Risk factors for major cardiovascular events in adult sepsis survivors: a population-based cohort study

SUPPLEMENTARY APPENDIX

Table S1. List and description of main ICES databases used

Database	Description
Discharge Abstract Database (DAD)	Patient-level demographic, diagnostic, procedural and treatment information on all acute care hospitalizations
National Ambulatory Care Reporting System (NACRS)	Patient-level demographic, diagnostic, procedural and treatment information for all National Ambulatory Care Reporting System (NACRS) hospital-based and community-based ambulatory care, including outpatient and community-based clinics and emergency departments
CENSUS (Ontario Census Area Profile)	Neighborhood level socioeconomic status
CCRS (Continuing care Reporting System)	Data on long term care residency
PCCF (Postal code conversion file)	Residence location information
INST (Ontario health care institutions)	Hospital type information
Ontario Registered Persons Database (RPDB)	Demographic, place of residence and vital status information
ONMARG (Ontario Marginalization Index)	Marginalization quintile
ORGD (Vital Statistics – Deaths)	Fact and cause of death
Ontario Health Insurance Plan Database (OHIP)	Claims for physician services paid for by the provincial government
OLIS (Ontario Laboratories Information System)	System that connects hospitals, community laboratories, public health laboratories and practitioners to facilitate the secure electronic exchange of laboratory test orders and results.
Ontario Cancer Registry (OCR)	Provincial registry of all individuals with incident cancer or have died of cancer
Congestive Heart Failure (CHF)	Validated ICES derived cohort
Ontario Hypertension Dataset (HYPER)	Validated ICES derived cohort
Ontario Diabetes Dataset (ODD)	Validated ICES derived cohort
COPD Dataset (COPD)	Validated ICES derived cohort

Table S2. Coding strategies for main variables of interest

Main variable of interest	Main components of coding algorithm[a] (ICD-10 codes unless otherwise specified)
Cohort creation	
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
Severe sepsis & septic shock (1)	R57.2 (septic shock); OR sepsis codes in addition to: 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
Prior cardiovascular disease (2, 3)	Any patient included in the CHF dataset, I21, I22, I60, I61, I63, I64, H34.1, I70, I73, I23, I24, I25, I00, I01, I02, I05, I06, I07, I08, I09, I30-I43, I46, I51, I71
Outcomes of interest	
Myocardial infarction (2, 4, 5)	I21, I22
Stroke (2, 6)	I60, I61, I63, I64, H34.1
Cardiovascular death (2)	I20, I21, I22, I23, I24, I25, I30, I31, I32, I34, I35, I36, I37, I39, I40, I41, I42, I43, I44, I45, I46, I47, I48, I49, I50, I51, I52, I70, I71, I72, I73, I74, I75
Selected risk factors and baseline characteristics	
Intensive care unit admission (7)	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)
High troponin (8)	OLIS codes 10839-9, 6598-7, 48425-3, 42757-5, 16255-2, 48426-1, 33204-9; high troponin defined as > 99th percentile for each assay
Acute kidney injury, renal replacement therapy	N17, N170, N171, N172, N178, N179, CCI code 1PZ21

Mechanical ventilation	CCI codes (1GZ31CBND, 1GZ31CAND, 1GZ31CRND, 1GZ31GPND, 1GZ31CAEP); Fee codes (G557, G558, G405, G406, G559, G407)
Hypertension	Patient included in HYPER database
Diabetes mellitus	Patient included in ODD database
Atrial fibrillation	I48

a. Main databases used included CIHI-DAD, NACRS, OLIS (for blood work results), ORGD (vital status) and additional ones as specified for individual covariables (e.g., HYPER, ODD, CHF databases).

Positive predictive values of the coding definitions for myocardial infarction and stroke are approximately 93% and 97% respectively (4, 6).

Table S3. A-priori considered domains for prespecified potential risk factors for the occurrence of major cardiovascular events in adult sepsis survivors

Domain	Risk factors	Additional comments and covariate selection
Baseline demographics and comorbid burden	Age, sex, income, long-term care resident, previous hospitalizations, Charlson comorbidity index score	For modelling, comorbid burden considered by including the individual comorbidities rather than a summary measure as the Charlson index (9)
Classic cardiovascular risk factors	Hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic kidney disease, smoking status, familiar history, prevalent cardiovascular disease, cholesterol levels	Pre-existing cardiovascular disease excluded; no data available on smoking status (but used proxy of chronic respiratory disease); no data on family history; cholesterol levels included in sensitivity analysis using laboratory data
Sepsis episode characteristics	Site of infection, acute kidney injury, severity of sepsis, platelet counts, troponin value, renal replacement therapy, invasive mechanical ventilation	Severity of sepsis defined as either intensive care unit admission, organ failure or septic shock; troponin included in sensitivity analysis using laboratory data

Table S4. Characteristics of adult sepsis survivors in Ontario (2008 – 2017)

Baseline characteristic	All sepsis Survivors (N = 268,259)	Major cardiovascular event		SMD
		Yes (N = 27,888)	No (N = 240,371)	
Demographic characteristics				
Age (years) – median (IQR)	72 (58 – 82)	80 (70 – 86)	70 (56 – 82)	0.59
Female sex – %	57.7	57.2	57.7	0.01
Income quintile – %				
1	24.2	24.8	24.1	0.02
2	21.3	21.3	21.3	0.00
3	19.2	19.4	19.2	0.01
4	18.0	17.7	18.0	0.01
5	16.7	16.1	16.8	0.02
Missing	0.6	0.6	0.5	0.01
Area-based material deprivation[1] – %				
Quintile 1 (least deprived) to 3	52.5	51.5	52.7	0.03
Quintile 4 to 5 (most deprived)	45.1	47.6	46.0	0.03
Missing	1.4	1.3	1.4	0.00
Long term care home resident – %	17.0	25.9	16.0	0.25
Previous hospitalizations – median (IQR)	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)	0.03
Baseline comorbid conditions				
Charlson comorbidity index score – median (IQR)	2 (1 – 4)	3 (1 – 5)	2 (0 – 4)	0.43
Hypertension – %	64.5	80.8	62.6	0.41
Diabetes mellitus – %	31.1	38.6	30.3	0.18
Dyslipidemia – %	16.4	16.2	16.4	0.01
Atrial fibrillation – %	4.6	8.0	4.2	0.16
Venous thromboembolism – %	2.4	2.2	2.4	0.01
Chronic liver disease – %	3.6	2.3	3.8	0.08
Chronic kidney disease – %	8.2	8.3	8.2	0.00
Chronic obstructive pulmonary disease – %	32.1	38.7	31.3	0.15
Dementia – %	17.5	23.5	16.8	0.17
Active malignancy – %	28.0	24.2	28.4	0.10
Pre-admission laboratory values (closest to admission date)				
Cholesterol LDL (mmol / l) – mean (SD)	2.5 (1.0)	2.4 (1.0)	2.5 (1.0)	0.07
Cholesterol HDL (mmol / l) – mean (SD)	1.3 (0.4)	1.6 (0.4)	1.4 (0.4)	0.07
Triglycerides (mmol / l) – mean (SD)	1.5 (1.0)	1.6 (1.1)	1.5 (1.0)	0.02
Sepsis episode characteristics				
Septic shock – %	23.0	23.9	22.9	0.02
Source of infection				
Pneumonia – %	32.1	32.9	32.0	0.02
Urosepsis – %	36.5	40.1	36.1	0.08

Acute kidney injury – %	11.6	13.4	11.3	0.06
Hemoglobin (g / l) – mean (SD)	103.1 (21.8)	104.5 (21.0)	102.3 (21.9)	0.07
White cell count ($x10^9$ / l) – mean (SD)	15.4 (13.3)	14.8 (11.7)	15.5 (13.3)	0.05
Platelet count ($x10^9$ / l) – mean (SD)	199.3 (104.2)	201.9 (102.7)	199.1 (104.3)	0.03
Creatinine (umol / l) – mean (SD)	116.2 (118.3)	124.3 (126.3)	115.4 (117.4)	0.07
Bilirubin (umol / l) – mean (SD)	18.7 (37.5)	15.5 (25.7)	18.9 (38.2)	0.09
High troponin[2] – %	3.7	4.3	3.6	0.03
Intensity of organ support				
Intensive care unit admission – %	17.6	15.2	17.9	0.07
Transfusion – %	16.1	13.6	16.4	0.08
Dialysis – %	1.9	2.3	1.8	0.03
Invasive mechanical ventilation – %	6.7	5.1	6.9	0.07
Non-invasive ventilation – %	8.7	6.8	8.9	0.08
Tracheostomy – %	1.4	0.9	1.4	0.05
Length of hospital stay (days) – median (IQR)	7 (4 – 15)	8 (4 – 16)	7 (4 – 15)	0.07

1. Income quintile and material deprivation are patient-level characteristics. Deprivation is an area-based index that seeks to show differences in marginalization between areas and understand inequalities in measures of health and well-being. Marginalization is based on four dimensions: residential instability, material deprivation, dependency, and ethnic concentration. The calculation of material deprivation factor scores includes variables for traditional socioeconomic status indicators such as income, education, and employment, and has been previously shown as the domain most strongly associated with health outcomes. Income calculation is based on demographic and geographic information.
2. High troponin defined as Troponin > 99^{th} percentile.

Rural setting available for 267,880 patients; Income quartile available for 266,777; Deprivation available for 264,575. Laboratory values available for the following number of patients: Hb 75,501; White cell count 73,446; Platelet count 75,567; Creatinine 113,736; Bilirubin 52,800; LDL 159,796; HDL 160,195; Triglycerides 160,536; Troponin 26,400. For hemoglobin and platelets, the results showcase lowest number during admission. For all laboratory values, if no information during admission was available the closest value was utilized.

SMD: absolute standardized mean difference; IQR: interquartile range; SD: standard deviation. Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. Index date defined as date of hospital discharge.

Table S5. Proportions of major cardiovascular events by follow-up timeframe[1]

	Year 1					Year 2	Year 3	Year 4	Year 5	Overall
	< 3 months	3 months to 6 months	6 months to 9 months	9 months to 12 months	Overall					
Number of cardiovascular events	4205	2449	2034	1925	10613	6271	4847	3535	2622	27,888
% (events / total at risk)	1.6	0.9	0.8	0.7	4.0	2.3	1.8	1.3	1.0	10.4

1. Total at risk comprised of 268,259 sepsis survivors. Proportions may not add up to the overall due to rounding.

Table S6. Factors (including laboratory values) associated with major cardiovascular events in adult sepsis survivors

Factor	Hazard ratio (95% CI)			Comment
	Complete case analysis[1]	Multiple imputation[2]	Cohort with a troponin value[3]	
Baseline characteristics and comorbid conditions				
Age (years)	1.36 (1.29 – 1.43)	1.46 (1.43 – 1.50)	1.42 (1.37 – 1.47)	Every 10 years
Male sex	1.22 (1.09 – 1.37	1.18 (1.11 – 1.20)	1.20 (1.11 – 1.29)	Yes vs. no
Income (quintiles)	0.96 (0.92 – 0.99)	0.98 (0.96 – 0.99)	0.98 (0.95 – 1.00)	Every 1 quintile
Chronic kidney disease	1.01 (0.83 – 1.24)	1.07 (0.98 – 1.18)	1.05 (0.90 – 1.22)	Yes vs. no
Chronic liver disease	1.17 (0.83 – 1.65)	1.17 (0.98 – 1.39)	1.37 (1.08 – 1.73)	Yes vs. no
Chronic obstructive pulmonary disease	1.26 (1.13 – 1.41)	1.16 (1.10 – 1.23)	1.23 (1.13 – 1.33)	Yes vs. no
Venous thromboembolic disease	0.92 (0.62 – 1.36)	1.15 (0.97 – 1.36)	1.00 (0.76 – 1.30)	Yes vs. no
Dementia	1.17 (1.02 – 1.35)	1.10 (1.03 – 1.18)	1.04 (0.94 – 1.15)	Yes vs. no
Active malignancy	1.12 (0.99 – 1.26)	1.05 (0.99 – 1.11)	1.07 (0.98 – 1.17)	Yes vs. no
Classic cardiovascular risk factors				
Diabetes mellitus	1.12 (1.00 – 1.26)	1.18 (1.11 – 1.25)	1.12 (1.04 – 1.22)	Yes vs. no
Hypertension	1.41 (1.19 – 1.66)	1.42 (1.32 – 1.53)	1.37 (1.23 – 1.53)	Yes vs. no
Atrial fibrillation	1.27 (1.05 – 1.55)	1.40 (1.27 – 1.53)	1.38 (1.21 – 1.57)	Yes vs. no
LDL cholesterol (mmol / l)	1.06 (1.00 – 1.12)	1.00 (0.97 – 1.03)	1.03 (0.99 – 1.08)	Every 1-unit increase
HDL cholesterol (mmol / l)	0.82 (0.72 – 0.94)	0.90 (0.84 – 0.96)	0.87 (0.78 – 0.96)	Every 1-unit increase
Sepsis episode characteristics and intensity of support				
Site of infection[2]				
Pneumonia	1.06 (0.92 – 1.23)	1.08 (1.01 – 1.15)	1.05 (0.96 – 1.16)	Vs. other infection
Urosepsis	1.13 (0.98 – 1.29)	0.98 (0.92 – 1.04)	1.10 (1.00 – 1.20)	Vs. other infection
Septic shock	1.18 (1.05 – 1.33)	1.07 (1.00 – 1.13)	1.11 (1.02 – 1.22)	Yes vs. no
High troponin	1.26 (1.13 – 1.42)	1.24 (1.05 – 1.46)	1.23 (1.13 – 1.33)	Yes vs. no
Intensive care unit admission	1.07 (0.90 – 1.28)	1.10 (1.00 – 1.21)	1.00 (0.88 – 1.14)	Yes vs. no
Invasive mechanical ventilation	0.73 (0.53 – 1.00)	0.87 (0.71 – 1.07)	0.92 (0.72 – 1.19)	Yes vs. no
Non-invasive ventilation	1.07 (0.79 – 1.46)	1.01 (0.84 – 1.21)	0.94 (0.78 – 1.25)	Yes vs. no
Tracheostomy placement	0.73 (0.45 – 1.17)	0.80 (0.57 – 1.12)	0.90 (0.66 – 1.24)	Yes vs. no
Transfusions	0.89 (0.73 – 1.07)	1.03 (0.94 – 1.13)	0.91 (0.79 – 1.04)	Yes vs. no
Hemoglobin (g / l)	1.00 (0.97 – 1.03)	1.00 (0.98 – 1.02)	1.01 (0.97 – 1.03)	Every 10-unit increase
White cell count (10^9 / l)	1.00 (0.95 – 1.05)	0.97 (0.94 – 1.00)	0.99 (0.97 – 1.02)	Every 10-unit increase
Platelet count (per ml)	1.04 (0.97 – 1.10)	1.01 (1.00 – 1.02)	1.05 (1.00 – 1.10)	Every 100-unit increase
Renal replacement therapy	1.10 (0.74 – 1.65)	1.25 (1.01 – 1.54)	1.04 (0.77 – 1.41)	Yes vs. no
Creatinine (umol / l)	1.03 (0.98 – 1.08)	1.06 (1.03 – 1.09)	1.03 (1.00 – 1.07)	Every 100-unit increase
Length of hospital stay (days)	1.01 (0.99 – 1.02)	1.00 (0.99 – 1.01)	1.01 (1.00 – 1.02)	Every 10 days

1. Based on 13,537 sepsis survivors with complete information on all laboratory values.
2. Cohort (62,803 sepsis survivors) using the years with maximum available laboratory data (2014 - 2017). Multiple imputation with chained equations for missing information. Models for missing covariates were linear (for continuous variables) and logistic (for class variables). All models included all available covariates including exposure and outcome. Laboratory values available as follows: Hemoglobin 57%; WBC: 55%; Platelets 57%; Creatinine 67%; Bilirubin 37%; LDL 79%; HDL 80%%: Triglycerides 80%; Troponin 22%.
3. Cohort constructed using those sepsis survivors (26,400) with at least one troponin measurement during hospitalization. Missing laboratory values were imputed using multiple imputation with chained equations as above in 2.

All models fitted using a cause-specific Cox proportional hazards model. Major cardiovascular event at 5 years defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

Table S7. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (restricting to septic shock or intensive care unit admission)

Factor	Hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.46 (1.43 – 1.49)	Every 10 years
Male sex	1.18 (1.13 – 1.23)	Yes vs. no
Income (quintiles)	0.96 (0.95 – 0.98)	Every 1 quintile
Chronic kidney disease	1.11 (1.04 – 1.19)	Yes vs. no
Chronic liver disease	1.16 (1.03 – 1.31)	Yes vs. no
Chronic obstructive pulmonary disease	1.22 (1.17 – 1.27)	Yes vs. no
Venous thromboembolic disease	1.13 (0.97 – 1.30)	Yes vs. no
Dementia	1.03 (0.97 – 1.09)	Yes vs. no
Active malignancy	1.04 (0.99 – 1.09)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.24 (1.18 – 1.29)	Yes vs. no
Hypertension	1.38 (1.30 – 1.46)	Yes vs. no
Atrial fibrillation	1.42 (1.32 – 1.53)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.12 (1.06. – 1.19)	Vs. other infection
Urosepsis	1.05 (0.99 – 1.10)	Vs. other infection
Invasive mechanical ventilation	0.94 (0.85 – 1.03)	Yes vs. no
Non-invasive ventilation	0.96 (0.88 – 1.05)	Yes vs. no
Tracheostomy placement	0.95 (0.83 – 1.09)	Yes vs. no
Transfusions	0.98 (0.93 – 1.04)	Yes vs. no
Renal replacement therapy	1.26 (1.13 – 1.41)	Yes vs. no
Length of hospital stay (days)	1.00 (1.00 – 1.01)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S8. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (restricting to patients without baseline kidney disease)

Factor	Hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.54 (1.52 – 1.56)	Every 10 years
Male sex	1.24 (1.21 – 1.28)	Yes vs. no
Income (quintiles)	0.98 (0.97 – 0.99)	Every 1 quintile
Chronic liver disease	1.22 (1.12 – 1.33)	Yes vs. no
Chronic obstructive pulmonary disease	1.21 (1.18 – 1.24)	Yes vs. no
Venous thromboembolic disease	1.14 (1.05 – 1.24)	Yes vs. no
Dementia	1.04 (1.00 – 1.07)	Yes vs. no
Active malignancy	1.04 (1.01 – 1.07)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.21 (1.18 – 1.25)	Yes vs. no
Hypertension	1.32 (1.27 – 1.36)	Yes vs. no
Atrial fibrillation	1.46 (1.39 – 1.53)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.07 (1.04 – 1.11)	Vs. other infection
Urosepsis	1.03 (1.00 – 1.06)	Vs. other infection
Septic shock	1.08 (1.05 – 1.12)	Yes vs. no
Intensive care unit admission	1.06 (1.01 – 1.11)	Yes vs. no
Invasive mechanical ventilation	0.92 (0.83 – 1.02)	Yes vs. no
Non-invasive ventilation	0.96 (0.87 – 1.05)	Yes vs. no
Tracheostomy placement	0.95 (0.82 – 1.09)	Yes vs. no
Transfusions	1.04 (1.00 – 1.09)	Yes vs. no
Renal replacement therapy	1.35 (1.20 – 1.51)	Yes vs. no
Length of hospital stay (days)	1.00 (1.00 – 1.01)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S9. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (restricting to patients without baseline cardiovascular prescriptions)[1]

Factor	Hazard ratio (95% CI)[2]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.52 (1.50 – 1.54)	Every 10 years
Male sex	1.24 (1.20 – 1.28)	Yes vs. no
Income (quintiles)	0.96 (0.95 – 0.97)	Every 1 quintile
Chronic kidney disease	1.14 (1.07 – 1.20)	Yes vs. no
Chronic liver disease	1.17 (1.07 – 1.28)	Yes vs. no
Chronic obstructive pulmonary disease	1.23 (1.19 – 1.27)	Yes vs. no
Venous thromboembolic disease	1.17 (1.04 – 1.31)	Yes vs. no
Dementia	1.03 (0.99 – 1.07)	Yes vs. no
Active malignancy	1.04 (1.00 – 1.07)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.35 (1.31 – 1.40)	Yes vs. no
Hypertension	1.36 (1.32 – 1.42)	Yes vs. no
Atrial fibrillation	1.52 (1.43 – 1.62)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[3]		
Pneumonia	1.07 (1.03 – 1.12)	Vs. other infection
Urosepsis	1.02 (0.98 – 1.06)	Vs. other infection
Septic shock	1.08 (1.04 – 1.12)	Yes vs. no
Intensive care unit admission	1.08 (1.03 – 1.14)	Yes vs. no
Invasive mechanical ventilation	0.94 (0.84 – 1.06)	Yes vs. no
Non-invasive ventilation	0.94 (0.84 – 1.04)	Yes vs. no
Tracheostomy placement	0.96 (0.82 – 1.13)	Yes vs. no
Transfusions	1.02 (0.97 – 1.07)	Yes vs. no
Renal replacement therapy	1.48 (1.33 – 1.64)	Yes vs. no
Length of hospital stay (days)	1.00 (1.00 – 1.00)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Prescription for either an antiplatelet agent, statin, or oral anticoagulant.
2. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
3. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S10. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (including discharge cardiovascular prescriptions)[1]

Factor	Hazard ratio (95% CI)[2]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.52 (1.50 – 1.53)	Every 10 years
Male sex	1.22 (1.19 – 1.25)	Yes vs. no
Income (quintiles)	0.98 (0.97 – 0.98)	Every 1 quintile
Chronic kidney disease	1.11 (1.06 – 1.16)	Yes vs. no
Chronic liver disease	1.22 (1.12 – 1.32)	Yes vs. no
Chronic obstructive pulmonary disease	1.20 (1.17 – 1.23)	Yes vs. no
Venous thromboembolic disease	1.11 (1.03 – 1.21)	Yes vs. no
Dementia	1.04 (1.01 – 1.07)	Yes vs. no
Active malignancy	1.03 (1.00 – 1.06)	Yes vs. no
Classic cardiovascular risk factors and prescriptions		
Diabetes mellitus	1.24 (1.21 – 1.27)	Yes vs. no
Hypertension	1.33 (1.29 – 1.38)	Yes vs. no
Atrial fibrillation	1.42 (1.36 – 1.49)	Yes vs. no
Statins	0.95 (0.92 – 0.98)	Yes vs. no
Antiplatelets	1.67 (1.58 – 1.77)	Yes vs. no
Oral anticoagulants	1.14 (1.09 – 1.19)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[3]		
Pneumonia	1.09 (1.05 – 1.12)	Vs. other infection
Urosepsis	1.02 (0.99 – 1.05)	Vs. other infection
Septic shock	1.07 (1.05 – 1.11)	Yes vs. no
Intensive care unit admission	1.05 (1.00 – 1.09)	Yes vs. no
Invasive mechanical ventilation	0.90 (0.82 – 0.99)	Yes vs. no
Non-invasive ventilation	0.96 (0.88 – 1.05)	Yes vs. no
Tracheostomy placement	0.94 (0.82 – 1.07)	Yes vs. no
Transfusions	1.05 (1.01 – 1.09)	Yes vs. no
Renal replacement therapy	1.51 (1.39 – 1.64)	Yes vs. no
Length of hospital stay (days)	1.00 (1.00 – 1.01)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Prescription for either an antiplatelet agent, statin, or oral anticoagulant.
2. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
3. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S11. Changes in the sub-distribution hazard (cumulative incidence function) of major cardiovascular events during 5 years of follow-up associated with baseline factors in adult sepsis survivors in Ontario (2008 – 2017)

Factor	Adjusted sub-distribution hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.41 (1.40 – 1.43)	Every 10 years
Male sex	1.14 (1.12 – 1.16)	Yes vs. no
Income (quintiles)	0.98 (0.97 – 0.99)	Every 1 quintile
Chronic kidney disease	1.06 (1.01 – 1.11)	Yes vs. no
Chronic liver disease	0.90 (0.83 – 0.98)	Yes vs. no
Chronic obstructive pulmonary disease	1.16 (1.13 – 1.19)	Yes vs. no
Venous thromboembolic disease	1.00 (0.93 – 1.09)	Yes vs. no
Dementia	0.80 (0.83 – 0.86)	Yes vs. no
Active malignancy	0.74 (0.72 – 0.76)	Yes vs. no
Long-term care home resident	1.21 (1.17 – 1.25)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.24 (1.21 – 1.27)	Yes vs. no
Hypertension	1.42 (1.37 – 1.47)	Yes vs. no
Atrial fibrillation	1.43 (1.37 – 1.49)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.05 (1.01 – 1.09)	Vs. other infection
Urosepsis	1.03 (1.00 – 1.06)	Vs. other infection
Septic shock	1.01 (0.98 – 1.04)	Yes vs. no
Intensive care unit admission	1.12 (1.08 – 1.17)	Yes vs. no
Invasive mechanical ventilation	1.01 (0.92 – 1.11)	Yes vs. no
Non-invasive ventilation	0.94 (0.91 – 1.03)	Yes vs. no
Tracheostomy placement	0.94 (0.82 – 1.08)	Yes vs. no
Transfusions	0.92 (0.89 – 0.96)	Yes vs. no
Renal replacement therapy	1.48 (1.36 – 1.61)	Yes vs. no
Length of hospital stay (days)	1.00 (0.99 – 1.00)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Fine and Gray model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S12. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (restricting to first half of study period)

Factor	Hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.55 (1.52 – 1.57)	Every 10 years
Male sex	1.23 (1.20 – 1.27)	Yes vs. no
Income (quintiles)	0.98 (0.97 – 0.99)	Every 1 quintile
Chronic liver disease	1.23 (1.10 – 1.37)	Yes vs. no
Chronic obstructive pulmonary disease	1.21 (1.17 – 1.25)	Yes vs. no
Venous thromboembolic disease	1.08 (0.96 – 1.21)	Yes vs. no
Dementia	1.05 (1.00 – 1.09)	Yes vs. no
Active malignancy	1.01 (0.97 – 1.05)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.25 (1.20 – 1.29)	Yes vs. no
Hypertension	1.33 (1.28 – 1.39)	Yes vs. no
Atrial fibrillation	1.47 (1.38 – 1.56)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.07 (1.02 – 1.11)	Vs. other infection
Urosepsis	1.02 (0.98 – 1.07)	Vs. other infection
Septic shock	1.05 (1.00 – 1.09)	Yes vs. no
Intensive care unit admission	1.01 (0.95 – 1.07)	Yes vs. no
Invasive mechanical ventilation	0.85 (0.75 – 0.98)	Yes vs. no
Non-invasive ventilation	1.07 (0.95 – 1.21)	Yes vs. no
Tracheostomy placement	1.09 (0.92 – 1.30)	Yes vs. no
Transfusions	1.05 (0.99 – 1.09)	Yes vs. no
Renal replacement therapy	1.43 (1.27 – 1.61)	Yes vs. no
Length of hospital stay (days)	0.99 (0.99 – 1.00)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S13. Factors associated with major cardiovascular events during 5 years of follow-up in adult sepsis survivors (restricting to second half of study period)

Factor	Hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.51 (1.48 – 1.53)	Every 10 years
Male sex	1.22 (1.18 – 1.26)	Yes vs. no
Income (quintiles)	0.97 (0.96 – 0.99)	Every 1 quintile
Chronic liver disease	1.20 (1.07 – 1.34)	Yes vs. no
Chronic obstructive pulmonary disease	1.19 (1.15 – 1.24)	Yes vs. no
Venous thromboembolic disease	1.19 (1.06 – 1.33)	Yes vs. no
Dementia	1.05 (1.02 – 1.10)	Yes vs. no
Active malignancy	1.06 (1.02 – 1.10)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.24 (1.19 – 1.28)	Yes vs. no
Hypertension	1.35 (1.28 – 1.42)	Yes vs. no
Atrial fibrillation	1.45 (1.36 – 1.54)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.10 (1.05 – 1.16)	Vs. other infection
Urosepsis	1.01 (0.97 – 1.06)	Vs. other infection
Septic shock	1.12 (1.08 – 1.17)	Yes vs. no
Intensive care unit admission	1.11 (1.04 – 1.18)	Yes vs. no
Invasive mechanical ventilation	0.96 (0.83 – 1.04)	Yes vs. no
Non-invasive ventilation	0.86 (0.76 – 0.98)	Yes vs. no
Tracheostomy placement	0.73 (0.59 – 0.92)	Yes vs. no
Transfusions	1.05 (0.99 – 1.11)	Yes vs. no
Renal replacement therapy	1.59 (1.40 – 1.80)	Yes vs. no
Length of hospital stay (days)	1.01 (1.00 – 1.01)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

Table S14. Factors associated with major cardiovascular events during 3-month follow-up in adult sepsis survivors

Factor	Hazard ratio (95% CI)[1]	Comment
Baseline characteristics and comorbid conditions		
Age (years)	1.53 (1.49 – 1.58)	Every 10 years
Male sex	1.15 (1.08 – 1.22)	Yes vs. no
Income (quintiles)	0.96 (0.94 – 0.98)	Every 1 quintile
Chronic liver disease	1.12 (0.92 – 1.36)	Yes vs. no
Chronic obstructive pulmonary disease	1.06 (1.00 – 1.13)	Yes vs. no
Venous thromboembolic disease	1.06 (0.87 – 1.29)	Yes vs. no
Dementia	1.23 (1.14 – 1.33)	Yes vs. no
Active malignancy	1.07 (1.00 – 1.14)	Yes vs. no
Classic cardiovascular risk factors		
Diabetes mellitus	1.16 (1.09 – 1.24)	Yes vs. no
Hypertension	1.25 (1.15 – 1.35)	Yes vs. no
Atrial fibrillation	1.63 (1.47 – 1.81)	Yes vs. no
Sepsis episode characteristics and intensity of support		
Site of infection[2]		
Pneumonia	1.06 (0.98 – 1.15)	Vs. other infection
Urosepsis	1.00 (0.92 – 1.08)	Vs. other infection
Septic shock	1.17 (1.09 – 1.25)	Yes vs. no
Intensive care unit admission	1.11 (0.99 – 1.24)	Yes vs. no
Invasive mechanical ventilation	0.77 (0.61 – 0.98)	Yes vs. no
Non-invasive ventilation	1.17 (0.95 – 1.45)	Yes vs. no
Tracheostomy placement	0.81 (0.56 – 1.17)	Yes vs. no
Transfusions	1.21 (1.10 – 1.32)	Yes vs. no
Renal replacement therapy	1.27 (1.01 – 1.59)	Yes vs. no
Length of hospital stay (days)	1.00 (0.99 – 1.01)	Every 10 days

Major cardiovascular event defined as the composite of myocardial infarction, stroke, or cardiovascular death. CI: confidence interval.

1. Based on a Cox proportional hazards model. Full model (i.e., all included co-variates) shown.
2. Site of infection modeled using the following categories: pneumonia, urosepsis, other infections.

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