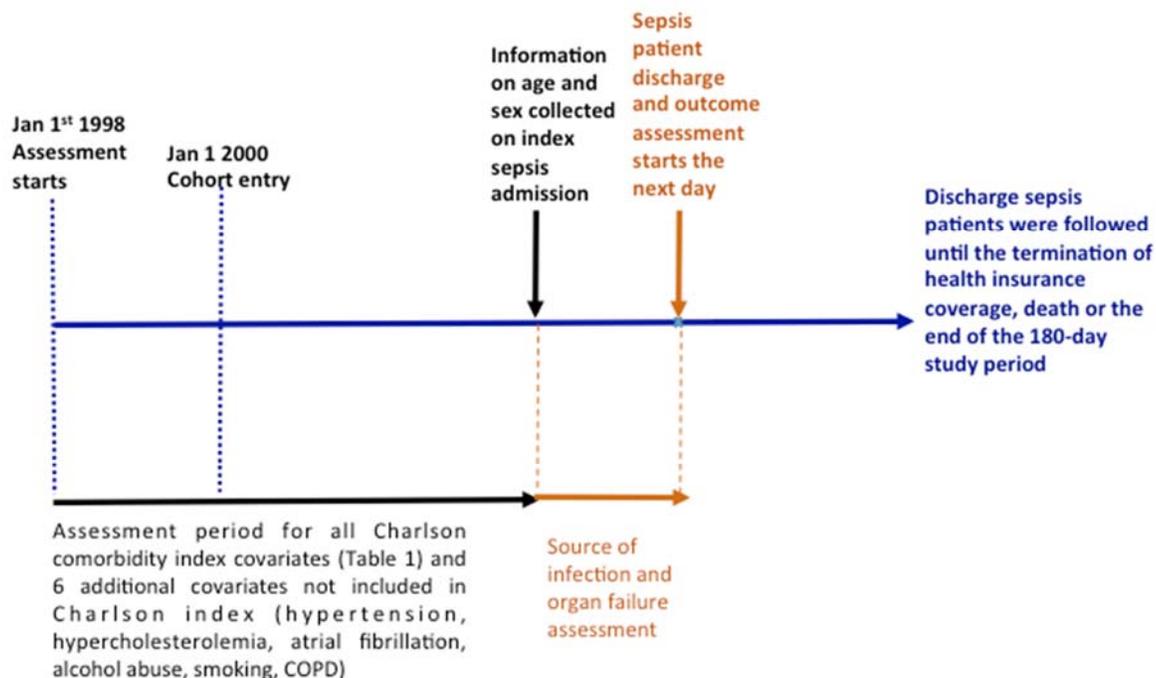# Appendix 1 (as supplied by the authors): Supplementary material

Figure 1: Timeline for covariate collection

Chronic comorbidities and risk factors for sepsis were collected between cohort inception to the index sepsis admission (black line). Age and sex of patients were assessed on the date of admission. Source of infections and organ failures were assessed during the index sepsis admission course (brown). Outcome assessment is for 180 days after hospital discharge.

List 1: Codes associated with infection

Codes associated with infection
Gastrointestinal infection
001, Cholera;
002, Typhoid/paratyphoid fever;
003, Other salmonella infection;
004, Shigellosis;
005, Other food poisoning;
008, Intestinal infection not otherwise classified;
009, Ill-defined intestinal infection;
562.01, Diverticulitis of small intestine without hemorrhage;
562.03, Diverticulitis of small intestine with hemorrhage;
562.11, Diverticulitis of colon without hemorrhage;
562.13, Diverticulitis of colon with hemorrhage;

Tuberculosis
010, Primary tuberculosis infection;
011, Pulmonary tuberculosis;
012, Other respiratory tuberculosis;
013, Central nervous system tuberculosis;
014, Intestinal tuberculosis; 015, Tuberculosis of bone and joint; 016, Genitourinary tuberculosis;
017, Tuberculosis not otherwise classified;
018, Miliary tuberculosis;

Zoonosis
020, Plague;
021, Tularemia;
022, Anthrax;
023, Brucellosis;
024, Glanders;
025, Melioidosis;
026, Rat-bite fever;
027, other bacterial zoonoses;

Other mycobacterial disease
030, Leprosy;
031, Other mycobacterial disease;

Syphilis
090, Congenital syphilis;
091, Early symptomatic syphilis;
092, Early syphilis latent;
093, Cardiovascular syphilis;
094, Neurosyphilis;
095, Other late symptomatic syphilis;
096, Late syphilis latent;
097, Other and unspecified syphilis;
102, Yaws;
103, Pinta;
104, Other spirochetal infection;

037, Tetanus;

Other bacterial diseases
040, Other bacterial diseases;
041, Bacterial infection in other diseases not otherwise specified;

Systematic fungal infection
110, Dermatophytosis;
111, Dermatomycosis not otherwise classified or specified;
112, Candidiasis;
114, Coccidioidomycosis;
115, Histoplasmosis;
116, Blastomycotic infection;
117, Other mycoses;
118, Opportunistic mycoses;
117.9, Disseminated fungal infection
112.5, Dissemintaed candidal infection
112.81, Disseminated fungal endocarditis
039, Actinomycotic infections;

CNS infection
320, Bacterial meningitis;
322, Meningitis, unspecified;
324, Central nervous system abscess;
325, Phlebitis of intracranial sinus;
036, Meningococcal infection;

Cardiovascular infection
420, Acute pericarditis;
421, Acute or subacute endocarditis;
451, Thrombophlebitis;

Upper respiratory tract infection
461, Acute sinusitis;
462, Acute pharyngitis;
463, Acute tonsillitis;
464, Acute laryngitis/ tracheitis;
465, Acute upper respiratory infection of multiple sites/not otherwise specified;
101, Vincent's angina;
034, Streptococcal throat/scarlet fever;
032, Diphtheria;

Lower respiratory tract infection
481, Pneumococcal pneumonia;
482, Other bacterial pneumonia;
485, Bronchopneumonia with organism not otherwise specified;
486, Pneumonia, organism not otherwise specified;
491.21, Acute exacerbation of obstructive chronic bronchitis;
494, Bronchiectasis;
510, Empyema;
513, Lung/mediastinum abscess;
033, Whooping cough;
484, Pneumonia classified in elsewhere
483, Pneumonia by other pathogens

Intra-abdominal infection

540, Acute appendicitis;
541, Appendicitis not otherwise specified;
542, Other appendicitis;
566, Anal and rectal abscess;
567, Peritonitis;
569.5, Intestinal abscess;
569.83, Perforation of intestine;
572.0, Abscess of liver;

Biliary tract infection
572.1, Portal pyremia;
575.0, Acute cholecystitis;

Genitourinary tract infection
590, Kidney infection;
597, Urethritis/urethral syndrome;
599.0, Urinary tract infection not otherwise specified;
601, Prostatic inflammation;
098, Gonococcal infections;

Gynecological infection
614, Female pelvic inflammation disease;
615, Uterine inflammatory disease;
616, Other female genital inflammation; 681, Cellulitis, finger/ toe;
098, Gonococcal infections;

Skin and appendix structure infection
682, Other cellulitis or abscess;
683, Acute lymphadenitis;
686, Other local skin infection;
035, Erysipelas;

Musculoskeletal infection
711.0, Pyogenic arthritis;
730, Osteomyelitis;

Primary bacteremia
790.7, Bacteremia;

Catheter related bloodstream infection
996.6, Infection or inflammation of device/graft;

Post-operative complication
998.5, Postoperative infection;

Nosocomial infection
999.3, Infectious complication of medical care not otherwise classified.

Septicemia
038.0, Streptococcal septicemia
038.1, Staphylococcal septicemia
038.2, Pneumococcal septicemia [Streptococcus pneumoniae septicemia]
038.3, Septicemia due to anaerobes
038.4, Septicemia due to other gram-negative organisms

038.8, Other specified septicemias
- o Excludes: septicemia (due to):
  - anthrax (022.3)
  - gonococcal (098.89)
  - herpetic (054.5)
  - meningococcal (036.2)
  - septicemic plague (020.2)

038.9, Unspecified septicemia

995.92, Severe sepsis

List 2: ICD-9-CM codes of organ dysfunction associated with sepsis

Cardiovascular dysfunction/Shock

785.5, Shock

458, Hypotension

Acute respiratory dysfunction

96.7, Mechanical ventilation

57001B, 57002B, 57023B, 57029C, use of ventilators

Central nervous system dysfunction

348.3, Neurologic Encephalopathy

293, Transient organic psychosis

348.1, Anoxic brain damage

Hematologic system dysfunction

287.4, Hematologic Secondary thrombocytopenia

287.5, Thrombocytopenia, unspecified

286.9, Other/unspecified coagulation defect

286.6, Defibrination syndrome

Hepatic system dysfunction

570, Hepatic Acute and subacute necrosis of liver

572.2, Hepatic encephalopathy

572.4, Hepatorenal syndrome

572.8, Other squeal of chronic liver disease

573.4, 573.8, Hepatic infarction

V42.7, Liver replaced by transplant

Renal system dysfunction

584, Acute renal failure

58014C, Use of CVVH

Table 1: Standardized difference between sepsis patients and matched population control

Characteristics	Standardized mean difference before PS-matching	Standardized difference after PS-matching
Male sex, n (%)	0.16	-0.01
Age, yrs,± SD	0.00035	0
Myocardial infarction	0.046	-0.0009
Congestive heart failure	0.167	-0.01
Peripheral vascular disease	-0.04	-0.02
Cerebrovascular disease	0.17	0.03
Dementia	0.20	0.03
Chronic pulmonary disease	0.06	-0.02
Rheumatologic disease	-0.05	-0.04
Peptic ulcer disease	-0.019	-0.05
Mild liver disease	-0.07	-0.04
Moderate or severe liver disease	0.04	0.01
Diabetes without chronic complications	0.06	0.002
Diabetes with chronic complications	0.07	-0.02
Hemiplegia or paraplegia	0.09	-0.01
Chronic renal disease	0.10	0.02
Leukemia and lymphoma	0.14	0.06
Metastatic solid tumor	0.11	-0.002
AIDS/HIV	-0.02	0

Table 2: Standardized difference between sepsis patients and matched hospital controls

Characteristics	Standardized mean difference before matching	Standardized difference after matching
Male sex, n (%)	-0.74	0
Age, yrs,± SD	1.07	0.05
Myocardial infarction	-0.05	0.04
Congestive heart failure	-0.15	0.15
Peripheral vascular disease	-0.09	0.08
Cerebrovascular disease	0.60	0.16
Dementia	-0.01	0.16
Chronic pulmonary disease	0.05	0.06
Rheumatologic disease	-0.03	0.03
Peptic ulcer disease	-0.14	0.01
Mild liver disease	0.07	0.05
Moderate or severe liver disease	-0.17	0.13
Diabetes without chronic complications	-0.09	0.15
Diabetes with chronic complications	-0.02	0.11
Hemiplegia or paraplegia	-0.08	0.15
Chronic renal disease	0.01	0.04
Leukemia and lymphoma	0.09	0.02
Metastatic solid tumor	0.04	-0.01
AIDS/HIV	0.05	0.004

Methods - free knot spline

We determine the turning point of the risk of MI/stroke after hospital discharge by using the "freeknotsplines" statistical package in R.[1,2] A free-knot spline may be described as a non-linear regression characterized by piecewise polynomials joined at locations called knots. The location of knots can be used to estimate partition boundaries characterizing groups experiencing differing, non-uniform relationship between exposure and outcome. In this case, we sought to determine the relationship between time after sepsis recovery and risk of cardiovascular events. The knot-search algorithm will automatically highlights the point where a monotonic relationship between the two variables (time and risk of MI/stroke) may change after specifying the number of knots a priori. We are interested to find out a date where the risk of MI/stroke after hospital discharge changes, and a single knot was specified. Therefore, in this study, the knot of the spline is the point or the date where the two phases of risk connect, and can be interpreted as the turning point of the risk of MI/stroke after hospital discharge.

References

1.   Steven Spiriti PS, Pierre Lecuyer. Freeknotsplines R package version 1.0 2012; https://cran.r-project.org/web/packages/freeknotsplines/. Accessed May 9, 2018.
2.   Spiriti S, Eubank R, Smith PW, Young D. Knot selection for least-squares and penalized splines. *Journal of Statistical Computation and Simulation.* 2013;83:1020-36.

Table 3: Characteristic of sepsis cohort.

Characteristics	Sepsis, N=42,316
Lower respiratory tract infection	21739 (51.4%)
Urinary tract infection	13100 (31.0%)
Intra-abdomen infection	2626 (6.21%)
Acute respiratory failure	27922 (66.0%)
Septic shock	12288 (29.0%)
Acute renal failure	7129 (16.9%)
30-day mortality	9469(22.38%)
ICU-admission	14636(34.59%)
Number of organ failure (median, inter quartile range)	1 (1)

Figure 1: Variation in the number of incident MI (A), Stroke (B), and MI and stroke (C) cases following days of hospital discharge for the sepsis cohort. X-axis is days of follow-up and Y-axis is events. ==AMI to be changed to MI in final==
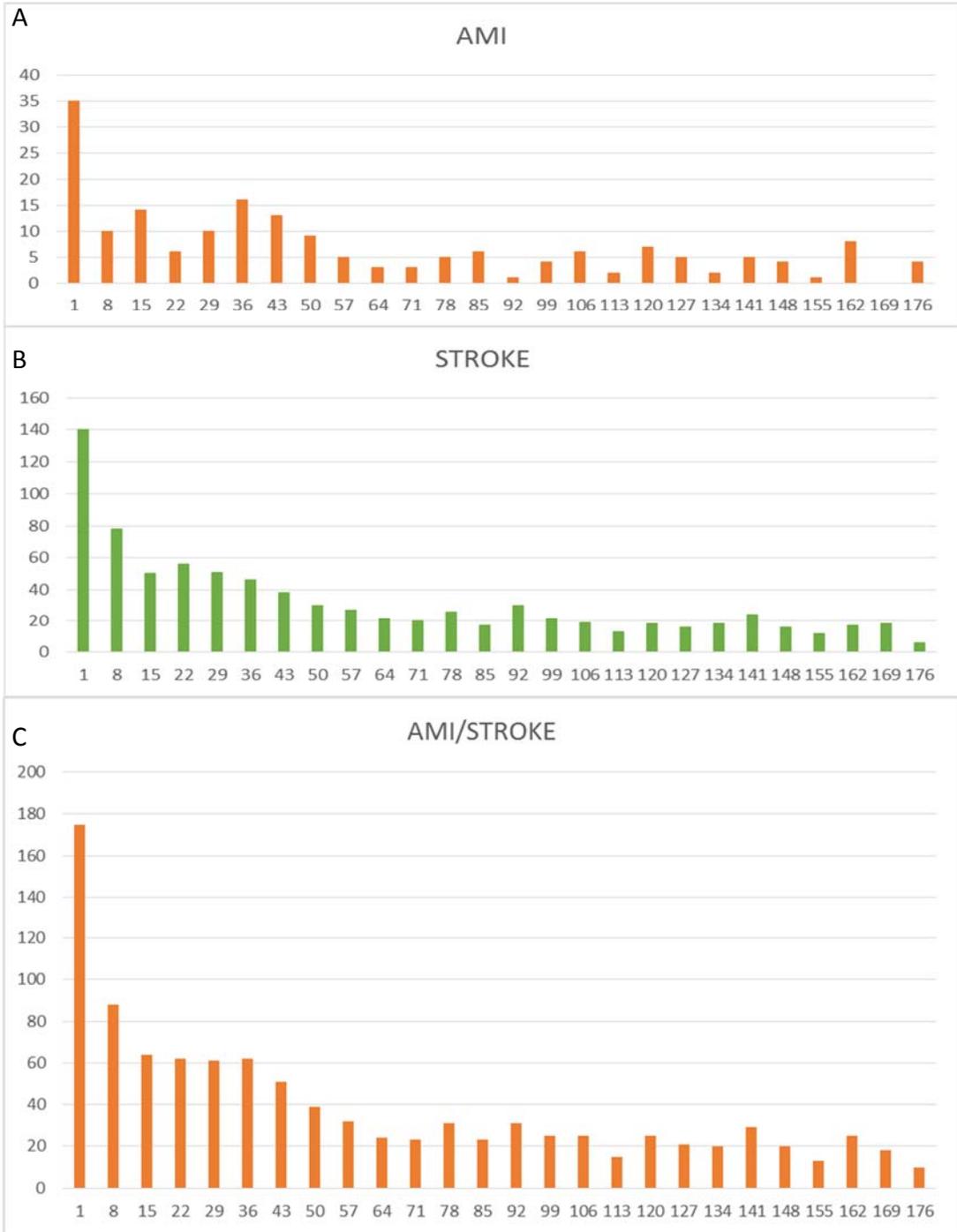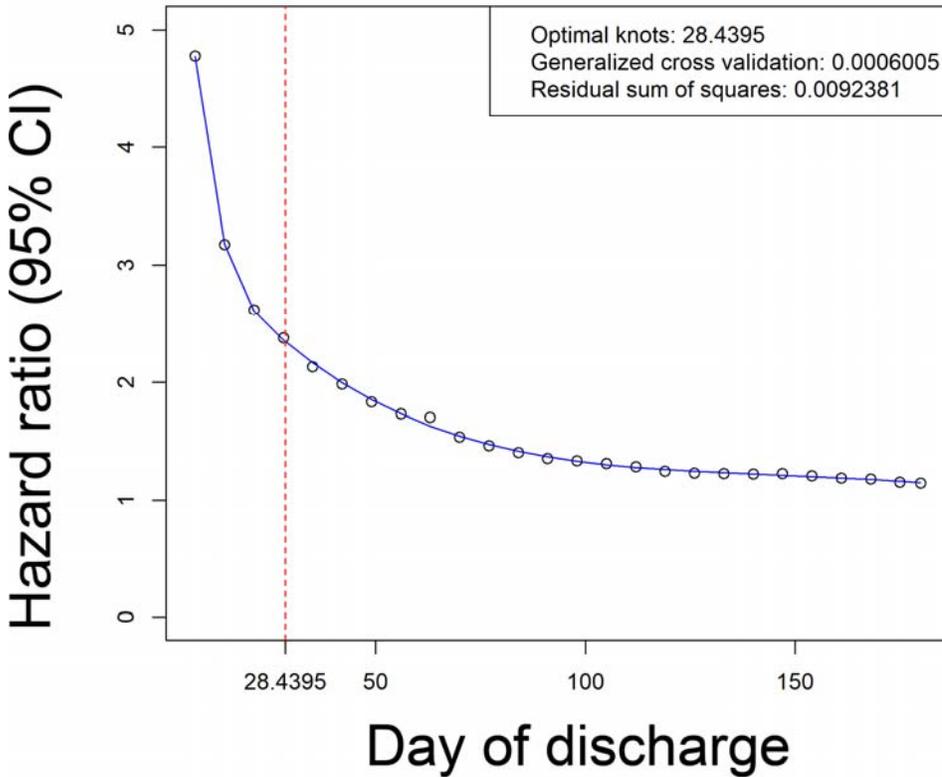
Figure 2: Time-dependent relative risk curves of MI and stroke fitted with free-knot splines. ((Upper panel) Comparison of sepsis patients to the non-sepsis individuals from the general population; (lower panel) comparison of sepsis patients to the non-sepsis hospitalized patients.
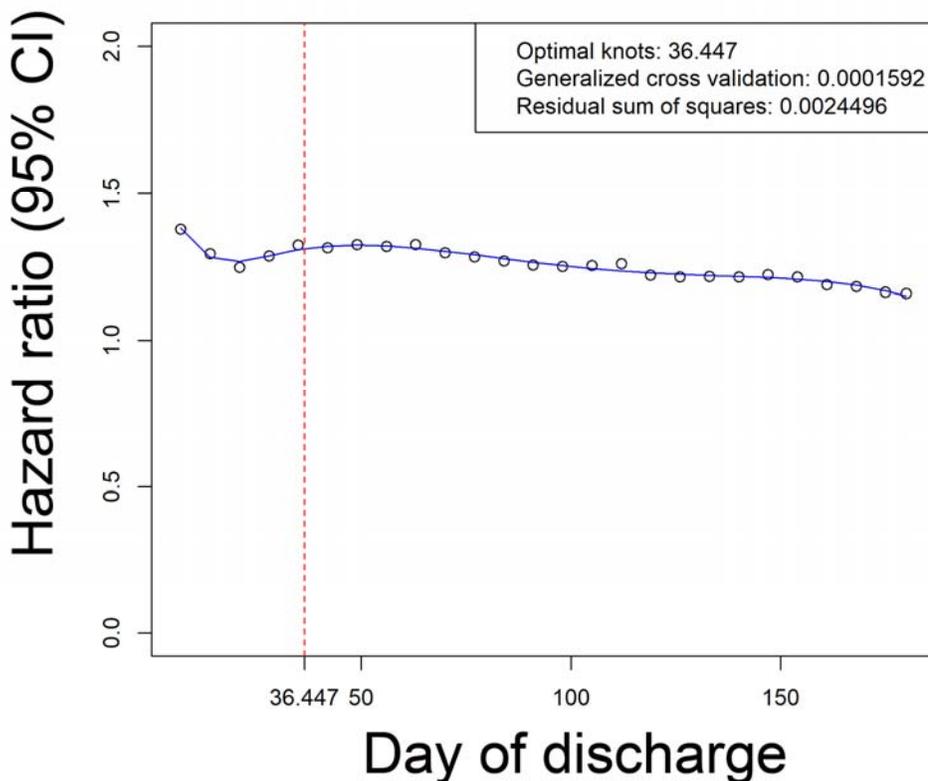
Table 4: Relative risk and risk difference of post-sepsis MI and stroke compared to non-sepsis patients, stratified by two age group.

Patient subgroups	HR (95% CI)	Risk difference (95% CI)	Number needed to harm
Age			
20-45	4.55 (1.75, 11.84)	0.0037 (0.0012,0.0061)	273
≥75	1.47 (1.30, 1.66)	0.0019(-0.0014, 0.0052)	529