**ONLINE SUPPLEMENT:**

**Epidemiology of Hospital-Onset versus Community-Onset Sepsis in U.S. Hospitals and Association with Mortality: A Retrospective Analysis Using Electronic Clinical Data**

**Supplemental Methods: Multiple Imputation Methods for Missing Data in Severity-of-Illness Covariates**

For missing covariates included in the logistic regression model comparing hospital-onset vs community-onset sepsis, the predicted mean matching method was used. This method imputes an observed value which is closest to the predicted value from the simulated regression model for each missing value. For the covariates included in the Cox regression model evaluating the effect of developing sepsis on mortality risk, a Markov Chain Monte Carlo method (Schafer, J.L. 1997, Analysis of Incomplete Multivariate Data, New York: Chapman and Hall.) that assumes multivariate normality was used for imputation; predicted values that were out of boundary were assigned the boundary values. The predicted mean matching method was not employed due to its associated computational burden in this setting with a very large sample size.

**Supplemental Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM)Codes Used to Identify Presumptive Infectious Source of Sepsis Cases**

|  |  |
| --- | --- |
| Infectious Source | ICD-9-CM Codes |
| Pneumonia | 480.0-480.9, 481, 482.0-482.9, 483.0-483.8, 484.1-484.8, 485, 486 |
| Urinary | 590.00, 590.01, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 590.9, 595.0, 595.2, 595.3, 595.4, 595.89, 595.9, 597.0, 597.80, 597.89, 598.00, 598.01, 599.0 |
| Intra-abdominal | 008.45, 009.0–009.3, 540.0–540.9, 541, 542, 543.9, 562.01, 562.03, 562.11, 562.13, 567.0–567.9, 569.5, 569.61, 569.71, 569.83, 572.0–572.8, 574.00–574.91,575.0–575.9, 576.0–576.9, 614.0–614.9 |
| Skin/Soft Tissue | 680-686, 035, 376.01, 728.86 |
| Septicemia/Bacteremia | 038.0-038.9, 790.7 |
| Central Nervous System | 027.0, 036, 320.0-321.1, 321.8, , 324.0 |
| Obstetric/Gynecologic | 614.0-614.5, 616.0-616.1, 616.3-616.4, 634.0, 635.0, 636.0, 637.0, 638.0, 639.0, 646.5, 646.6, 647.9, , 658.4, 659.3, 670, 675 |

**Supplemental Table 2. Cerner HealthFacts Study Hospital Characteristics**

|  |  |
| --- | --- |
| Hospital Characteristic | Hospitals (Total N=136) |
| Region |  |
|  Northeast | 30 (22.1%) |
|  Midwest | 26 (19.1%) |
|  West | 32 (23.5%) |
|  South  | 48 (35.3%) |
| Bed Size |  |
|  <200 | 88 (64.7%) |
|  200-499 | 39 (28.7%) |
|  >500 | 9 (6.6%) |
| Teaching Status |  |
|  Teaching | 49 (36.0%) |
|  Nonteaching | 81 (59.6%) |
|  Unknown | 6 (4.4%) |

**Supplemental Table 3. Logistic and Cox Regression Models to Estimate Risk of Death from Hospital-Onset Sepsis versus Community-Onset Sepsis and No Sepsis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Odds Ratio for Mortality (HO vs CO-Sepsis)(95% CI) | p-value | Hazard Ratio for Mortality (HO-Sepsis vs No Sepsis)(95% CI) | p-value |
| Age (years) | 1.02 (1.02-1.02) | <0.001 | 1.04 (1.04-1.04) | <0.001 |
| Male Sex | 0.97 (0.93-1.01) | 0.106 | 1.08 (1.06-1.10) | <0.001 |
| Race |  |  |  |  |
|  White  | Referent | N/A | Referent | N/A |
|  Black | 1.13 (1.07-1.19) | <0.001 | 0.92 (0.89-0.94) | <0.001 |
|  Other | 1.07 (1.00-1.15) | 0.060 | 0.97 (0.93-1.01) | 0.153 |
| Comorbidities |  |  |  |  |
|  Acquired Immunodeficiency Syndrome | 1.43 (1.12-1.82) | 0.004 | 1.37 (1.15-1.62) | <0.001 |
|  Alcohol Abuse | 0.82 (0.75-0.90) | <0.001 | 0.82 (0.78-0.87) | <0.001 |
|  Anemia | 0.74 (0.71-0.78) | <0.001 | 0.80 (0.78-0.82) | <0.001 |
|  Arthritis | 1.01 (0.90-1.13) | 0.864 | 0.96 (0.90-1.03) | 0.280 |
|  Blood Loss | 0.68 (0.57-0.80) | <0.001 | 0.66 (0.60-0.73) | <0.001 |
|  Cardiac Arrhythmia | 1.18 (1.13-1.23) | <0.001 | 1.07 (1.05-1.10) | <0.001 |
|  Congestive Heart Failure | 1.05 (1.00-1.101 | 0.031 | 1.19 (1.16-1.23) | <0.001 |
|  Chronic Lung Disease | 0.97 (0.92-1.01) | 0.230 | 1.01 (0.98-1.04) | 0.574 |
|  Coagulopathy | 1.04 (0.98-1.11) | 0.177 | 0.88 (0.85-0.91) | <0.001 |
|  Depression | 0.84 (0.78-0.90) | <0.001 | 0.78 (0.75-0.81) | <0.001 |
|  Diabetes without Complications | 0.85 (0.81-0.89) | <0.001 | 0.93 (0.90-0.95) | <0.001 |
|  Diabetes with Complications | 0.91 (0.84-0.99) | 0.032 | 0.74 (0.71-0.78) | <0.001 |
|  Drug Use | 0.72 (0.64-0.82) | <0.001 | 0.86 (0.79-0.93) | <0.001 |
|  Hypertension with Complications | 0.79 (0.76-0.83) | <0.001 | 0.70 (0.68-0.72) | <0.001 |
|  Hypothyroidism | 0.90 (0.85-0.96) | 0.002 | 0.88 (0.85-0.91) | <0.001 |
|  Liver Disease | 1.45 (1.34-1.58) | <0.001 | 1.48 (1.40-1.55) | <0.001 |
|  Lymphoma | 1.46 (1.29-1.65) | <0.001 | 1.24 (1.15-1.34) | <0.001 |
|  Fluid and Electrolyte Disorders | 0.95 (0.92-0.99) | 0.024 | 1.08 (1.05-1.11) | <0.001 |
|  Metastatic Disease | 2.30 (2.13-2.48) | <0.001 | 2.59 (2.50-2.68) | <0.001 |
|  Neurologic Disease | 1.04 (0.98-1.09) | 0.183 | 1.14 (1.10-1.17) | <0.001 |
|  Obesity | 0.78 (0.73-0.84) | <0.001 | 0.78 (0.75-0.82) | <0.001 |
|  Paralysis | 0.85 (0.78-0.92) | <0.001 | 0.90 (0.86-0.94) | <0.001 |
|  Peripheral Vascular Disease | 1.20 (1.12-1.28) | <0.001 | 0.98 (0.94-1.01) | 0.221 |
|  Psychiatric Disease | 0.76 (0.69-0.84) | <0.001 | 0.65 (0.61-0.69) | <0.001 |
|  Pulmonary Circulatory Disease | 1.31 (1.22-1.41) | <0.001 | 1.17 (1.13-1.22) | <0.001 |
|  Renal Failure | 1.20 (1.14-1.27) | <0.001 | 1.14 (1.11-1.18) | <0.001 |
|  Solid Tumor | 1.33 (1.21-1.47) | <0.001 | 1.41 (1.34-1.48) | <0.001 |
|  Peptic Ulcer Disease | 0.68 (0.26-1.75) | 0.419 | 0.55 (0.32-0.94) | 0.029 |
|  Valvular Disease | 1.01 (0.94-1.08) | 0.857 | 0.81 (0.76-0.81) | <0.001 |
|  Weight Loss | 1.02 (0.96-1.08) | 0.561 | 0.79 (0.76-0.81) | <0.001 |
| Parameter | **Odds Ratio for HO vs CO-Sepsis****(95% CI)** | **p-value** | **Hazard Ratio for HO-Sepsis vs No Sepsis****(95% CI)** | **p-value** |
|  Leukemia | 1.76 (1.52-2.02) | <0.001 | 1.86 (1.71-2.02) | <0.001 |
|  Solid Organ Transplant | 0.90 (0.76-1.06) | 0.207 | 0.86 (0.78-0.96) | 0.005 |
|  Stem Cell Transplant | 1.40 (0.99-1.99) | 0.057 | 0.83 (0.66-1.05) | 0.114 |
| Admission from Healthcare Facility | 1.17 (1.10-1.23) | <0.001 | 1.16 (1.13-1.20) | <0.001 |
| Infectious Diagnosisa |  |  |  |  |
|  Central Nervous System | 1.28 (0.92-1.76) | 0.132 | N/A | - |
|  Intra-abdominal | 1.00 (0.90-1.12) | 0.955 | N/A | - |
|  Obstetric-Gynecologic | 0.76 (0.51-1.14) | 0.189 | N/A | - |
|  Pneumonia | 1.44 (1.29-1.60) | <0.001 | N/A | - |
|  Septicemia/Bacteremia | 1.96 (1.77-2.22) | <0.001 | N/A | - |
|  Skin/Soft Tissue | 0.85 (0.76-0.96) | 0.010 | N/A | - |
|  None of the above / Unknown | 1.45 (1.30-1.63) | <0.001 | N/A | - |
|  2 or more infections | 0.91 (0.80-1.03) | 0.165 | N/A | - |
| Positive Blood Cultures | 1.03 (0.98-1.09) | 0.184 |  |  |
| Suspected Infection on Admissiona | N/A | N/A | 0.99 (0.97-1.02) | 0.664 |
| Severity of Illnessb |  |  |  |  |
|  Temperature (Maximum) | 0.93 (0.92-0.95) | <0.001 | 0.89 (0.89-0.90) | <0.001 |
|  Systolic Blood Pressure (Minimum) | 1.00 (1.00-1.00) | <0.001 | 0.99 (0.99-1.00) | <0.001 |
|  Respiratory Rate (Maximum) | 1.01 (1.00-1.01) | <0.001 | 1.01 (1.01-1.01) | <0.001 |
|  Glasgow Coma Scale (Minimum) | 0.95 (0.94-0.96) | <0.001 | 0.89 (0.89-0.89) | <0.001 |
|  Mechanical Ventilation (yes/no) | 2.32 (2.21-2.44) | <0.001 | 1.84 (1.77-1.91) | <0.001 |
|  ICU Admission (yes/no) | 1.09 (1.05-1.14) | <0.001 | 1.13 (1.10-1.17) | <0.001 |
|  Number of Vasopressors | 1.49 (1.45-1.53) | <0.001 | 1.13 (1.12-1.15) | <0.001 |
|  Albumin (Minimum)  | 0.68 (0.65-0.70) | <0.001 | 0.66 (0.64-0.67) | <0.001 |
|  Hematocrit (Minimum) | 1.00 (1.00-1.00) | 0.684 | 1.02 (1.02-1.02) | <0.001 |
|  Platelets (Minimum) | 1.00 (1.00-1.00) | <0.001 | 1.00 (1.00-1.00) | 0.416 |
|  Sodium (Minimum) | 1.01 (1.00-1.01) | <0.001 | 1.01 (1.01-1.01) | <0.001 |
|  Anion Gap (Maximum) | 1.04 (1.03-1.04) | <0.001 | 1.06 (1.06-1.06) | <0.001 |
|  Aspartate Aminotransferase (Maximum) | 1.00 (1.00-1.00) | 0.025 | 1.00 (1.00-1.00) | <0.001 |
|  Total Bilirubin (Maximum) | 1.06 (1.05-1.06) | <0.001 | 1.05 (1.04-1.05) | <0.001 |
|  Creatinine (Maximum) | 1.01 (1.00-1.02) | 0.172 | 1.04 (1.03-1.04) | <0.001 |
|  International Normalized Ratio (Maximum) | 1.03 (1.01-1.04) | 0.002 | 1.05 (1.04-1.05) | <0.001 |
|  Lactate (Maximum) | 1.10 (1.09-1.11) | <0.001 | 1.05 (1.04-1.04) | <0.001 |
|  White Blood Cell Count (Maximum) | 1.00 (1.00-1.01) | <0.001 | 1.00 (1.00-1.01) | <0.001 |
| Hospital-Onset Sepsis | **2.09 (1.98-2.21)** | **<0.001** | **3.04 (2.92-3.17)** | **<0.001** |

Notes:

1. The two sets of columns show the results of the two different models: 1) logistic regression model estimating the adjusted odds of mortality in hospital-onset vs community-onset sepsis, and 2) Cox regression model estimating the adjusted hazard of mortality for patients initially admitted without sepsis who subsequently develop hospital-onset sepsis. For each covariate, the adjusted odds ratio or hazard ratio for mortality (specific to each model) is presented.
2. Admission year and hospital characteristics (region, bed size, and teaching status) were included in the model but are not shown above.

a Infectious diagnoses were only included in the logistic regression model comparing hospital-onset vs community-onset sepsis. Suspected infection on admission (clinical cultures + antibiotics) was only included in the Cox regression model examining the risk of death associated with developing hospital-onset sepsis in patients admitted without sepsis.

b Severity of illness parameters were taken as the worst values within +/-1 day of sepsis onset for the comparison of hospital-onset vs community-onset sepsis, and within +/- 1 day of admission for the comparison of hospital-onset sepsis vs no sepsis.

**Supplemental Table 4. Quantity of Missing Data for Physiologic Parameters for Logistic Regression and Cox Regression Models**

|  |  |  |
| --- | --- | --- |
| Parametera | Admitted without Sepsis (Cox Regression Model)  | Community or Hospital-Onset Sepsis (Logistic Regression Model) |
|  | **2009-2015****(n=2,132,412)** | **2013-2015 (n=892,449)** | **2009-2015****(n=95,154)** | **2013-2015 (n=35,568)** |
| Laboratory Data |  |  |  |  |
|  Creatinine | 371565(17.4%) | 154,616 (17.3%) | 1,180 (1.2%) | 388(1.1%) |
|  Platelets | 209,244(9.8%) | 80,942 (9.1%) | 2,263(2.4%) | 376(1.1%) |
|  Total Bilirubin | 943,918 (44.3%) | 398,355 (44.6%) | 14,470(15.2%) | 4,777 (14.0%) |
|  White Blood Cell  Count | 206,224 (9.7%) | 90,943(10.9%) | 7,582(8.0%) | 2,397 (6.7%) |
|  Lactate | 1,945,895 (91.3%) | 785,641 (88.0%) | 44,027 (46.3%) | 12,849 (36.1%) |
|  Aspartate  Aminotransferase | 954,282 (44.8%) | 383,024(42.9%) | 31,195(32.8%) | 9,636 (27.1%) |
|  Hematocrit | 172,540(8.1%) | 80,942 (9.1%) | 7,114(7.5%) | 2,257 (6.3%) |
|  Sodium | 388,932(18.2%) | 167,576 (18.8%) | 6,422(6.7%) | 2,232 (6.3%) |
|  Anion Gap | 390,474 (18.3%) | 166,644 (18.7%) | 6,777(7.1%) | 2,360 (6.6%) |
|  Albumin | 933,395(43.8%) | 397,820 (44.6%) | 28,772 (30.2%) | 9,765(27.5%) |
|  International  Normalized Ratio | 1,163,756 (54.6%) | 494,159 (55.4%) | 44,784 (45.0%) | 14,772 (41.5%) |
| Vital Signs / Mental Statusb |  |  |  |  |
|  Systolic Blood  Pressure | 779,128 (36.5%) | 79,600 (8.9%) | 40,362 (42.4%) | 2,156 (6.1%) |
|  Respiratory Rate | 805,131(37.8%) | 100,110 (11.2%) | 40,663 (42.7%) | 2,379 (6.7%) |
|  Temperature | 870,991(40.8%) | 138,766 (15.5%) | 44,473(46.7%) | 4,748 (13.3%) |
|  Glasgow Coma  Scale | 1,208,820 (56.7%) | 348,313 (39.0%) | 52,440(55.1%) | 9,421 (26.5%) |

a Parameters were measured within +/-1 day of admission for the Cox regression model (which included all patients admitted without community-onset sepsis, and evaluated the hazard ratio associated with developing hospital-onset sepsis) and within +/-1 day of sepsis onset for the logistic regression model (which compared the odds of death associated with hospital-onset versus community-onset sepsis).

b There were substantially fewer missing data for vital signs and Glasgow Coma Scale measurements in the cohort in years 2013-2015; thus, a sensitivity analysis was done for the Cox and logistic regression models limiting to patients in those years.

**Supplemental Table 5. Risk of Death with Hospital-Onset Sepsis in Primary Models and Sensitivity Analyses**

|  |  |  |
| --- | --- | --- |
|  | Odds Ratio for Mortality (HO vs CO-Onset Sepsis)(95% CI) | Hazard Ratio for HO-sepsis vs No Sepsis(95% CI) |
| Full 2009-2015 Cohort with Multiple Imputation (Primary Analysis)a | 2.09 (1.98-2.20) | 3.04 (2.92-3.17) |
| 2013-2015 Cohort with Multiple Imputationb | 2.09 (1.92-2.29) | 3.27 (3.07-3.48) |
| 2013-2015 Cohort with SOFA Scorec | 2.11 (2.01-2.21) | 3.16 (2.97-3.37) |
| 2009-2015 Cohort with Non-Missing Covariatesd | 2.63 (2.22-3.13) | 2.55 (2.28-2.84) |

The two sets of columns show the results of the two different models: 1) logistic regression model estimating the adjusted odds of mortality in hospital-onset vs community-onset sepsis, and 2) Cox regression model estimating the adjusted hazard of mortality for patients initially admitted without sepsis who subsequently develop hospital-onset sepsis.

a The primary model included all patients in the study cohort from January 2009-Sept 2015. Multiple imputation was used to account for missing data for covariates.

b A sensitivity analysis was conducted limiting the cohort to patients admitted from January 2013-Sept 2015 since the availability of vital signs and Glasgow Coma Scale was substantially higher in later years. Multiple imputation was used to account for missing data for covariates.

c A sensitivity analysis was conducted amongst the Jan 2013-Sept 2015 cohort using the Sequential Organ Failure Assessment (SOFA) score to adjust for severity of illness instead of each individual covariate (i.e., vital signs, laboratory data, Glasgow Coma Scale, mechanical ventilation, vasopressors). The SOFA score was calculated on the day of sepsis onset for the hospital-onset vs community-onset logistic regression model, and on the day of admission for the hospital-onset sepsis vs no sepsis Cox regression model. Other baseline characteristics (demographics, comorbidities) and hospital characteristics were included in the models.

d A sensitivity analysis was conducted amongst the entire Jan 2009-Sept 2015 cohort limited to patients with no missing covariates (N=13,615 for the logistic regression hospital-onset vs community-onset sepsis model, and N=65,327 for the Cox regression model).