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History of diabetes may delay antibiotic administration in patients with severe sepsis presenting to emergency departments

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Abstract

Clinical manifestations of sepsis differ between patients with and without diabetes mellitus (DM), and these differences could influence the clinical behaviors of medical staff. Therefore, we aimed to investigate whether pre-existing DM was associated with the time to antibiotics or sepsis care protocols.

This was a retrospective cohort study.

It conducted at 53 intensive care units (ICUs) in Japan.

Consecutive adult patients with severe sepsis admitted directly to ICUs form emergency departments from January 2016 to March 2017 were included.

The primary outcome was time to antibiotics.

Of the 619 eligible patients, 142 had DM and 477 did not have DM. The median times (interquartile ranges) to antibiotics in patients with and without DM were 103 minutes (60–180 minutes) and 86 minutes (45–155 minutes), respectively ($P = .05$). There were no significant differences in the rates of compliance with sepsis protocols or with patient-centred outcomes such as in-hospital mortality.

The mortality rates of patients with and without DM were 23.9% and 21.6%, respectively (*P* = .55). Comparing patients with and without DM, the gamma generalized linear model-adjusted relative difference indicated that patients with DM had a delay to starting antibiotics of 26.5% (95% confidence intervals (95%CI): 4.6–52.8, *P* = .02). The gamma generalized linear model-adjusted relative difference with multiple imputation for missing data of sequential organ failure assessment was 19.9% (95%CI: 1.0–42.3, *P* = .04). The linear regression model-adjusted beta coefficient indicated that patients with DM had a delay to starting antibiotics of 29.2 minutes (95%CI: 6.8–51.7, *P* = .01). Logistic regression modelling showed that pre-existing DM was not associated with in-hospital mortality (odds ratio, 1.26; 95%CI: 0.72–2.19, *P* = .42).

Pre-existing DM was associated with delayed antibiotic administration among patients with severe sepsis or septic shock; however, patient-centred outcomes and compliance with sepsis care protocols were comparable.

Abbreviations: CCI = Charlson Comorbidity Index, DM = diabetes mellitus, ED = emergency department, FORECAST = Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma, ICUs = intensive care units, JAAM = Japanese Association for Acute Medicine, SOFA = sequential organ failure assessment, VFDs = ventilator-free days.

Keywords: bundle, comorbidity, diabetes mellitus, protocols, sepsis

1. Introduction

Diabetes mellitus (DM) is one of the most common comorbidities in the world. Although it is known to increase the likelihood of infectious complications, including sepsis,[1] its influence on patient-centred outcomes in patients who develop sepsis remains unclear.[2–4] The complexities of DM in older patients with comorbidities who develop acute infection can make it difficult to

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identify the development of sepsis and to provide an accurate prognosis. Patients with DM are also known to have different patterns of sepsis and different clinical manifestations,[5] even if outcomes do not differ to those in patients without DM. For example, the risk of sepsis and the resulting complications and prognosis in DM have been reported to vary with the underlying infection.[5,6] Also, the incidence of acute kidney injury was reportedly higher in patients with DM than in those without DM who developed sepsis,[3,4] whereas respiratory failure and acute respiratory distress syndrome were less likely.[4]

The different clinical manifestations of sepsis in DM could influence the decision making of medical staff, and better understanding this problem may be a key to disentangling the complicated relationship between these diseases. If we can identify a potentially modifiable factor that is unique to patients with diabetes who present with sepsis, it would enable us to improve sepsis management for these patients. Therefore, we aimed to investigate whether pre-existing DM was associated with the time to antibiotics and the compliance rate of sepsis care protocols.

2. Methods

2.1. Design, setting, and participants

We conducted a secondary analysis of the sepsis cohort from the Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORE-CAST) study in Japan.[7] The FORECAST used a multicenter, prospective cohort of acutely ill patients from 59 intensive care units and was conducted between January 2016 and March 2017. In this research, we included adult patients (age ≥16 years) with severe sepsis based on 2003 Sepsis-2 criteria,[8] and excluded those who ordered "do not attempt resuscitation" or those with post-cardiopulmonary arrest resuscitation status at the time of sepsis recognition. We only included patients admitted to intensive care units (ICUs) directly from emergency departments because this ensured that we got temporally accurate sequence of events, such as time to antibiotics and bundle compliance. Finally, we excluded patients if the time to antibiotics was unknown, if the time to antibiotics exceeded 720 minutes, or if data for in-hospital mortality were missing.

The study protocol was reviewed and approved by the ethics committee of all participant institutes in the Japanese Association for Acute Medicine (JAAM) FORECAST group, Japan (IRB No.014–0306 on Hokkaido University, the representative for FORECAST group). This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committees of Osaka University Hospital. The ethics committee waived the need for informed consent because of the anonymous and retrospective nature of this study.

2.2. Data collection

Data were obtained from the FORECAST database, which was compiled from routine clinical records by the FORECAST investigators during the patient's original hospital stay. The exposure variable of primary interest was the presence of DM in the medical history. Other variables included the patients' demographic data, admission sources, comorbidities (Charlson Comorbidity Index; CCI), activities of daily living, organ dysfunction scores, infection characteristics, laboratory data, and blood culture results. In addition, we obtained data on

compliance with established sepsis care protocols, such as the measurement of serum lactate levels within 3 hours,[9] and recorded the time to antibiotics. Time to antibiotics was the primary outcome, but secondary patient-centred outcomes were also assessed, including in-hospital mortality, length of stay, ICU-free days, and ventilator-free days (VFDs).

2.3. Data definitions

Time zero for the start times of antibiotics or bundle compliance was when a physician recognised severe sepsis or septic shock. Time to antibiotics was the time at which antibiotics were first administered. History of DM was derived from CCI. The modified CCI was calculated without including DM. Septic shock and organ dysfunction were defined according to the Sepsis-2 criteria.[8] Suspected sites of infection in the FORECAST database initially included 11 foci: lung, intra-abdominal, urinary tract, soft tissue, wound, osteo-articular, endocardium, catheter-related, implant device-related, central nervous system, and undifferentiated. However, the number of patients in some categories was small, so these were consolidated into 7 main clinical categories: lung, intra-abdominal, urinary tract, soft tissue (soft tissue and wound), bloodstream-related (osteo-articular, endocardial, catheter-related, and implant device-related), central nervous system, and undifferentiated. VFD was defined as the number of days within the first 28 days after enrolment during which a patient was able to breathe without the help of a ventilator. VFD of patients who died during the study period was assigned as 0. ICU-free days were similarly calculated.[10]

2.4. Analysis

Descriptive statistics are presented as counts (proportions) for categorical variables and medians (interquartile ranges) or means ± standard deviations for continuous variables, as appropriate.

First, we compared baseline patient characteristics and demographic data, infection characteristics, organ dysfunction, and sepsis severity scores between patients with and without DM. Time to antibiotics is displayed using kernel density plots after comparing patients with and without DM. We also compared compliance with sepsis care protocols as well as the patient-centred outcomes between the groups. The analyses were repeated to compare patients with DM-related complications, DM alone, and no DM.

Next, we developed regression models to evaluate whether pre-existing DM was associated with delayed antibiotic administration, using generalized linear models with log-link functions to account for the right-skewed distributions. The results of the Park test[11] indicated a γ-distribution to be most appropriate for our data. Age, CCI (excluding DM), suspected infection site, and sequential organ failure assessment (SOFA) score were used for adjustment based on previous reports of their clinical importance (chosen a priori). We also carefully checked for interactions between DM and the CCI (excluding DM) and assessed each variable for multi-collinearity. We then reported the adjusted relative difference for the time to antibiotics. An additional analysis of patients with and without DM-related complications was performed and reported for all 3 groups (i.e., DM-related complications, DM alone, and no DM), using the same covariates for adjustment. Finally, we performed logistic regression analysis to evaluate the relationship between in-hospital mortality and a

history of pre-existing DM. Age, CCI (excluding DM), suspected site of infection, and the SOFA score were used for adjustment. These analyses are reported with their 95% confidence intervals (95%CIs).

2.5. Sensitivity analysis

Because 20% data of SOFA score, which is one of the most important variables in sepsis, was missing, we performed another sensitivity analysis by multiple imputations to handle missing data of SOFA. Supplemental Table 1 (Additional file 1, http://links.lww.com/MD/D917) shows characteristics of patients with and without missing data of SOFA. To impute the missing data, we constructed multiple ordered logistic regression models, including variables potentially related to the fact that the data were missing, those correlated with that outcome and those that had less missing data. The results across 20 imputed data sets were combined by averaging and standard errors were adjusted to reflect within-imputation and between-imputation variabilities.

Moreover, we used linear regression model for primary analysis as another sensitivity analysis because the results of the gamma generalized linear model were difficult to interpret. The same variables used in as the primary analysis were used.

All P-values were two-sided, with values of <.05 considered statistically significant. Statistical analyses were performed with Stata software, version 15.1 (StataCorp, TX).

3. Results

Of 676 patients with severe sepsis at the time of ICU admission from the emergency department (ED), we excluded 57 (8.4%) who did not meet our inclusion criteria or who had missing data. Of the remaining 619 patients from 53 ICUs, 142 had DM, and 477 did not (Supplemental Figure 1, http://links.lww.com/MD/D916). Baseline characteristics, comorbidities, organ failure, APACHE II scores, and SOFA scores were comparable between the groups with and without DM (Table 1).

However, patients with DM had fewer abdominal infections, more soft tissue infections, and higher C-reactive protein and procalcitonin levels than their peers without DM (all $P<.01$). Supplemental Table 2 (Additional file 2, http://links.lww.com/MD/D918) shows characteristics of patients with sepsis categorized into those with DM-related complications, those without DM-related complications and those without DM.

Overall, the median time to antibiotics was 89 minutes (47–160 minutes), with median times of 103 minutes (60–180 minutes) for patients with DM, and 86 minutes (45–155 minutes) for patients without DM ($P=.05$) (Fig. 1). After stratifying patients with DM by the presence ($n=35$) or absence ($n=107$) of complications, the median times to antibiotics were 119 minutes (63–180 minutes) and 98 minutes (52–180 minutes), respectively, compared with 86 minutes (45–155 minutes) ($P=.14$) in those without DM. There was no significant difference in compliance with sepsis protocols between the groups with and without DM (Table 2), even after stratification for the presence or absence of DM-related complications (Supplemental Table 3: Additional file 3, http://links.lww.com/MD/D919).

The crude mortality was 22.1%, with mortality rates of 23.9% and 21.6% in patients with and without DM, respectively ($P=.55$) (Table 3). The mortality rates among patients with DM-related complications, without DM-related complications, and

without DM were 31.4%, 21.5%, and 21.6%, respectively ($P=.39$) (Supplemental Table 4: Additional file 4, http://links.lww.com/MD/D920). Additional file 4 shows outcomes among patients with sepsis categorized into those with DM-related complications, those without DM-related complications and those without DM. In addition, there were no significant differences in patient-centred outcomes, such as the length of hospital stay, between patients with and without DM (Table 3).

The gamma generalized linear model-adjusted relative difference for the time to antibiotics showed that the DM group had a 26.5% delay (95%CI: 4.6–52.8; $P=.02$) in receiving antibiotics when compared with the group that had no history of DM (Table 4). The gamma generalized linear model-adjusted relative difference with multiple imputation for missing data of SOFA was 19.9% delay (95%CI: 1.0–42.3, $P=.04$). The linear regression model-adjusted beta coefficient indicated that patients with DM had a delay to starting antibiotics of 29.2 minutes (95% CI: 6.8–51.7, $P=.01$). The linear regression model-adjusted beta coefficient with multiple imputation for missing data of SOFA was 22.0 minutes delay (95%CI: 1.8–42.3, $P=.03$). After stratifying the DM group into those with and without complications, antibiotic administration was delayed in the latter (relative difference [95%CI]: 26.7% [1.8%–56.8%]; $P=.03$) but not in the former (relative difference [95%CI]: 26.7% [−8.8 to 76.2]; $P=.16$) relative to patients without DM (Table 4). The logistic regression model showed that a history of pre-existing DM was not associated with in-hospital mortality among patients with severe sepsis or septic shock (odds ratio, 1.26; 95% confidence interval, 0.72–2.19, $P=.42$) (Table 5).

4. Discussion

4.1. Summary

We performed secondary analyses of patients with severe sepsis and septic shock using data from a multicentre prospective cohort study in Japan. Our results show that pre-existing DM was related to delayed antibiotic administration among these patients. By contrast, patient-centred outcomes and compliance with sepsis care protocols were comparable between patients with and without DM.

Limited information exists about personal factors related to delays in the delivery of sepsis care protocols. To date, most studies have reported varied results when looking into the socioeconomic factors or systems that delay or block access,[12–15] including our previous research.[7] In the present study, however, we found that personal factors may be related to treatment delays. Therefore, we may need to consider not only improvements to systems but also to the identification of those who need special attention in the management of sepsis.

A small delay of 17 minutes in the median time to start antibiotics (103 and 83 minutes with and without DM, respectively; 26.5% delay by the gamma generalized linear model adjustment; 29.2 minutes delay by the linear regression model) may be important, considering recent bundle guidance recommends starting antibiotics within 1 hour.[16] On the other hand, it has been still controversial the relationship between mortality and time to antibiotics as well as our other secondary analysis which included all patients with sepsis (from EDs, wards, and inside ICUs) in the FORECAST study.[17] There was no significant difference in patient-centred outcomes according to time to antibiotics in this study, either. Since the protocols on

Table 1

Characteristics of patients with sepsis according to the presence or absence of DM (n = 619).

Characteristics		DM (n = 142)	No DM (n = 477)	P-value
Age, yr	At admission	74 (66–81)	76 (66–83)	.18
Male		83 (58.5)	288 (60.4)	.68
BMI, kg/m²		22.6 ± 4.6	21.6 ± 4.8	.05
Coexisting conditions	Myocardial infarction	8 (5.6)	17 (3.7)	.27
	Congestive heart failure	15 (10.6)	45 (9.4)	.69
	Peripheral vascular disease	4 (2.8)	9 (1.9)	.50
	Cerebrovascular disease	19 (13.4)	58 (12.2)	.70
	Dementia	14 (9.9)	53 (11.1)	.67
	COPD	8 (5.6)	41 (8.6)	.25
	Connective tissue disease	6 (4.2)	27 (5.7)	.50
	Peptic ulcer disease	4 (2.8)	17 (3.6)	.67
	Chronic kidney disease	13 (9.2)	27 (5.7)	.14
	Hemiplegia	5 (3.5)	18 (3.8)	.89
	Malignancy (solid)	14 (9.9)	64 (13.4)	.26
	Malignancy (leukemia)	0 (0)	3 (0.6)	.34
	Malignancy (lymphoma)	2 (1.4)	3 (0.6)	.36
	Metastatic tumour	1 (0.7)	6 (1.3)	.58
	Mild liver disease	5 (3.5)	19 (4.0)	.80
	Moderate to severe liver disease	1 (0.7)	12 (2.5)	.19
	AIDS	0 (0)	1 (0.2)	.59
Medication	Immunosuppressant	3 (2.1%)	10 (2.1%)	.991
	Steroid	14 (9.9%)	47 (9.9%)	.998
Non-diabetic CCI		1 (0–2)	1 (0–2)	.32
ADL	Dependent	36 (25.4)	124 (26.1)	.87
Suspected infection site	Lung (n = 209)	52 (36.6)	157 (32.9)	.41
	Abdomen (n = 138)	19 (13.4)	119 (24.9)	<.01
	Urinary tract (n = 138)	31 (21.8)	107 (22.4)	.88
	Soft tissue (n = 63)	24 (16.9)	39 (8.2)	<.01
	Central nervous system (n = 11)	3 (2.1)	8 (1.7)	.73
	Blood stream-related (n = 29)	6 (4.2)	23 (4.8)	.77
	Others (n = 31)	7 (4.9)	24 (5.0)	.96
Vital signs	Systolic BP (mm Hg)	107 (84–131)	97 (80–124)	.05
	Pulse rate (beats/min)	112 ± 26	113 ± 25	.72
	Respiratory rate (breaths/min)	24 (21–30)	26.5 (23–31)	.01
	Body temperature (Celsius)	37.5 (36.5–38.9)	37.8 (36.6–38.8)	.42
	Consciousness (GCS)	14 (9–15)	14 (9.5–15)	.85
Fever (body temperature ≥37.0)		91 (64.1)	334 (70.0)	.18
qSOFA ≥ 2		94 (66.7)	341 (74.6)	.29
Bacteraemia		89 (69.0)	269 (60.9)	.19
Septic shock	Yes	84 (59.2)	289 (60.6)	.76
Organ dysfunction on arrival	Hyperlactatemia (>2 mmol/L)	104 (73.2)	351 (73.6)	.93
	Acute kidney injury (Cre > 2 mg/dL)	59 (41.5)	171 (35.8)	.22
	Hyperbilirubinemia (>2.0 mg/dL)	22 (15.5)	88 (18.4)	.42
	Thrombocytopenia (<100,000/μL)	39 (27.5)	113 (23.7)	.36
	Coagulopathy (PT INR > 1.5)	18 (12.7)	80 (16.8)	.24
ARDS at arrival[*]		21 (17.2)	78 (18.4)	.77
Mechanical ventilation		53 (39.0)	160 (34.6)	.35
APACHE II score		23 (16–29)	22 (17–29)	.76
SOFA score		8 (6–11)	9 (6–11)	.62
Laboratory data at ED	White blood cell count (10³ cells/μL)	12.6 (6.6–18.6)	10.9 (5.9–18.0)	.22
	WBC differentials, band (%)	2 (0–31.5)	7 (0–35.5)	.40
	Hematocrit (%)	34.9 ± 7.4	35.7 ± 7.5	.26
	Total protein (g/dL)	5.9 ± 1.0	6.1 ± 1.0	.09
	Albumin (g/dL)	2.8 ± 0.7	2.9 ± 0.7	.09
	Lactate (mmol/L)	3.3 (2–5.6)	3.7 (2.1–5.9)	.13
	C-reactive protein (mg/dL)	17.4 (8.3–27.9)	14.1 (5.2–23.6)	.01
	Procalcitonin (ng/mL)	23.5 (1.9–90.2)	8.3 (1.7–37.7)	.04
	Serum glucose (g/dL)	202 (136–289)	130 (103–168)	<.01

Reported counts (proportions) for categorical variables and median (interquartile range) or mean ± standard deviation (SD) for continuous variables, where appropriate. *Missing data:* BMI = 17; ADL = 1; bacteraemia = 1; systolic BP = 17; pulse rate = 1; respiratory rate = 1; body temperature = 21; consciousness = 5; bacteraemia = 48; ARDS = 73; mechanical ventilation = 21; APACHE II score = 94; SOFA score = 125; white blood cell count = 2; WBC differentials = 423; hematocrit = 2; total protein = 26; albumin = 14; lactate = 17; C-reactive protein = 7; procalcitonin = 305; serum glucose = 9. ADL = activities of daily living, AIDS = acquired immune deficiency syndrome, APACHE = acute physiology and chronic health evaluation, ARDS = acute respiratory distress syndrome, BMI = body mass index, BP = blood pressure, CCI = Charlson Comorbidity Index, COPD = chronic obstructive pulmonary disease, Cre = creatinine, DM = diabetes mellitus, GCS = Glasgow coma scale, IV = intravenous, SOFA = sequential organ failure assessment.

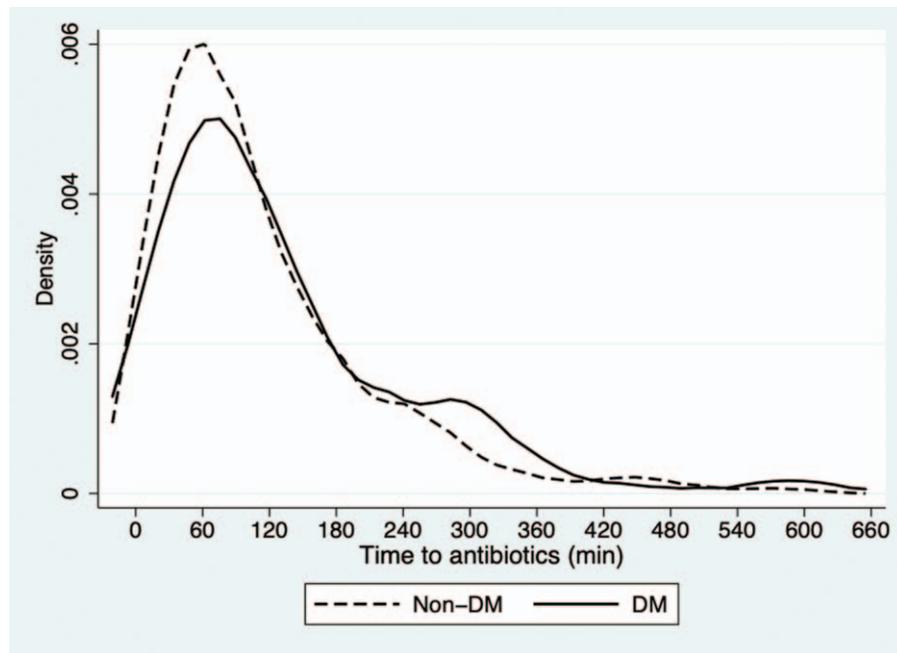[*] ARDS was defined by Berlin criteria.

Figure 1. Kernel density plot for the time to first antibiotic administration from the emergency department. The distributions for patients with and without DM are shown by solid and a dashed line, respectively. DM = diabetes mellitus.

Table 2

Compliance with sepsis care protocols among patients with sepsis according to the presence or absence of DM (n=619).

	Compliance rate		
Applicable elements of the sepsis bundle	DM	No DM	*P*-value
Entire 3-h resuscitation bundle*	70 (70.7)	253 (71.7)	.85
P1. Serum lactate obtained	138 (97.2)	464 (97.5)	.85
P2. Broad-spectrum antibiotic given	130 (91.5)	413 (86.9)	.14
P3. Blood cultures obtained before broad-spectrum antibiotic administration	137 (96.5)	455 (96.0)	.79
P4. 30 mg/kg crystalloid fluid bolus delivered (yes/cases with indication)*	76 (76.8)	293 (82.8)	.17
Other sepsis care protocols			
P5. Vasopressors use followed initial fluid bolus if needed to maintain MAP ≥ 65 mm Hg (yes/cases with indication)	83 (81.4)	285 (87.2)	.14
P6. Re-measured lactate if initial lactate elevated (yes/cases with indication)	98 (88.3)	346 (89.4)	.74

Data are reported as counts (proportions).
* Septic shock or lactate > 4 mmol/L. *Missing data:* P1 = 1; P2 = 2; P3 = 3; P4 = 5; P5 = 3; P6 = 4. Number of cases with indication for P4, P5, and P6: P4 = 453; P5 = 437; P6 = 498. DM = diabetes mellitus, MAP = mean arterial pressure.

Table 3

Outcomes among patients with sepsis according to the presence or absence of DM (n=619).

Outcomes		DM (n=142)	No DM (n=477)	*P*-value
In-hospital mortality		34 (23.9)	103 (21.6)	.55
	With shock (n=373)	26 (31.0)	77 (26.6)	.44
	Without shock (n=246)	8 (13.8)	26 (13.8)	.99
Survivor dispositions	Home (vs transfer)	46 (42.6)	155 (41.4)	.83
ICU-free days		20 (12–25)	21 (12–25)	.59
Ventilator-free days		21 (0–28)	22 (0–28)	.59
Length of hospital stay		22 (12–36)	21 (11–37)	.69

Data are reported as counts (proportions) for categorical data and as medians (interquartile ranges) for continuous variables. *Missing data:* Survival dispositions = 137; ICU-free days = 126; ventilator-free days = 9. DM = diabetes mellitus, ICU = intensive care unit.

Table 4

Model-adjusted relative difference in time to antibiotics among septic patients with DM (1. total, and 2. stratified by DM complications) with reference to those without DM (n = 494).

		Relative difference (%)	95%CI		P-value
1. Total	DM (ref. non-DM)	26.5	4.6	52.8	.02
(multiple imputation model for missing data of SOFA)	DM (ref. non-DM)	19.9	1.0	42.3	.04
2. Stratified	Non-DM		Reference		
	DM with complications	26.7	−8.8	76.2	.16
	DM without complications	26.4	1.8	56.8	.03

Adjusted for age CCI without DM, SOFA score, infection site (lung, abdomen, urinary tract, soft tissue, blood stream-related CNS, and others) by the gamma generalized linear model.
CCI = Charlson Comorbidity Index, CNS = central nervous system, DM = diabetes mellitus, SOFA = sequential organ failure assessment.

resuscitation, such as fluid bolus delivered and vasopressor use are a trigger for vital signs, it is naturally not related to the history of DM. We expected that protocols related to infection, such as the rate of blood culture and broad-spectrum antibiotics would decline; however, the median of time to antibiotics was 103 minutes and 86 minutes, and considering the rate of blood culture was about 90% or more in our study,[7] it was not a comparison that could show a significant difference within 3 hours protocol. However, further studies are required in this topic.

Notably, there was no statistical significance in sepsis care, such as time to antibiotics and bundles when patients with DM were stratified by the presence or absence of complications. The study may have been underpowered to show such differences because of the small number of patients with DM-related complications. However, similar model-adjusted relative differences in time to antibiotics imply that the delay in starting antibiotics and the prognosis of septic patients with DM were not affected by these complications.

Our study might be underpowered to detect the effect of diabetes on mortality. A previous report indicated that glucose variability, and not pre-existing DM, is independently associated with in-hospital mortality for patients with sepsis.[18,19] This suggests that the management of glucose level of a patient is more important than considering it as comorbidity.

We were not able to investigate the mechanism of the observed association between diabetes and antibiotic timing from our results. Diabetic patients seemed to have slightly less derangement of some vital signs, which may have reduced the urgency that clinicians felt when initiating antibiotics after sepsis recognition. We believe that both systemic and local host factors

contributed. For example, DM has typically been associated with specific infection sites, such as the skin and soft tissue,[5] and it is known that patients with DM are more susceptible to particular infections. Presumably, hyperglycemia-related impairment of the immune response may influence the development of infection and the resulting unmeasured clinical features, such as vague presentations.[20] Further studies are needed to investigate the relationship between clinical features, the causative organisms, and the immune response, and how these interact to delay treatment among patients with DM.

Moreover, patients with diabetes may have lower threshold to meet sepsis criteria with less severe illness. Although clinicians will have experienced that DM is associated with severe infection and worse outcomes, our results did not show a difference in mortality between patients with and without DM. The Sepsis-2 criteria, which we used as an inclusion criterion, cannot distinguish acute from chronic organ failure, and severity scores were similar between patients with and without DM in our cohort. We clinically presumed that patients with DM had more chronic organ failures than those without DM regardless of CCI. Thus, the DM cohort might also have included those with less severe sepsis or pseudo-sepsis if pre-existing organ failures were considered sepsis-related, and this could have affected the mortality rate. Given that patients with DM received antibiotics for sepsis after a delay, their clinical course might have been affected and have altered our clinical impressions. Severe sepsis continues to be an underdiagnosed and undertreated condition (i.e., there is low bundle compliance), with its influence on mortality still debated.[21] The contribution of DM to sepsis outcomes remains a major problem given that it is the most common major comorbidity.

4.2. Limitations

This study has several important limitations. First, the nature of the secondary study design meant that we could not make causal inferences between the observed characteristics and outcomes. Second, for the sepsis care protocols, we considered time zero to be the time of sepsis recognition instead of the time of arrival at the ED. Although previous reports have often used sepsis recognition as time zero, this approach may have caused bias.[22] Third, the presence of disparities in the use and timing of sepsis care protocols between institutions cannot be excluded, although other sepsis care protocols were comparable between groups. Fourth, we could not separate patients with type 1 and type 2 DM, which may have affected the results.[5] Fifth, we did not have specific data of immunity such as end stage renal disease although we have data of comorbidities which was deprived from CCI. Finally, in-hospital mortality data may have been optimistic

Table 5

Logistic regression model for in-hospital mortality comparing patients with DM and those without DM (n = 494).

		Odds ratio	95%CI	
DM		1.26	0.72	2.19
Age		1.02	1.00	1.04
CCI without DM		1.16	0.99	1.35
SOFA score		1.23	1.15	1.32
Infection site	Lung		Reference	
	Abdomen	0.71	0.38	1.34
	Urinary tract	0.63	0.32	1.25
	Soft tissue	0.90	0.38	2.15
	Blood steam-related	1.44	0.51	4.08
	CNS	7.76	1.76	34.27
	Others	1.27	0.46	3.46

CCI = Charlson Comorbidity Index, CNS = central nervous system, DM = diabetes mellitus, SOFA = sequential organ failure assessment.

because we did not follow-up the kinds of facilities where the patients were transferred from study hospitals, although survivors are mainly transferred to skilled nursing facilities from acute care hospitals in Japan.

5. Conclusions

In conclusion, a history of DM was associated with delayed antibiotic administration in patients with severe sepsis and septic shock. However, compliance with sepsis care protocols was comparable. This study has important implications for the management of sepsis in patients with diabetes in Japan.

Author contributions

All authors meet the ICMJE authorship criteria. TA contributed to the acquisition of data, conceived and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. TS, HI, and AK contributed to the conceiving and designing this study, interpreted the data, and revised the manuscript for important intellectual content. AS contributed to the acquisition of data, conducted data cleaning, interpreted the data, and revised the manuscript for important intellectual content. SK, SG, and AH contributed to the acquisition of data, jointly conceived and designed this study, interpreted the data, and revised the manuscript for important intellectual content. All of the authors contributed to the acquisition of data, and reviewed, discussed, and approved the final manuscript.

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