Pre-existing diabetes and all-cause mortality in adult patients with sepsis: A population-based cohort study

Federico Angriman MD MPH PhD; Jutamas Saoraya MD PhD; Patrick R. Lawler MD MPH; Baiju R. Shah MD PhD; Claudio M. Martin MD MSc; Damon C. Scales MD PhD

on behalf of the Sepsis Canada Network

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Table S1. Coding strategies for main variables of interest

Main variable of interest[1]	**Main components of algorithm (ICD-10 codes unless otherwise specified)**	**Code significance - Examples**
Sepsis diagnosis(1)	A039, A021, A207, A217, A227, A239, A241, A267, A280, A282, A327, A392, A393, A394, A40, A400, A401, A402, A403, A408, A409, A41, A410, A411, A412, A413, A415, A4150, A4151, A4152, A4158, A418, A4180, A4188, A419, A427, B007, B377, P360, P361, P362, P363, P364, P365, P368, P369, P352, P372, P375, A047, B9548, B956, J189, J440, N390	Enterocolitis, other sepsis, sepsis due to specific microorganisms, pneumonia, urinary tract infection
Severe sepsis(1,2)	R57.2 (septic shock) OR Sepsis codes + J96.0, J96.9, J80, R09.2, R57.0, R57.1, R57.2, R57.8, R57.9, I95.1, I95.9, N17.0, N17.1, N17.2, N17.8, N17.9, K72.0, K72.9, K76.3, F05.0, F05.9, G93.1, G93.4, G93.80, D69.5, D69.6, D65	Septic shock, acute respiratory failure, cardiogenic shock, shock unspecified, acute renal failure, hepatic failure, delirium, encephalopathy, thrombocytopenia
Intensive care unit admission(3)	CCI codes (1.GZ.31.CA-ND; 1.GZ.31.CR-ND; 1.GZ.31.GP-ND); SCU codes (10, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 95, 98)	Special care unit codes and procedure codes for mechanical ventilation
Pre-existing diabetes(4)	Any patient included in the ODD database	Either type 1 or type 2 diabetes mellitus

1. Note that the labeling of “sepsis” and “severe sepsis” follows the Jolley implementation of administrative codes to define sepsis, rather than clinical definitions of sepsis that have been published (e..g., Sepsis-2 criteria). For details, please see Jolley 2015. The sensitivity and specificity for sepsis in the ICU and non-ICU population are 1) 47% and 98%, and 2) 60% and 95% respectively.

Table S2. Characteristics of hospital stay and outcome information

	Pre-existing diabetes		Crude risk ratio or mean difference (95% CI)[1]
	YES (N = 183,585)	NO (N = 319,870)	
Hospital stay characteristics			
Intensive care unit admission – %	21.5	18.9	1.13 (1.12 – 1.15)
Multiple organ dysfunction score – mean (SD)*	4.2 (3.1)	4.0 (3.2)	0.20 (0.16 – 0.25)
Septic shock – %	4.6	4.1	1.12 (1.09 – 1.15)
Length of stay, days – median (IQR)*	7 (4 – 14)	7 (4 – 14)	0.70 (0.56 – 0.84)
Organ support measures			
Invasive mechanical ventilation – %	8.2	7.6	1.08 (1.06 – 1.10)
New renal replacement therapy – %	2.4	1.4	1.66 (1.60 – 1.73)
30- and 90-day outcomes			
All-cause mortality at 30 days – %	13.9	14.1	0.98 (0.97 – 1.00)
All-cause mortality at 90 days – %	21.4	21.5	1.00 (0.99 – 1.01)

* Estimates shown as mean difference for the comparison of diabetes yes vs. no.

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no)

CI: confidence interval; IQR: interquartile range; SD: standard deviation

Table S3. Baseline characteristics of adult patients with diabetes and a first episode of sepsis with or without previous metformin treatment

Baseline characteristic	NO metformin (N = 2,248)	Metformin (N = 45,144)	SMD
Demographic characteristics			
Age (years) – mean (SD	80.8 (7.4)	78.9 (7.5)	0.25
Female sex – %	54.0	50.4	0.07
Rural setting – %	12.0	12.1	0.00
Income quintile – %[1]			
1	14.1	14.3	0.01
2	15.9	17.2	0.04
3	19.0	19.1	0.00
4	23.6	22.4	0.03
5	26.6	25.9	0.02
Material deprivation – %[2]			
Quintile 1 to 3	49.0	50.8	0.03
Quintile 4 to 5	50.2	48.2	0.04
Baseline comorbidities			
Charlson score – median (IQR)[3]	1 (0 – 3)	1 (0 – 3)	0.08
Frailty index – mean (SD)[4]	0.2 (0.08)	0.2 (0.09)	0.13
Hypertension – %	90.2	89.4	0.03
Atrial fibrillation – %	6.5	8.0	0.06
Coronary heart disease – %	10.5	11.7	0.04
Stroke – %	4.3	5.4	0.05
Congestive heart failure – %	32.5	28.4	0.09
Venous thromboembolism – %	0.7	1.0	0.04
Chronic liver disease – %	1.3	1.4	0.01
Chronic obstructive pulmonary disease – %	35.9	36.6	0.01
Dementia – %	17.1	21.9	0.12
Active malignancy – %	13.4	12.7	0.02
Previous hospitalizations – median (IQR)	1 (0 – 2)	1 (0 – 2)	0.09
Antidiabetic management			
Glycated hemoglobin – mean (SD)	7.3 (1.4)	7.2 (1.4)	0.02
Thiazolidinediones	16.4	2.0	0.52
Meglitinides	2.5	0.2	0.20
α-Glucosidase inhibitors	7.8	0.9	0.35
Sulfonylureas	79.6	9.6	1.98
Additional insulin therapy	9.4	19.1	0.28
Sepsis episode characteristics			
Pneumonia as source of infection – %	41.3	41.2	0.00
Urosepsis – %	46.0	47.6	0.03
Intensive care unit admission – %	19.5	19.6	0.00
MODS score – median (IQR)[5]	3 (1 – 5)	3 (1 – 6)	0.09
Length of hospital stay – median (IQR)	8 (4 – 15)	7 (4 – 14)	0.10

SMD: absolute standardized mean difference; IQR: interquartile range; SD: standard deviation.

1. Missing for 0.5% of patients
2. Missing for 1.0% of patients
3. Based on the Deyo adaptation
4. Based on the preoperative frailty index derived by McIsaac et.al.
5. Multiple organ dysfunction score at intensive care unit admission

Table S4. Characteristics of hospital stay and main outcome information for study participants with or without prior metformin use

	Prior metformin use		Crude Odds ratio[1] (95% CI)	Adjusted Odds ratio[2] (95% CI)
	NO (N = 2,248)	YES (N = 45,144)		
Primary outcome				
All-cause mortality at 90 days – %	22.4	20.1	0.87 (0.78 – 0.96)	0.89 (0.80 – 0.99)
Organ support measures				
Invasive mechanical ventilation – %	6.3	6.4	1.03 (0.86 – 1.22)	1.06 (0.71 – 1.59)
New renal replacement therapy – %	1.1	1.3	1.15 (0.77 – 1.72)	0.98 (0.82 – 1.17)

1. Based on a crude logistic regression model including metformin as a binary indicator
2. Based on a logistic regression model including metformin as a binary indicator (i.e., yes vs. no) in addition to all a-priori defined confounders (e.g., age, sex, rural setting, income, frailty, baseline comorbidities, and source of infection).

CI: confidence interval

Table S5. Mediation analysis

Effect	Risk ratio (95% CI)
Natural direct effect	0.87 (0.85 – 0.88)
Natural indirect effect	0.95 (0.94 – 0.96)

Percentage mediated = 21% (95% CI: 19 – 28).
CI: confidence interval

Statistical details for the analysis of metformin use:

We included adults older than 65 years of age with pre-existing diabetes mellitus with a first hospitalization for sepsis in Ontario from 2008 to 2019. We included this age range to ensure that outpatient drug prescriptions were captured by the Ontario Drug Benefits (ODB) program and database. We excluded patients who 1) were not on any oral antidiabetic agent at the time of index admission, 2) had pre-existing chronic kidney disease or a creatinine greater than 2.0 mg / dl prior to hospitalization (and hence potentially not eligible as per current guidelines to receive metformin), and 3) those patients without any blood-work prior to hospitalization (and hence without information on degree of metabolic control as measured by the HbA1c or kidney function as measured by serum creatinine).

Our main exposure of interest was the prevalent use of metformin before the index hospital admission (first episode of sepsis). Following standard pharmacoepidemiologic practice, prevalent use of metformin was defined as having at least one prescription within 90 days prior to hospitalization. Prevalent use (also within 90 days of hospitalization) of any other oral antidiabetic agent was the comparator of interest. Additional insulin treatment or combined oral antidiabetic regimens were allowed in both arms. The primary outcome of interest was all-cause mortality at 90 days after hospital admission.

Baseline characteristics were summarized using proportions for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, as appropriate. Baseline characteristics of patients with or without prior metformin use were compared using standardized mean differences. Standardized mean differences (SMD) greater than 10% were considered relevant. To adjust for measured confounding at baseline, we performed outcome regression modelling using a multivariable logistic regression model. Specifically, we fitted a logistic model with the main exposure and all potential confounders, which were selected based on subject matter knowledge and a conceptual model. The vector of potential confounders included age, sex, income quintile and deprivation, burden of comorbidities, metabolic control, and additional antidiabetic treatments. Since after exclusions missing data was present for less than 1% of the analytical sample, we performed a complete case analysis. The association between prior metformin use and outcomes of interest (i.e., all-cause mortality and receipt of invasive mechanical ventilation and renal replacement therapy within the hospitalization) was summarized using odds ratios (OR) alongside 95% confidence intervals (CI).

The mediation analysis was performed using PROC causalmed in SAS. For this analysis, we included the same study cohort as in our main analysis, with diabetes as the main exposure and 90-day mortality as the outcome of interest. Metformin was considered as the mediator, and we included the same set of confounders as in the primary analysis. Modified Poisson regression models were used, and results shown as natural direct and indirect effects (as risk ratios with 95% confidence intervals), as well as percentage mediated.

Table S6. Baseline characteristics of **matched*** adult patients with a first episode of sepsis with or without pre-existing diabetes in Ontario (2008 – 2019)

Baseline characteristic	**Patients with pre-existing diabetes (N = 182,554)**	**Patients without a diabetes diagnosis (N = 182,554)**	**SMD**
Demographic characteristics			
Age (years) – mean (SD)	74.9 (12.6)	74.9 (12.6)	0.00
Female sex – %	50.8	52.5	0.03
Rural setting – %	12.8	15.5	0.08
Income quintile – %[1]			
1	27.0	25.2	0.04
2	22.5	22.5	0.00
3	19.3	19.4	0.00
4	16.9	17.7	0.02
5	14.3	15.2	0.02
Material deprivation – %[2]			
Quintile 1 to 3	49.4	52.5	0.06
Quintile 4 to 5	49.4	46.7	0.05
Baseline comorbidities			
Charlson score – median (IQR)[3]	1 (0 – 3)	0 (0 – 2)	0.40
Frailty index – mean (SD)[4]	0.2 (0.1)	0.2 (0.1)	0.52
Hypertension – %	85.7	75.0	0.27
Atrial fibrillation – %	8.7	8.1	0.02
Coronary heart disease – %	14.1	10.7	0.10
Stroke – %	5.3	4.4	0.04
Congestive heart failure – %	31.8	23.6	0.19
Venous thromboembolism – %	1.5	1.9	0.03
Chronic liver disease – %	2.8	2.6	0.01
Chronic kidney disease – %	10.9	3.9	0.27
Chronic pulmonary disease – %	38.1	40.3	0.04
Dementia – %	18.2	18.2	0.00
Active malignancy – %	12.7	17.7	0.14
Previous hospitalizations – median (IQR)	1 (0 – 3)	1 (0 – 3)	0.01
Source of infection			
Pneumonia as source of infection – %	41.7	45.7	0.08
Urosepsis – %	43.5	39.7	0.08

SMD: absolute standardized mean difference; IQR: interquartile range; SD: standard deviation.

* Matching algorithm (greedy method, 1:1, with a caliper on the logit scale of 0.15) based on a disease risk score. Specifically, we estimated a propensity score (formally a disease risk score) using logistic regression with diabetes (yes vs. no) as the dependent variable. This model included as independent variables the same vector of confounders than the standardization performed for the main analysis (including age, sex, income, baseline comorbidities, and frailty index).

1. Missing for less than 1% of patients
2. Missing for less than 1% of patients
3. Based on the Deyo adaptation
4. Based on the preoperative frailty index derived by McIsaac et.al.

Table S7. Characteristics of hospital stay and main outcome information for **matched** study participants

	Pre-existing diabetes		Adjusted risk ratio or mean difference (95% CI)[1]
	YES (N = 182,554)	NO (N = 182,554)	
Hospital stay characteristics			
Intensive care unit admission – %	21.5	19.2	1.20 (1.18 – 1.22)
Multiple organ dysfunction score – mean (SD)*	4.2 (3.1)	4.0 (3.1)	0.19 (0.13 – 0.25)
Septic shock – %	4.6	4.0	1.22 (1.18 – 1.26)
Length of stay, days – median (IQR)*	7 (4 – 14)	7 (4 – 14)	0.04 (-0.12, 0.21)
Organ support measures			
Invasive mechanical ventilation – %	8.2	7.4	1.17 (1.14 – 1.20)
New renal replacement therapy – %	2.4	1.4	1.87 (1.77 – 1.96)
30- and 90-day outcomes			
All-cause mortality at 30 days – %	13.9	15.3	0.81 (0.79 – 0.82)
All-cause mortality at 90 days – %	21.4	23.5	0.82 (0.81 – 0.83)

* Estimates shown as mean difference for the comparison of diabetes yes vs. no.

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no), in addition to all covariates that were imbalanced at baseline (i.e., standardized mean differences > 10%) and robust standard errors accounting for the matching procedure. CI: confidence interval

Table S8. Main sensitivity analyses (crude measures of association)

Outcome of interest	Crude risk ratio (95% CI)[1]			
	Restricting to patients with ICU admission	**HbA1c >7% vs. no diabetes**	**HbA1c ≤ 7% vs. no diabetes**	**Including all sepsis associated hospitalizations**
Primary outcome				
All-cause mortality at 90 days – %	1.02 (1.00 – 1.04)	0.87 (0.85 – 0.88)	1.06 (1.05 – 1.07)	1.03 (1.02 – 1.04)
Organ support measures				
Invasive mechanical ventilation – %	0.96 (0.94 – 0.97)	1.22 (1.18 – 1.25)	1.06 (1.03 – 1.09)	1.03 (1.02 – 1.05)
New renal replacement therapy – %	1.41 (1.34 – 1.48)	1.98 (1.86 – 2.10)	1.57 (1.48 – 1.67)	1.59 (1.55 – 1.65)

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no)
ICU: intensive care unit; CI: confidence interval

Table S9. Main sensitivity analyses (adjusted measures of association)

Outcome of interest	Adjusted risk ratio (95% CI)[1]				
	Restricting to patients with ICU admission	**Pre-existing diabetes with HbA1c >7% vs. no diabetes**	**Pre-existing diabetes with HbA1c ≤ 7% vs. no diabetes**	**Including all sepsis associated hospitalizations**	**Adjusting for calendar time**
Primary outcome					
All-cause mortality at 90 days – %	0.92 (0.90 – 0.93)	0.78 (0.76 – 0.80)	0.85 (0.84 – 0.87)	0.83 (0.82 – 0.84)	0.82 (0.81 – 0.83)
Organ support measures					
Invasive mechanical ventilation – %	0.98 (0.96 – 1.00)	1.03 (1.00 – 1.07)	1.05 (1.01 – 1.09)	1.02 (1.01 – 1.04)	1.05 (1.03 – 1.07)
New renal replacement therapy – %	1.48 (1.39 – 1.57)	1.49 (1.39 – 1.60)	1.46 (1.37 – 1.56)	1.45 (1.40 – 1.51)	1.54 (1.47 – 1.62)

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no), in addition to same vector of potential confounders as main analysis

ICU: intensive care unit; CI: confidence interval

Table S10. Changes in exposure and control groups based on HbA1c levels

Group	Mean HbA1c	Adjusted risk ratio (95% CI)[1]		
		All-cause mortality at 90-days	Renal replacement therapy	Invasive mechanical ventilation
No pre-existing diabetes without HbA1c measurement	N/A	Reference	Reference	Reference
No pre-existing diabetes with HbA1c < 5.7%	5.3%	0.92 (0.91 – 0.94)	1.06 (0.99 – 1.14)	0.97 (0.94 – 1.00)
No prior diabetes diagnosis but with HbA1c >= 5.7% and < 6.5%	5.9%	0.85 (0.82 – 0.89)	1.12 (0.97 – 1.30)	0.95 (0.88 – 1.00)
No prior diabetes diagnosis but with HbA1c >= 6.5%	6.9%	0.79 (0.74 – 0.84)	1.19 (0.96 – 1.48)	0.91 (0.83 – 1.00)
Pre-existing diabetes with HbA1c <= 7%	6.2%	0.73 (0.67 – 0.79)	1.26 (0.95 – 1.68)	0.89 (0.78 – 1.01)
Pre-existing diabetes with HbA1c > 7%	8.6%	0.68 (0.61 – 0.74)	1.34 (0.94 – 1.92)	0.86 (0.73 – 1.01)

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no), in addition to same vector of potential confounders as main analysis
CI: confidence interval

Table S11. Impact of length of pre-existing diabetes on clinical outcomes

Group	Adjusted risk ratio (95% CI)[1]		
	All-cause mortality at 90-days	**Renal replacement therapy**	**Invasive mechanical ventilation**
Length of pre-existing diabetes (every 5 years)	0.76 (0.75 – 0.77)	0.99 (0.96 – 1.01)	0.90 (0.89 – 0.91)

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no), in addition to same vector of potential confounders as main analysis
CI: confidence interval

Table S12. Main outcome analysis by source of infection

Outcome of interest	Adjusted risk ratio (95% CI)[1]	
	Restricted to patients with pneumonia	Restricted to patients with urosepsis
Primary outcome		
All-cause mortality at 90 days – %	0.81 (0.79 – 0.82)	0.81 (0.79 – 0.83)
Organ support measures		
Invasive mechanical ventilation – %	1.11 (1.07 – 1.15)	0.97 (0.92 – 1.02)
New renal replacement therapy – %	1.67 (1.53 – 1.82)	1.52 (1.37 – 1.68)

1. Based on a modified Poisson regression model with diabetes as a binary indicator (i.e., yes vs. no), in addition to same vector of potential confounders as main analysis
CI: confidence interval

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