Epidemiology of sepsis in Korea: a population-based study of incidence, mortality, cost and risk factors for death in sepsis

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Objective To investigate the epidemiology of sepsis in Korea and identify risk factors for death in sepsis.

Methods We conducted a longitudinal, population-based epidemiological study of sepsis in Korea from 2005 to 2012 using the National Health Insurance Service-National Sample Cohort, a population-based cohort representing 2.2% of the Korean population. The primary objective was to assess the incidence, mortality and cost of sepsis. The secondary objective was to identify the risk factors for death in sepsis. Claim records of admitted adult patients (aged ≥15 years) were analyzed. Sepsis was defined as 1) bacterial or fungal infection or the conditions they often complicate, 2) prescription of intravenous antibiotics, and 3) presence of any organ dysfunction. Comorbidities were defined using the Charlson/Deyo method. Risk factors for 6-month mortality were assessed using multivariable logistic regression.

Results A total of 22,882 cases were identified. Both incidence and 6-month mortality increased from 265.7 (95% confidence interval [CI], 254.7 to 277.1) to 453.1 (95% CI, 439.0 to 467.5) per 100,000 person-years (P-trend <0.001) and from 26.5% (95% CI, 24.4% to 28.8%) to 30.1% (95% CI, 28.4% to 31.9%), respectively. After standardization, the increasing trend of incidence was slower but still significant (P-trend <0.001), while that for mortality was not (P-trend 0.883). The average cost increased by 75.5% (P-trend <0.001). Multivariable logistic regression identified various risk factors for mortality.

Conclusion The burden of sepsis in Korea was high and is expected to increase considering the aging population. Proactive measures to curtail this increase should be sought and implemented.

Keywords Sepsis; Epidemiology; Incidence; Mortality; Risk factors

Capsule Summary

What is already known
The incidence of sepsis and mortality have increased worldwide. The epidemiological characteristics of sepsis in Korea are yet unknown.

What is new in the current study
Although the incidence of sepsis in Korea has increased, the mortality rate has remained steady.

Table 1. Patient characteristics of the study population

Characteristics	2005	2006	2007	2008	2009	2010	2011	2012	Total	P-value
No. of cases/person-year	2,194/825,502	2,256/820,204	2,398/842,444	2,672/832,170	2,921/837,177	2,887/846,853	3,639/855,428	3,915/863,820	22,882/6,723,598	
Age group (yr)										<0.001
15–64	972 (44.3)	978 (43.4)	957 (39.9)	1,084 (40.6)	1,172 (40.1)	1,089 (37.7)	1,307 (35.9)	1,295 (33.1)	8,854 (38.7)	
65–74	573 (26.1)	588 (26.1)	626 (26.1)	670 (25.1)	747 (25.6)	698 (24.2)	818 (22.5)	901 (23.0)	5,621 (24.6)	
75–84	499 (22.7)	522 (23.1)	614 (25.6)	658 (24.6)	726 (24.9)	793 (27.5)	1,037 (28.5)	1,207 (30.8)	6,056 (26.5)	
≥85	150 (6.8)	168 (7.4)	201 (8.4)	260 (9.7)	276 (9.4)	307 (10.6)	477 (13.1)	512 (13.1)	2,351 (10.3)	
Sex, male	1,273 (58.0)	1,239 (54.9)	1,352 (56.4)	1,519 (56.8)	1,622 (55.5)	1,654 (57.3)	1,948 (53.5)	2,112 (53.9)	12,719 (55.6)	0.003
Comorbidities										
Chronic pulmonary disease	473 (21.6)	500 (22.2)	505 (21.1)	585 (21.9)	636 (21.8)	600 (20.8)	723 (19.9)	811 (20.7)	4,833 (21.1)	0.384
Neoplasm	230 (10.5)	246 (10.9)	249 (10.4)	297 (11.1)	289 (9.9)	281 (9.7)	378 (10.4)	453 (11.6)	2,423 (10.6)	0.251
Chronic liver disease	151 (6.9)	119 (5.3)	144 (6.0)	163 (6.1)	207 (7.1)	162 (5.6)	202 (5.6)	234 (6.0)	1,382 (6.0)	0.067
Renal disease	55 (2.5)	49 (2.2)	74 (3.1)	94 (3.5)	105 (3.6)	90 (3.1)	151 (4.1)	198 (5.1)	816 (3.6)	<0.001
Diabetes melitus	173 (7.9)	193 (8.6)	246 (10.3)	287 (10.7)	322 (11.0)	342 (11.8)	410 (11.3)	554 (14.2)	2,527 (11.0)	<0.001
Peripheral vascular disease	31 (1.4)	30 (1.3)	34 (1.4)	40 (1.5)	46 (1.6)	57 (2.0)	62 (1.7)	89 (2.3)	389 (1.7)	0.051
Rheumatological disease	8 (0.4)	24 (1.1)	12 (0.5)	16 (0.6)	16 (0.5)	28 (1.0)	22 (0.6)	32 (0.8)	158 (0.7)	0.036
Charlson comorbidity index										<0.001
0	1,170 (53.3)	1,160 (51.4)	1,224 (51.0)	1,318 (49.3)	1,420 (48.6)	1,419 (49.2)	1,783 (49.0)	1,773 (45.3)	11,267 (49.2)	
1	544 (24.8)	584 (25.9)	580 (24.2)	613 (22.9)	739 (25.3)	723 (25.0)	880 (24.2)	940 (24.0)	5,603 (24.5)	
2	220 (10.0)	246 (10.9)	285 (11.9)	347 (13.0)	361 (12.4)	372 (12.9)	487 (13.4)	539 (13.8)	2,857 (12.5)	
>2	260 (11.9)	266 (11.8)	309 (12.9)	394 (14.7)	401 (13.7)	373 (12.9)	489 (13.4)	663 (16.9)	3,155 (13.8)	
Presented to emergency room	1,274 (58.1)	1,329 (58.9)	1,425 (59.4)	1,492 (55.8)	1,618 (55.4)	1,658 (57.4)	2,070 (56.9)	2,262 (57.8)	13,128 (57.4)	0.041
Medical department	1,520 (69.3)	1,560 (69.1)	1,686 (70.3)	1,884 (70.5)	2,059 (70.5)	2,018 (69.9)	2,630 (72.3)	2,855 (72.9)	16,212 (70.9)	0.007
Surgical department	668 (30.4)	694 (30.8)	708 (29.5)	782 (29.3)	855 (29.3)	865 (30.0)	1,002 (27.5)	1,053 (26.9)	6,627 (29.0)	0.006
Income level										<0.001
Lower	376 (17.1)	324 (14.4)	398 (16.6)	502 (18.8)	518 (17.7)	446 (15.4)	1,064 (29.2)	1,102 (28.1)	4,730 (20.7)	
Lower-middle	326 (14.9)	323 (14.3)	332 (13.8)	344 (12.9)	398 (13.6)	415 (14.4)	392 (10.8)	432 (11.0)	2,962 (12.9)	
Middle	372 (17.0)	387 (17.2)	422 (17.6)	492 (18.4)	509 (17.4)	490 (17.0)	496 (13.6)	472 (12.1)	3,640 (15.9)	
Upper-middle	475 (21.6)	490 (21.7)	516 (21.5)	533 (19.9)	594 (20.3)	547 (18.9)	619 (17.0)	670 (17.1)	4,444 (19.4)	
Upper	645 (29.4)	732 (32.4)	730 (30.4)	801 (30.0)	902 (30.9)	989 (34.3)	1,068 (29.3)	1,239 (31.6)	7,106 (31.1)	
Hospital size (no. of beds)										<0.001
<100	59 (2.7)	75 (3.3)	59 (2.5)	89 (3.3)	98 (3.4)	100 (3.5)	74 (2.0)	72 (1.8)	626 (2.7)	
100–299	399 (18.2)	417 (18.5)	451 (18.8)	531 (19.9)	580 (19.9)	650 (22.5)	808 (22.2)	801 (20.5)	4,637 (20.3)	
300–599	501 (22.8)	418 (18.5)	528 (22.0)	585 (21.9)	618 (21.2)	650 (22.5)	889 (24.4)	971 (24.8)	5,160 (22.6)	
600–999	645 (29.4)	668 (29.6)	739 (30.8)	779 (29.2)	856 (29.3)	813 (28.2)	1,002 (27.5)	1,136 (29.0)	6,638 (29.0)	
≥1,000	590 (26.9)	678 (30.1)	621 (25.9)	688 (25.7)	769 (26.3)	674 (23.3)	866 (23.8)	935 (23.9)	5,821 (25.4)	

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Table 1. Continued

Characteristics	2005	2006	2007	2008	2009	2010	2011	2012	Total	P-value
Organ dysfunction										
Respiratory	1,163 (53.0)	1,172 (52.0)	1,286 (53.6)	1,400 (52.4)	1,482 (50.7)	1,459 (50.5)	1,851 (50.9)	2,041 (52.1)	11,854 (51.8)	0.218
Hemodynamic	1,024 (46.7)	1,075 (47.7)	1,160 (48.4)	1,251 (46.8)	1,393 (47.7)	1,359 (47.1)	1,731 (47.6)	1,799 (46.0)	10,792 (47.2)	0.679
Sepsis-induced cardiomyopathy	5 (0.2)	7 (0.3)	11 (0.5)	10 (0.4)	20 (0.7)	18 (0.6)	25 (0.7)	46 (1.2)	142 (0.6)	<0.001
Hematologic	266 (12.1)	231 (10.2)	257 (10.7)	275 (10.3)	309 (10.6)	299 (10.4)	356 (9.8)	391 (10.0)	2,384 (10.4)	0.210
Renal	261 (11.9)	301 (13.3)	303 (12.6)	327 (12.2)	363 (12.4)	374 (13.0)	479 (13.2)	584 (14.9)	2,992 (13.1)	0.013
Hepatic	198 (9.0)	167 (7.4)	176 (7.3)	230 (8.6)	206 (7.1)	188 (6.5)	194 (5.3)	159 (4.1)	1,518 (6.6)	<0.001
Metabolic	29 (1.3)	27 (1.2)	37 (1.5)	39 (1.5)	33 (1.1)	37 (1.3)	61 (1.7)	65 (1.7)	328 (1.4)	0.469
Neurologic	115 (5.2)	121 (5.4)	130 (5.4)	179 (6.7)	180 (6.2)	182 (6.3)	275 (7.6)	331 (8.5)	1,513 (6.6)	<0.001
No. of organ dysfunctions										0.351
1	1,585 (72.2)	1,651 (73.2)	1,701 (70.9)	1,962 (73.4)	2,138 (73.2)	2,147 (74.4)	2,670 (73.4)	2,846 (72.7)	16,700 (73.0)	
2	420 (19.1)	423 (18.8)	495 (20.6)	481 (18.0)	559 (19.1)	519 (18.0)	699 (19.2)	747 (19.1)	4,343 (19.0)	
3	134 (6.1)	132 (5.9)	152 (6.3)	152 (5.7)	173 (5.9)	163 (5.6)	193 (5.3)	229 (5.8)	1,328 (5.8)	
≥4	55 (2.5)	50 (2.2)	50 (2.1)	77 (2.9)	51 (1.7)	58 (2.0)	77 (2.1)	93 (2.4)	511 (2.2)	
Site of infection										0.001
Respiratory	1,122 (51.1)	1,189 (52.7)	1,307 (54.5)	1,431 (53.6)	1,529 (52.3)	1,559 (54.0)	1,951 (53.6)	2,167 (55.4)	12,255 (53.6)	
CNS	14 (0.6)	19 (0.8)	20 (0.8)	12 (0.4)	18 (0.6)	30 (1.0)	18 (0.5)	19 (0.5)	150 (0.7)	
Gastrointestinal	444 (20.2)	445 (19.7)	441 (18.4)	508 (19.0)	570 (19.5)	541 (18.7)	714 (19.6)	720 (18.4)	4,383 (19.2)	
Genitourinary	122 (5.6)	147 (6.5)	183 (7.6)	188 (7.0)	202 (6.9)	218 (7.6)	259 (7.1)	310 (7.9)	1,629 (7.1)	
Musculoskeletal, skin and soft tissue	114 (5.2)	87 (3.9)	99 (4.1)	130 (4.9)	154 (5.3)	146 (5.1)	164 (4.5)	174 (4.4)	1,068 (4.7)	
Endocarditis	5 (0.2)	7 (0.3)	4 (0.2)	9 (0.3)	8 (0.3)	8 (0.3)	11 (0.3)	11 (0.3)	63 (0.3)	
Device-related	16 (0.7)	5 (0.2)	9 (0.4)	14 (0.5)	12 (0.4)	7 (0.2)	15 (0.4)	24 (0.6)	102 (0.4)	
Unspecified	357 (16.3)	357 (15.8)	335 (14.0)	380 (14.2)	428 (14.7)	378 (13.1)	507 (13.9)	490 (12.5)	3,232 (14.1)	
Septic shock	1,014 (46.2)	1,063 (47.1)	1,146 (47.8)	1,227 (45.9)	1,367 (46.8)	1,320 (45.7)	1,694 (46.6)	1,739 (44.4)	10,570 (46.2)	0.242
Length of stay										
Median (IQR)	12.0 (7.0–24.0)	13.0 (7.0–26.0)	14.0 (7.0–26.0)	13.0 (7.0–27.0)	12.0 (7.0–25.0)	13.0 (7.0–26.0)	13.0 (7.0–28.0)	14.0 (7.0–29.0)	13.0 (7.0–26.0)	<0.001
Mean±SD	24.7±44.5	27.0±48.3	26.6±43.1	27.3±48.8	25.6±47.2	29.2±55.4	32.5±62.3	36.3±69.7	29.3±55.0	
Cost (10,000 KRW)										
Median (IQR)	209.8 (113.9–449.5)	240.5 (131.1–539.8)	283.5 (144.8–604.8)	263.8 (140.6–633.2)	264.8 (144.3–617.5)	292.6 (151.2–645.9)	306.3 (158.0–675.1)	309.9 (163.1–731.5)	276.0 (144.2–621.8)	<0.001
Mean±SD	425.3±628.1	513.9±804.3	548.6±801.2	574.2±959.5	593.9±951.3	620.2±1,002.5	681.2±1,079.9	743.3±1,226.6	605.6±984.8	
ICU admission	747 (34.0)	722 (32.0)	806 (33.6)	792 (29.6)	896 (30.7)	821 (28.4)	1,139 (31.3)	1,208 (30.9)	7,131 (31.2)	<0.001
6-month mortality	582 (26.5)	628 (27.8)	696 (29.0)	790 (29.6)	831 (28.4)	881 (30.5)	1,089 (29.9)	1,243 (31.7)	6,740 (29.5)	0.001

Values are presented as number (%) unless otherwise indicated.
CNS, central nervous system; IQR, interquartile range; SD, standard deviation; KRW, Korean won; ICU, intensive care unit.

records within three years prior to the first sepsis record using the Charlson/Deyo method.[22-24] Ancillary variables including household income level, emergency room (ER) presentation, type of admitting department, and hospital capacity measured by the number of beds were also included in the analyses. Length of stay, overall cost, intensive care unit (ICU) admission and 6-month mortality were included as outcome measures. We excluded the claim records beginning more than a year after the event when calculating the length of stay and cost because we thought prolonged admission more than a year after the index event would hardly be due to the index event. The detailed coding schemes are available in the Appendix 1.

Statistical analysis

Both crude and standardized annual incidence of sepsis in the adult population (aged ≥ 15 years) were calculated. The standardized annual incidence based on the sex-age distribution of the 2010 Korean census was estimated by direct standardization.[25] Similarly, both crude and standardized 6-month mortality were calculated using the direct standardization method based on the sex-age distribution sepsis cases for the year 2010. The average (both mean and median) cost per case and the total national cost for each year were estimated in Korean won (KRW). The standardized annual average cost based on the sex-age distribution of sepsis cases from 2010 was also calculated. The trend analyses for dichotomous events were conducted using logistic regression,
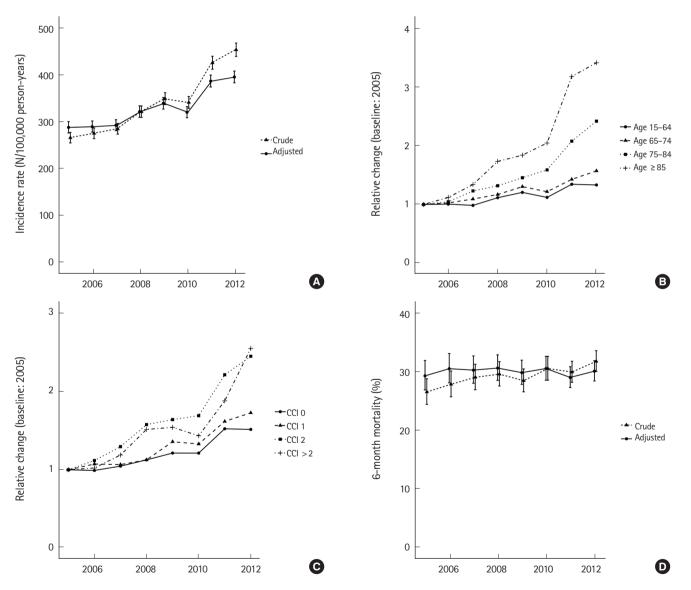

Fig. 2. Eight-year trend of sepsis incidence and mortality. (A) Crude and adjusted incidence rate of sepsis. (B) Relative change of incidence of sepsis according to the age group. (C) Relative change of incidence of sepsis according to the comorbidity. (D) Crude and adjusted 6-month mortality of sepsis. CCI, Charlson comorbidity index.

and those for continuous variables were conducted using linear regression.

Survival curves for the sepsis patients during the first six months were plotted using the Kaplan-Meier method and comparisons between groups were made using the log-rank test. To identify independent risk factors for mortality, we performed multivariable logistic regression analyses using two different model-building schemes. The first involved comprehensive modeling using all available variables and data. The second involved parsimonious modeling with a variable selection scheme based on Bayesian information criterion using 80% of randomly selected cases (training set) which was later tested using the remaining 20% of cases (test set). The results of the logistic regression were presented as odds ratios and their 95% confidence intervals (CIs). All data handling and statistical analyses were performed using R ver. 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From 2005 to 2012, a total of 22,882 sepsis cases were identified from the cohort (Table 1). More than half of the patients (14,028; 61.3%) were older than 65 years and had at least one comorbidity (11,615; 50.8%). Over half of the cases initially presented to the ER (13,128; 57.4%) and over two-thirds were treated in the medical department (16,212; 70.9%). Their income levels showed a polarized pattern with almost half of the cases (11,836; 51.7%) in the lowest and highest income classes. Majority of the cases (17,619; 77.0%) were treated in larger hospitals with capacities of 300 beds or higher. The most common type of organ dysfunc-

tion was respiratory failure (11,854; 51.8%) followed by hemodynamic failure (10,792; 47.2%) and the most common site of infection was the respiratory system (12,255; 53.6%). Almost half of the cases were complicated by septic shock (10,570; 46.2%) and almost one-third of the cases involved ICU admission (7,131; 31.2%). The median length of stay was 13 (interquartile range, 7 to 26) days and the median cost was 276 (interquartile range, 144.2 to 621.8) × 10,000 KRW and the 6-month mortality rate was 29.5%.

Fig. 2 shows the eight-year trend of sepsis incidence and mortality. There was a significant increase in crude incidence rate of sepsis from 265.7 (254.7 to 277.1) per 100,000 person-years in 2005 to 453.1 (439.0 to 467.5) per 100,000 person-years in 2012 (P-trend < 0.001). After standardization for both age and sex, the increase was less remarkable but still significant with 287.7 (275.8 to 300.1) in 2005 to 395.1 (382.7 to 407.8) in 2012 (P-trend < 0.001). The increase was more remarkable in the elderly population and the patients with significant comorbidity burdens. The crude mortality rate also gradually increased from 26.5% (24.4% to 28.8%) to 30.1% (28.4% to 31.9%) during the period (P-trend < 0.001). However, the trend was not significant after sex-age standardization (from 29.3% [95% CI, 26.9% to 31.9%] to 30.5 [95% CI, 28.5% to 32.6%]; P-trend = 0.883). The crude mortality rate among patients with septic shock also gradually increased from 32.2% (28.8% to 35.9%) to 38.5% (35.6% to 41.5%) during the period (P-trend < 0.001, Supplementary Fig. 1). However, the trend was not significant after sex-age standardization (from 36.8% [95% CI, 32.8% to 41.8%] to 36.9 [95% CI, 34.1% to 39.9%]; P-trend 0.564).
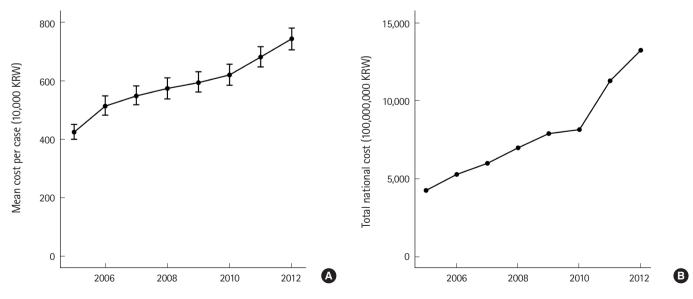

Fig. 3. Eight-year trend of national expenditure on sepsis. (A) Mean cost per case of sepsis. (B) Total national cost of sepsis. KRW, Korean won.
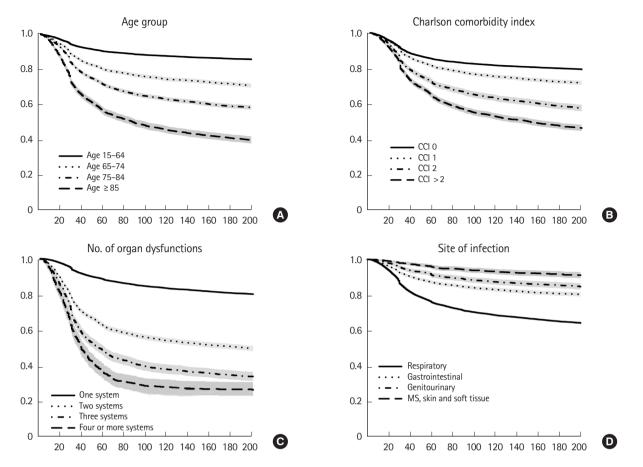
Fig. 4. Differential survival probability by age, comorbidity burden, organ dysfunction, and the site of infection. (A) Survival according to the age group. (B) Survival according to the comorbidity. (C) Survival according to the number of organ dysfunction. (D) Survival according to the site of infection. CCI, Charlson comorbidity index; MS, musculoskeletal.

The standardized average cost per case increased by 75.5% from 422.5 (95% CI, 396.9 to 448.1) × 10,000 KRW in 2005 to 741.7 (95% CI, 701.5 to 781.9) × 10,000 KRW in 2012 (P-trend < 0.001) (Fig. 3). The estimated total national expenditure on sepsis was tripled (311.8%) during the same period with the estimated total amount of expenditure at 13,226.5 × 100,000,000 KRW in 2012 (P-trend < 0.001).

Fig. 4 shows the differential survival probabilities by age, comorbidity burden, organ dysfunction and site of infection. Older age, higher comorbidity burden, multiple organ dysfunction and primary respiratory infection were associated with higher mortality rates through the first 6 months (P < 0.001 for all). To identify independent risk factors for 6-month mortality, we performed multivariable logistic regression using two different model-building schemes. The first, using all predictors and cases, showed that older age, higher comorbidity burden, ER presentation, admission to the medical department, multiple organ dysfunction, central nervous system or unspecified site of infection (vs. respiratory system), and the development of septic shock were independently

associated with increased mortality (Table 2). In contrast, female sex; higher income level; larger hospital capacity; and gastrointestinal, genitourinary, musculoskeletal, skin and soft tissue and device-related infections were associated with lower mortality. The second model was developed using 80% of the data (training set) using Bayesian information criterion for variable selection showed similar results, with patient age, sex, comorbidity level, admitting department, hospital capacity, organ dysfunction, site of infection, and the development of septic shock identified as independent predictors (Table 3 and Fig. 5). Its performance in predicting the 6-month mortality was tested in the remaining 20% of data (test set) which yielded an area under the receiver operating characteristic curve of 0.840 (95% CI, 0.829 to 0.852) (Fig. 6).

DISCUSSION

This study is the first longitudinal, population-based study of sepsis in Korea. We found that sepsis is a relatively common condition with very high mortality in Korea as in other countries. Its

Table 2. Multivariable logistic regression model for 6-month mortality

Characteristics			OR	95% CI	P-value
Year	2006 (vs. 2005)		1.10	0.94–1.29	0.234
	2007		1.04	0.89–1.22	0.589
	2008		1.05	0.90–1.22	0.511
	2009		1.01	0.87–1.18	0.851
	2010		1.10	0.95–1.28	0.208
	2011		0.97	0.84–1.11	0.631
	2012		1.00	0.87–1.15	0.998
Age (yr)	65–74 (vs. <65)		1.95	1.77–2.15	<0.001
	75–84		3.68	3.34–4.05	<0.001
	≥85		9.25	8.18–10.45	<0.001
Sex, female			0.70	0.66–0.76	<0.001
Charlson comorbidity index	1 (vs. 0)		1.08	0.98–1.18	0.104
	2 (vs. 0)		2.39	2.16–2.65	<0.001
	>2 (vs. 0)		4.22	3.81–4.66	<0.001
ER visit (vs. all other presentation)			1.12	1.03–1.21	0.005
Medical departments (vs. all others)			2.09	1.89–2.31	<0.001
Income level	Lower-middle (vs. lower)		1.04	0.92–1.17	0.563
	Middle		1.01	0.90–1.13	0.904
	Upper-middle		0.92	0.82–1.02	0.115
	Upper		0.85	0.77–0.94	0.001
Hospital size (beds)	100–299 (vs. <100)		1.12	0.89–1.42	0.329
	300–599		0.75	0.59–0.96	0.019
	600–999		0.55	0.43–0.69	<0.001
	≥1,000		0.51	0.40–0.65	<0.001
No. of organ dysfunctions	2 (vs. 1)		2.90	2.65–3.17	<0.001
	3		6.30	5.45–7.28	<0.001
	≥4		10.28	8.18–12.91	<0.001
Site of infection	CNS (vs. respiratory)		1.69	1.12–2.55	0.012
	Gastrointestinal		0.69	0.62–0.77	<0.001
	Genitourinary		0.48	0.41–0.57	<0.001
	Musculoskeletal, skin & soft tissue		0.47	0.37–0.60	<0.001
	Endocarditis		0.93	0.48–1.79	0.829
	Device-related		0.19	0.07–0.47	<0.001
	Unspecified		1.30	1.17–1.46	<0.001
Septic shock (vs. no septic shock)			1.79	1.64–1.95	<0.001

OR, odds ratio; CI, confidence interval; ER, emergency room; CNS, central nervous system.

Table 3. Parsimonious multivariable logistic regression model derived from training set

Characteristics			OR	95% CI	P-value
Age (yr)	65–74 (vs. <65)		1.91	1.71–2.12	<0.001
	75–84		3.63	3.27–4.02	<0.001
	≥85		9.16	8.01–10.48	<0.001
Sex, female			0.70	0.64–0.76	<0.001
Charlson comorbidity index	1 (vs. 0)		1.10	1.00–1.21	0.058
	2 (vs. 0)		2.33	2.08–2.62	<0.001
	>2 (vs. 0)		3.98	3.56–4.45	<0.001
Medical departments (vs. all others)			2.12	1.90–2.37	<0.001
Hospital size (beds)	100–299 (vs. <100)		1.28	0.98–1.66	0.070
	300–599		0.88	0.68–1.15	0.346
	600–999		0.66	0.51–0.86	0.002
	≥1,000		0.60	0.46–0.79	<0.001
No. of organ dysfunctions	2 (vs. 1)		2.87	2.60–3.17	<0.001
	3		6.17	5.27–7.23	<0.001
	≥4		11.28	8.73–14.58	<0.001
Site of infection	CNS (vs. respiratory)		1.89	1.20–2.98	0.006
	Gastrointestinal		0.70	0.62–0.78	<0.001
	Genitourinary		0.50	0.41–0.60	<0.001
	Musculoskeletal, skin & soft tissue		0.44	0.34–0.58	<0.001
	Endocarditis		0.95	0.46–1.95	0.884
	Device-related		0.23	0.09–0.59	0.002
	Unspecified		1.30	1.15–1.47	<0.001
Septic shock (vs. no septic shock)			1.79	1.63–1.97	<0.001

OR, odds ratio; CI, confidence interval; CNS, central nervous system.

there was universal healthcare coverage by the National Health Insurance Service in Korea throughout the study period, there could be significant disparities in care as shown in previous studies of cardiovascular and cancer-related mortalities in the Korean population.[27-29]

Another risk factor was smaller hospital capacity. It is possible that smaller hospitals have narrower ranges of available diagnostic tests and limited capacity for prompt source control which requires duty surgeons or interventional radiologists. It is also possible that the availability of critical care specialists and devices for the treatment of severe organ dysfunction (i.e., continuous renal replacement therapy equipment for acute kidney injury) could also be different. However, there has been no surveillance or any official report on the level of sepsis care provided by hospitals in Korea.

In this study, the age-sex-adjusted mortality rate was about 30%. This is consistent with the findings of previous population-based studies in which the mortality rate of 'severe sepsis' ranged from 26% to 40%.[4,6,9,15,19,30-32] However, these are clearly higher than the 10% mortality rate used to define 'sepsis' in the Sepsis-3 definition paper.[1] This difference could be due to methodological differences in identifying organ dysfunctions. Organ dysfunctions

overall incidence was increasing and the increase was most prominent in the old age and high comorbidity populations. This rapid increase among old and debilitated sepsis patients was accompanied by the overall increase in mortality. The increase in incidence rate and the cost per case were accompanied by more than a triple increase in national expenditure on sepsis. Considering that population aging is still an ongoing process in Korea, we believe these trends will continue for a while.[26]

We found several interesting but worrisome risk factors for mortality from sepsis. The association between lower family income level and higher mortality can be the sign of disparities in the quality of critical care according to income levels. Although
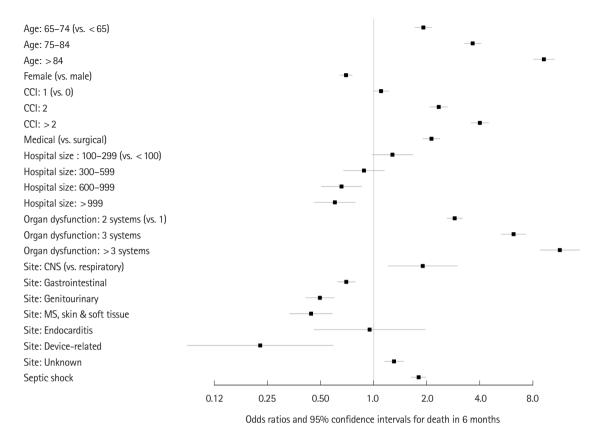
Fig. 5. Predictors of the 6-month mortality model of sepsis. CCI, Charlson comorbidity index; CNS, central nervous system; MS, musculoskeletal.
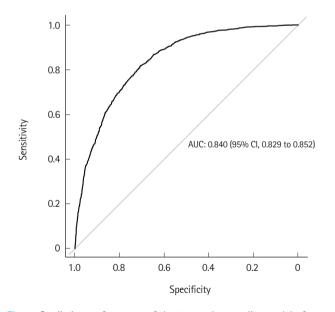

Fig. 6. Predictive performance of the 6-month mortality model of sepsis. AUC, area under the receiver operating characteristic curve; CI, confidence interval.

in population-based studies are identified based-on diagnostic and intervention codes. Because only significant clinical/laboratory derangements would lead to any entry of related diagnostic codes or application of interventions, organ dysfunctions identified in population-based studies must be more severe.

Lastly, the association between ER presentation and increased mortality could be an important finding. More than half of the patients received their initial care in the ER and their outcomes were worse than the other patients. Currently, we do not know whether this is due to the severity of diseases among ER patients or the quality of care provided in the ERs. However, we believe that the ER should be regarded as a critical intervention point for sepsis care as the ward and ICU have been, because the initial treatment of more than half of sepsis cases would be initiated in the ER and there might be a lot of room for improvement.

The coding scheme used in this study is unique in several aspects. First, the coding system was based on the ICD-10 in contrast to previous studies that were based on the ICD-9. Second, we used a more comprehensive set of diseases for case definition. Third, we limited the cases that were treated with intravenous antibiotics. Fourth, we applied several new operational definitions for organ dysfunction as described in the Appendix 1.

This study has several limitations. First, this study was based on claim data in which the accuracy of diagnostic codes was limited and significant over- or under-coding could be present. Sec-

ond, it was impossible to accurately know the timing of clinical events. Although the sequence of events based on the order of the fragmented claim records of each admission case was considered, the sequence of events within each claim record was not available. Third, the operational definition used to define sepsis cases was arbitrary and could lead to possible misclassifications. Lastly, the overall cost and mortality rate were all-cause estimates. Therefore, it should be considered that a significant proportion of them would be attributable to non-sepsis conditions.

Despite these limitations, this study, as other population-based studies using claim data, allowed for the examination of health care utilization and expenditure of sepsis in a real-world setting of Korea. For the first time, it estimated the overall burden of sepsis and the overall trend in the epidemiology of sepsis in Korea using nationally representative cohort data. It also identified risk factors for death in sepsis some of which may have implications for our health care delivery system.

In conclusion, sepsis is relatively common and is associated with a high mortality rate in Korea. Although the current national burden of sepsis is already high, it is expected to increase at a fast pace because of the ongoing population aging in Korea. Proactive measures to curtail this increase in societal burden should be sought and implemented.

CONFLICT OF INTEREST

Kyuseok Kim is an editorial board member of Clinical Experimental and Emergency Medicine; however, he did not involve in the paper reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1 is available from: https://doi.org/10.15441/ceem.18.007.

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Appendix 1. Definition of a sepsis case

Admission cases with 1) bacterial or fungal infection or the conditions that are often complicated by such infections (e.g. surgical abdomen) as indicated by the primary or the first secondary diagnostic codes, 2) prescription of intravenous antibiotics and 3) presence of organ dysfunction involving at least one system.

Coding conventions for both diagnostic and procedure codes:
    a) Dot (.) is omitted from diagnostic codes (i.e. J38.3 → J383)
    b) If there are more than a code in the same hierarchy (i.e. J38 and J383), the parent codes indicate only themselves specifically, but not its children (i.e. J38x).
    c) The code at the end of each of hierarchy, including those without any parent, indicate both themselves and their children (i.e. J37x for J37)

1) Korean Classification of Diseases sixth revision codes used for identification of infectious conditions

A00, Cholera; A01, Typhoid and paratyphoid fevers; A02, Other salmonella infections; A03, Shigellosis; A04, Other bacterial intestinal infections; A05, Other bacterial foodborne intoxications, NEC; A09, Other gastroenteritis and colitis of infectious and unspecified origin; A20, Plague; A21, Tularaemia; A23, Brucellosis; A24, Glanders and Melioidosis; A25, Rat-bite fevers; A26, Erysipeloid; A27, Leptospirosis; A28, Other zoonotic bacterial diseases, NEC; A31, Infection due to other mycobacteria; A32, Listeriosis; A35, Other tetanus; A36, Diphtheria; A37, Whooping cough; A38, Scarlet fever; A39, Meningococcal infection; A40, Streptococcal sepsis; A41, Other sepsis; A42, Actinomycosis; A43, Nocardiosis; A44, Bartonellosis; A46, Erysipelas; A48, Other bacterial diseases, NEC; A49, Bacterial infection of unspecified site; A54, Gonococcal infection; A55, Chlamydial lymphogranuloma (venereum); A56, Other sexually transmitted chlamydial diseases; A57, Chancroid; A58, Granuloma inguinale; A63, Other predominantly sexually transmitted diseases, NEC; A64, Unspecified sexually transmitted disease; A68, Relapsing fevers; A69, Other spirochaetal infections; A70, Chlamydia psittaci infection; A74, Other diseases caused by chlamydiae; A75, Typhus fever; A77, Spotted fever (tick-borne rickettsioses); A78, Q fever; A79, Other rickettsioses; B37, Candidiasis; B38, Coccidioidomycosis; B39, Histoplasmosis; B40, Blastomycosis; B41, Paracoccidioidomycosis; B42, Sporotrichosis; B43, Chromomycosis and pheomycotic abscess; B44, Aspergillosis; B45, Cryptococcosis; B46, Zygomycosis; B48, Other mycoses, NEC; B49, Unspecified mycosis; B99, Other and unspecified infectious diseases; D71, Progressive septic granulomatosis; D733, Abscess of spleen; D738, Perisplenitis; E060, Abscess of thyroid; E321, Abscess of thymus; G00, Bacterial meningitis, NEC; G01, Meningitis in bacterial diseases classified elsewhere; G02, Meningitis in other infectious and parasitic diseases classified elsewhere; G03, Meningitis due to other and unspecified causes; G04, Encephalitis, myelitis and encephalomyelitis; G05, Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere; G06, Intracranial and intraspinal abscess and granuloma; G07, Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere; G08, Intracranial and intraspinal phlebitis and thrombophlebitis; H050, Acute inflammation of orbit; H440, Purulent endophthalmitis; H441, Other endophthalmitis; H600, Abscess of external ear; H601, Cellulitis of external ear; H602, Malignant otitis externa; H603, Other infective otitis externa; H608, Other otitis externa; H609, Otitis externa, unspecified; H610, Perichondritis of external ear; H620, Otitis externa in bacterial diseases classified elsewhere; H622, Otitis externa in mycoses; H623, Otitis externa in other infectious and parasitic diseases classified elsewhere; H624, Otitis externa in other diseases classified elsewhere; H66, Suppurative and unspecified otitis media; H67, Otits media in diseases classified elsewhere; H70, Mastoiditis and related conditions; H750, Mastoiditis in infectious and parasitic diseases classified elsewhere; I30, Acute pericarditis; I32, Pericarditis in diseases classified elsewhere; I33, Acute and subacute endocarditis; I38, Endocarditis, valve unspecified; I39, Endocarditis and heart valve disorders in disease classified elsewhere; I518, Carditis (acute, chronic); I80, Phlebitis and thrombophlebitis; I831, Varicose veins of lower extremities with inflammation; I832, Varicose veins of lower extremities with both ulcer and inflammation; I88, Nonspecific lymphadenitis; I891, Lymphangitis; J01, Acute sinusitis; J02, Acute pharyngitis; J03, Acute tonsillitis; J04, Acute laryngitis and tracheitis; J05, Acute obstructive laryngitis (croup) and epiglottitis; J13, Pneumonia due to Streptococcus

pneumoniae; J14, Pneumonia due to Hemophilus in fluenzae; J15, Bacterial pneumonia, NEC; J16, Pneumonia due to other infectious organisms, NEC; J17, Pneumonia in diseases classified elsewhere; J18, Pneumonia, organism unspecified; J20, Acute bronchitis; J21, Acute bronchiolitis; J22, Unspecified acute lower respiratory infection; J340, Abscess, furuncle and carbuncle of nose; J36, Peritonsillar abscess; J383, Abscess of vocal cord(s); J387, Abscess of larynx; J390, Retropharyngeal and parapharyngeal abscess; J391, Other abscess of pharynx; J440, Chronic obstructive pulmonary disease with acute lower respiratory infection; J441, Chronic obstructive pulmonary disease with acute exacerbation, unspecified; J690, Pneumonitis due to food and vomit; J85, Abscess of lung and mediastinum; J86, Pyothorax; J90, Pleurisy with effusion; J91, Pleural effusion in conditions classified eleswhere; J950, Sepsis of tracheostomy stoma; J985, Mediastinitis; J986, Diaphragmatitis; K044, Acute apical periodontitis of pulpal origin; K046, Periapical abscess with sinus; K047, Periapical abscess without sinus; K050, Acute gingivitis; K052, Acute periodontitis; K102, Inflammatory conditions of jaws; K103, Alveolitis of jaws; K112, Sialoadenitis; K113, Abscess of salivary gland; K122, Cellulitis and abscess of mouth; K140, Abscess of tongue; K221, Fungal ulcer of oesophagus; K223, Perforation of oesophagus; K251, Acute gastric ulcer with perforation; K252, Acute gastric ulcer with both hemorrhage and perforation; K255, Chronic or unspecified gastric ulcer with perforation; K256, Chronic or unspecified gastric ulcer with both hemorrhage and perforation; K261, Acute duodenal ulcer with perforation; K262, Acute duodenal ulcer with both hemorrhage and perforation; K265, Chronic or unspecified duodenal ulcer with perforation; K266, Chronic or unspecified duodenal ulcer with both hemorrhage and perforation; K271, Acute peptic ulcer, site unspecified with perforation; K272, Acute peptic ulcer, site unspecified with both hemorrhage and perforation; K275, Chronic or unspecified peptic ulcer, site unspecified with perforation; K276, Chronic or unspecified peptic ulcer, site unspecified with both hemorrhage and perforation; K281, Acute gastrojejunal ulcer with perforation; K282, Acute gastrojejunal ulcer with both hemorrhage and perforation; K285, Chronic or unspecified gastrojejunal ulcer with perforation; K286, Chronic or unspecified gastrojejunal ulcer with both hemorrhage and perforation; K35, Acute appendicitis; K36, Other appendicitis; K37, Unspecified appendicitis; K383, Fistula of appendix; K388, Intussusception of appendix; K401, Bilateral inguinal hernia, with gangrene; K404, Unilateral or unspecified inguinal hernia, with gangrene; K411, Bilateral femoral hernia, with gangrene; K414, Unilateral or unspecified femoral hernia, with gangrene; K421, Umbilical hernia with gangrene; K431, Ventral hernia with gangrene; K441, Diaphragmatic hernia with gangrene; K451, Other specified abdominal hernia with gangrene; K461, Unspecified abdominal hernia with gangrene; K550, Acute vascular disorders of intestine; K551, Chronic vascular disorders of intestine; K559, Vascular disorders of intestine, unspecified; K561, Intussusception; K562, Volvulus; K563, Gallstone ileus; K564, Other impaction of intestine; K565, Intestine adhesions (bands) with obstruction; K566, Other and unspecified intestinal obstruction; K567, Ileus, unspecified; K57, Diverticulitis of intestine (small, large); K60, Fissure and fistula of anal and rectal regions; K61, Abscess of anal and rectal regions; K630, Abscess of intestine; K631, Perforation of intestine (nontraumatic); K632, Fistula of intestine; K65, Peritonitis; K67, Disorders of peritoneum in infectious diseases classified elsewhere; K75, Other inflammatory liver diseases; K770, Liver disorders in infectious and parasitic diseases classified elsewhere; K800, Calculus of gallbladder with acute cholecystitis; K801, Calculus of gallbladder with other cholecystitis; K803, Calculus of bile duct with cholangitis; K804, Calculus of bile duct with cholecystitis; K81, Cholecystitis; K820, Obstruction of gallbladder; K822, Perforation of gallbladder; K823, Fistula of gallbladder; K830, Cholangitis; K831, Obstruction of bile duct; K832, Perforation of bile duct; K833, Fistula of bile duct; K85, Acute pancreatitis; K868, Pancreatic necrosis NOS; K931, Megacolon in Chagas¡¯s disease (B57.3+); L00, Staphylococcal scalded skin syndrome; L01, Impetigo; L02, Cutaneous abscess, furuncle and carbuncle; L03, Cellulitis; L04, Acute lymphadenitis; L050, Pilonidal cyst with abscess; L08, Other local infections of skin and subcutaneous tissue; M00, Pyogenic arthritis; M01, Direct infections of joint in infectious and parasitic diseases classified elsewhere; M462, Osteomyelitis of vertebra; M463, Infection of intervertebral disc (pyogenic); M464, Discitis, unspecified; M465, Other infective spondylopathies; M491, Brucella spondylitis (A23.-+); M492, Enterobacterial spondylitis (A01-A04+); M493, Spondylopathy in other infectious and parasitic diseases classified elsewhere; M600, Infective myositis; M630, Myositis in bacterial diseases classified elsewhere; M632, Myositis in other infectious diseases classified elsewhere; M650, Abscess of tendon sheath; M651, Other infective (teno) synovitis; M680, Synovitis and tenosynovitis in bacterial diseases classified elsewhere; M710, Abscess of bursa; M711, Other infective bursitis; M715, Other bursitis NEC; M719, Bursitis NOS; M726, Necrotising fasciitis; M728, Abscess of fascia; M730, Gonococcal bursitis (A54.4+); M86, Osteomyelitis; M901, Periostitis in other infectious diseases classified elsewhere; M902, Osteopathy in other infectious diseases classified elsewhere; N10, Acute pyelonephritis; N12, Pyelonephritis NOS; N136, Pyonephrosis; N151, Renal and perinephric abscess; N159, Infection of kidney, NOS; N20, Calculous pyelonephritis; N390, Urinary tract infection, site not specified; N41, Inflammatory diseases of prostate; N431, Infected hydrocele; N45, Orchitis and epididymitis; N482, Other inflammatory disorders of penis; N49, Inflammatory disorders of male genital organs, NEC; N510, Gonococcal prostatitis (A54.2+); N511, Chlamydial epididymitis (A56.1+); N512, Balanitis in diseases classified elsewhere; N61, Inflammatory disorders of breast; N70, Salpingitis and oophoritis; N71, Inflammatory disease of uterus, except cervix; N72, Inflammatory

disease of cervix uteri; N73, Other female pelvic inflammatory diseases; N74, Female pelvic inflammatory disorders in diseases classified elsewhere; N751, Abscess of Bartholin¡¯s gland; N758, Bartholinitis; N76, Other inflammation of vagina and vulva; N77, Vulvovaginal ulceration and inflammation in diseases classified elsewhere; N82, Fistulae involving female genital tract; N980, Infection associated with artificial insemination; R02, Gangrene, NEC; R091, Pleurisy; R50, Fever of other and unknown origin; R572, Septic shock; R578, Endotoxic shock; R65, Systemic Inflammatory Response Syndrome; T793, Post-traumatic wound infection, NEC; T801, Phlebitis following infusion, transfusion and therapeutic injection; T802, Infections following infusion, transfusion and therapeutic injection; T814, Infection following a procedure, NEC; T826, Infection and inflammatory reaction due to cardiac valve prosthesis; T827, Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts; T835, Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary system; T836, Infection and inflammatory reaction due to prosthetic device, implant and graft in genital tract; T845, Infection and inflammatory reaction due to internal joint prosthesis; T846, Infection and inflammatory reaction due to internal fixation device (any site); T847, Infection and inflammatory reaction due to other internal orthopedic prosthetic devices, implants and grafts; T857, Infection and inflammatory reaction due to other internal prosthetic devices,implants and grafts; T874, Infection of amputation stump; T880, Infection following immunization; U80, Agent resistant to penicillin and related antibiotics; U81, Agent resistant to vancomycin and related antibiotics; U88, Agent resistant to multiple antibiotics; U89, Agent resistant to other and unspecified antibiotics

2) Intravenous antibiotics (generic/product codes for intravenous form was used for actual case definition, not included in the appendix)

amikacin, amoxicillin, amphotericin, ampicillin, anidulafungin, arbekacin, astromycin, azithromycin, aztreonam, caspofungin, cefamandole, cefazolin, cefbuperazone, cefepime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, cefotaxime, cefotetan, cefotiam, cefoxitin, cefpiramide, cefpirome, cefsulodin, ceftazidime, ceftezole, ceftizoxime, ceftriaxone, cefuroxime, cephalothin, cephazedone, cephradine, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, colistin, doripenem, ertapenem, flomoxef, fluconazole, fosfomycin, gemifloxacin, gentamicin, imipenem, isepamicin, itraconazole, kanamycin, levofloxacin, lincomycin, linezolid, meropenem, metronidazole, micafungin, moxifloxacin, nafcillin, netilmicin, ofloxacin, ornidazole, panipenem, penicillin, pentamidine, piperacillin, ribostamycin, sisomicin, spectinomycin, streptomycin, sulfamethoxazole, teicoplanin, ticarcillin, tigecycline, tobramycin, vancomycin, voriconazole

3) Types of organ dysfunction

Types of organ dysfunction	Codes	Conditions
Hemodynamic	R572	Septic shock
	I95	Hypotension
	I958	Other hypotension
	I959	Hypotension, unspecified
	R57	Shock, NEC
	R578	Other shock
	R579	Shock, unspecified
	T811	Shock (endotoxic, hypovolemic) during or following a procedure
	Extra #1	Use of vasopressor (norepinephrine, dopamine, dobutamine, vasopressin, epinephrine)
Respiratory	J80	Adult respiratory distress syndrome
	J81	Pulmonary edema
	J96	Respiratory failure, NEC
	J960	Acute respiratory failure
	J969	Respiratory failure, unspecified
	R0902	Hypoxemia
	R230	Cyanosis
	Z991	Dependence on respirator

(Continued to the next page)

Continued

Types of organ dysfunction	Codes	Conditions
	Extra #1	Combination of oxygen delivery, arterial blood gas analysis and lower respiratory infection (A15, A16, A202, A212, A221, A241, A310, A37, A420, A430, A481, A70, B371, B380, B381, B382, B390, B391, B392, B400, B401, B402, B410, B420, B440, B441, B450, B460, J13, J14, J15, J16, J17, J18, J20, J21, J22, J40, J440, J441, J690, J85, J86, J90, J91, R091)
	Extra #2	Mechanical ventilation (M5830, M585) without general anesthesia (L010, L050, L6, L7)
Neurologic	F05	Delirium, not induced by alcohol and other psyhoactive substances
	F06	Other mental disorders due to brain damage and dysfunction and to physical disease
	F09	Organic psychosis NOS
	G931	Anoxic brain damage, NEC
	G934	Encephalopathy, unspecified
	G9380	Metabolic encephalopathy
	R40	Somnolence, stupor and coma
	R400	Somnolence
	R401	Stupor
	R410	Disorientation, unspecified
Hematologic	D65	Disseminated intravascular coagulation (defibrination syndrome)
	D68	Other coagulation defects
	D688	Other specified coagulation defects
	D689	Coagulation defect, unspecified
	D69	Purpura and other hemorrhagic conditions
	D695	Secondary thrombocytopenia
	D696	Thrombocytopenia, unspecified
	R233	Spontaneous ecchymoses
	R791	abnormal coagulation lab
Hepatic	K72	Hepatic failure, NEC
	K762	Central hemorrhagic necrosis of liver
	K763	Infarction of liver
	R17	Unspecified jaundice
Renal	N17	Acute renal failure
	N19	Unspecified renal failure
	N990	Postprocedural renal failure
	R34	Anuria and oliguria
	R944	Abnormal results of kidney function studies
	Z992	Dependence on renal dialysis
	Extra #1	New initiation of hemodialysis / continuous renal replacement therapy (O701, O702, O703, O704, O705) without preexisting dependence on HD (registered kidney disability grade 1)
Sepsis-induced cardiomyopathy	I428	Other cardiomyopathies
	I429	Cardiomyopathy, unspecified
	I430	Cardiomyopathy in infectious and parasitic diseases classified elsewhere
	I5181	Takotsubo syndrome (Stress induced cardiomyopathy)
Metabolic	E872	Acidosis

Supplementary Fig. 1. Eight-year trend of sepsis mortality in patients with septic shock.