**Online Supplement**

**Title**: Epidemiology and Outcomes of Cancer-Related and Non-Cancer-Related Sepsis Hospitalizations

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Risk of Mortality in the Pediatric & Adolescent Population

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Risk Differencein the Pediatric and Adolescent Population

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| **Supplemental Table 1**: Variable Definitions | |
| Variable | Definition |
| Sepsis | Defined by explicit sepsis ICD-9 codes 995.92 785.52 and Dombrovskiy criteria (infection plus organ dysfunction)  ICD-9 codes used for organ dysfunction: 518.81 518.82 786.09 799.1 785.50 785.51 785.52 785.59 427.5 458.0 458.8 458.9 796.3 287.4 287.5 286.6 286.9 584.5 584.6 584.7 584.8 584.9 570 572.2 573.4 293.0 348.1 348.3 780.01  ICD-9 codes for infection: 038.0 038.1 038.2 038.3 038.4 038.8 038.9 003.1 020.2 036.6 054.5 112.5 995.91 995.92 785.52 |
| Cancer | HCUP CCS codes used to identify malignancy:  11 (Cancer of head and neck);12 (Cancer of esophagus); 13 (Cancer of stomach); 14 (Cancer of colon); 15 (Cancer of rectum and anus); 16 (Cancer of liver and intrahepatic bile duct); 17 (Cancer of pancreas); 18 (Cancer of other GI organs; peritoneum); 19 (Cancer of bronchus; lung); 20 (Cancer; other respiratory and intrathoracic); 21 (Cancer of bone and connective tissue); 22 (Melanomas of skin); 23 (Other non-epithelial cancer of skin); 24 (Cancer of breast); 25 (Cancer of uterus); 26 (Cancer of cervix); 27 (Cancer of ovary); 28 (Cancer of other female genital organs); 29 (Cancer of prostate); 30 (Cancer of testis); 31 (Cancer of other male genital organs); 32 (Cancer of bladder); 33 (Cancer of kidney and renal pelvis); 34 (Cancer of other urinary organs); 35 (Cancer of brain and nervous system); 36 (Cancer of thyroid); 37 (Hodgkin`s disease); 38 (Non-Hodgkin`s lymphoma); 39 (Leukemias); 40 (Multiple myeloma); 41 (Cancer; other and unspecified primary); 42 (Secondary malignancies); 43 (Malignant neoplasm without specification of site) |
| Solid tumor | CCS codes 11-36 correspond to solid tumor |
| Hematologic tumor | CCS codes 37-40 correspond to hematologic malignancy |
| Other tumor | CCS codes 40-43 correspond to other or NOS malignancies |
| **Site of Infection** | ICD-9 codes or CCS codes were used to identify site, first diagnosis was the only one considered. |
| Respiratory | CCS codes: 122 (pneumonia); 123 (Influenza); 125 (bronchitis); 126 (other upper respiratory infections); 129 (aspiration pneumonitis);  ICD9 codes: 510 (empyema); 510.0 (empyema with fistula); 510.9 (Empyema without fistula); 513.0 (abscess of lung) |
| Bacteremia/Fungemia | ICD9 codes: 790.7 (Bacteremia); 771.81 (newborn sepsis); 999.32 (catheter associated blood stream infection); 112.5 (disseminated candida); 999.31 (infection due to central venous catheter) |
| Genitourinary | CCS codes: 159 (urinary tract infections)  ICD-9 codes: 590.0 (pyelonephritis); 590.1 (pyelonephritis); 590.10 (pyelonephritis NOS); 590.80 (pyelonephritis NOS); 590.81 (pyelonephritis in other disease); 590.11 (pyelonephritis with necrosis); 601.9 (prostatitis NOS); 601.0 (prostatitis); 646.6 (infections of genitourinary tract in pregnancy) |
| Gastrointestinal | CCS codes: 142 (appendicitis); 146 (diverticulitis); 148 (peritonitis and intestinal abscess)  ICD-9 codes: 576.1 (cholangitis); 008.5 (bacterial enteritis NOS); 003.0 (salmonella enteritis); 009.0 (infections enteritis NOS); 009.1 (enteritis of infectious origin); 008.45 (clostridium dificile); 009 (ill-defined intestinal infections); 008.41 (staphylococcal enteritis); 572.0 (liver abscess); 567.22 (peritoneal abscess); 569.83 (perforation of intestine); 777.5 (necrotizing enterocolitis of newborn); 004.0 (shigella dysentery) |
| Skin/soft tissue | CCS codes: 197 (skin and subcutaneous soft tissue infections)  ICD-9 codes: 728.86 (necrotizing fasciitis); 785.4 (gangrene); 683 (lymphadenitis); 682.9 (cellulitis NOS) |
| Joint/bone | CCS code: 201 (infective arthritis and osteomyelitis) |
| CNS | CCS codes: 76 (meningitis); 77 (encephalitis); 78 (other CNS infections) |
| Cardiovascular | ICD-9 codes: 424.99 (endocarditis nec); 424.90 (endocarditis NOS); 424.91 (endocarditis in other diseases); 424.9 (endocarditis valve unspecified); 421 (acute and subacute endocarditis); 421.9 (acute/subacute endocarditis NOS) |
| **Individual Organ Failures** | ICD-9 codes used for organ dysfunction in Dombrovskiy methodology |
| Pulmonary | 518.81 (acute respiratory failure); 518.82 (other pulmonary insufficiency); 786.09 (respiratory abnormality nec); 799.1 (respiratory arrest) |
| Cardiovascular | 785.50 (shock NOS); 785.51 (cardiogenic shock); 785.52 (septic shock); 785.59 (shock without trauma nec); 427.5 (cardiac arrest); 458.0 (orthostatic hypotension); 458.8 (hypotension NEC); 458.9 (hypotension NOS) |
| Renal | 584.5 (acute kidney failure NOS); 584.6 (acute kidney failure, cortical necrosis); 584.7 (acute kidney failure, medullary necrosis ); 584.8 (acute kidney failure NEC) |
| Liver | 570 (acute necrosis of liver); 572.2 (hepatic encephalopathy); 573.4 (hepatic infarction) |
| Neurologic | 293.0 (delirium due to other conditions); 348.1 (anoxic brain damage); 348.3 (encephalopathy not elsewhere specified); 780.01 (coma) |
| Hematologic | 287.4 (secondary thrombocytopenia); (thrombocytopenia NOS); 286.6 (defibrination syndrome); 286.9 (coagulation defect NOS/NEC) |

HCUP CCS – Healthcare Utilization Project Clinical Classification Software Codes; ICD-9 – International Classification of Diseases, 9th revision; NOS – not otherwise specified; NEC – not elsewhere classifiable

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| **Supplemental Table 2.** Pediatric Chronic Conditions Characteristics\* | | | |
|  | Non-cancer-related sepsis hospitalizations (N=4,405) | Cancer-related sepsis hospitalizations (N=1,045) | *p* |
| Technology Dependent | 1,714 (38.9%) | 278 (26.6%) | <0.001 |
| Gastrointestinal | 1,364 (31.0%) | 163 (15.6%) | <0.001 |
| Neurologic & Neuromuscular | 1,283 (29.1%) | 117 (11.2%) | <0.001 |
| Cardiovascular | 871 (19.8%) | 181 (17.3%) | 0.07 |
| Metabolic | 759 (17.2%) | 291 (27.9%) | <0.001 |
| Renal/Urologic | 646 (14.7%) | 155 (14.8%) | 0.9 |
| Hematologic/Immunologic | 621 (14.1%) | 594 (56.8%) | <0.001 |
| Congenital/Genetic | 615 (14.0%) | 49 (4.7%) | <0.001 |
| Respiratory | 541 (12.3%) | 35 (3.4%) | <0.001 |
| Transplantation | 259 (5.9%) | 210 (20.1%) | <0.001 |
| Neonatal | 66 (1.5%) | <11 (<1.0%) | <0.001 |
| None | 1,293 (29.4%) | <11 (<1.0%) | <0.001 |
| \* Malignancy excluded given this was also the exposure | | | |

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| **Supplemental Table 3**. Comparison of Sepsis Outcomes from 1995-2014\* | | |
| Category | 19951 | 2013-2014 |
| Cancer-Related Sepsis Mortality (%) | 43.4% | 27.9% |
| Proportion of Cancer Among Sepsis Hospitalizations (%) | 12% | 21.2% |
| Proportion of Sepsis Among Cancer Hospitalizations (%) | 5% | 5.7% |
| \* Angus method was used to identify sepsis in the 1990’s. Dombrovskiy method is used in the current study.  1. Derived from Table 2 of Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001 | | |

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| **Supplemental Table 4.** Payer Type | | | |
|  | Non-cancer-related sepsis hospitalizations (N=869,722) | Cancer-related sepsis hospitalizations (N=234,641) | *p* |
| Payer type, N(%) | | | <0.001 |
| Medicare | 583,766 (67.1%) | 162,312 (69.2%) |  |
| Private | 123,953 (14.2%) | 41,803 (17.8%) |  |
| Medicaid | 107,143 (12.3%) | 20,553 (8.8%) |  |
| Self-Pay | 27,654 (3.2%) | 3,189 (1.4%) |  |
| Other | 23,658 (2.7%) | 6,058 (2.6%) |  |
| Missing | 1,156 (0.1%) | 346 (0.2%) |  |

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| **Supplemental Table 5.** Charlson Comorbidity Index Characteristics\* | | | |
|  | Non-cancer-related sepsis hospitalizations (N=865,233) | Cancer-related sepsis hospitalizations (N=234,641) | *p* |
| Chronic kidney disease | 276,374 (31.9%) | 64,902 (27.7%) | <0.001 |
| Congestive heart failure | 249,743 (28.9%) | 48,981 (21.0%) | <0.001 |
| Chronic respiratory disease | 236,579 (27.3%) | 61,226 (26.2%) | <0.001 |
| Uncomplicated diabetes | 234,241 (27.1%) | 52,757 (22.6%) | <0.001 |
| Myocardial infarction | 103,450 (12.0%) | 22,662 (9.7%) | <0.001 |
| Cerebrovascular disease | 85,385 (9.9%) | 14,967 (6.4%) | <0.001 |
| Complicated diabetes | 70,248 (8.1%) | 10,372 (4.4%) | <0.001 |
| Peripheral vascular disease | 53,405 (6.2%) | 10,008 (4.3%) | <0.001 |
| Mild liver disease | 41,034 (4.7%) | 8,260 (3.5%) | <0.001 |
| Severe liver disease | 36,009 (4.2%) | 8,964 (3.8%) | <0.001 |
| Rheumatologic disease | 32,697 (3.8%) | 6,313 (2.7%) | <0.001 |
| Hemiplegia | 21,394 (2.5%) | 3,588 (1.5%) | <0.001 |
| Peptic ulcer disease | 19,296 (2.2%) | 4,498 (1.9%) | <0.001 |
| Dementia | 12,538 (1.4%) | 1,967 (0.8%) | <0.001 |
| HIV | 8,209 (1.0%) | 1,699 (0.7%) | <0.001 |
| None | 184,057 (21.3%) | 65,870 (28.2%) | <0.001 |
| \*Malignancy excluded given this was also the exposure | | | |

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| **Supplemental Table 6.** Comparison of Sepsis Mortality by Site and Organ Dysfunctions | | |
| Variable | Cancer-Related Sepsis Mortality (%) | Non-Cancer-Related Sepsis Mortality (%) |
| Sepsis source |  |  |
| Pulmonary | 34.1% | 23.7% |
| Gastrointestinal | 27.3% | 21.6% |
| Genitourinary | 17.4% | 12.7% |
| Missing | 34.1% | 26.2% |
| Organ Dysfunctions |  |  |
| 1 | 14.0% | 8.3% |
| 2 | 31.5% | 21.5% |
| 3+ | 57.2% | 44.1% |
| Received Mechanical Ventilation | 46.6% | 32.6% |

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| **Supplemental Table 7.** Sepsis Hospitalization Demographics by Tumor Class | | | | |
|  | Solid Tumor (N=148,845) | Hematologic Tumor (N=43,074) | Other Tumor (N=42,722) | *p* |
| **Patient Characteristics** | | | | |
| Age (years), median (IQR) | 74 (64-83) | 69 (58-78) | 67 (58-76) | <0.001 |
| Gender, N(%) |  |  |  | <0.001 |
| Male | 82,664 (55.5%) | 25,421 (59.0%) | 22,644 (53.0%) |  |
| Payer type, N(%) |  | | | <0.001 |
| Medicare | 109,771 (73.8%) | 27,179 (63.1%) | 25,362 (59.4%) |  |
| Private | 22,028 (14.8%) | 9,647 (22.4%) | 10,128 (23.7%) |  |
| Medicaid | 11,133 (7.5%) | 4,317 (10.0%) | 5,103 (12.0%) |  |
| Self-Pay | 1,815 (1.2%) | 616 (1.4%) | 758 (1.8%) |  |
| Other | 3,697 (2.5%) | 1,142 (2.7%) | 1,219 (2.9%) |  |
| Missing | 180 (0.1%) | 97 (0.2%) | 69 (0.2%) |  |
| Charlson Comorbidity Index |  |  |  | <0.001 |
| Median (IQR) | 2 (1-4) | 2 (0-4) | 2 (0-3) |  |
| Pediatric CCC v2 (Revised) |  |  |  | <0.001 |
| Median (IQR) | 3 (2-3) | 2 (2-3) | 2 (1-3) |  |
| **Hospitalization Characteristics** | | | | |
| Organ dysfunction count  Median (IQR) | 1 (1-2) | 2 (1-3) | 2 (1-2) | <0.001 |
| Individual Organ Dysfunctions, N(%) |  |  |  |  |
| Renal | 88,278 (59.3%) | 24,922 (57.9%) | 24,281 (56.8%) | <0.001 |
| Cardiovascular | 66,731 (44.8%) | 22,001 (51.1%) | 21,827 (51.1%) | <0.001 |
| Pulmonary | 52,886 (35.5%) | 18,081 (42.0%) | 16,759 (39.2%) | <0.001 |
| Hematologic | 25,753 (17.3%) | 12,843 (29.8%) | 8,540 (20.0%) | <0.001 |
| Liver | 7,183 (4.8%) | 2,324 (5.4%) | 2,910 (6.8%) | <0.001 |
| Neurologic | 6,681 (4.5%) | 1,976 (4.6%) | 1,967 (4.6%) | 0.48 |
| None | 7,854 (5.3%) | 1,459 (3.4%) | 1,861 (4.4%) | <0.001 |
| Site of Infection, N(%) |  |  |  | <0.001 |
| Respiratory | 54,010 (36.3%) | 18,260 (42.4%) | 16,284 (38.1%) |  |
| Genitourinary | 40,492 (27.2%) | 6,921 (16.1%) | 9,137 (21.4%) |  |
| Gastrointestinal | 19,520 (13.1%) | 4,373 (10.2%) | 5,715 (13.4%) |  |
| Skin/soft tissue | 7,021 (4.7%) | 2,364 (5.5%) | 1,505 (3.5%) |  |
| Bacteremia/Fungemia | 3,208 (2.2%) | 1,961 (4.6%) | 1,256 (2.9%) |  |
| Joint/bone | 1,182 (0.8%) | 361 (0.8%) | 217 (0.5%) |  |
| Central Nervous System | 684 (0.5%) | 378 (0.9%) | 171 (0.4%) |  |
| Cardiovascular | 232 (0.2%) | 76 (0.2%) | 48 (0.1%) |  |
| Missing or Unknown | 22,496 (15.1%) | 8,380 (19.5%) | 8,389 (19.6%) |  |
| Hospital Length of Stay (days), med (IQR) | 7 (4-13) | 9 (5-19) | 7 (4-13) | <0.001 |

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| |  |  |  | | --- | --- | --- | | **Supplemental Table 8.** Unadjusted In-hospital Sepsis Mortality by Cancer Type | | | |  | Mortality | Odds Ratio (95% CI) | | Cancer Types |  |  | | Solid Tumor | 36,386 (24.5%) | ref | | Hematologic Tumor | 13,172 (30.6%) | 1.4 (1.3-1.4) | | Other (not specified) | 15,861 (37.1%) | 1.8 (1.8-1.9) | |

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| **Supplemental** **Table 9.** Adjusted In-hospital Sepsis Mortality by Cancer Type\*\* | | |
| Tumor Types | Odds Ratio (95% CI) | Adjusted Difference in Probability (95% CI) |
| Solid Primary | ref | ref |
| Hematologic Primary | 1.4 (1.3-1.4) | 6.3% (5.8%-6.8%) |
| Other (not specified) | 1.8 (1.8-1.9) | 12.2% (11.7%-12.7% |
| \*\* adjusted for payer type, gender, age, income, site of infection, complicated diabetes, severe liver disease, cerebrovascular disease, myocardial infarction, congestive heart failure, chronic kidney disease, and chronic respiratory disease | | |

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| **Supplemental Table 10.** Unadjusted Sepsis Mortality by Tumor Type | | |
|  | Mortality | Odds Ratio (95% CI) |
| Head and Neck | 1,871 (24.3%) | 1.2 (1.1-1.3) |
| Esophagus | 1,291 (35.6%) | 2.1 (1.9-2.2) |
| Stomach | 1,348 (36.2%) | 2.1 (2.0-2.2) |
| Colon | 5,718 (26.3%) | 1.3 (1.3-1.4) |
| Rectum and Anus | 1,511 (23.9%) | 1.1 (1.1-1.2) |
| Liver and bile duct | 2,565 (38.0%) | 2.3 (2.2-2.4) |
| Pancreas | 2,531 (33.7%) | 1.9 (1.8-2.0) |
| Other GI organs, peritoneum | 1,178 (26.0%) | 1.3 (1.2-1.4) |
| Bronchus, Lung | 11,262 (37.1%) | 2.2 (2.2-2.3) |
| Other respiratory and intrathoracic | 119 (35.4%) | 2.0 (1.6-2.5) |
| Bone and connective tissue | 537 (30.7%) | 1.6 (1.5-1.8) |
| Melanoma | 874 (21.3%) | 1.0 (0.9-1.1) |
| Non-epithelial skin cancer | 1,872 (18.2%) | 0.8 (0.8-0.9) |
| Breast | 6,507 (24.8%) | 1.2 (1.2-1.3) |
| Uterus | 1,304 (25.4%) | 1.3 (1.2-1.3) |
| Cervix | 640 (17.0%) | 0.8 (0.7-0.8) |
| Ovary | 1,335 (28.6%) | 1.5 (1.4-1.6) |
| Other female genital organs | 250 (20.8%) | 1.0 (0.8-1.1) |
| Prostate | 6,168 (21.2%) | 1.0 (0.9-1.0) |
| Testis | 165 (20.6%) | 1.0 (0.8-1.1) |
| Other male genital organs | 63 (18.9%) | 0.9 (0.6-1.1) |
| Bladder | 2,557 (18.2%) | 0.8 (0.8-0.9) |
| Kidney and renal pelvis | 1,673 (22.2%) | 1.1 (1.0-1.1) |
| Other urinary organs | 117 (19.2%) | 0.9 (0.7-1.1) |
| Brain and nervous system | 663 (29.0%) | 1.5 (1.4-1.7) |
| Thyroid | 406 (20.8%) | 1.0 (0.9-1.1) |
| Hodgkin’s lymphoma | 565 (29.4%) | 1.5 (1.4-1.7) |
| Non-Hodgkin’s lymphoma | 5,433 (30.2%) | 1.6 (1.6-1.7) |
| Leukemias | 6,686 (33.1%) | 1.8 (1.8-1.9) |
| Multiple myeloma | 2,398 (27.4%) | 1.4 (1.3-1.5) |
| Cancer, other and unspecified primary | 930 (25.0%) | 1.2 (1.1-1.3) |
| Secondary malignancies | 24,101 (37.9%) | 2.4 (2.3-2.4) |
| Malignant neoplasm without specification of site | 3,397 (42.4%) | 2.7 (2.6-2.9) |

**Supplemental Figure Title 1**: Cancer-Related versus Non-Cancer-Related Sepsis Relative Risk of Mortality in the Pediatric & Adolescent Population

**Supplemental Figure Legend 1**: Solid black line indicates relative risk of mortality. Dashed lines indicate 95% confidence limits. Grey bars indicate the distribution of sepsis hospitalizations by age.

Adjusted for: gender, payer type, income quartile, site of infection, comorbidities: neuromuscular, cardiovascular, respiratory, gastrointestinal, renal, hematologic/immunologic, transplant, tech dependent and metabolic.

**Supplemental Figure Title 2**: Cancer-Related versus Non-Cancer-Related Sepsis Mortality Risk Differencein the Pediatric and Adolescent Population

**Supplemental Figure Legend 2**: Solid black line indicates risk difference in mortality. Dashed lines indicate 95% confidence limits. Grey bars indicate the distribution of sepsis hospitalizations by age.

Adjusted for: gender, payer type, income quartile, site of infection, comorbidities: neuromuscular, cardiovascular, respiratory, gastrointestinal, renal, hematologic/immunologic, transplant, tech dependent and metabolic.