Trajectory of Type 2 Diabetes in Sepsis Outcome: Impacts of Diabetic Complication Burdens, Initial Glucose Level, and HbA1c: Population-Based Cohort Study Combining with Nationwide and Hospital-Based Database

Running title: Type 2 diabetes and sepsis outcome

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Type 2 diabetes and sepsis outcome

1 **Abstract**

2 **Background**

3 Diabetic patients have an increased risk of infections; however, the association between type 2
4 diabetes and hospital outcomes of sepsis remains controversial when the diabetes severity is not
5 considered. We examined this association using nationwide and hospital-based databases
6 concomitantly.

7 **Methods**

8 The first part of this study was conducted using 2 nationwide databases: the Longitudinal Cohort
9 of Diabetes Patients and the Longitudinal Health Insurance Database 2000. The diabetic
10 complication burden was evaluated using the adapted Diabetes Complications Severity Index score
11 (aDCSI score). In the second part, we used the hospital-based database with laboratory data, such
12 as initial blood glucose and HbA1c levels, to make comparisons between surviving and dead
13 patients with type 2 diabetes and sepsis.

14 **Results**

15 The nationwide study included 19,719 type 2 diabetic sepsis patients and an equal number of
16 non-diabetic patients. The diabetic sepsis patients had an increased odds ratio (OR) of 1.14 (95%
17 CI 1.1-1.19) for hospital mortality. The OR for mortality increased as the complication burden
18 increased (diabetic sepsis patients with aDCSI scores of 0, 1, 2, 3, 4, and ≥5 had ORs of 0.91, 0.87,
19 1.14, 1.25, 1.56, and 1.77 for mortality, respectively (all *P*<0.001 and *P* for trend <0.001)).

20   A total of 1,054 diabetic sepsis patients were included from the hospital-based database. Initial
21 blood glucose levels in the surviving and dead diabetic sepsis patients did not differ significantly:
22 273.9 ± 180.3 versus 266.1 ± 200.2 (mg/dL) (*P*=0.095). Moreover, the surviving diabetic sepsis
23 patients did not have a lower HbA1c (%): 8.4 ± 2.6 versus 8.0 ± 2.5 (*P*=0.078).

24 **Conclusions**

25 In the case of type 2 diabetic sepsis patients, the diabetes-related complication burden is the
26 major determinant of hospital mortality rather than the diabetes itself. Contrary to popular belief,
27 initial blood glucose and HbA1c levels may not be as important as previously thought.

28

1 Introduction

2   Sepsis is a leading cause of mortality in critical care worldwide.[1-3] In addition to mortality, sepsis
3   may also induce acute organ dysfunction, and even cause long-term post-sepsis cardiovascular
4   diseases.[4] The reported incidence of sepsis varies; however, it presents an undoubtedly
5   increasing trend that is reflected in the aging population and greater recognition of this condition.
6   Treating sepsis patients causes significant national financial burdens.

7   Diabetes is an important comorbid condition in sepsis because of its high prevalence.[5] It has
8   generally been believed that diabetic patients are more prone to infections than the general
9   population.[6] However, the influence of diabetes on the outcome of sepsis remains inconclusive.
10 Higher mortality rates in the patients with diabetes were reported[7-12]; however, some others
11 found no influence[13-16], and even protective effects of diabetes in sepsis.[17-20]

12 The most frequently proposed study limitations of this debate were the study designs: the
13 epidemiological studies using large cohorts can avoid the selection bias that is frequently observed
14 in hospital-based studies, however, detailed clinical information is usually not available. Most
15 importantly, many studies failed to consider the influence of diabetic complication severity.

16 HbA1c is commonly used to measure blood glucose control in diabetic patients and has also
17 been proposed as an independent predictor for hospital mortality in sepsis patients.[21] However,
18 its importance in diabetic sepsis patients requires further study due to limited information.
19 Hyperglycemia was shown to impair polymorphonuclear neutrophil function and cytokine
20 production. However, it was reported that high initial glucose levels were not associated with
21 increased mortality in the diabetic sepsis patients.[22] Furthermore, tight glucose control did not
22 seem to be significantly associated with reduced hospital mortality in critical patients.[23, 24] The
23 influence of HbA1c and initial glucose levels on the outcome of sepsis deserves further
24 investigation.

25 In the current study, using the representative nationwide database and the hospital-based
26 database from multi-centers with laboratory data, we examined the association between type 2
27 diabetes and sepsis outcomes, and specifically focused on (1) whether diabetes itself increases the
28 risk of mortality in hospitalized sepsis patients or depends on the diabetes complication burdens
29 and (2) whether initial blood glucose levels and HbA1c affect the hospital course and outcomes.

1   **Methods**

2   **Data sources and study participants**

3   *Nationwide database*

4   In the first part of this study, we conducted a nationwide cohort study using data from the
5   National Health Insurance Research Database (NHIRD). The diagnosis codes of the International
6   Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are used in the NHIRD
7   to identify specific diagnoses. Sepsis patients were retrieved using the ICD-9-CM codes 038. The
8   specificity of a sepsis diagnosis in the NHIRD has been validated in previous studies.[25] The
9   infection site classification was performed similar to Angus et al. (Supplement Table 1).[26]

10   The patients were classified as using certain drugs if they took them for more than one month
11   within a one-year period prior to the index hospitalization. The index date was defined as the first
12   date of index hospitalization. The drug codes are shown in Supplement Table 2. The procedures
13   during hospitalization were defined by using the claims data (Supplement Table 3).

14   Initially, we used the Longitudinal Cohort of Diabetes Patients (LHDB) of the NHIRD, which
15   contains randomized selected data (120,000 patients / year) from patients with newly diagnosed
16   diabetes to retrieve the study cohort of type 2 diabetic first episode sepsis patients.[27] The
17   patients in the study cohort should have been diagnosed to have type 2 diabetes prior to the index
18   hospitalization to allow for the evaluation of diabetic complication status by using the adapted
19   Diabetes Complications Severity Index score (aDCSI score) (Supplement Table 4).[28, 29] *(The
20   original form of DCSI score had some missing and we had corrected in the supplement table)*

21   The Diabetes Complications Severity Index (DCSI) was first developed by Young et al.[28] The
22   DCSI is a useful tool to adjust for the baseline severity of diabetic complications and to predict
23   hospitalization and mortality. The aDCSI score was modified from the DCSI score and had been
24   validated in the NHIRD.[30] The aDCSI score included seven categories of complications:
25   cardiovascular disease, nephropathy, neuropathy, retinopathy, peripheral vascular disease, stroke,
26   and metabolic emergency events.

27   The comparison cohort, which was composed of non-diabetic first episode sepsis patients, was
28   retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 used
29   in this study contains the medical information of 1 million beneficiaries, randomly sampled from
30   the registry of all beneficiaries in 2000. This study was approved by the Institutional Review Board
31   of China Medical University (CMUH104-REC2-115).

Type 2 diabetes and sepsis outcome

1   *Hospital-based database*

2   In the second part of this study, we retrieved data on the type 2 diabetic first episode sepsis
3   patients between 2006 and 2012 from the electronic databases of three medical centers. Most of
4   these diabetic sepsis patients were included in the LHDB. Laboratory data, including initial blood
5   glucose level, HbA1c, and initial lactate level; hospital outcomes, including ICU (intensive care unit)
6   admission, hospital and 28-day mortalities; the received procedures (including mechanical
7   ventilation and emergent hemodialysis); blood culture results were collected for further analysis.
8   This study was approved by the Institutional Review Board of Taichung Veterans General Hospital
9   (No. CE13233).

10   The participant selection process of the nationwide and hospital-based databases was showed
11   in Supplement Figure 1 and Supplement Figure 2. Only type 2 diabetic patients were included for
12   further study. In the hospital-based database, the initial blood glucose level was obtained on the
13   admission day ether in the emergency department or ward before receiving any acute
14   glucose-lowering injection therapy, that is, insulin; the HbA1c level should be obtained in a period
15   of three days around the admission day.

16   **Statistical analyses**

17   In the hospital-based database, the type 2 diabetic and non-diabetic sepsis patients were matched
18   by age and gender. In the nationwide database, the study cohort from the LHDB and the
19   comparison cohort from the LHID2000 were matched by the propensity score matching method.
20   For each patient, we calculated the propensity score using the multivariate logistic regression by
21   entering age, gender, income, urbanization level, hospital level, baseline comorbidities, and
22   infection site.

23   Differences in demographic characteristics, comorbidities, medications, and laboratory data
24   were examined using Chi-square, Mann-Whitney and two-sample t-tests. Odds ratios (ORs) with
25   95% confidence intervals (95% CIs) were calculated in the logistic regression model. The
26   Kaplan-Meier analysis with log-rank test was conducted to compare the hospital outcome in
27   patients with different initial blood glucose levels and HbA1c. The statistical analyses were
28   performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, USA). A P value of 0.05
29   was considered significant.

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1   **Sensitivity analysis**

2   Because of limited cases with the data of HbA1c using the strict criteria of three days around the

3   admission date, we further conducted a sensitivity analysis. The HbA1c data was re-collected with

4   a wider time period of one month prior to the admission date to re-examine the effect of HbA1c.

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3   admission date, we further conducted a sensitivity analysis. The HbA1c data was re-collected with

4   a wider time period of one month prior to the admission date to re-examine the effect of HbA1c.

Type 2 diabetes and sepsis outcome

1 Results

2 *First part: nationwide database*

3 From the LHDB and LHID2000 between 1999 and 2012, after propensity score matching, 19,719
4 type 2 diabetic and an equal number of non-diabetic first episode sepsis patients were retrieved as
5 the study and comparison cohorts. The demographic characteristics, comorbidities, medications,
6 infection sites, and received procedures of the study and comparison cohorts were showed in
7 Supplement Table 5.

8   Before matching, the diabetic sepsis patients had a higher prevalence of genitourinary tract
9 infection (33.65% versus 27.71%) and soft tissue/musculoskeletal system infection related sepsis
10 (5.77% versus 4.54%) (both *P*<0.0001). Also, the diabetic sepsis patients more frequently received
11 respiratory support (mechanical ventilation: 39.42% versus 38.18%; non-invasive positive pressure
12 ventilation: 7.12% versus 6.75%, both *P*<0.0001) and emergent dialysis (11.56% versus 8.28%,
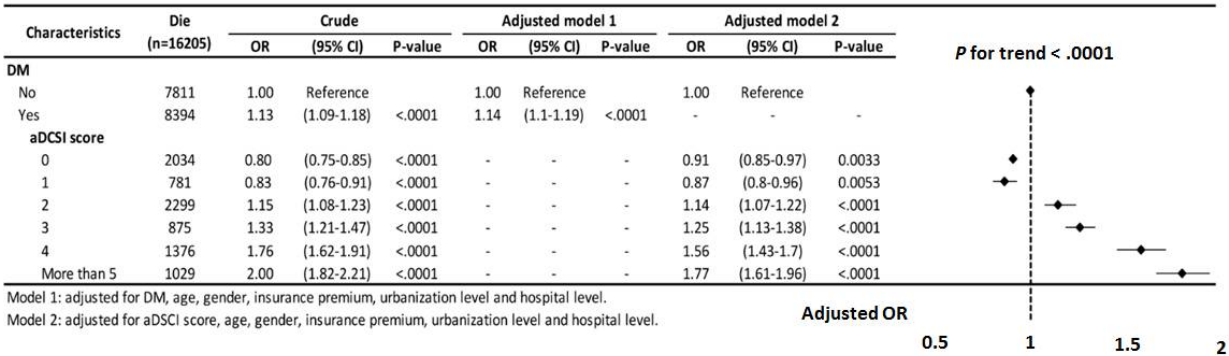13 *P*<0.0001, respectively).

14   After matching, in the further multivariate analysis, type 2 diabetic sepsis patients had an
15 increased OR of 1.14 (95% confidence level [CI] 1.1-1.19, *P*<0.0001) for mortality after adjusting
16 for age, gender, insurance premium (as a proxy for household income), urbanization level, and
17 hospital level (Supplement Table 6).

18   In the analysis according to diabetic complication burdens, the patients with aDCSI scores of 0, 1,
19 2, 3, 4, and ≥5 had ORs of 0.91 (95% CI, 0.85-0.97), 0.87 (95% CI, 0.8-0.96), 1.14 (95% CI,
20 1.07-1.22), 1.25 (95% CI, 1.13-1.38), 1.56 (95% CI, 1.43-1.7), and 1.77 (95% CI, 1.61-1.96) for
21 mortality during sepsis, respectively (all *P*<0.001 and *P* for trend <0.001) (Figure 1). In the
22 subgroup analysis stratified by age (every 10 years), the type 2 diabetic sepsis patients with higher
23 aDCSI scores had increased ORs for mortality compared to those with lower scores, particularly in
24 the 30-39 age group (Supplement Figure 3).

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Type 2 diabetes and sepsis outcome

1   Figure 1 Logistic regression analysis analyzing the odds ratios of hospital mortality in sepsis
2   patients with type 2 diabetes and different diabetic complication burdens (aDCSI scores).

Characteristics	Die (n=16205)	Crude			Adjusted model 1			Adjusted model 2			
		OR	(95% CI)	P-value	OR	(95% CI)	P-value	OR	(95% CI)	P-value	
DM											*P* for trend < .0001
No	7811	1.00	Reference		1.00	Reference		1.00	Reference		
Yes	8394	1.13	(1.09-1.18)	<.0001	1.14	(1.1-1.19)	<.0001	-	-	-	
aDCSI score											
0	2034	0.80	(0.75-0.85)	<.0001	-	-	-	0.91	(0.85-0.97)	0.0033	
1	781	0.83	(0.76-0.91)	<.0001	-	-	-	0.87	(0.8-0.96)	0.0053	
2	2299	1.15	(1.08-1.23)	<.0001	-	-	-	1.14	(1.07-1.22)	<.0001	
3	875	1.33	(1.21-1.47)	<.0001	-	-	-	1.25	(1.13-1.38)	<.0001	
4	1376	1.76	(1.62-1.91)	<.0001	-	-	-	1.56	(1.43-1.7)	<.0001	
More than 5	1029	2.00	(1.82-2.21)	<.0001	-	-	-	1.77	(1.61-1.96)	<.0001	

Model 1: adjusted for DM, age, gender, insurance premium, urbanization level and hospital level.
Model 2: adjusted for aDSCI score, age, gender, insurance premium, urbanization level and hospital level.

Adjusted OR

0.5   1   1.5   2

3

Second part: hospital-based database

5   From the hospital-based database, we initially included 4,984 sepsis patients between 2006 and
6   2012. After matching for age and gender, there were 1,054 type 2 diabetic and 2,108 non-diabetic
7   sepsis patients included for further analysis. The type 2 diabetic sepsis patients had a higher
8   prevalence of receiving hemodialysis (23.2% versus 16.9%, *P*<0.001) during hospitalization (Table
9   1). The type 2 diabetic sepsis patients had higher hospital mortality rate (45.2% versus 42.3%,
10   *P*=0.138) and 28-day mortality rate (35.5% versus 32.8%, *P*=0.147) compared to the non-diabetic
11   sepsis patients. The type 2 diabetic sepsis patients had higher prevalence of gram-positive coccus
12   bacteremia (16.8% versus 14.4%, *P*=0.089) but lower prevalence of gram-negative bacillus
13   bacteremia (19.1% versus 20.7%, *P*=0.294) compared to the non-diabetic sepsis patients, although
14   the *P* value did not reach the significance.

Type 2 diabetes and sepsis outcome

Table 1 Demographic characteristics, comorbidities, laboratory data, hospital course, and outcomes of matched type 2 diabetic and non-diabetic sepsis patients

Variables	Total (n=3162)	DM		*P* value
		Yes (n=1054)	No (n=2108)	
Age¶	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
Septic shock	1867(59.0)	616(58.4)	1251(59.3)	0.655
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
Length of ICU stay¶	15.6±14.3	14.6±13.8	16.0±14.6	0.020
APACH II score (n=557 vs 1063)¶	25.0±7.0	25.3±7.1	24.9±7.0	0.292
Length of hospital stay¶	23.5±25.5	23.0±27.5	23.7±24.4	0.214
Comorbidities				
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¶	3.4±2.7	3.7±2.4	3.2±2.8	<0.001
Bacterial cultures				
GPC	481 (15.2)	177 (16.8)	304 (14.4)	0.089
GNB	638 (20.2)	201 (19.1)	437 (20.7)	0.294
Laboratory data				
Glucose	191.4±141.8	270.4±189.4	149.1±80.8	<0.001
WBC (x10³)	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 (x10⁶)	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

Chi-Square test. ¶Mann-Whitney test. Continuous data were expressed as mean ± SD. Categorical data were expressed as number (percentage).

1   Acute physiologic and chronic health (APACH), Charlson comorbidity index (CCI),Chronic kidney
2   disease (CKD), Chronic liver disease (CLD), Chronic obstructive pulmonary disease (COPD),
3   Gram-negative bacillus (GNB), Gram-positive coccus (GPC), Hypertension (HTN), Intensive care
4   unit (ICU), Ischemic heart disease (IHD), Peripheral arterial occlusion disease (PAOD)

5

6   In the univariate and further multivariate logistic regression analyses, type 2 diabetes was
7   associated with an increased risk of hospital mortality during the sepsis course (adjusted OR=1.31,
8   95% CI, 1.11-1.54, *P*=0.002) (Supplement Table 7). But the Kaplan-Meier analysis with log-rank test
9   did not show a significant difference of hospital course of mortality between the type 2 diabetic
10 and non-diabetic sepsis patients (*P*=0.122) (Figure 2A).

11   The 1,054 type 2 diabetic sepsis patients were divided into surviving and dead groups for
12 further comparison (Supplement Table 8). Initial blood glucose levels in the surviving and dead
13 diabetic sepsis patients did not differ significantly: 273.9 ± 180.3 versus 266.1 ± 200.2 (mg/dL)
14 (*P*=0.095) (Figure 2B). Furthermore, the surviving diabetic sepsis patients did not have lower
15 HbA1c (%) than the dead diabetic sepsis patients: 8.4 ± 2.6 versus 8.0 ± 2.5 (*P*=0.078). In the
16 further logistic regression analysis, the univariate analysis which included age, gender, CCI score
17 and important laboratory data, showed an OR of 1.00 (95% CI, 1.00-1.00, *P*=0.532) for initial
18 glucose levels and 0.94 (95% CI, 0.86-1.02, *P*=0.143) for HbA1c (Supplement Table 9). The
19 Kaplan-Meier analysis with log-rank test also showed that the hospital mortality during the sepsis
20 course did not differ between type 2 diabetic sepsis patients with different initial blood glucose
21 levels (≤200, 201-400, and >400 mg/dL) and HbA1c (≤7 and >7%) (Figure 3) (Supplement Table 10
22 and Supplement Table 11).

23 Figure 2A The Kaplan-Meier analysis with log-rank test for hospital course of mortality between
24 the type 2 diabetic and non-diabetic sepsis patients. Figure 2B Comparison of Initial blood glucose
25 levels in the surviving and dead diabetic sepsis patients.

Type 2 diabetes and sepsis outcome

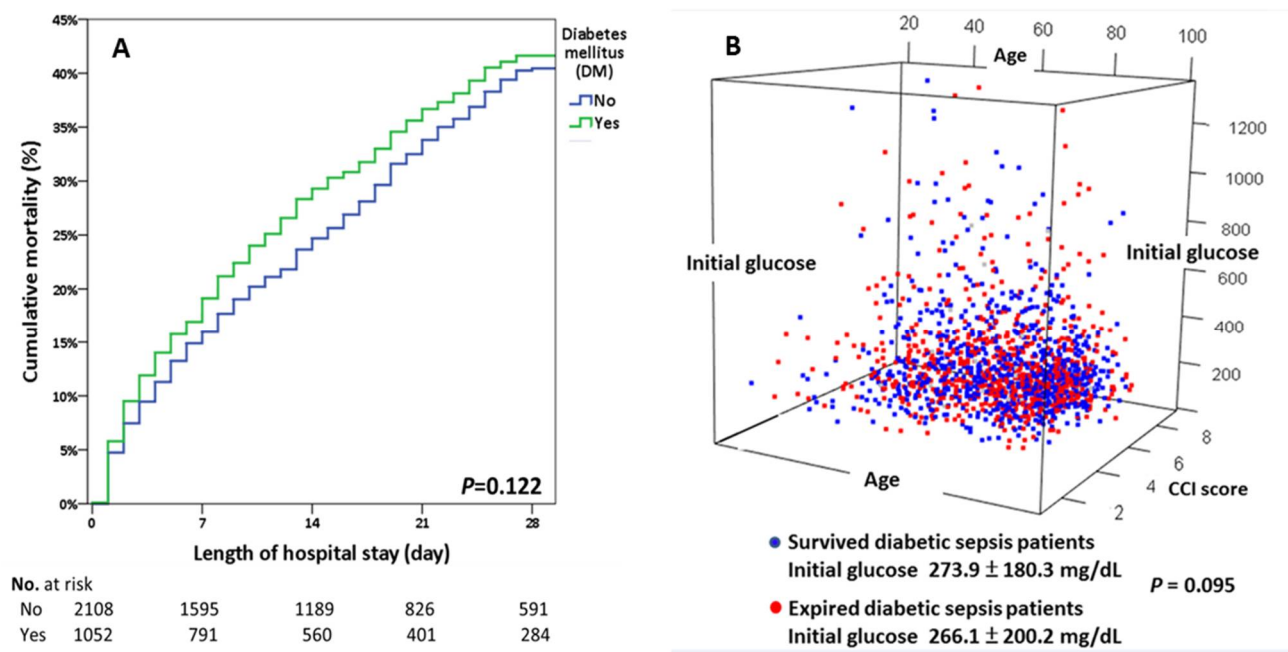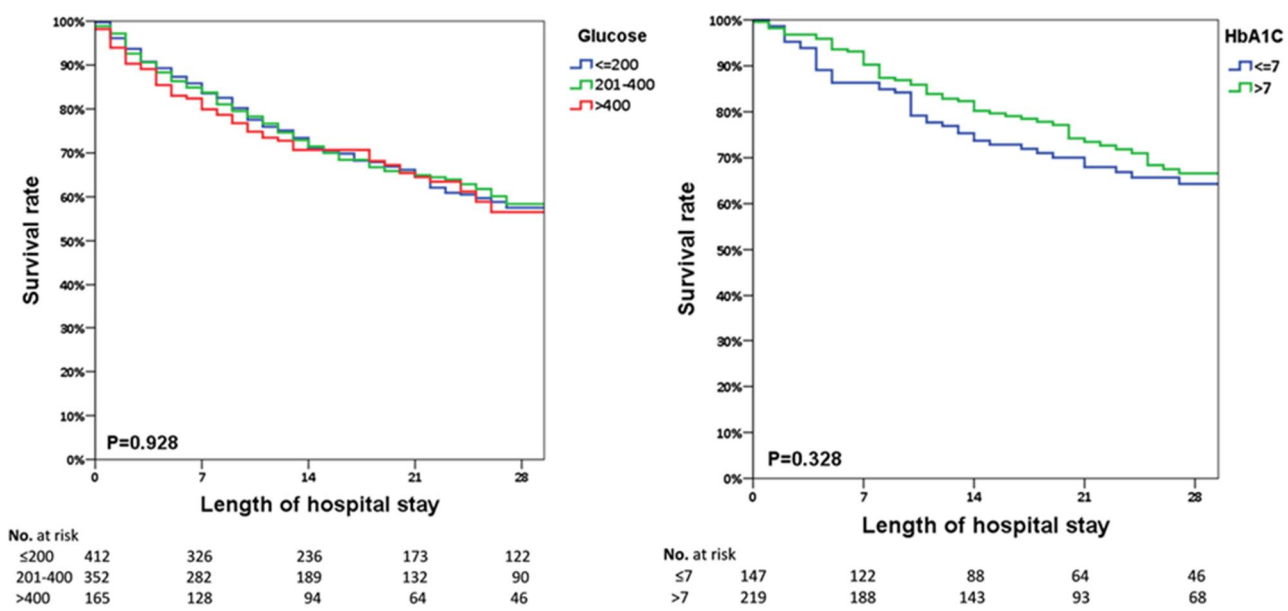4   Figure 3 Kaplan-Meier analysis with log-rank test for type 2 diabetic sepsis patients with different
5   initial blood glucose levels and HbA1c.

Type 2 diabetes and sepsis outcome

1   In the sensitivity analysis, using a wider time period of one month prior to the admission date

2   for HbA1c collection, the hospital mortality during the sepsis course between the type 2 diabetic

3   sepsis patients with HbA1c ≤7 and >7% did not differ significantly (47.2% versus 44.3%, *P*=0.471)

4   (Supplement Table 12) (Supplement Figure 4).

5

Type 2 diabetes and sepsis outcome

1   **Discussion**

2   In the current study, we demonstrated that the outcome of type 2 diabetic sepsis patients was

3   mainly determined by the diabetic complication burdens (represented as the aDCSI score).

4   Somewhat surprisingly, neither the recent glucose control (HbA1c) nor the initial glucose level was

5   associated with hospital mortality in the sepsis course. Physicians should not infer the outcome of

6   a diabetic sepsis patient merely via the recent poor glucose control or initial high glucose level;

7   rather, they should consider the diabetic complication burdens.

8   Donnelly et al. demonstrated that diabetes was associated with an increased risk of

9   hospitalization due to infection diseases. However, diabetes itself and insulin use were not

10   associated with increased 28-day hospital mortality.[31] Dianna et al. demonstrated that diabetic

11   patients had an excess risk of dying from a range of infection diseases.[32] Both studies used a

12   large cohort; however, their conclusions were conflicting. We infer that the difference was induced

13   by the lack of severity classification of diabetic complications. In our current study, we introduced

14   the utilization of aDCSI score and the results showed that the sepsis outcomes of diabetic patients

15   were mainly determined by the complication burdens of diabetes. This inference was supported

16   by the dose-responsive effect in the trend test in our study.

17   In this study, we found that the OR for hospital mortality elevated as the aDCSI score increased,

18   and presented in a dose-responsive manner. In the type 2 diabetic sepsis patients with an aDCSI

19   score of ≤ 1 even had a reverse OR for hospital mortality. However, we did not found an obviously

20   shorter disease course of diabetes (from the first diagnosis date of type 2 diabetes to the index

21   hospitalization date) in the patients with an aDCSI score of ≤1 (median duration = 294 days)

22   compared to those with an aDCSI score of >2 (median duration = 306 days). From this result, we

23   can infer that in type 2 diabetic sepsis patients, diabetes-related complication burdens are the

24   major determinant of hospital mortality, but not merely the diabetes itself.

25   HbA1c is a widely used marker that reflects the average glucose level within 120 days. It was

26   reported that HbA1c was a major outcome predictor in diabetic sepsis patients.[21] However, our

27   study results did not support this argument. There are many studies supporting the influence of

28   long-term glycemic control on diabetic complication development.[33, 34] Long-term poor

29   glycemic control makes diabetic patients prone to infection diseases because of their impaired

30   immune functions.[31] However, the hospital outcome of diabetic sepsis patients presenting with

31   higher HbA1c may be not as poor as we initially thought because these patients may receive more

32   aggressive blood sugar control in the initial stage of sepsis with insulin.

33   Hyperglycemia frequently occurs in sepsis patients as a stress response by stimulating

1 gluconeogenesis, which uses recycled pyruvate and lactate.[35-37] Hyperglycemia may have
2 protective effects in patients because high blood glucose levels increase the diffusion gradient in
3 tissues with abnormal microvasculature caused by sepsis. Our study may indirectly support the
4 above argument. The study by van Vught et al. demonstrated that admission hyperglycemia was
5 associated with adverse outcomes in sepsis course, irrespective of the presence of diabetes.[38]
6 However, our study demonstrated that a high blood glucose level at admission was not associated
7 with the hospital outcome.

8   Our study has the strengths. We examined the association between type 2 diabetes and sepsis
9 outcomes by concomitantly using the representative nationwide database (LHDB and LHID2000)
10 and the hospital-based database from medical centers (details in the appendix) with laboratory
11 data. Using this method, we longitudinally linked the long-term accumulated diabetic complication
12 burdens, HbA1c (as a representation of recent glucose control), and initial blood glucose levels at
13 admission to describe the complex trajectory of the disease course in these type 2 diabetic sepsis
14 patients. Our study which evaluated the diabetic complication burdens by using aDCSI score rather
15 than simply adjusting for baseline comorbidities was of important innovation in this topic. Also, in
16 this study of the nationwide database, we used the claims data for procedures such as mechanical
17 ventilation, hemodialysis and so on; therefore the accuracy is much better than the use of ICD
18 codes for acute organ dysfunction. Finally, the detailed information such as blood culture results in
19 the hospital-based database provided a richer understanding in the complex interplay between
20 type 2 diabetes and sepsis, rather than simple taxonomy.

21   This study has limitations. First, although we were able to link the individual patient's medical
22 information between the hospital-based database and the nationwide database to create a
23 convincing longitudinal cohort study. However, due to the increasing conflict of health database
24 utilization in Taiwan, we abandoned this idea to avoid further severe conflicts. Second, HbA1c was
25 usually measured at the physician's discretion and we initially included only one third of the whole
26 type 2 diabetic sepsis patients with data of HbA1c (366 in 1054), that might induce a significant
27 bias. We therefore use a wider time period of one month to substitute three days as the inclusion
28 criteria to examine the effect of HbA1c on sepsis outcome. However, the OR of HbA1c and
29 hospitalization course remained unchanged in using the larger sample size (953 in 1054).

1   **Conclusion**

2   In type 2 diabetic sepsis patients, diabetes-related complication burdens are the major
3   determinant of hospital mortality, rather than the diabetes itself. Initial blood glucose levels and
4   HbA1c may not be associated with the hospital outcome of sepsis.

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1   **Figure Legends**

2   **Figure 1** Logistic regression analysis analyzing the odds ratios of hospital mortality in

3   sepsis patients with type 2 diabetes and different diabetic complication burdens

4   (aDCSI scores).

5   **Figure 2A** The Kaplan-Meier analysis with log-rank test for hospital course of

6   mortality between the type 2 diabetic and non-diabetic sepsis patients. **Figure 2B**

7   Comparison of Initial blood glucose levels in the surviving and dead diabetic sepsis

8   patients.

9   **Figure 3** Kaplan-Meier analysis with log-rank test for type 2 diabetic sepsis patients

10   with different initial blood glucose levels and HbA1c.

11

12   **Table**

13   **Table 1** Demographic characteristics, comorbidities, laboratory data, hospital course,

14   and outcomes of matched type 2 diabetic and non-diabetic sepsis patients.

15

16   **Additional Files**

17   **Supplement Figures**

18   **Supplement Figure 1**

19   The participant selection process of combined nationwide and hospital-based

20   databases.

21   **Supplement Figure 2**

22   The participant selection process of the hospital-based database.

23   **Supplement Figure 3**

24   The stratification analysis by age (every 10 years) according to dichotomized aDCSI

25   scores (0-2 and ≥3).

1 **Supplement Figure 4**

2 Kaplan-Meier analysis with log-rank test to determine the difference of survival rate

3 in HbA1c ≤7and >7 by using a wider collection time period of one month prior to the

4 admission date.

5 **Supplement Tables**

6 **Supplement Table 1**

7 Classification of infection sites by ICD-9-CM codes

8 **Supplement Table 2**

9 ATC drug codes

10 **Supplement Table 3**

11 Procedure codes in the national health insurance database

12 **Supplement Table 4**

13 adapted Diabetes Complications Severity Index score (aDCSI score) by ICD-9-CM

14 Codes

15 **Supplement Table 5**

16 Nationwide database: demographic characteristics, comorbidities, and medications

17 in type 2 diabetic and non-diabetic sepsis patients before and after propensity score

18 matching

19 **Supplement Table 6**

20 Nationwide database: odds ratio of mortality related to type 2 diabetes and its

21 complication severity in different adjusted mode

22 **Supplement Table 7**

23 Hospital-based database: odds ratio of type 2 diabetes and baseline comorbidities

24 for sepsis mortality in type 2 diabetic and non-diabetic sepsis patients

1   **Supplement Table 8**

2   Hospital-based database: demographic characteristics, laboratory data, and hospital

3   course of survived and dead type 2 diabetic sepsis patients

4   **Supplement Table 9**

5   Hospital-based database: odds ratio of demographic characteristics and laboratory

6   data for sepsis mortality in type 2 diabetic sepsis patients

7   **Supplement Table 10**

8   Hospital-based database: comparison of hospital mortality between type 2 diabetic

9   sepsis patients with different HbA1c

10   **Supplement Table 11**

11   Hospital-based database: comparison of hospital mortality between type 2 diabetic

12   sepsis patients with different initial glucose level

13   **Supplement Table 12**

14   Hospital-based database: comparison of hospital mortality between type 2 diabetic

15   sepsis patients with different HbA1c level

Type 2 diabetes and sepsis outcome

1   ## Declarations

2   **Ethics approval and consent to participate:**

3   This study was approved by two Institutional Review Board :

4   (1) The Institutional Review Board of Taichung Veterans General Hospital (No. CE13233) for the
5   hospital-based database study.

6   (2) The Institutional Review Board of China Medical University (CMUH104-REC2-115) for the
7   nationwide database (LHID2000 and LHDB) study.

8   **Consent for publication:**

9   Not applicable.

10   **Availability of data and material:**

11   The datasets analyzed during the current study are not publicly available because it needed special
12   apply to the national health insurance database of Taiwan.

13   **Competing interests:**

14   None of the authors have any conflicts of interest to disclose. We confirm that we have read the
15   Journal's position on issues involved with unethical publication and affirm that this study is
16   consistent with those guidelines.

17   **Funding:**

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Type 2 diabetes and sepsis outcome

1   **Authors' contributions:**

2   The authors' individual contributions are as follows. Conception and design: Ming-Shun Hsieh,

3   Chorng-Kuang How, Yi-Tzu Lee, and Chen-June Seak. Data analysis and interpretation: Jen-Huai

4   Chiang, Vivian Chia-Rong Hsieh, and Chiann-Yi Hsu. Manuscript writing: Ming-Shun Hsieh. Final

5   approval and critical revision: Pau-Chung Chen, Sung-Yuan Hu, and Sheng-Hsiang Ma. All authors

6   read and approved the final manuscript. (more detail in the submission system)

13   **Appendix**

14   **The hospital-based database was collected from the following three medical centers:**

15   1. **Taipei Veterans General Hospital**

16   Ming-Shun Hsieh; Chorng-Kuang How; Yi-Tzu Lee;

17   2. **Taichung Veterans General Hospital**:

18   Sung-Yuan Hu; Chiann-Yi Hsu;

19   3. **Lin-Kou Medical Center, Chang Gung Memorial Hospital:**

20   Chen-June Seak;

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