used to determine crude and adjusted hazard ratios (HRs) for mortality during the follow-up period by cohort for the total sample. After adjusting for patient age, gender, and selected comorbidities, HCE (HCE ≥ 2 , adjusted HR 3.29, 95 % CI 2.98–3.63; HCE = 1, adjusted HR 4.64, 95 % CI 3.92–5.49) was still an independent risk factor for mortality in the total sample (Table 5). Other risk factors for mortality included older age (≥ 18 years old), male gender,

renal disease, stroke, cancer, COPD, CHF, and liver disease.

Discussion

Our study analyzed follow-up claim data on 7693 HCE patients and 15,386 comparison patients. Our results suggest that HCE raises the risk of subsequent mortality. This present study found that the incidence rate of mortality was significantly high during the entire follow-up period after HCE. The risks of mortality were 54.43, 4.85, 3.96, 3.66, 2.27, 1.72, 2.21, and 2.05 times higher in the HCE group than in the comparison group during the first 1 month after HCE, the first 6 months after, 6–12 months after, 1–2 years

Table 4 Risk of death for patients with HHS and without HHS

Characteristics	With HHS				Without HHS				IRR (95 % CI)	P value
	n	Death	PY [#]	Rate*	n	Death	PY [#]	Rate*		
All	2378	442	13,841.44	31.9331	4756	255	32,142.30	7.9335	4.03 (3.45–4.70)	<0.0001
Age at index date (years)										
Pediatric (0–17 years)	5	0	43.52	0	31	1	256.46	3.9	–	–
Young adult (18–39 years)	249	37	1795.56	20.61	573	18	4718.03	3.82	5.40 (3.08–9.49)	<0.0001
Middle age (40–64 years)	2124	405	12,002.36	33.74	4152	236	27,167.81	8.69	3.88 (3.30–4.56)	<0.0001
Gender										
Male	1497	301	8938.9	33.67	2954	196	20,528.94	9.55	3.53 (2.95–4.22)	<0.0001
Female	881	141	4902.54	28.76	1802	59	11,613.36	5.08	5.66 (4.18–7.67)	<0.0001
Comorbidity										
HTN	898	141	4698.01	30.01	1613	90	10,089.94	8.92	3.36 (2.58–4.38)	<0.0001
Renal disease	68	18	267.63	67.26	114	14	635.32	22.04	3.06 (1.52–6.14)	0.0017
CAD	239	41	1258	32.59	376	28	2387.5	11.73	2.78 (1.72–4.49)	<0.0001
Stroke	167	42	669.47	62.74	211	17	1272.45	13.36	4.70 (2.67–8.25)	<0.0001
Cancer	97	52	290.02	179.3	134	35	614.82	56.93	3.15 (2.05–4.83)	<0.0001
COPD	108	31	566.25	54.75	205	17	1329.78	12.78	4.28 (2.37–7.74)	<0.0001
CHF	37	12	128.37	93.48	48	6	278.95	21.51	4.35 (1.63–11.58)	0.0033
Liver disease	287	107	1267.74	84.4	521	57	3494.39	16.31	5.17 (3.75–7.14)	<0.0001
Follow-up period										
0–1 month	2378	99	191.51	516.96	4756	3	395.44	7.59	68.14 (21.61–214.90)	<0.0001
1–6 months	2263	55	913.91	60.18	4734	17	1948.53	8.72	6.90 (4.00–11.88)	<0.0001
6–12 months	2146	38	1039.86	36.54	4613	14	2271.2	6.16	5.93 (3.21–10.94)	<0.0001
1–2 years	2030	64	1931.14	33.14	4459	20	4329.36	4.62	7.17 (4.34–11.85)	<0.0001
2–4 years	1826	67	3325.66	20.15	4194	70	7745.94	9.04	2.23 (1.59–3.12)	<0.0001
4–6 years	1502	48	2672.49	17.96	3571	50	6466.93	7.73	2.32 (1.56–3.45)	<0.0001
6–8 years	1163	38	2028.38	18.73	2878	45	5038.20	8.93	2.18 (1.58–2.99)	<0.0001
≥8 year	863	33	1738.49	18.98	2124	36	3946.70	9.12	2.08 (1.30–3.34)	0.0024

HHS hyperosmolar hyperglycemic state, IRR incidence rate ratio, HTN hypertension, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, CHF congestive heart failure

* Rate Per 1000 person-years

PY person-years

after, 2–4 years after, 4–6 years after, 6–8 years after, and ≥8 years. In the age subgroups, HCE patients of middle age and young adult had a higher mortality than comparisons, but not in the pediatric subgroup. Individual analysis of DKA and HHS also showed the similar result with combination of both. After adjusting for potential confounding factors, the risk of mortality associated with HCE was still near four times that of patients without HCE. Early referral of patients with HCE for proper patient education, better access to medical care, effective communication with a health care provider during an intercurrent (occurring during and modifying the course of another disease) illness [1], and secondary prevention of mortality, such as controlling renal disease, stroke, cancer, COPD, CHF, and liver disease, may be done as soon as possible.

The most common precipitating factor of HCE is poor compliance [1, 9]. A recent study [13] reported that the mean glycosylated hemoglobin (HbA1c) of patients with HCE was 11.8 %; therefore, the occurrence of HCE indicated uncontrolled diabetes, which may have long-term effects that contribute to various complications such as renal disease, CAD, and stroke [1]. Even more, uncontrolled diabetes is associated with all-cause mortality and cardiovascular mortality [17]. Resources need to be redirected toward prevention by funding better access to care and educational programs tailored to individual needs, including ethnic and personal health care beliefs [1]. Recent studies suggest that any type of education for nutrition has resulted in reduced hospitalization [18]. In fact, the guidelines for diabetes self-management education

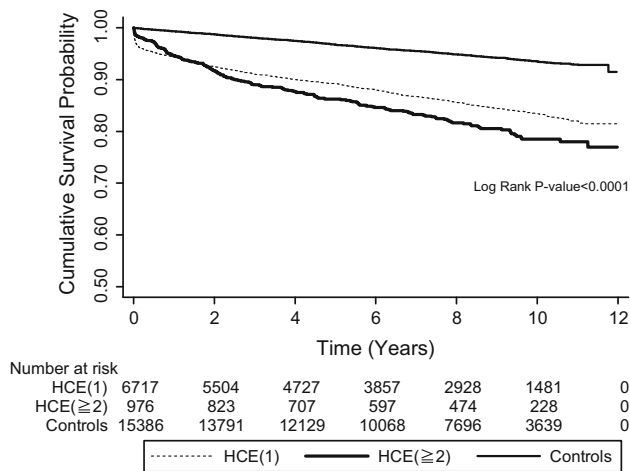


Fig. 2 Survival rate for patients with HCE and patients without HCE during the follow-up period. *HCE* hyperglycemic crisis episode

were developed by a recent task force to identify ten detailed standards for diabetes self-management education [19].

Older age is an independent mortality predictor in the total sample. In the pediatric population, HCE patients did not have a higher mortality. However, it does not suggest that HCE did not increase the subsequent mortality in the pediatric population. The mortality number in HCE patients and comparisons was too few (2 and 3, respectively) which may cause statistically insignificant (Table 2). Other explanations for the lower mortality in the pediatric population are that more than half of children got HCE as the initial diagnosis of DM [20] and adult HCE were always due to poor compliance, infection, and long-term DM [9]. It needs further study with more number to clarify this issue.

The present study showed that cancer patients with comorbid DM who also had HCE had higher all-cause mortality than did comparisons. CLUE II (Give Us a Clue to Cancer and Heart Disease), a recent community-based, prospective study [21] provides support for the association between cancer and DM. This study revealed that of patients who developed cancer, adults with DM had a higher cancer mortality risk [HR 1.34 (95 % CI 1.002–1.79)] and all-cause mortality risk [1.61 (1.29–2.01)]. Despite there being no direct results about patients with HCE comorbid with cancer in the CLUE II study, it seems reasonable to conclude that uncontrolled diabetes leads to poorer outcomes in patients with cancer.

There is a significant increase in the risk of COPD with increasing baseline HbA1c in patients with DM [22]. The lung is also a target organ for diabetic microangiopathy in patients with both type 1 and type 2 DM [23], and decrements in lung function have been reported in patients with

DM over the past two decades [24–26]. Decrements in the lung function of patients with DM are believed to be the consequence of biochemical alterations in the connective tissue constituents of the lung, particularly collagen and elastin, as well as microangiopathy due to the nonenzymatic glycosylation of proteins induced by chronic hyperglycemia [27, 28].

The CHF problem is magnified in people with diabetes, in whom incidence rates are two to five times greater than those in the general population [29]. Poorer glycemic control was an important predictor of CHF development [30]. DM not only increases the risk of CHF, but also accelerates its occurrence [30] and even mortality.

Liver disease is an important cause of death for people with DM [30]. In the population-based Verona Diabetes Study [31], cirrhosis was the fourth leading cause of death and accounted for 4.4 % of DM-related deaths. The standardized mortality ratio, i.e., the relative rate of an event compared with the background rate, for cirrhosis was 2.52 compared with 1.34 for cardiovascular disease [31]. In another prospective cohort study [32], cirrhosis accounted for 12.5 % of deaths in patients with DM. DM is also the most common cause of liver disease in the United States [33]. Cryptogenic cirrhosis, of which DM is, by far, the most common cause, has become the third leading indication for liver transplantation in the United States [33]. Thus, patients with DM have a high prevalence of liver disease and patients with liver disease have a high prevalence of DM [33].

The major difference of long-term mortality after HCE between non-elderly and elderly was that HCE significantly increases the subsequent mortality risk even more than 8 years in the non-elderly but limited to ≤ 6 years in the elderly [15]. The elderly have more comorbidities which may dilute the HCE effect on the long-term mortality after 6 years.

Because of the increased long-term mortality, prevention for HCE is paramount especially in the patients who have previous HCE. The prevention strategies include proper patient and family member education such as emphasizing the important of keeping insulin treatment and sick day management [1], better access and effective communication to medical care such as early contact with the health care provider [1], keeping attention to probable infection [9], and controlling concurrent comorbidities such as renal disease, stroke, cancer, COPD, CHF, and liver disease.

There are several limitations to this study. First, the comorbidities relied on the claim data and ICD-9-CM diagnosis codes, which may have resulted in potential disease misclassification. Second, although we stratified our patients by age, gender, and comorbidities, like other studies that have used administrative data, we did not control for some unmeasured confounding variables: type

Table 5 Crude and adjusted hazard ratios of Cox proportional hazard regressions and 95 % confidence intervals for death during the follow-up period for the study cohort

Cohort	Crude hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)
HCE		
≥2 (449/1729)	3.89 (3.29–4.59)*	3.29 (2.98–3.63)*
1 (2480/11,056)	3.09 (2.81–3.41)*	4.64 (3.92–5.49)*
Without (2661/25,570)	1.000	1.000
Age (years)		
0–17	1.000	1.000
18–39	3.20 (1.31–7.79)*	2.98 (1.22–7.27)*
40–64	8.31 (3.45–19.99)*	6.58 (2.73–15.86)*
Gender		
Male	1.50 (1.36–1.66)*	1.63 (1.47–1.80)*
Female	1.000	1.000
Comorbidity		
HTN		
Yes versus No	1.21 (1.09–1.34)*	0.93 (0.84–1.04)
Renal disease		
Yes versus No	2.42 (1.87–3.14)*	2.05 (1.55–2.70)*
CAD		
Yes versus No	1.41 (1.20–1.67)*	1.12 (0.94–1.35)
Stroke		
Yes versus No	2.25 (1.86–2.71)*	1.95 (1.60–2.37)*
Cancer		
Yes versus No	6.03 (5.14–7.06)*	5.35 (4.45–6.30)*
COPD		
Yes versus No	1.75 (1.45–2.11)*	1.46 (1.20–1.77)*
CHF		
Yes versus No	3.90 (2.93–5.19)*	2.75 (2.00–3.77)*
Liver disease		
Yes versus No	2.54 (2.26–2.86)*	2.30 (2.04–2.60)*
Area		
Northern	1.000	1.000
Central	1.01 (0.88–1.16)	1.00 (0.87–1.16)
Southern	1.23 (1.11–1.37)*	1.11 (1.00–1.23)
Eastern	1.10 (0.80–1.52)	1.07 (0.77–1.48)
Monthly income (NTD)		
<15,840	2.44 (2.08–2.86)*	2.5 (2.13–2.94)*
15,840–25,000	1.09 (0.98–1.19)	1.04 (0.93–1.15)
>25,000	1.000	1.000

CI confidence interval, HCE hyperglycemic crisis episode, HTN hypertension, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, CHF congestive heart failure, NTD new Taiwan dollars

* Rate Per 1000 person-years

PY person-years

of DM, antidiabetes treatment, etc. Third, some important sociodemographic characteristics, such as education level, stress level, body mass index, and alcohol drinking habits, results of clinical examinations, and laboratory data such as HbA1c, and cause of death were not available in the NHIRD. Therefore, we could not adjust for these variables

as contributing factors in this study. Fourth, we were unable to take into account the severity of the diseases, which reduced our chances of showing the severity-related effects of comorbidities. Fifth, despite our database being national, our findings may not be generalizable to cohorts in other nations.

Conclusions

In summary, our study shows that non-elderly patients with HCE had a significantly higher mortality risk than did controls during the entire follow-up period and beyond. HCE signified uncontrolled diabetes, which may have long-term effects that contribute to various complications, including death. Strategies for prevention such as education, better access to medical care, effective communication with a healthcare provider, and control of comorbidities are needed as soon as possible.

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Conflict of interest No potential conflicts of interest relevant to this article were reported.

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