

Additional File 1

Association between the timing of ICU admission and mortality in patients with hospital-onset sepsis: a nationwide prospective cohort study

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Figure S1. Distribution of the Propensity Score Before (left) and After (right) Matching

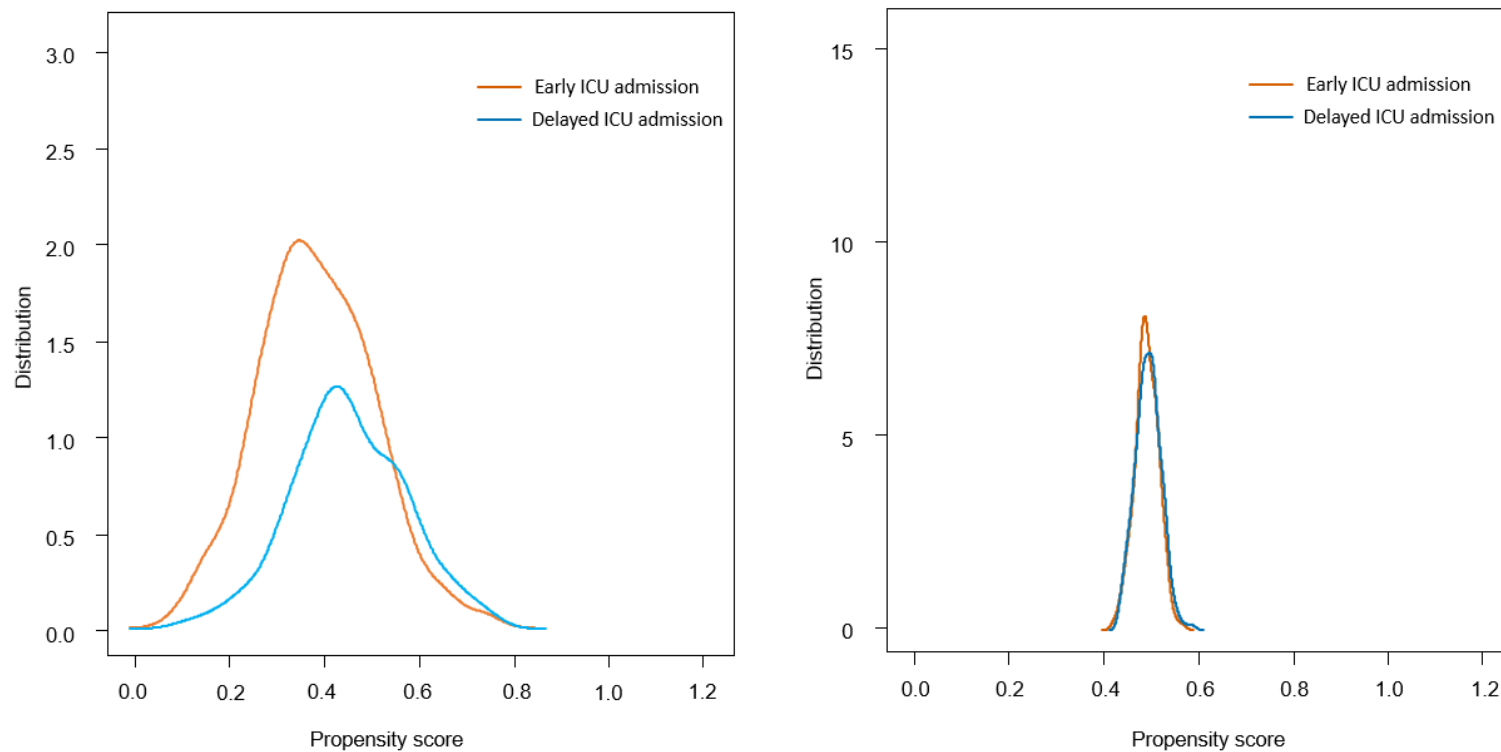


Figure S2. Time to ICU admission and In-hospital Mortality

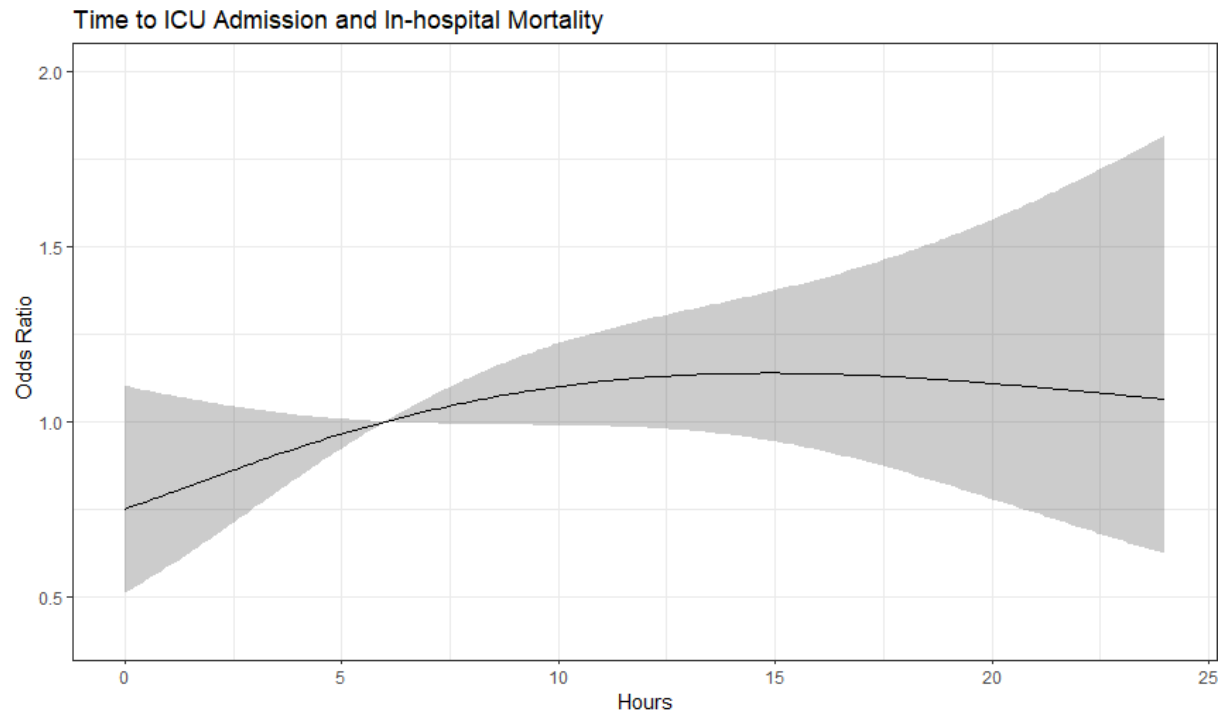


Figure S2. Restricted cubic spline plot of the association between the time to ICU admission and in-hospital mortality
The plot was adjusted for age and initial sequential organ failure assessment (SOFA) scores. The shaded areas represent the 95% confidence intervals (CI).

Figure S3. Rapid Response System by Operating Hours

Rapid Response System by Operating Hours

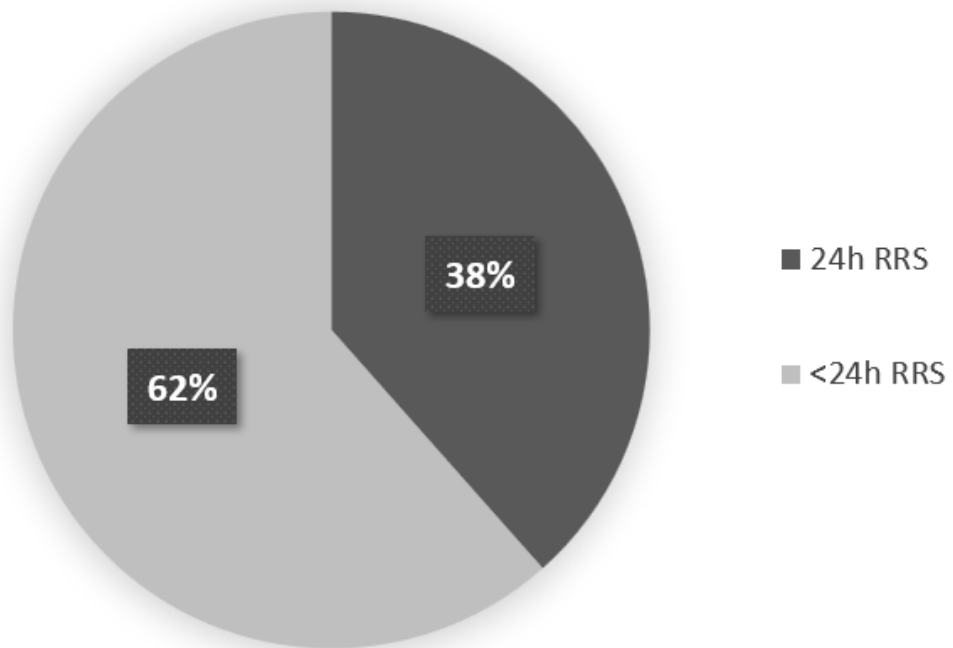


Figure S4. Initial Antibiotic Therapy at Each Hospital

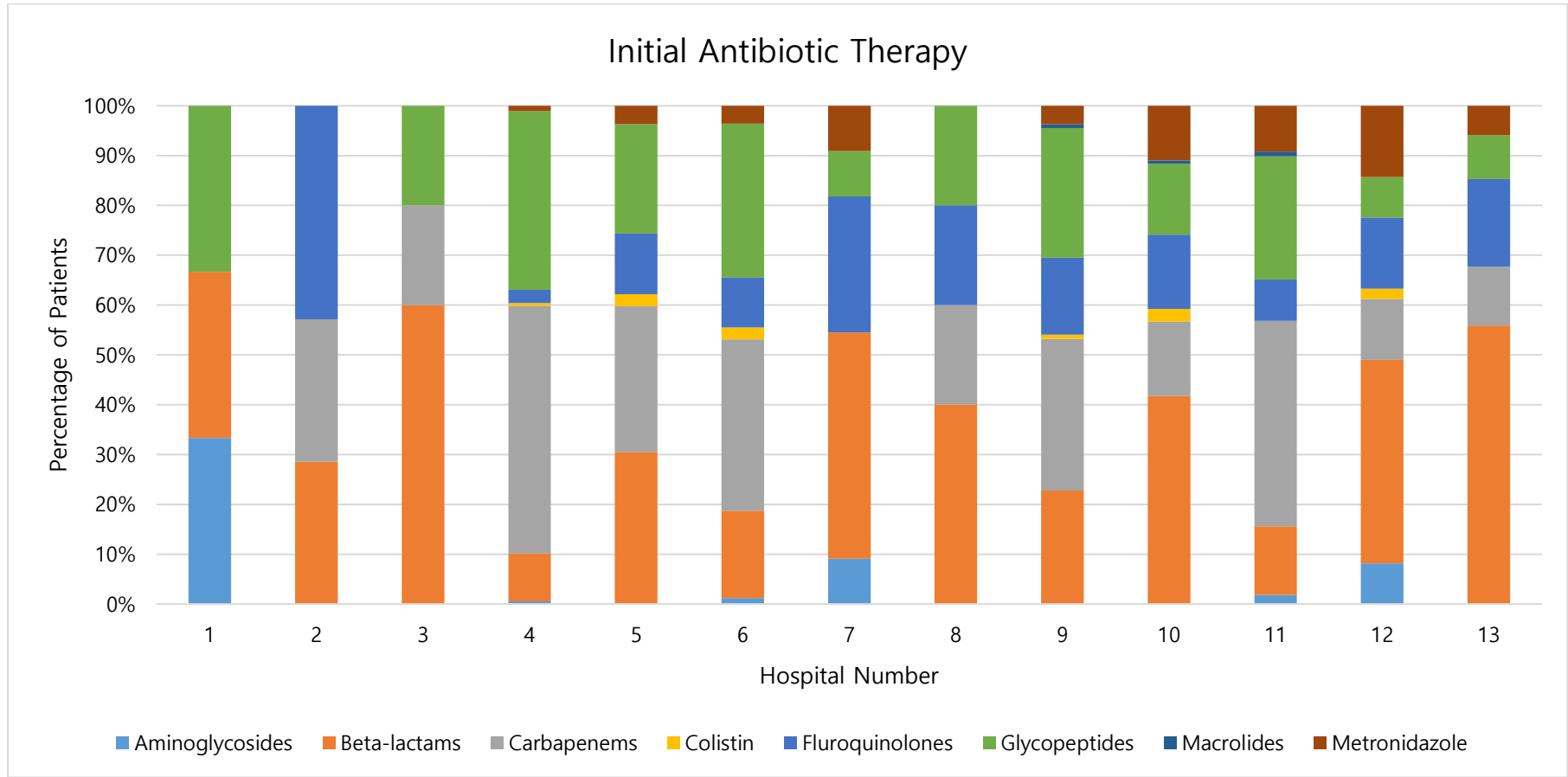


Figure S5. Source of Infection at Each Hospital

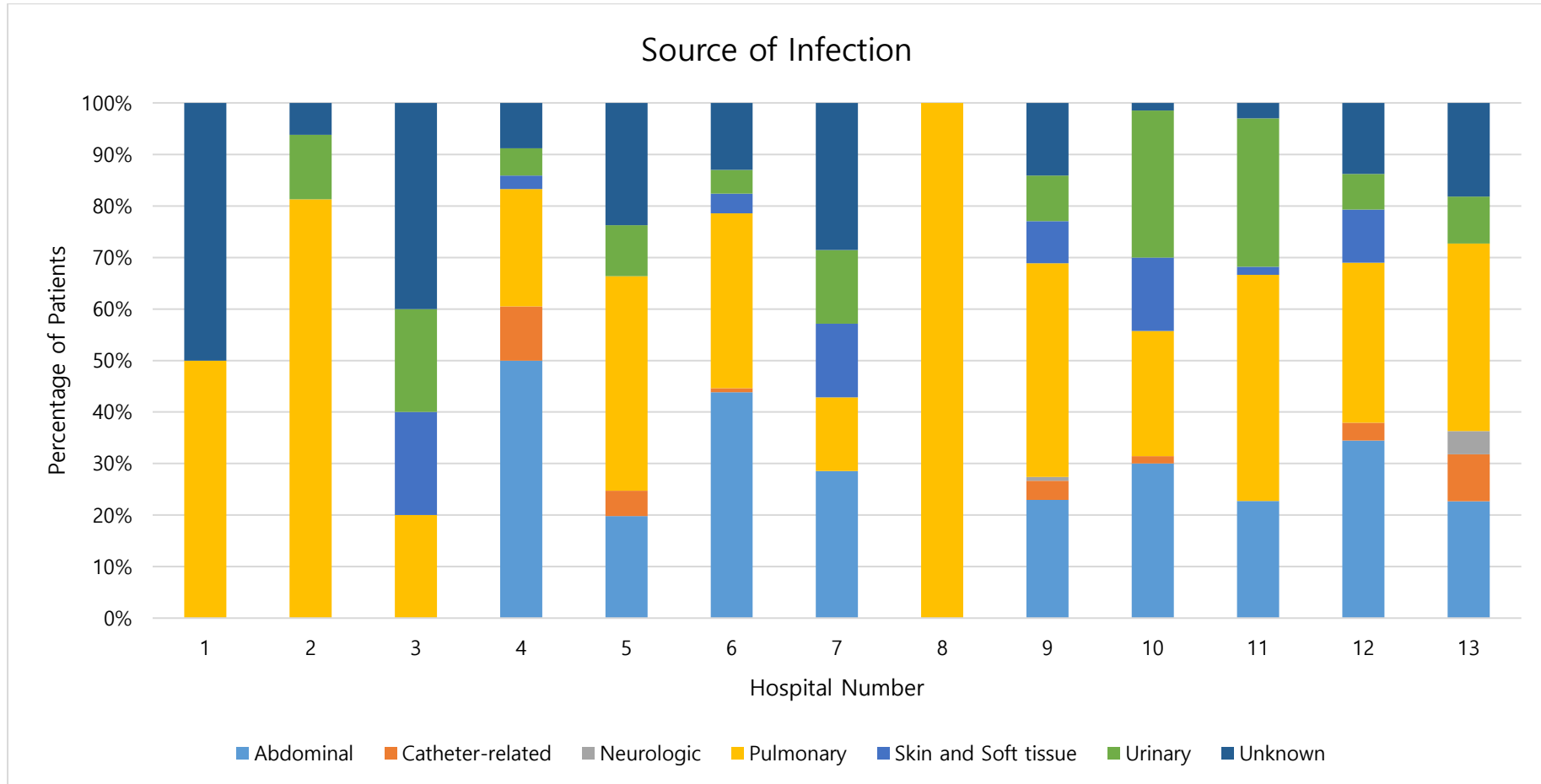


Table S1. Activation Criteria of Rapid Response System at Participating Hospitals

| Center | Activation criteria |
|--|--|
| Korea University Anam Hospital | A. Screening criteria - MEWS ≥ 2 |
| Seoul National University Bundang Hospital | - Systolic blood pressure: <90 mmHg - Heart rate: $<50, >140$ /min - Respiratory rate: $<10, >30$ /min - Body temperature: $<36^{\circ}\text{C}, >39^{\circ}\text{C}$ - SpO ₂ : $<90\%$ - ABG: pH <7.25 , PaCO ₂ >50 mmHg, PaO ₂ <55 mmHg - Lactate >4 mmol/L - Total CO ₂ <15 mmol/L |
| Samsung Medical Center | A. Calling criteria - Airway: compromised, stridor - Respiratory: respiratory rate ≥ 30 , SpO ₂ $<85\%$ for 5 min, pH <7.3 and PaCO ₂ >50 mmHg, use of accessory respiratory muscles - Cardiovascular: systolic blood pressure <85 mmHg, heart rate >130 , acute chest pain, symptomatic arrhythmia - Neurologic: altered mental status of sudden onset, unexplained agitation, seizure - Others: subjective assessment of physician or nurse B. Screening criteria - MEWS ≥ 7 |
| Seoul National University Hospital | A. Calling criteria - Respiratory: respiratory rate ≤ 8 or ≥ 28 , SpO ₂ $\leq 90\%$ for 5 minutes, sudden onset dyspnea - Cardiovascular: heart rate ≤ 40 or ≥ 130 , systolic blood pressure ≤ 80 or ≥ 200 , systolic blood pressure $80\text{--}90$ mmHg with symptoms, chest pain unresponsive to sublingual nitroglycerin - Neurologic: sudden onset of altered consciousness, sudden paralysis, new onset seizure, prolonged agitation (≥ 10 minutes) not fully explained by medical conditions - Others: color change of peripheral extremities, subjective assessment of physician or nurse B. Screening criteria - Heart rate: $<41, >129$ /min - Respiratory rate: $<9, >27$ /min - Systolic blood pressure: $<81, >199$ mmHg - SpO ₂ : $<90\%$ |
| Asan Medical Center | A. Calling criteria - Airway: compromised, stridor |

| | |
|--------------------------------------|--|
| | <ul style="list-style-type: none"> - Respiratory: respiratory rate <6 or >30/min, SpO₂ <90% on high flow FiO₂ ≥40% or O₂ ≥6 L/min - Cardiovascular: heart rate <40 or >140/min, systolic blood pressure <90 mmHg - Neurologic: sudden change in mental status, seizure - Others: subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - Systolic blood pressure <86 mmHg - Sudden change in mental status or unexplained agitation - Hypoxemia with oxygen requirement of >9 L/min or FiO₂ > 35% - Respiratory rate >27 or <8/min - Heart rate >140 or <40 - Unexplained severe metabolic acidosis: pH <7.3, lactate >2 mmol/L, total CO₂ <12 mmol/L - PaCO₂ > 50 mmHg or PaO₂ ≤ 55 mmHg - Subjective assessment of attending physician or nurse |
| Ulsan University Hospital | <p>A. Calling criteria</p> <ul style="list-style-type: none"> - Airway: compromised, stridor, wheezing - Respiratory: respiratory rate ≤6 or ≥30/min, SpO₂ <90% on O₂ ≥6 L/min or high flow FiO₂ ≥40% - Cardiovascular: heart rate < 40 or ≥140/min, systolic blood pressure < 90 mmHg - Neurologic: sudden change in mental status, seizure - Others: subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - Airway: compromised, stridor, wheezing - Breathing: respiratory rate ≤6 or ≥30/min, SpO₂ <90% on O₂ ≥6 L/min or high flow FiO₂ ≥40% - Cardiovascular: heart rate < 40 or ≥140/min, systolic blood pressure ≤ 85 mmHg - Neurologic: sudden change in mental status, seizure - Others: pH ≤7.33, HCO₃ ≤15 mmol/L, lactate ≥2 mmol/L, potassium ≥6 mmol/L, total CO₂ ≤15 mmol/L, glucose ≤50 mg/dL, patients recently discharged from the ICU |
| Chonnam National University Hospital | <ul style="list-style-type: none"> - Systolic blood pressure <80 mmHg, heart rate <40 or >140/min, respiratory rate ≤10 or ≥ 30/min, SpO₂ ≤85% - ABG: pH <7.3, pCO₂ >50 mmHg, pO₂ <60 mmHg - Sudden change in mental status - Symptomatic arrhythmia |
| Jeonbuk National University Hospital | <p>A. Screening criteria</p> <ul style="list-style-type: none"> - NEWS ≥ 5 |

| | |
|--|---|
| Chungnam National University Hospital | <p>A. Calling criteria</p> <ul style="list-style-type: none"> - Airway: obstruction, stridor - Respiratory: respiratory rate <8 or >30/min, pH <7.3 and PaCO₂ > 60 mmHg, SpO₂ <90% on facial mask or high flow nasal cannula - Cardiovascular: heart rate <40 or >140/min, systolic blood pressure <90 mmHg, lactate >2 mmol/L - Neurologic: sudden change in mental status, unexplained agitation, seizure - Subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - based on NEWS |
| Chungnam National University Sejong Hospital | <p>A. Calling criteria</p> <ul style="list-style-type: none"> - Airway: obstruction, stridor - Respiratory: respiratory rate <8 or >30/min, pH <7.3 and PaCO₂ > 60 mmHg, SpO₂ <90% on facial mask or high flow nasal cannula - Cardiovascular: heart rate <40 or >140/min, systolic blood pressure <90 mmHg, lactate >2 mmol/L - Neurologic: sudden change in mental status, unexplained agitation, seizure - Subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - based on NEWS |
| Hanyang University Guri Hospital | <p>A. Calling criteria</p> <ul style="list-style-type: none"> - Airway: airway obstruction sign, stridor - Respiratory: respiratory rate <8 or >30/min, pH <7.3 and PaCO₂ >60 mmHg, SpO₂ <90% on facial mask or high flow nasal cannula - Cardiovascular: heart rate <40 or >140/min, systolic blood pressure <90 mmHg, lactate >2 mmol/L - Neurologic: sudden change in mental status, unexplained agitation, seizure - Subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - MEWS ≥4 - Systolic blood pressure ≤80 or ≥200 mmHg, heart rate ≤40 or ≥130/min, respiratory rate <9 or ≥30/min, SpO₂ ≤90% - ABG: pH ≤7.3, pCO₂ ≥50 mmHg, pO₂ ≤60 mmHg, HCO₃ ≤14 mmEq/L, lactate ≥4.0 mmol/L - Chemistry: potassium ≥6.0 mmol/L, total CO₂ ≤14 mmol/L |
| Daegu Catholic University Hospital | <p>A. Calling criteria</p> <ul style="list-style-type: none"> - Respiratory: respiratory rate <8 or ≥30/min, pH <7.3 and PaCO₂ >60 mmHg, SpO₂ <90% on facial mask - Cardiovascular: heart rate <40 or ≥140/min, systolic blood pressure <80 mmHg - Neurologic: sudden mental change, unexplained agitation for ≥10 minutes - Subjective assessment of attending physician or nurse <p>B. Screening criteria</p> <ul style="list-style-type: none"> - NEWS ≥ 5 |

Yeungnam University Medical Center

A. Screening criteria

- NEWS ≥ 5
- Respiratory rate <10 or ≥ 30 /min
- Heart rate <40 or ≥ 140 /min
- Systolic blood pressure ≤ 80 mmHg
- SpO₂ $\leq 90\%$

ABG, Arterial blood gas analysis; FiO₂, fraction of inspired oxygen; MEWS, modified early warning score; NEWS, national early warning score; PaCO₂, partial pressure of carbon dioxide in arterial blood; PaO₂, partial pressure of oxygen in arterial blood; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; SpO₂, oxygen saturation

Table S2. In-hospital Mortality According to the Timing of ICU admission

| Group | No. of deaths / Total no. of patients (%) | <i>P</i> -value | Unadjusted OR (95% CI) | Adjusted OR (95% CI) ^a |
|--|---|-----------------|------------------------|-----------------------------------|
| Unmatched cohort | | | | |
| Early admission | 181/470 (38.5) | 0.44 | 1.14 (0.84–1.54) | 1.36 (0.99–1.87) |
| Delayed admission | 119/286 (41.6) | | | |
| Propensity-score-matched cohort | | | | |
| Early admission | 83/239 (34.7) | 0.13 | 1.35 (0.93–1.96) | 1.38 (0.94–2.03) |
| Delayed admission | 100/239 (41.8) | | | |

OR, odds ratio; CI, confidence interval

^a In the unmatched cohort, odds ratios were adjusted for age and initial sequential organ failure assessment (SOFA) scores and center variables. In the propensity score-matched cohort, the odds ratios were adjusted for age, SOFA scores, center variables and propensity scores.

Table S3. Secondary Outcomes According to the Timing of ICU Admission

| Outcome | Early admission (N = 470) | Delayed admission (N = 286) | P-value |
|---|--------------------------------------|--|----------------|
| Median hospital length of stay (IQR), days | | | |
| In-hospital survivors | 27 (16–46) | 26 (15–48) | 0.93 |
| In-hospital non-survivors | 10 (2–29) | 12 (4–24) | 0.21 |
| Median ICU length of stay (IQR), days | | | |
| ICU survivors | 5 (3–11) | 4 (2–9) | 0.35 |
| ICU non-survivors | 4 (2–14) | 5 (2–12) | 0.30 |
| Discharge, n/total (%)^a | | | 0.23 |
| At home | 211/289 (73.0) | 113/167 (67.7) | |
| Transfer at another hospital | 78/289 (27.0) | 54/167 (32.3) | |

ICU, intensive care unit; IQR, interquartile range

^a Analysis was performed only in patients who survived until discharge

Table S4. Sepsis Bundle Compliance According to the Timing of ICU Admission

| Variable | Unmatched cohort | | | Propensity Score-Matched Cohort | | |
|--|------------------|-------------------|---------|---------------------------------|-------------------|---------|
| | Early admission | Delayed admission | P-value | Early admission | Delayed admission | P-value |
| | (N = 470) | (N = 286) | | (N = 239) | (N = 239) | |
| 1-Hour Bundle Compliance | | | | | | |
| Lactate measurement | 273 (58.1) | 134 (46.9) | 0.003 | 142 (59.4) | 121 (50.6) | 0.066 |
| Blood cultures | 285 (60.6) | 170 (59.4) | 0.760 | 137 (57.3) | 147 (61.5) | 0.402 |
| Administration of antibiotics ^a | 172/368 (46.7) | 104/248 (41.9) | 0.248 | 85/185 (45.9) | 85/208 (40.9) | 0.359 |
| Crystalloid infusion ^b | 205/283 (72.4) | 111/138 (80.4) | 0.093 | 99/135 (73.3) | 99/126 (78.6) | 0.385 |
| Vasopressor use ^c | 167/279 (59.9) | 64/134 (47.8) | 0.026 | 78/135 (57.8) | 62/122 (50.8) | 0.316 |
| 3-Hour Bundle Compliance | | | | | | |
| Lactate measurement | 344 (73.2) | 169 (59.1) | <0.001 | 179 (74.9) | 153 (64.0) | 0.013 |
| Blood cultures | 359 (76.4) | 202 (70.6) | 0.087 | 176 (73.6) | 175 (73.2) | 1.000 |
| Administration of antibiotics ^a | 260/368 (70.7) | 160/248 (64.5) | 0.113 | 130/185 (70.3) | 135/208 (64.9) | 0.282 |
| Crystalloid infusion ^b | 208/283 (73.5) | 112/138 (81.2) | 0.090 | 101/135 (74.8) | 100/126 (79.4) | 0.462 |
| Vasopressor use ^c | 219/279 (78.5) | 85/134 (63.4) | 0.002 | 102/135 (75.6) | 78/122 (63.9) | 0.056 |

^a Initiation of antibiotic therapy on patients who were not previously on antibiotics

^b Patients with either hypotension (mean blood pressure < 65 mmHg) or lactate ≥ 4 mmol/L

^c Patients with hypotension despite fluid resuscitation

Table S5. Time to ICU Admission by Rapid Response System Operating Hours

| Outcome | 24-Hour RRS (N = 446) | Part-time RRS^a (N = 310) | P-value |
|---|----------------------------------|--|----------------|
| Time to ICU Admission (IQR), hours | 3.8 (1.6–9.5) | 3.4 (1.1–10.4) | 0.22 |
| Timing of ICU Admission, n (%) | | | |
| Early Admission | 274 (61.4%) | 196 (63.2%) | 0.67 |
| Delayed Admission | 172 (38.6%) | 114 (36.8%) | |

RRS, rapid response system; ICU, intensive care unit; IQR, interquartile range

^a RRS that operated <24 hours

Table S6. Initial Antibiotic Therapy and Source of Infection According to the Timing of ICU Admission

| Variable | Early admission (N = 470) | Delayed admission (N = 286) | P-value |
|--|--------------------------------------|--|----------------|
| Initial Antibiotic Therapy | | | |
| Aminoglycoside | 12 (2.6) | 3 (1) | 0.19 |
| Beta-lactam | 201 (42.8) | 124 (43.4) | 0.88 |
| Carbapenem | 280 (59.6) | 175 (61.2) | 0.70 |
| Colistin | 12 (2.6) | 10 (3.5) | 0.51 |
| Fluroquinolone | 106 (22.6) | 59 (20.6) | 0.59 |
| Glycopeptide | 240 (51.1) | 126 (44.1) | 0.07 |
| Macrolide | 1 (0.2) | 3 (1) | 0.16 |
| Metronidazole | 44 (9.4) | 25 (8.7) | 0.80 |
| Source of Infection | | | |
| Abdominal | 174 (37) | 92 (32.2) | 0.18 |
| Catheter-related | 14 (3) | 12 (4.2) | 0.41 |
| Neurologic | 0 (0) | 2 (0.7) | 0.14 |
| Pulmonary | 169 (36) | 104 (36.4) | 0.94 |
| Skin and soft tissue | 27 (5.7) | 13 (4.5) | 0.51 |
| Urinary | 50 (10.6) | 32 (11.2) | 0.81 |
| Systemic infections with unknown focus | 48 (10.2) | 44 (15.4) | 0.04 |

ICU, intensive care unit