

# Hospital outcomes and cumulative burden from complications in type 2 diabetic sepsis patients: a cohort study using administrative and hospital-based databases

Ming-Shun Hsieh, Sung-Yuan Hu, Chong-Kuang How, Chen-June Seak, Vivian Chia-Rong Hsieh, Jin-Wei Lin and Pau-Chung Chen 

## Abstract

**Background:** The association between type 2 diabetes and hospital outcomes of sepsis remains controversial when severity of diabetes is not taken into consideration. We examined this association using nationwide and hospital-based databases.

**Methods:** The first part of this study was mainly conducted using a nationwide database, which included 1.6 million type 2 diabetic patients. The diabetic complication burden was evaluated using the adapted Diabetes Complications Severity Index score (aDCSI score). In the second part, we used laboratory data from a distinct hospital-based database to make comparisons using regression analyses.

**Results:** The nationwide study included 19,719 type 2 diabetic sepsis patients and an equal number of nondiabetic sepsis patients. The diabetic sepsis patients had an increased odds ratio (OR) of 1.14 (95% confidence interval 1.1–1.19) for hospital mortality. The OR for mortality increased as the complication burden increased [aDCSI scores of 0, 1, 2, 3, 4, and  $\geq 5$  with ORs of 0.91, 0.87, 1.14, 1.25, 1.56, and 1.77 for mortality, respectively (all  $p < 0.001$ )].

The hospital-based database included 1054 diabetic sepsis patients. Initial blood glucose levels did not differ significantly between the surviving and deceased diabetic sepsis patients:  $273.9 \pm 180.3$  versus  $266.1 \pm 200.2$  mg/dl ( $p = 0.095$ ). Moreover, the surviving diabetic sepsis patients did not have lower glycated hemoglobin (HbA1c; %) values than the deceased patients:  $8.4 \pm 2.6$  versus  $8.0 \pm 2.5$  ( $p = 0.078$ ).

**Conclusions:** For type 2 diabetic sepsis patients, the diabetes-related complication burden was the major determinant of hospital mortality rather than diabetes *per se*, HbA1c level, or initial blood glucose level.

**Keywords:** diabetes complication severity index score, diabetes mellitus, sepsis

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## Introduction

Sepsis is a leading cause of mortality in critical care worldwide.<sup>1–3</sup> In addition to mortality, sepsis may also cause long-term postsepsis cardiovascular disease.<sup>4</sup> The reported incidence of sepsis varies; however, an undoubtedly increasing trend has been reported, reflecting the aging population and greater recognition of this condition. Furthermore,

treating sepsis patients creates a significant national financial burden.

Diabetes is an important comorbid condition in sepsis because of its high prevalence.<sup>5</sup> Diabetic patients are generally believed to be more prone to infections than the general population.<sup>6</sup> However, the influence of diabetes on the

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outcome of sepsis remains inconclusive. Higher mortality rates in patients with diabetes have been reported;<sup>7–12</sup> however, other studies have found no effect of diabetes<sup>13–16</sup> or even protective effects of diabetes on sepsis.<sup>17–20</sup> Within this debate, the most frequently proposed study limitation was study design. Epidemiological studies using large cohorts can avoid the selection bias that is frequently observed in hospital-based studies, but detailed clinical information is usually not available. Most importantly, many studies have failed to consider the influence of diabetic complication severity.

Hemoglobin A1C (HbA1c) is commonly used to measure blood glucose control in diabetic patients and has also been proposed as an independent predictor of hospital mortality in sepsis patients.<sup>21</sup> However, its importance in diabetic sepsis patients requires further study because of limited data. Hyperglycemia has been shown to impair polymorphonuclear neutrophil function and cytokine production. However, high initial glucose levels were not reported to be associated with increased mortality in diabetic sepsis patients.<sup>22</sup> Furthermore, tight glucose control did not seem to be significantly associated with reduced hospital mortality in critical patients.<sup>23,24</sup> The influences of HbA1c and initial glucose levels on the outcome of sepsis deserve further investigation.

In the current study, using a representative nationwide database and a hospital-based database from multiple centers with laboratory data, we examined the association between type 2 diabetes and sepsis outcomes, specifically focusing on (a) whether type 2 diabetes itself increases the risk of mortality in hospitalized sepsis patients or whether risk of mortality depends on diabetic complication burdens, and (b) whether initial blood glucose level and HbA1c affect the hospital outcome.

## Methods

### *Data sources and study participants*

In this study, we used two distinct databases: (a) the National Health Insurance Research Database (NHIRD), which included the Longitudinal Cohort of Diabetes Patients (LHDB) and the Longitudinal Health Insurance Database 2000

(LHID 2000); and (b) the hospital-based database from multiple centers.

Because the hospital-based database lacked longitudinal information for each type 2 diabetic individual, we used the LHDB and LHID 2000 to resolve this limitation. The LHDB and LHID 2000 recorded all the medical information for each individual, such as outpatient (at clinics or hospitals) and emergency department visits (at every hospital) and hospitalizations that were not limited to a single medical facility. Therefore, data from the NHIRD avoided recall bias and could be used in the longitudinal cohort study.

In contrast, the hospital-based database from multiple centers could provide laboratory data, such as HbA1c, initial blood glucose level, and culture results. However, the information was restricted to a single facility, and important information from other clinics or hospitals might be missed.

### *Nationwide database*

In the first part of this study, we conducted a nationwide cohort study using data from the NHIRD. The diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are used in the NHIRD to identify specific diagnoses. Data for sepsis patients were retrieved using the ICD-9-CM code 038 plus a main infection diagnosis with antibiotics prescription. The accuracy of sepsis diagnosis in the NHIRD has been validated in previous studies.<sup>25</sup> The infection site classification was conducted following the criteria developed by Angus and colleagues.<sup>26</sup>

The patients were classified as using certain drugs if they took the drugs for more than 1 month within a 1-year period prior to the index hospitalization (the first admission for sepsis). The index date was defined as the first day of index hospitalization. The drugs, procedures, special modalities, intensive care unit (ICU) admission, and length of hospital stay were recorded using the claims data of the NHIRD.

Initially, we used the LHDB of the NHIRD, which contains randomized selected data (a total of 1.68 million enrollees from 1999 to 2012) from patients with newly diagnosed diabetes to

retrieve the study cohort of type 2 diabetic first-episode sepsis patients.<sup>27</sup> The patients in the study cohort had to have been diagnosed with type 2 diabetes at least 1 year prior to the index hospitalization to allow for the evaluation of diabetic complication burden by using the adjusted Diabetes Complications Severity Index score (aDCSI score).<sup>28,29</sup>

The Diabetes Complications Severity Index (DCSI) was first developed by Young and coworkers.<sup>28</sup> The DCSI is a useful tool for adjusting for the baseline severity of diabetic complications and predicting hospital mortality. The aDCSI score was modified from the DCSI score and had been validated in the NHIRD.<sup>30</sup> The aDCSI score included seven categories of complications: cardiovascular disease, nephropathy, neuropathy, retinopathy, peripheral vascular disease, stroke, and metabolic emergency events.

The comparison cohort, which was composed of nondiabetic first-episode sepsis patients, was retrieved from the LHID 2000. The LHID 2000 used in this study contains medical information for 1 million beneficiaries, randomly sampled from the registry of all beneficiaries in 2000. The study cohort from the LHDB and the comparison cohort from the LHID 2000 were matched in a 1:1 ratio by propensity scoring. For each patient, we calculated the propensity score using multivariate logistic regression by entering age, sex, income, urbanization level, hospital level, baseline comorbidities, and infection sites from the LHDB and LHID 2000. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

#### *Hospital-based database*

In the second part of this study, we retrieved the first-episode data of type 2 diabetic and nondiabetic sepsis patients from 2006 to 2012 in the electronic databases of three medical centers, Taipei and Taichung Veterans General Hospitals, and the Lin-Kou Medical Center of Chang Gung Memorial Hospital. The type 2 diabetic and nondiabetic sepsis patients were matched by age and sex. Laboratory data, including initial blood glucose level, HbA1c, and initial lactate level; hospital courses, including ICU admission and total and 28-day hospital mortality; received procedures (including mechanical ventilation and hemodialysis); and blood culture results were collected for

further analysis. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-02-003BC), Taichung Veterans General Hospital (CE18102A), and Lin-Kou Medical Center of Chang Gung Memorial Hospital (201701502B0C501).

The selection process of participants from the nationwide and hospital-based databases is shown in Supplement Figure 1. Most of the enrolled type 2 diabetic sepsis patients in the hospital database from multiple centers could be traced and linked to the nationwide database by a specific matching method.<sup>31</sup> However, matching was not allowed in Taiwan at the time of this study. Regarding the data in the hospital-based database, initial blood glucose levels were measured on the day of admission, either in the emergency department or on the ward, before patients received any acute glucose-lowering injection therapy (i.e. insulin). HbA1c levels were assessed during a 1-month period prior to the admission day.

*Statistical analyses.* Differences in demographic characteristics, comorbidities, medications, and laboratory data were examined using the chi-square test, the Mann-Whitney test and a two-sample *t* test. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated using a logistic regression model. A Kaplan-Meier analysis with the log-rank test was performed to compare hospital outcomes among type 2 diabetic sepsis patients with different initial blood glucose levels and HbA1c values. Statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, USA). A *p* value of 0.05 was considered indicative of significance.

## **Results**

#### *First part: nationwide database*

After propensity-score matching, data collected between 1999 and 2012 for 19,719 type 2 diabetic first-episode sepsis patients and an equal number of nondiabetic first-episode sepsis patients were retrieved as the study and comparison cohorts from the LHDB and LHID 2000. Demographic characteristics, comorbidities, medications, infection sites, and received procedures of the study and comparison cohorts are shown in Table 1.

**Table 1.** Nationwide database: demographic characteristics, comorbidities, and medications in type 2 diabetic and nondiabetic sepsis patients before and after propensity-score matching.

Patient characteristics	All sepsis patients (n = 120,439)	Before matching			p value	PS matching			Standardized difference	
		Non-DM (n = 21,576, 17.91%)	DM (n = 98,863, 82.09%)			Non-DM (n = 19,719)	DM (n = 19,719)			
		n	%	n	%	n	%	n	%	
<b>Sex</b>										
Female	54,767	8913	41.31	45,854	46.38	7990	40.52	7884	39.98	0.011
Male	65,672	12,663	58.69	53,009	53.62	11729	59.48	11835	60.02	0.011
<b>Age, years</b>										
20–29 years	1529	953	4.42	576	0.58	530	2.69	164	0.83	0.142
30–39 years	3892	1439	6.67	2453	2.48	1077	5.46	631	3.2	0.111
40–49 years	9638	2106	9.76	7532	7.62	1814	9.20	1755	8.9	0.01
50–59 years	17,755	2587	11.99	15,168	15.34	2318	11.76	2910	14.76	0.089
60–69 years	22,552	2996	13.89	19,556	19.78	2814	14.27	3694	18.73	0.12
70–79 years	33,327	5179	24	28,148	28.47	5012	25.42	5404	27.41	0.045
≥80 years	31,746	6316	29.27	25,430	25.72	6154	31.21	5161	26.17	0.112
Mean (SD)*	68.90 (15.08)	66.89 (18.53)		69.33 (14.17)		68.64 (17.39)		68.80 (14.88)		0.01
<b>Insurance premium (NT dollars)</b>										
<20,000	75,927	16,048	74.38	59,879	60.57	14,576	73.92	14433	73.19	0.016
20,000 ≤ insurance premium < 40,000	36,824	4558	21.13	32,266	32.64	4256	21.58	4365	22.14	0.013
40,000 ≤ insurance premium < 60,000	5930	890	4.12	5040	5.1	820	4.16	839	4.25	0.005
60,000 ≤ insurance premium	1758	80	0.37	1678	1.7	67	0.34	82	0.42	0.012

(Continued)

Table 1. (Continued)

Patient characteristics	All sepsis patients (n = 120,439)				Before matching				PS matching			
	Non-DM (n = 21,576, 17.91%)		DM (n = 98,863, 82.09%)		p value		Non-DM (n = 19,719)		DM (n = 19,719)		Standardized difference	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>Urbanization level</b>						<0.0001						
1 (highest)	29,506	25.1	24,099	24.38	5407	24.38	4902	24.86	4884	24.77	0.002	0.002
2	33,242	27.31	27,358	27.67	5884	27.67	5362	27.19	5306	26.91	0.006	0.006
3	19,906	16.18	16,419	16.61	3487	16.61	3180	16.13	3186	16.16	0.001	0.001
4	19,589	15.96	16,150	16.34	3439	16.34	3199	16.22	3250	16.48	0.007	0.007
5 (lowest)	18,166	15.45	14,837	15.01	3329	15.01	3076	15.6	3093	15.69	0.002	0.002
<b>Hospital level</b>						<0.0001						
Medical center	38,933	35.09	31,363	31.72	7570	31.72	6836	34.67	6856	34.77	0.002	0.002
Regional hospital	54,017	43.15	44,710	45.22	9307	45.22	8554	43.38	8554	43.38	0	0
District hospital	27,484	21.76	22,790	23.05	4694	23.05	4329	21.95	4309	21.85	0.002	0.002
<b>Baseline comorbidities</b>												
HTN	86,491	59.24	73,709	74.56	12,782	74.56	12,446	63.12	12360	62.68	0.009	0.009
Hyperlipidemia	51,971	24.49	46,687	47.22	5284	47.22	5182	26.28	5148	26.11	0.004	0.004
COPD	52,796	44.40	43,217	43.71	9579	43.71	9484	48.10	9524	48.30	0.004	0.004
CLD	39,563	30.61	32,958	33.34	6605	33.34	6518	33.05	6502	32.97	0.002	0.002
CKD	46,873	24.85	41,511	41.99	5362	41.99	5324	27.00	5334	27.05	0.001	0.001
PAOD	16,240	9.44	14,204	14.37	2036	14.37	2016	10.22	2014	10.21	0	0
IHD	51,633	31.76	44,781	45.30	6852	45.30	6783	34.40	6758	34.27	0.003	0.003
Stroke	52,615	37.69	44,484	45.00	8131	45.00	8056	40.85	8071	40.93	0.002	0.002
Cancer	33,639	20.63	29,187	29.52	4452	29.52	4422	22.43	4387	22.25	0.004	0.004

(Continued)

Table 1. (Continued)

Patient characteristics	All sepsis patients (n = 120,439)			Before matching			PS matching			Standardized difference	
	n	Non-DM (n = 21,576, 17.91%)		DM (n = 98,863, 82.09%)	p value	Non-DM (n = 19,719)		DM (n = 19,719)			
		n	%			n	%	n	%		
<b>Drugs</b>											
NSAIDs	59,580	10,021	46.45	49,559	50.13	<0.0001	9588	48.62	9401	47.67	0.019
Aspirin	13,350	1980	9.18	11,370	11.50	<0.0001	1938	9.83	2150	10.90	0.035
Statins	18,869	1014	4.70	17,855	18.06	<0.0001	995	5.05	2178	11.05	0.222
Biguanides	42,469	-	-	42,469	42.96	-	-	-	7600	38.54	-
DPP-4 inhibitors	4759	-	-	4759	4.81	-	-	-	659	3.34	-
Sulfonylureas	47,483	-	-	47,483	48.03	-	-	-	8631	43.77	-
TZDs	6443	-	-	6443	6.52	-	-	-	961	4.87	-
Other OADs	18,113	-	-	18,113	18.32	-	-	-	2911	14.76	-
Insulin	34,201	-	-	34,201	34.59	-	-	-	6297	31.93	-
Immunosuppressants	447	74	0.34	373	0.38	0.4526	71	0.36	52	0.26	0.017
Steroids	29,167	4676	21.67	24,491	24.77	<0.0001	4578	23.22	4681	23.74	0.012
<b>Infection site</b>											
Respiratory	44,511	8375	38.82	36,136	36.55	<0.0001	7876	39.94	7420	37.63	0.047
Genitourinary	39,244	5979	27.71	33,265	33.65	<0.0001	5419	27.48	6266	31.78	0.094
Gastrointestinal	9562	1817	8.42	7745	7.83	<0.0001	1607	8.15	1672	8.48	0.012
Soft tissue/musculoskeletal	6682	979	4.54	5703	5.77	<0.0001	868	4.40	1239	6.28	0.084
Central nervous	785	135	0.63	650	0.66	<0.0001	111	0.56	139	0.70	0.018
Cardiovascular	801	164	0.76	637	0.64	<0.0001	143	0.73	135	0.68	0.005
Device related	1924	286	1.33	1638	1.66	<0.0001	278	1.41	275	1.39	0.001
Others	10,006	1970	9.13	8036	8.13	<0.0001	1745	8.85	1726	8.75	0.003

(Continued)

Table 1. (Continued)

Patient characteristics	All sepsis patients (n = 120,439)	Before matching				p value	PS matching			
		Non-DM (n = 21,576, 17.91%)		DM (n = 98,863, 82.09%)			Non-DM (n = 19,719)		DM (n = 19,719)	
		n	%	n	%		n	%	n	%
<b>aDCSI score</b>										
0	24,134	-	-	24,134	24.41	-	-	5905	29.95	-
1	11,625	-	-	11,625	11.76	-	-	2218	11.25	-
2	25,030	-	-	25,030	25.32	-	-	5340	27.08	-
3	10,782	-	-	10,782	10.91	-	-	1876	9.51	-
4	14,575	-	-	14,575	14.74	-	-	2568	13.02	-
≥5	12,171	-	-	12,171	12.86	-	-	1812	9.19	-
<b>Procedures</b>										
Nasogastric tube feeding	71,665	12,314	57.07	59,351	60.03	<0.0001				
Central venous catheter insertion	49,283	8335	38.63	40,948	41.42	<0.0001				
Blood transfusion	61,611	10,919	50.61	50,692	51.27	<0.0001				
Hemodialysis	13,219	1786	8.28	11,433	11.56	<0.0001				
ICU admission	59,583	10,060	46.63	49,523	50.09	0.0002				
NIPPV	8499	1456	6.75	7043	7.12	<0.0001				
Mechanical ventilation	47,205	8237	38.18	38,968	39.42	<0.0001				
Results were obtained using the Chi-square test.										
*Results were obtained using the two-sample t test.										
PS matching include variables of age, sex, insurance premium, urbanization level, hospital level, baseline comorbidities, and infection site.										
aDCSI, adapted Diabetes Complications Severity Index; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitor; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; NIPPV, non-invasive positive pressure ventilation; NT dollars, national Taiwan dollars; OADs, oral antidiabetic drugs; PAOD, peripheral arterial occlusion disease; PS, propensity score; TZD, thiazolidinedione.										

Before matching, the type 2 diabetic sepsis patients had a higher prevalence of sepsis in the genitourinary tract (33.65% versus 27.71%) and soft tissue/musculoskeletal system (5.77% versus 4.54%, both  $p < 0.0001$ ). Additionally, the diabetic sepsis patients more frequently received respiratory support (mechanical ventilation: 39.42% versus 38.18%; noninvasive positive pressure ventilation: 7.12% versus 6.75%, both  $p < 0.0001$ ) and dialysis (11.56% versus 8.28%,  $p < 0.0001$ ) compared with the nondiabetic sepsis patients.

After propensity-score matching in a multivariate analysis, type 2 diabetic sepsis patients had an increased OR of 1.14 (95% CI 1.10–1.19,  $p < 0.0001$ ) for mortality after adjusting for age, sex, insurance premium (as a proxy for household income), urbanization level, and hospital level (Table 2).

According to diabetic complication burdens in the regression analysis of the main model, the patients with aDCSI scores of 0, 1, 2, 3, 4, and  $\geq 5$  had ORs of 0.91 (95% CI 0.85–0.97), 0.87 (95% CI 0.80–0.96), 1.14 (95% CI 1.07–1.22), 1.25 (95% CI 1.13–1.38), 1.56 (95% CI 1.43–1.70), and 1.77 (95% CI 1.61–1.96) for hospital mortality of sepsis, respectively (all  $p < 0.001$  and  $p$  for trend  $< 0.001$ ). In the subgroup analysis, the type 2 diabetic sepsis patients with higher aDCSI scores had increased ORs for mortality compared with those with lower scores in every age subgroup (per 10 years), especially in the range of 30–39 years (Supplement Figure 2).

We also stratified the sepsis patients according to infection site, and we found that the type 2 diabetic sepsis patients had increased adjusted ORs in every origin except the gastrointestinal system (adjusted OR of 2.29 (95% CI 1.36–3.86) for the central nervous system, adjusted OR of 1.26 (95% CI 1.18–1.35) for the respiratory system, adjusted OR of 1.88 (95% CI 1.14–3.10) for the cardiovascular system, adjusted OR of 1.58 (95% CI 1.46–1.72) for the genitourinary system, adjusted OR of 1.32 (95% CI 1.08–1.61) for soft tissue, and adjusted OR of 0.99 (95% CI 0.86–1.14) for the gastrointestinal system; Supplement Table 1).

### Second part: hospital-based database

From the hospital-based database, we initially included data for 4984 sepsis patients collected

between 2006 and 2012. After matching for age and sex, 1054 type 2 diabetic sepsis patients and 2108 nondiabetic sepsis patients were included for further analysis.

The type 2 diabetic sepsis patients had a higher initial creatinine level ( $2.4 \pm 2.1$  versus  $1.9 \pm 1.8$ ,  $p < 0.001$ ) and prevalence of receiving hemodialysis during hospitalization (23.2% versus 16.9%,  $p < 0.001$ ; Table 3). Furthermore, the type 2 diabetic sepsis patients had a higher ICU admission rate (57.5% versus 55.3%,  $p = 0.249$ ) and acute physiologic and chronic health II (APACH II) score ( $25.3 \pm 7.1$  versus  $24.9 \pm 7.0$ ,  $p = 0.292$ ) than the nondiabetic sepsis patients, although the  $p$  value did not reach significance. Accordingly, the type 2 diabetic sepsis patients had a higher hospital mortality rate (45.2% versus 42.3%,  $p = 0.138$ ) and 28-day mortality rate (35.5% versus 32.8%,  $p = 0.147$ ) than the nondiabetic sepsis patients. The type 2 diabetic sepsis patients had a higher prevalence of Gram-positive coccus bacteremia (16.8% versus 14.4%,  $p = 0.089$ ) but a lower prevalence of Gram-negative bacillus bacteremia (19.1% versus 20.7%,  $p = 0.294$ ) than the nondiabetic sepsis patients.

In the univariate and multivariate logistic regression analyses, type 2 diabetes was associated with an increased risk of hospital mortality during the sepsis course (adjusted OR = 1.31, 95% CI 1.11–1.54,  $p = 0.002$ ). This result was similar to that obtained for the nationwide database. The Kaplan–Meier analysis with log-rank test also showed a difference in hospital mortality between the type 2 diabetic and nondiabetic sepsis patients [ $p = 0.122$ ; Figure 1(a)].

The 1054 type 2 diabetic sepsis patients were divided into two groups, surviving and deceased patients, for further comparison. Initial blood glucose levels between the surviving and deceased diabetic sepsis patient groups did not differ significantly:  $273.9 \pm 180.3$  versus  $266.1 \pm 200.2$  [mg/dl;  $p = 0.095$ ; Figure 1(b)]. Furthermore, the surviving diabetic sepsis patients did not have lower HbA1c (%) levels than the deceased diabetic sepsis patients:  $8.4 \pm 2.6$  versus  $8.0 \pm 2.5$  ( $p = 0.078$ ; Supplement Table 2). The univariate analysis, another logistic regression analysis that included age, sex, Charlson comorbidity index score, and important laboratory data, showed an OR of 1.00 (95% CI 1.00–1.00,  $p = 0.532$ ) for initial glucose levels and 0.94 (95% CI 0.86–1.02,  $p = 0.143$ ) for



**Table 2.** Nationwide database: odds ratio of mortality related to type 2 diabetes and its complication severity in different adjusted models.

Characteristics	Die (n = 16205)	Crude		Adjusted model 1		Adjusted model 2		
		OR	p value	OR	(95% CI)	OR	(95% CI)	p value
<b>DM</b>								
No	7811	1.00	Reference	1.00	Reference	1.00	Reference	
Yes	8394	1.13	(1.09–1.18)	1.14	(1.1–1.19)	–	–	–
<b>aDCSI score</b>								
0	2034	0.80	(0.75–0.85)	–	–	0.91	(0.85–0.97)	0.0033
1	781	0.83	(0.76–0.91)	–	–	0.87	(0.8–0.96)	0.0053
2	2299	1.15	(1.08–1.23)	–	–	1.14	(1.07–1.22)	<0.0001
3	875	1.33	(1.21–1.47)	–	–	1.25	(1.13–1.38)	<0.0001
4	1376	1.76	(1.62–1.91)	–	–	1.56	(1.43–1.7)	<0.0001
≥5	1029	2.00	(1.82–2.21)	–	–	1.77	(1.61–1.96)	<0.0001
<b>Sex</b>								
Female	5685	1.00	Reference	1.00	Reference	1.00	Reference	
Male	10,520	1.45	(1.39–1.51)	1.56	(1.5–1.63)	1.55	(1.49–1.62)	<0.0001
<b>Age, years</b>								
20–29 years	121	1.00	Reference	1.00	Reference	1.00	Reference	
30–39 years	385	1.38	(1.1–1.73)	1.37	(1.09–1.72)	1.38	(1.1–1.74)	0.0053
40–49 years	1090	2.08	(1.69–2.57)	2.07	(1.68–2.56)	2.11	(1.71–2.61)	<0.0001
50–59 years	1616	2.12	(1.73–2.6)	2.19	(1.78–2.69)	2.21	(1.8–2.72)	<0.0001
60–69 years	2372	2.72	(2.22–3.33)	2.72	(2.22–3.33)	2.71	(2.21–3.32)	<0.0001
70–79 years	4635	3.80	(3.11–4.64)	3.69	(3.02–4.51)	3.57	(2.92–4.37)	<0.0001
≥80 years	5986	5.32	(4.36–6.49)	5.33	(4.36–6.52)	5.10	(4.17–6.24)	<0.0001

(Continued)

Table 2. (Continued)

Characteristics	Die (n = 16205)	Crude		Adjusted model 1		Adjusted model 2			
		OR	[95% CI]	p value	OR	[95% CI]	OR	[95% CI]	p value
<b>Insurance premium (NT dollars)</b>									
<20000	12,766	1.00	Reference		1.00	Reference	1.00	Reference	
20,000 ≤ insurance premium < 40,000	2937	0.66	[0.63-0.69]	<0.0001	0.71	[0.68-0.75]	0.72	[0.68-0.76]	<0.0001
40,000 ≤ insurance premium < 60,000	458	0.49	[0.43-0.54]	<0.0001	0.60	[0.54-0.68]	0.62	[0.55-0.69]	<0.0001
60,000 ≤ insurance premium	44	0.53	[0.37-0.76]	0.0005	0.67	[0.47-0.96]	0.70	[0.49-1]	0.0521
<b>Urbanization level</b>									
1 (highest)	4004	1.00	Reference		1.00	Reference	1.00	Reference	
2	4274	0.97	[0.91-1.02]	0.2171	1.00	[0.94-1.06]	1.01	[0.95-1.07]	0.86
3	2655	1.03	[0.97-1.1]	0.3179	1.05	[0.98-1.12]	1.06	[0.99-1.13]	0.1103
4	2692	1.03	[0.97-1.1]	0.2939	1.03	[0.96-1.1]	1.04	[0.97-1.11]	0.2698
5 (lowest)	2580	1.04	[0.97-1.11]	0.2565	1.06	[0.99-1.14]	1.07	[1-1.15]	0.0409
<b>Hospital level</b>									
Medical center	5705	1.00	Reference		1.00	Reference	1.00	Reference	
Regional hospital	6894	0.94	[0.9-0.99]	0.0152	0.88	[0.84-0.92]	0.87	[0.83-0.92]	<0.0001
District hospital	3606	1.00	[0.95-1.06]	0.9066	0.83	[0.78-0.88]	0.81	[0.77-0.86]	<0.0001
<b>Baseline comorbidities</b>									
HTN	10,716	1.27	[1.21-1.32]	<0.0001	0.95	[0.89-1.01]	-	-	-
Hypertlipidemia	3820	0.79	[0.76-0.83]	<0.0001	0.90	[0.84-0.96]	-	-	-
COPD	8647	1.42	[1.37-1.48]	<0.0001	0.91	[0.86-0.97]	-	-	-

(Continued)

Table 2. (Continued)

Characteristics	Die (n = 16205)	Crude		Adjusted model 1		Adjusted model 2	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
CLD	5444	1.05	(1-1.09)	1.09	(1.03-1.16)	-	-
CKD	5031	1.41	(1.35-1.47)	0.99	(0.93-1.06)	-	-
PAOD	1910	1.33	(1.25-1.42)	1.08	(0.99-1.18)	-	-
IHD	6116	1.29	(1.24-1.35)	0.95	(0.89-1.01)	-	-
Cancer	4836	2.06	(1.97-2.16)	3.02	(2.83-3.22)	-	-
Stroke	7409	1.40	(1.35-1.46)	1.21	(1.16-1.27)	-	-
<b>Procedures</b>							
Nasogastric tube feeding	13,777	7.84	(7.46-8.25)	-	-	-	-
Central venous catheter insertion	9973	4.74	(4.54-4.95)	-	-	-	-
Blood transfusion	11,716	4.01	(3.84-4.19)	-	-	-	-
Hemodialysis	2236	2.83	(2.63-3.04)	-	-	-	-
ICU admission	10,893	3.87	(3.71-4.03)	-	-	-	-
NIPPV	1591	2.14	(1.98-2.32)	-	-	-	-
Mechanical ventilation	10,564	6.62	(6.33-6.92)	-	-	-	-
Cardiopulmonary cerebral resuscitation	3893	10.36	(9.52-11.27)	-	-	-	-
<p>Model 1: adjusted for DM, age, sex, insurance premium, urbanization level, hospital level, and baseline comorbidities.  Model 2: adjusted for aDSCI score, age, sex, insurance premium, urbanization level, and hospital level.  In model 2, baseline comorbidities were not put into the model for adjustment because of the collinearity.  aDSCI, adapted Diabetes Complications Severity Index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease;  DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; NIPPV, non-invasive positive pressure ventilation, NT dollars, national Taiwan dollars;  OR, odds ratio; PAOD, peripheral arterial occlusion disease.</p>							

**Table 3.** Demographic characteristics, comorbidities, laboratory data, hospital course, and outcomes of matched type 2 diabetic and nondiabetic sepsis patients.

Variables	Total (n = 3162)	DM		p value
		Yes (n = 1054)	No (n = 2108)	
Age <sup>¶</sup>	70.4 ± 13.1	70.3 ± 12.9	70.4 ± 13.1	0.779
Male	1956 (61.9)	652 (61.9)	1304 (61.9)	1.000
Hospital mortality	1368 (43.3)	476 (45.2)	892 (42.3)	0.138
28-day mortality	1066 (33.7)	374 (35.5)	692 (32.8)	0.147
Hemodialysis	602 (19.0)	245 (23.2)	357 (16.9)	<0.001
Mechanical ventilation	1897 (60.0)	658 (62.4)	1239 (58.8)	0.053
ICU admission	1771 (56.0)	606 (57.5)	1165 (55.3)	0.249
APACH II score (n = 557 versus 1063) <sup>¶</sup>	25.0 ± 7.0	25.3 ± 7.1	24.9 ± 7.0	0.292
Length of ICU stay <sup>¶</sup>	15.6 ± 14.3	14.6 ± 13.8	16.0 ± 14.6	0.020
Length of hospital stay <sup>¶</sup>	23.5 ± 25.5	23.0 ± 27.5	23.7 ± 24.4	0.214
<b>Comorbidities</b>				
HTN	931 (29.4)	463 (43.9)	468 (22.2)	<0.001
Hyperlipidemia	54 (1.7)	36 (3.4)	18 (0.9)	<0.001
COPD	287 (9.1)	72 (6.8)	215 (10.2)	0.002
CLD	244 (7.7)	81 (7.7)	163 (7.7)	1.000
CKD	1019 (32.2)	410 (38.9)	609 (28.9)	<0.001
PAOD	80 (2.5)	43 (4.1)	37 (1.8)	<0.001
IHD	124 (3.9)	55 (5.2)	69 (3.3)	0.010
Cancer	958 (30.3)	226 (21.4)	732 (34.7)	<0.001
Stroke	273 (8.6)	120 (11.4)	153 (7.3)	<0.001
CCI score <sup>¶</sup>	3.4 ± 2.7	3.7 ± 2.4	3.2 ± 2.8	<0.001
<b>Bacterial cultures</b>				
GPC	481 (15.2)	177 (16.8)	304 (14.4)	0.089
GNB	638 (20.2)	201 (19.1)	437 (20.7)	0.294
<b>Laboratory data</b>				
Glucose	191.4 ± 141.8	270.4 ± 189.4	149.1 ± 80.8	<0.001
WBC (×10 <sup>3</sup> )	13.2 ± 13.5	14.2 ± 12.1	12.7 ± 14.1	<0.001
Hb	12.0 ± 2.7	12.2 ± 2.6	12.0 ± 2.7	0.057
PLT (×10 <sup>6</sup> )	1.9 ± 1.3	2.1 ± 1.6	1.9 ± 1.2	<0.001
Cr	2.1 ± 1.9	2.4 ± 2.1	1.9 ± 1.8	<0.001
Bilirubin	0.9 ± 2.0	0.8 ± 1.9	0.9 ± 2.0	<0.001
Lactate	31.7 ± 31.3	32.9 ± 34.0	31.0 ± 29.7	0.259

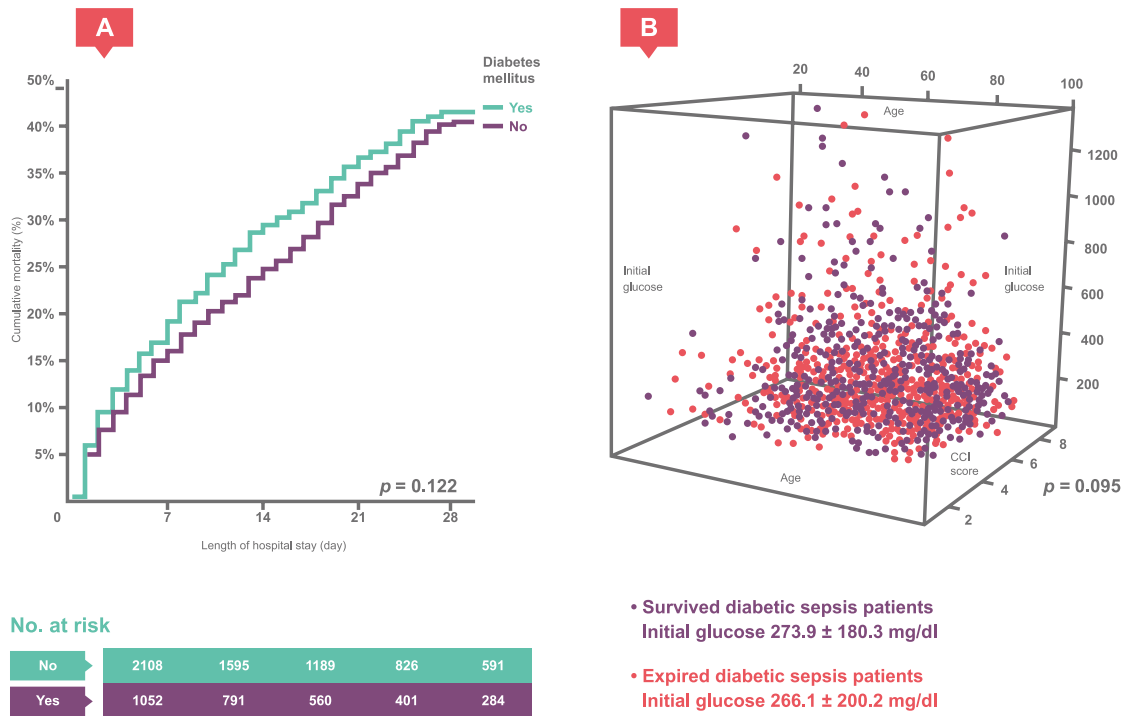
Results were obtained using the Chi-square test.

<sup>¶</sup>Results were obtained using the Mann-Whitney test.

Continuous data are expressed as mean ± SD. Categorical data are expressed as numbers (percentage).

APACH, acute physiologic and chronic health; CCI, Charlson comorbidity index; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; GNB, Gram-negative bacillus (GNB); GPC, Gram-positive coccus; Hb, hemoglobin; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; PAOD, peripheral arterial occlusion disease; PLT, platelets; SD, standard deviation; WBC, white blood count.

## Diabetic Sepsis Patients Initial Glucose



**Figure 1.** Diabetic sepsis patients' initial glucose.

(a) The Kaplan–Meier analysis with log-rank test showed the difference in the hospital course of mortality between the type 2 diabetic and nondiabetic sepsis patients. (b) Scatter plot of initial blood glucose levels in the surviving and deceased type 2 diabetic sepsis patients, which did not differ significantly:  $273.9 \pm 180.3$  mg/dl versus  $266.1 \pm 200.2$  mg/dl ( $p=0.095$ ).

HbA1c. The Kaplan–Meier analysis with log-rank test also showed that hospital mortality did not differ among type 2 diabetic sepsis patients with different initial blood glucose levels ( $\leq 200$ , 201–400, and  $>400$  mg/dl) and HbA1c values ( $\leq 7$  and  $>7\%$ ) [Figure 2(a) and (b)].

### Sensitivity analysis

We analyzed multiple models adjusted for drugs, procedures, and infection sites to examine the stability of the main model, that is, the multivariate analysis based on the aDCSI score. The models showed that the hospital mortality rate of sepsis increased as the aDCSI score increased (Supplement Table 3).

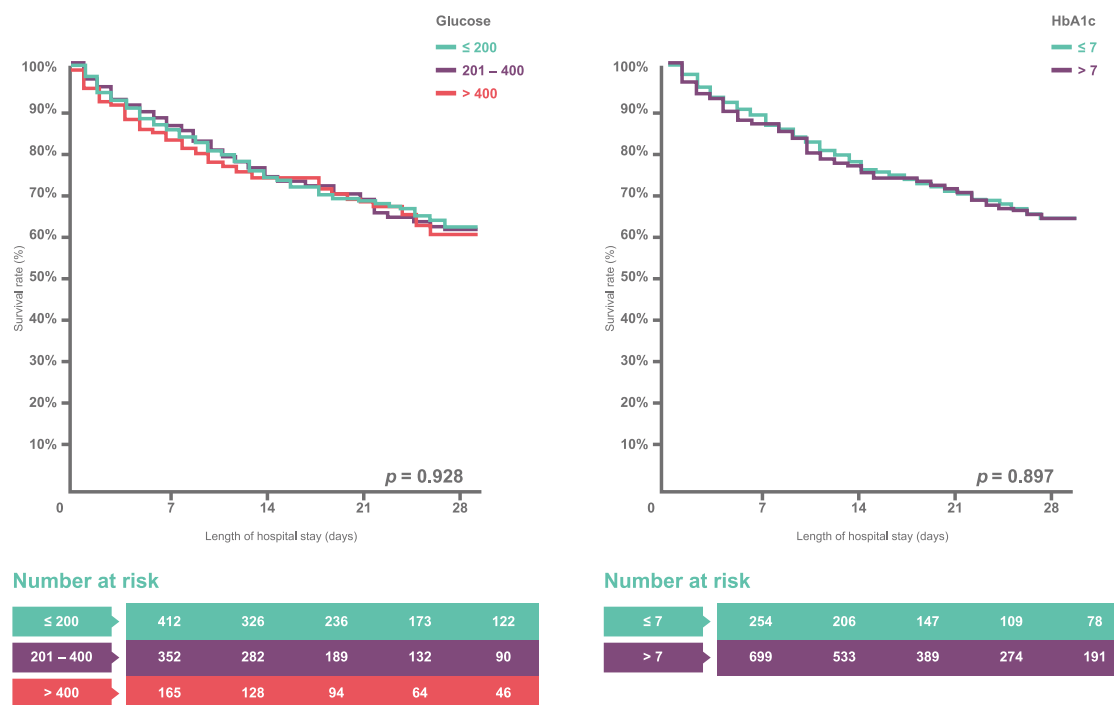
In the sensitivity analysis, we used a stricter inclusion criterion for HbA1c collection: the HbA1c needed to be collected within 3 days of admission. A total of 366 (sample size reduced from 953 to 366) type 2 diabetic sepsis patients were included.

The difference in hospital mortality rate remained unchanged (a hospital mortality rate of 39.5% for HbA1c  $\leq 7$  and 35.2% for HbA1c  $> 7$ ). In addition, we conducted another sensitivity analysis that excluded the outlier subjects with initial blood sugar levels  $> 600$  or  $< 50$  mg/dl. The study results remained unchanged (for initial blood glucose levels  $\leq 200$ , 201–400, and  $>400$  mg/dl, the hospital mortality rates were 48.2%, 41.2%, and 48.1%, respectively,  $p=0.136$ ).

### Discussion

In this study, we demonstrated that the outcome of type 2 diabetic sepsis patients was mainly determined by the cumulative diabetic complication burden (represented by the aDCSI score) rather than diabetes itself. The above argument was reinforced by the reverse ORs found in the type 2 diabetic sepsis patients with an aDCSI score  $\leq 1$ . In other words, if type 2 diabetic patients have few complications, they may not

## Survival Rate in Glucose and HbA1c



**Figure 2.** Survival rate *versus* glucose and HbA1c. (a) The Kaplan–Meier analysis with log-rank test for the hospital course of mortality among type 2 diabetic sepsis patients with different initial blood glucose levels at admission ( $\leq 200$ , 201–400, and  $> 400$ ). (b) The Kaplan–Meier analysis with log-rank test for the hospital course of mortality between type 2 diabetic sepsis patients with HbA1c levels  $> 7$  and  $\leq 7$ .

have an inferior hospital outcome of sepsis compared with nondiabetic patients. Furthermore, somewhat surprisingly, neither recent glucose control (HbA1c) nor the initial blood glucose level was associated with hospital mortality during the sepsis course. In conclusion, clinicians should not infer the outcome of a type 2 diabetic sepsis patient merely on the basis of recent glucose control or initial glucose level; rather, they should consider the cumulative diabetic complication burden. The stereotype of the impact of type 2 diabetes in sepsis should be modified.

This study contributes at least two important novelties in clinical practice. First, we described the trajectory of type 2 diabetic sepsis patients from the past (cumulative diabetic complication burdens) to the recent past (blood glucose control within the prior 3 months, HbA1c) and the present (initial blood glucose at admission). The connections were bridged by using the nationwide diabetic patient database and the

multicenter hospital databases concurrently. Second, we evaluated the severity of type 2 diabetic patients by using the aDCSI score, which is specific for the evaluation of diabetic complication burdens, and we explored its use in sepsis outcome predictions.

Donnelly and colleagues demonstrated that diabetes was associated with an increased risk of hospitalization due to infectious diseases. However, diabetes itself and insulin use were not associated with increased 28-day hospital mortality.<sup>32</sup> Nonetheless, Dianna and coworkers demonstrated that patients with diabetes had an excess risk of dying from a range of infectious diseases.<sup>33</sup> Both studies used a large cohort, but their conclusions were conflicting. We infer that the difference was due to the lack of a classification of diabetes severity. In our study, we introduced the use of the aDCSI score, and the results showed that the sepsis outcomes of diabetic patients were mainly determined by the complication burden of

diabetes. Our argument was also supported by the dose–response effect in the trend test for the ORs of patients with different aDCSI scores. Therefore, judging the sepsis outcome only by the existence of diabetes is not sufficient.

HbA1c is a widely used marker that reflects the average glucose level within the previous 120 days. Furthermore, HbA1c was reported a major outcome predictor in diabetic sepsis patients.<sup>21</sup> However, our study results did not support this argument. Many studies support the influence of long-term glycemic control on diabetic complication development.<sup>34,35</sup> Poor long-term glycemic control makes diabetic patients prone to infectious diseases because of their impaired immune functions.<sup>32</sup> In this study, HbA1c levels were assessed during a 1-month period prior to the admission day. In Taiwan, because of the convenience and high quality of medical care, the diabetes specialists were easily accessed without the need of long waiting. Patients could receive antidiabetic drug adjustment according to the HbA1c level in the outpatient department on time. Furthermore, the diabetic sepsis patients presenting with higher HbA1c levels may receive more aggressive blood sugar control with insulin in the initial stage of sepsis. Although, the hospital outcome of diabetic sepsis patients with higher HbA1c was not be as poor as initially thought, more evidence was needed to document this result.

Hyperglycemia frequently occurs in sepsis patients as a stress response that stimulates gluconeogenesis, which uses recycled pyruvate and lactate.<sup>36–38</sup> Hyperglycemia may have protective effects in patients because high blood glucose levels increase the diffusion gradient in tissues with abnormal microvasculature caused by sepsis. Our study may indirectly support the above argument. A study by van Vught and colleagues demonstrated that admission hyperglycemia was associated with adverse outcomes in sepsis, irrespective of the presence of diabetes.<sup>39</sup> However, our study demonstrated that a high blood glucose level at admission was not associated with hospital outcome. We inferred that the initial blood glucose level was an important risk factor for mortality in non-diabetic sepsis patients but not in type 2 diabetic sepsis patients.

Our study has the following strengths. In the study of the nationwide database, we used claims data for procedures such as mechanical

ventilation, hemodialysis, and blood transfusion. The accuracy of this approach is far superior to using only ICD-9 or 10 codes for acute organ dysfunction. Furthermore, detailed information, such as blood culture results and APACH II scores, in the hospital-based database provided a richer understanding of the complex interplay between type 2 diabetes and sepsis, rather than simple taxonomy.

This study is not without limitations. We were able to link the individual patient's medical information between the hospital-based database and the nationwide diabetic patient database to create a convincing longitudinal cohort study. However, due to the increasing conflict surrounding health-care database use in Taiwan, we abandoned this idea to avoid further severe debates. Second, some may challenge our use of a previous sepsis definition, originating from the systemic inflammatory response syndrome (SIRS) criteria, rather than the sepsis-3 definition. However, we believe that the central idea of this study would not change. We retrieved the study cohort by using ICD-9 codes not only for sepsis (038) but also for main infection origins, such as pneumonia or biliary tract infection. Therefore, we are confident that all the retrieved sepsis patients in our study were truly infected and did not have other conditions, such as pancreatitis, burn injury, or trauma, which would similarly induce SIRS reactions. Furthermore, as noted by Cortes-Puch I and coworkers, 'Moreover, these previous definitions and the SIRS criteria have been widely adopted for use at the bedside and for hospital and state-wide quality improvement initiatives worldwide. Numerous controlled trials have relied on them, and this scientific database should not be discarded until unequivocal evidence indicates that superior diagnostic criteria exist.'<sup>40</sup> We believe that our study could still provide valuable information to clinicians. Finally, the first sodium–glucose cotransporter-2 (SGLT2) inhibitor (Empagliflozin) was available in Taiwan since 2014. However, our nationwide database only included the data from 1999 to 2012. Therefore, we could not discuss the potential risk of serious urinary tract infections and genital infections in type 2 diabetic patients using SGLT2 inhibitors.

## Conclusion

In type 2 diabetic sepsis patients, hospital mortality was mainly determined by the diabetes-related

complication burden rather than the diabetes itself. Furthermore, initial blood glucose and HbA1c levels may not be as important as previously thought. Early intervention in type 2 diabetic patients could clearly improve the sepsis outcome, especially in the early stage of diabetes with few diabetic complications.

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The authors' individual contributions are as follows: conception and design: Ming-Shun Hsieh, Sung-Yuan Hu and Chorng-Kuang How. Data analysis and interpretation: Jin-Wei Lin, Ming-Shun Hsieh, Chen-June Seak and Vivian Chia-Rong Hsieh. Manuscript writing: Ming-Shun Hsieh. Final approval and critical revision: Pau-Chung Chen. All authors read and approved the final manuscript.

### Availability of data and material

The data that support the findings of this study are available from NHIRD but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of NHIRD.

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### Conflict of interest statement

The authors declare no conflicts of interest in preparing this article. They confirm that they have read the journal's position on issues involved with unethical publication and affirm that this study is consistent with those guidelines.

### Ethics approval and consent to participate

This study was conducted by using the NHIRD in Taiwan. The NHIRD contains deidentified secondary data for research; our study was exempted from the requirement of informed consent from participants. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

### Novelty statements

This study contributes at least two important novelties in clinical practice. Here, we described the trajectory of type 2 diabetic sepsis patients from the past (cumulative diabetic complication burdens) to the recent past (blood glucose control within the previous 3 months, HbA1c) and the present (initial blood glucose at admission).

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### Supplemental material

Supplemental material for this article is available online.

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