

Online Appendix

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Supplementary table 1. Characteristics of patients hospitalized with sepsis, stratified by three periods between 2002 and 2012(N= total number of sepsis patients)

Characteristic	2002 n=86,422	2003 n=89,440	2004 n=97,982	2005 n=106,499	2006 n=110,200	2007 n=116,064	2008 n=120,621	2009 n=124,603	2010 n=131,691	2011 n=137,156	2012 n=138,899
Age	67.32 ±16.93	67.85 ±16.41	68.3 ±16.54	69.27 ±16.26	69.18 ±16.26	69.47 ±16.47	69.78 ±16.63	69.59 ±16.58	70.2 ±16.44	69.85 ±16.82	70.71 ±16.54
Male sex (%)	86422 (59.71%)	89440 (59.26%)	97982 (59.86%)	106499 (59.88%)	110200 (59.57%)	116064 (59.16%)	120621 (58.99%)	124603 (58.88%)	131691 (58.62%)	137156 (58.68%)	138899 (58.12%)
Infection site											
Lower respiratory tract infection	47450 (23.66%)	47773 (23.82%)	50953 (25.41%)	54367 (27.11%)	61562 (24.17%)	62811 (24.66%)	64920 (25.48%)	65460 (25.7%)	73081 (32.48%)	76470 (33.98%)	75477 (33.54%)
Genitourinary tract infection	29580 (23.69%)	30708 (24.6%)	31528 (25.25%)	33036 (26.46%)	37854 (23.51%)	39794 (24.72%)	41026 (25.48%)	42326 (26.29%)	46741 (33.03%)	46369 (32.76%)	48409 (34.21%)
Intra-abdominal infection	5408 (24.92%)	5466 (25.19%)	5393 (24.85%)	5437 (25.05%)	6294 (23.02%)	6682 (24.44%)	7053 (25.8%)	7306 (26.73%)	7930 (32.92%)	8090 (33.58%)	8072 (33.51%)
Skin and skin structure infection	4506 (24.5%)	4491 (24.42%)	4564 (24.82%)	4827 (26.25%)	5537 (23.63%)	5824 (24.86%)	5926 (25.29%)	6145 (26.22%)	7056 (33.33%)	6967 (32.91%)	7145 (33.75%)
Systematic fungal infection	2429 (27.07%)	2283 (25.45%)	2123 (23.66%)	2138 (23.82%)	2632 (23.15%)	2784 (24.48%)	2936 (25.82%)	3020 (26.56%)	3372 (32.42%)	3425 (32.94%)	3602 (34.64%)
Musculoskeletal infection	1710 (29.04%)	1516 (25.74%)	1380 (23.43%)	1283 (21.78%)	1534 (21.57%)	2260 (31.78%)	1659 (23.32%)	1659 (23.32%)	2027 (31.47%)	1914 (29.72%)	2500 (38.81%)
Biliary tract infection	934 (21.46%)	1099 (25.25%)	1209 (27.78%)	1110 (25.51%)	1447 (27.69%)	1005 (19.23%)	1461 (27.95%)	1313 (25.13%)	1812 (39.53%)	1637 (35.69%)	1136 (24.78%)

Supplementary table 2. Covariates with associated hazard ratios in the outcome Cox regression model.

	Hazard Ratio (95% Confidence Interval)	P-value
Number of sources of infection		
1	Ref	
2	1.36(1.31,1.42)	<.0001
>= 3	1.19(1.14,1.25)	<.0001
Demographics		
Gender male (female =0)	1.33(1.28,1.38)	<.0001
Age	1.02(1.01,1.02)	<.0001
Age squared	1.00(1.00,1.00)	0.2302
Hospital status		
Tertiary medical centers	Ref	0.0002
Teaching hospitals	1.02(0.96,1.08)	
Large community nonteaching hospitals	0.96(0.9,1.02)	
Small community hospitals	0.86(0.78,0.95)	
Living area		
Urban Area	Ref	<.0001
Metro Area	0.92(0.88,0.96)	
Suburban Area	0.74(0.7,0.78)	
Countryside Area	0.71(0.66,0.75)	
Insurance premium level		
Dependent	Ref	0.0014
\$1-\$19,999	1(0.95,1.06)	
\$20,000-\$39,999	1.07(1.00,1.13)	
>=\$40,000	0.93(0.85,1.01)	
Comorbidities		
Hypertension	1.11(1.05,1.16)	<.0001
Chronic pulmonary disease	0.91(0.87,0.95)	<.0001
Congestive heart failure	0.93(0.88,0.99)	0.0123
Hemiplegic stroke	0.98(0.94,1.03)	0.4399
Complicated diabetes	0.91(0.87,0.96)	<.0001
Chronic kidney disease	1.01(0.96,1.06)	0.7897
Chronic liver disease	1.02(0.98,1.06)	0.3654
Alcohol-related disease	1.02(0.92,1.14)	0.7075
Any tumor	1.24(1.18,1.3)	<.0001
Metastatic cancer	1.28(1.15,1.42)	<.0001
Peripheral vascular disorder	0.95(0.9,1.01)	0.1001
Coagulopathy	1.03(0.94,1.12)	0.5616
Dementia	0.94(0.89,1)	0.0521
Psychosis	0.95(0.9,1.02)	0.1358
HIV/AIDS	2.58(1.83,3.63)	<.0001
Charlson comorbidity score	1.13(1.1,1.15)	<.0001
Charlson Score Squared	1.00(0.99,1)	<.0001
Health care utilization		
Number of OPD visit	1.00(1.00,1.00)	<.0001
Number of ED visit	1.01(1,1.01)	0.0479
Number of hospitalization	1.02(1.01,1.03)	<.0001

Supplementary Methods

Acute organ/system dysfunction includes cardiovascular/shock, respiratory, central nervous system, hematologic, hepatic, renal and metabolic system dysfunction. Cardiovascular dysfunction/Shock was identified by the presence of shock (785.5) or hypotension (458). Acute respiratory dysfunction was defined by both ICD-9 CM code (96.7) insurance reimbursement codes for mechanical ventilation. Central nervous system dysfunction was defined by the presence of neurologic encephalopathy (348.3), transient organic psychosis (293), and anoxic brain damage (348.1). Hematologic system dysfunction was defined by hematologic secondary thrombocytopenia (287.4), unspecified thrombocytopenia (287.5), other/unspecified coagulation defect (286.9), and defibrination syndrome (286.6).

Renal system dysfunction was defined by acute renal failure (584) and claims codes for acute dialysis therapy. Hepatic system dysfunction was defined by acute and subacute necrosis of liver (570), hepatic encephalopathy (572.2), hepatorenal syndrome (572.4), other sequelae of chronic liver disease (573.4), hepatic infarction (573.8) and liver replaced by transplant (V42.7). In addition to the above organ dysfunction defined by Angus et al, we also included patients with metabolic system dysfunction as defined by the presence of diabetic ketoacidosis (250.1), and hyperosmolar hyperglycemic state (250.2) as the spectrum of sepsis-related organ dysfunction. Gastrointestinal failure was not included due to difficulty in definition by ICD-9 code.

Supplementary appendix 1. ICD-9-CM codes of different infection site associated with sepsis

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

Genitourinary tract infection

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

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

Skin and skin 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

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, Disseminated candidal infection
112.81, Disseminated fungal endocarditis
039, Actinomycotic infections

Biliary tract infection

572.1, Portal pyremia

575.0, Acute cholecystitis

Supplementary Appendix 2. ICD-9-CM/procedure 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 sequel 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

Metabolic system dysfunction

250.1, Diabetic ketoacidosis
250.2, Hyperosmolar hyperglycemic state