High 28-day mortality in critically ill patients with sepsis and concomitant active cancer

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Abstract
Objective: This study was performed to explore the characteristics and outcomes of patients with sepsis accompanied by active cancer who were admitted to the intensive care unit (ICU).

Methods: The baseline characteristics, infection profiles, and outcomes of patients with sepsis were retrospectively analyzed according to the presence of concomitant active cancer. The association between concomitant active cancer and 28-day mortality was explored.

Results: Of 23,956 patients with sepsis, 1574 (6.6%) had concomitant active cancer. The most common type was digestive (30.7%). The 28-day mortality ranged from 41.9% to 81.5%. Patients with active cancer had a significantly higher Simplified Acute Physiology Score II and significantly shorter length of ICU stay. Respiratory (32.9%), genitourinary (31.0%), and bloodstream (17.0%) infections were most common. Escherichia coli was the most frequent gram-negative pathogenic bacteria. The 28-day mortality rate was significantly higher in patients with than without active cancer. Concomitant active cancer was associated with increased 28-day mortality in patients with sepsis. Hematological malignancy was associated with a significantly higher risk of death than solid tumors.

Conclusions: Concomitant active cancer was associated with higher 28-day mortality in patients with sepsis requiring ICU admission. Hematological malignancy was associated with a higher risk of death than solid tumors.
Keywords
Sepsis, outcome, active cancer, intensive care unit, mortality, Simplified Acute Physiology Score II

Introduction
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, as described in the Sepsis-3 definition. Although the mortality rate of patients with sepsis has decreased during the past several decades, the incidence of sepsis has steadily increased, and the mortality rate remains ≥20%. This has led to a nationwide economic burden of $17 billion annually in the United States.

Increasing evidence has demonstrated that patients’ immune status plays an essential role in the pathogenesis and progression of sepsis and that boosting immunity improves survival. It is generally acknowledged that immunocompromised patients are susceptible to infection and have a worse prognosis. Additionally, cancer and sepsis have been shown to share many immunological defects, including increased production of the immunosuppressive cytokine interleukin 10 and programmed cell death-1 and its ligand with T-cell exhaustion. Therefore, the likelihood that patients with sepsis and concomitant active cancer are generally severely immunosuppressed and thus tend to have worse outcomes is an idea with intuitive appeal. However, no comprehensive data on whether active cancer compromises the outcome of sepsis in the intensive care unit (ICU) are available. Thus, using a large clinical database, we explored the characteristics and outcomes of patients with sepsis and concomitant cancer who were admitted to the ICU.

Material and methods

Data source and extraction
This study was an analysis of a publicly available ICU database called Medical Information Mart for Intensive Care III (MIMIC III, version 1.4). MIMIC III is a large, single-center database containing information of 46,520 patients admitted to Beth Israel Deaconess Medical Center (a teaching hospital of Harvard Medical School in Boston, MA, USA) from 2001 to 2012. Access of the MIMIC III database for research purposes was approved by the institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and the Beth Israel Deaconess Medical Center after completion of a National Institutes of Health Web-based course called “Protecting Human Research Participants.” Because this was a retrospective study and all patients were de-identified, informed consent was waived by the ethics committee of Beth Israel Deaconess Medical Center. Data were extracted from MIMIC III using structure query language (SQL) with pgAdmin 4 PostgreSQL 9.6 (PostgreSQL Global Development Group).

Inclusion criteria and definitions
Patients older than 16 years were included in the present study. Those meeting the diagnostic criteria for sepsis were extracted from the database. Sepsis was defined as infection or suspected infection plus a ≥2-point increase in the Sequential
Sepsis-related Organ Failure Assessment (SOFA) score. Infection or suspected infection was defined as one of the following: 1) any of the following terms in the patient’s medical record according to the Ninth Revision of the International Classification of Diseases: “infection,” “pneumonia,” “meningitis,” “peritonitis,” “bacteremia,” “sepsis,” or “septic,” and 2) a positive microbiological culture. Patients with active cancer were defined as those in the immediate postoperative period after resection of a tumor and those with a newly diagnosed tumor.

Other extracted information were age, sex, ethnicity, comorbidities, SOFA score, Simplified Acute Physiology Score II (SAPS II), length of stay in the ICU, causative agents, and site of infection. The primary endpoint was the 28-day mortality rate. The secondary endpoint was the length of stay in the ICU.

Statistical analysis

The Kolmogorov–Smirnov test and histograms were performed to test the normality of the distribution of quantitative variables. Normally distributed quantitative variables are presented as mean ± standard deviation, and skewed variables are described as median and interquartile range. Chi-square analysis or Fisher’s exact test was performed to compare categorical variables. Quantitative variables were compared using analysis of variance or the t test for normally distributed data and the Kruskal–Wallis test or Mann–Whitney test for non-normally distributed data.

Covariates with a p value of <0.05 in the univariate analysis were incorporated into a Cox multivariable regression model to determine the risk factors associated with 28-day mortality. A Kaplan–Meier curve and risk-adjusted survival curve were plotted from the model.

All analyses were performed using R 3.3.3 (http://www.r-project.org/), and a p value of <0.05 was considered statistically significant.

Results

Characteristics of the study population

A total of 23,956 patients satisfied the Sepsis-3 definition, and 1574 (6.6%) had active cancer (Table 1). Among them, the types of cancer were digestive (30.7%), respiratory (20.1%), hematological (19.0%), neural (8.6%), urinary (4.4%), bone (3.8%), genital (2.4%), peritoneal (2.0%), head and neck (2.0%), pleural (1.7%), and others (5.3%) (Figure 1). The 28-day mortality rate of patients with sepsis and concomitant active cancer ranged from 41.9% to 81.5%. Patients with digestive, respiratory, and hematological malignancies had 28-day mortality rates of 50.9%, 69.0%, and 70.2%, respectively, while those with pleural cancer had the highest mortality rate of 81.5% (Figure 1).

Approximately half of the patients were male and >65 years old. The ethnicity of the vast majority of patients was white (71.7%). Notably, about one-quarter of patients had septic shock. Patients with active cancer had a higher SAPS II score and shorter length of stay in the ICU (median scores: 44 vs. 41, p < 0.001; median length of stay: 3.3 vs. 3.8 days, p < 0.001). As expected, the 28-day mortality rate was significantly higher in patients with than without active cancer (63.0% vs. 36.5%, respectively; p < 0.001) (Table 1).

Infection profile of patients with sepsis

Respiratory (27.2%), genitourinary (33.9%), and bloodstream (18.6%) infection were the three leading types of infection. Nearly one-third of patients with
sepsis and concomitant active cancer had a genitourinary infection (Table 1).

Among the 23,956 patients with sepsis, 18,327 (76.5%) had data regarding a microbiological culture (Table 2). Among the causative agents, *Escherichia coli* was the most frequent gram-negative pathogenic bacteria, followed by *Pseudomonas aeruginosa*. With respect to gram-positive bacteria, *Staphylococcus* was the most important. Most fungal infections were caused by yeast (Table 2). Interestingly, the rates of detection of *P. aeruginosa* (5.1% vs. 2.2%, \(p = 0.002\)), *Enterobacter cloacae* (3.9% vs. 1.6%, \(p = 0.004\)), *Viridans streptococcus* (4.5% vs. 2.3%, \(p = 0.023\)), and *Enterococcus faecium* (12.3% vs. 5.4%, \(p < 0.001\)) in blood were significantly higher for patients with than without active cancer (Table 2).

### Table 1. Baseline characteristics and clinical presentation of patients with sepsis with or without active cancer admitted to intensive care units (n = 23,956)

| Characteristics                      | Total (n = 23,956) | Without active cancer (n = 22,382) | With active cancer (n = 1574) | \(p\) value |
|--------------------------------------|--------------------|----------------------------------|-------------------------------|------------|
| Male                                 | 12,879 (53.8)      | 11,971 (53.5)                    | 908 (57.7)                    | <0.001     |
| Age of >65 years                     | 13,144 (54.9)      | 12,314 (55.0)                    | 830 (52.7)                    | 0.083      |
| Ethnicity                            |                    |                                  |                               |            |
| White                                | 17,178 (71.7)      | 15,996 (71.5)                    | 1182 (75.1)                   | <0.001     |
| Black                                | 2461 (10.3)        | 2355 (10.5)                      | 106 (6.7)                     |            |
| Asian                                | 583 (2.4)          | 520 (2.3)                        | 63 (4.0)                      |            |
| Hispanic                             | 751 (3.1)          | 716 (3.2)                        | 35 (2.2)                      |            |
| Others                               | 2983 (12.5)        | 2795 (12.5)                      | 188 (11.9)                    |            |
| Comorbidity                          |                    |                                  |                               |            |
| Hypertension                         | 8712 (36.4)        | 8120 (36.3)                      | 592 (37.6)                    | 0.301      |
| Diabetes mellitus                    | 7182 (30.0)        | 6861 (30.7)                      | 321 (20.4)                    | <0.001     |
| Congestive heart failure             | 7755 (32.4)        | 7464 (33.3)                      | 291 (18.5)                    | <0.001     |
| COPD                                 | 2448 (10.2)        | 2347 (10.5)                      | 101 (6.4)                     | <0.001     |
| Chronic kidney disease               | 4712 (19.7)        | 4540 (20.3)                      | 172 (10.9)                    | <0.001     |
| Infection site                       |                    |                                  |                               | <0.001     |
| Respiratory                          | 7893 (32.9)        | 7317 (32.7)                      | 576 (36.6)                    |            |
| Genitourinary                        | 7419 (31.0)        | 6998 (31.3)                      | 421 (26.7)                    |            |
| Bloodstream                          | 4070 (17.0)        | 3820 (17.1)                      | 250 (15.9)                    |            |
| Gastrointestinal                     | 844 (3.5)          | 783 (3.5)                        | 61 (3.9)                      |            |
| Abdominal                            | 546 (2.3)          | 461 (2.1)                        | 85 (5.4)                      |            |
| Skin and soft tissue                 | 425 (1.8)          | 406 (1.8)                        | 19 (1.2)                      |            |
| Device-related                       | 423 (1.8)          | 407 (1.8)                        | 16 (1.0)                      |            |
| Others/unspecified                   | 2336 (9.8)         | 2190 (9.8)                       | 146 (9.3)                     |            |
| Septic shock                         | 6001 (25.1)        | 5720 (25.6)                      | 281 (17.9)                    | <0.001     |
| Mechanical ventilation on ICU admission | 4217 (17.6)     | 3953 (17.7)                      | 264 (16.8)                    | 0.389      |
| SAPS II                              | 41 (32–51)         | 41 (32–51)                       | 44 (36–54)                    | <0.001     |
| SOFA score                           | 5 (3–8)            | 5 (3–8)                          | 5 (3–8)                       | 0.012      |
| ICU length of stay, days             | 3.7 (1.9–8.6)      | 3.8 (1.9–8.7)                    | 3.3 (1.8–7.3)                 | <0.001     |
| 28-day mortality, %                  | 38.2               | 36.5                             | 63.0                          | <0.001     |

Data are presented as n (%) or median (interquartile range).

COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.
Table 2. Causative agents of sepsis in patients with or without active cancer admitted to intensive care units (n = 18,327)

| Causative agents | All specimens (n = 18,327) | Blood cultures (n = 5300) |
|------------------|-----------------------------|---------------------------|
|                  | Without active cancer (n = 17,165) | With active cancer (n = 1162) | p value | Without active cancer (n = 4966) | With active cancer (n = 334) | p value |
| Gram-negative    |                             |                           |          |                             |                           |          |
| *Escherichia coli* | 2579 (15.0) | 168 (14.5) | 0.630 | 457 (9.2) | 38 (11.4) | 0.221 |
| *Pseudomonas aeruginosa* | 1547 (9.0) | 106 (9.1) | 0.942 | 111 (2.2) | 17 (5.1) | 0.002 |
| *Klebsiella pneumoniae* | 1366 (8.0) | 82 (7.1) | 0.296 | 228 (4.6) | 16 (4.8) | 0.973 |
| *Klebsiella oxytoca* | 279 (1.6) | 26 (2.2) | 0.144 | 43 (0.9) | 5 (1.5) | 0.226 |
| *Corynebacterium diphtheria* | 828 (4.8) | 57 (4.9) | 0.956 | 238 (4.8) | 18 (5.4) | 0.719 |
| *Proteus mirabilis* | 525 (3.1) | 24 (2.1) | 0.067 | 56 (1.1) | 1 (0.3) | 0.264 |
| *Haemophilus* | 512 (3.0) | 24 (2.1) | 0.088 | 10 (0.2) | 0 (0.0) | >0.999 |
| *Enterobacter spp.* |                              |                           |          |                             |                           |          |
| *Enterobacter cloacae* | 509 (3.0) | 49 (4.2) | 0.021 | 80 (1.6) | 13 (3.9) | 0.004 |
| *Enterobacter aerogenes* | 175 (1.0) | 12 (1.0) | 0.999 | 15 (0.3) | 1 (0.3) | >0.999 |
| *Xanthomonas* | 321 (1.9) | 23 (2.0) | 0.878 | 25 (0.5) | 3 (0.9) | 0.418 |
| *Serratia marcescens* | 307 (1.8) | 25 (2.2) | 0.433 | 54 (1.1) | 4 (1.2) | 0.784 |

(continued)
Risk factors associated with 28-day mortality

A Cox proportional hazard regression model was established to determine the risk factors associated with 28-day mortality. As shown in Table 3, the following factors were significantly associated with increased 28-day mortality: an age of >65 years (p < 0.001), diabetes mellitus (p = 0.027), congestive heart failure (p < 0.001), chronic kidney disease (p < 0.001), septic shock (p < 0.001), and the presence of active cancer (p < 0.001). The following infection sites were risk factors with skin and soft tissue infection as the reference: respiratory (p < 0.001), genitourinary (p = 0.006), bloodstream (p < 0.001), gastrointestinal (p < 0.001), and abdominal (p = 0.012).

Figure 2 shows the crude and adjusted Kaplan–Meier survival curves of 28-day
Table 3. Independent predictors of 28-day mortality in all patients with sepsis (n = 23,956)

| Factors                        | Univariate       | Multivariate     |
|--------------------------------|------------------|------------------|
|                                | HR (95% CI)      | p value          | HR (95% CI)      | p value          |
| **Sex**                        |                  |                  |                  |                  |
| Male                           | 1.031 (0.989–1.074) | 0.152            | -                | -                |
| **Age**                        |                  |                  |                  |                  |
| >65 years                      | 1.845 (1.767–1.927) | <0.001           | 1.663 (1.590–1.740) | <0.001           |
| **Comorbidity**                |                  |                  |                  |                  |
| Diabetes mellitus              | 1.181 (1.130–1.233) | <0.001           | 1.053 (1.006–1.101) | 0.027            |
| Congestive heart failure       | 1.510 (1.448–1.575) | <0.001           | 1.224 (1.190–1.301) | <0.001           |
| COPD                           | 1.082 (1.013–1.154) | 0.018            | 0.975 (0.912–1.041) | 0.446            |
| Chronic kidney disease         | 1.571 (1.499–1.647) | <0.001           | 1.405 (1.337–1.477) | <0.001           |
| Septic shock                   | 1.440 (1.377–1.505) | <0.001           | 1.341 (1.282–1.402) | <0.001           |
| Concomitant active cancer      | 2.168 (2.029–2.316) | <0.001           | 2.386 (2.231–2.551) | <0.001           |
| **Site of infection**          |                  |                  |                  |                  |
| Skin and soft tissue           | Reference        |                  | Reference        |                  |
| Respiratory                    | 1.746 (1.439–2.119) | <0.001           | 1.461 (1.204–1.774) | <0.001           |
| Genitourinary                  | 1.665 (1.371–2.021) | <0.001           | 1.313 (1.081–1.594) | 0.006            |
| Bloodstream                    | 2.043 (1.679–2.485) | <0.001           | 1.738 (1.428–2.115) | <0.001           |
| Gastrointestinal               | 2.105 (1.694–2.614) | <0.001           | 1.611 (1.298–2.000) | <0.001           |
| Abdominal                      | 1.696 (1.341–2.145) | <0.001           | 1.353 (1.069–1.711) | 0.012            |
| Device-related                 | 1.465 (1.138–1.887) | 0.003            | 1.254 (0.976–1.611) | 0.076            |
| Others/unspecified             | 0.994 (0.804–1.229) | 0.956            | 0.970 (0.789–1.193) | 0.774            |

COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval

Figure 2. Crude and adjusted Kaplan–Meier curves of 28-day survival probability in patients with sepsis according to (a) the presence or absence of active cancer and (b) the presence of solid or hematological malignancies. ICU, intensive care unit
mortality according to cancer category. Active cancer was associated with increased 28-day mortality, and hematological cancer was associated with a higher risk of death than solid tumors (p < 0.001 with log-rank test for both).

Discussion

In the present study, active cancer was associated with a higher 28-day mortality rate among patients with sepsis admitted to the ICU (hazard ratio: 2.369, p < 0.001). Moreover, hematological malignancy was associated with a higher risk of death than solid tumors.

Among patients with active cancer, the most common types were genitourinary, respiratory, and bloodstream cancers, which is consistent with a previous study. However, because all infections were hospital-acquired in that study, the incidence rate of respiratory infection reached to 54.6%. With respect to causative agents, Escherichia coli was the most frequent gram-negative bacteria. Notably, patients with sepsis and concomitant active cancer were more susceptible to Clostridium difficile infection (6.7% vs. 5.3%, p = 0.047). Anaerobic bacteremia, usually caused by C. difficile in patients with cancer, accounted for 0.5% to 9.0% of all hospitalized patients in a previous study and posed a threat to patients with cancer. This is probably because patients undergoing chemotherapy and radiation for treatment of cancer often experience diarrhea, causing intestinal mucous membrane barrier dysfunction and secondary C. difficile infection.

Patients with cancer account for nearly 15% of ICU admissions in Europe, and cancer is a potential risk factor for devastating infection. Zahar et al. demonstrated that hematological and gastrointestinal cancers were the most common underlying diseases for anaerobic bacteremia. Likewise, we found that active cancer was significantly associated with increased 28-day mortality and that the presence of hematological malignancy had an even more negative impact on survival, in contrast to solid tumors (Figure 2). A recent prospective multicentric analysis that focused on candidemia secondary to underlying malignancy demonstrated that patients with hematological malignancy had a higher rate of early death (day < 8) and a higher 30-day mortality rate than those with solid tumors (34.2% vs. 30.3% and 51.3% vs. 48.1%, respectively). Another large retrospective study on the outcomes of patients with cancer admitted to ICUs in England, Wales, and Northern Ireland showed that compared with patients with solid tumors, those with hematological malignancies had a longer length of stay in the ICU (median: 6 vs. 4 days), higher ICU mortality rate (41.3% vs. 17.1%), and higher hospital mortality rate (53.6% vs. 26.4%). These findings are consistent with our results.

Given that cancer and sepsis share some immunological defects, concomitant active cancer in patients with sepsis might even worsen patients' immune system function and hence worsen the prognosis. Therefore, for patients with active cancer and concomitant sepsis, especially for those with already compromised organ dysfunction, it is reasonable for physicians and patients' families to weigh the potential benefits of therapy and possible futile aggressive interventions to optimize the choice of treatment strategy.

Although this was a large study on the correlation between cancer and sepsis, the study still has several potential limitations. First, all data were obtained from a single-center database, which may result in concerns regarding the generalization of the conclusions. Second, to protect patient confidentiality, all dates in the database have been shifted. Thus, we could not
analyze the chronological trend from 2001 to 2012. Third, owing to the nature of the retrospective analysis, long-term survival outcomes were not accessible for most patients in the database.

In conclusion, higher 28-day mortality was found in patients with sepsis and concomitant active cancer than in those without active cancer. Moreover, hematological malignancies were associated with a high risk of death. Large multicenter prospective studies on long-term survival are needed to confirm these findings.

Author contributions
Yong-gang Wang: Study design, data acquisition, chart abstraction, data analysis/interpretation, manuscript drafting.
Jian-cang Zhou: Chart abstraction, data analysis/interpretation, manuscript revision.
Kang-song Wu: Study conception and design, data analysis/interpretation, manuscript revision.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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