Temporal Trends in Sepsis Incidence and Mortality in Patients With Cancer in the US Population

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Background Few population-based studies assess the impact of cancer on sepsis incidence and mortality.
Objectives To evaluate epidemiological trends of sepsis in patients with cancer.
Methods This retrospective cohort study included adults (≥20 years old) identified using sepsis-indicator *International Classification of Diseases* codes from the Nationwide Inpatient Sample database (2006-2014). A generalized linear model was used to trend incidence and mortality. Outcomes in patients with cancer and patients without cancer were compared using propensity score matching. Cox regression modeling was used to calculate hazard ratios for mortality rates.
Results The study included 13 996 374 patients, 13.6% of whom had cancer. Gram-positive infections were most common, but the incidence of gram-negative infections increased at a greater rate. Compared with patients without cancer, those with cancer had significantly higher rates of lower respiratory tract (35.0% vs 31.6%), intra-abdominal (5.5% vs 4.6%), fungal (4.8% vs 2.9%), and anaerobic (1.2% vs 0.9%) infections. Sepsis incidence increased at a higher rate in patients with cancer than in those without cancer, but hospital mortality rates improved equally in both groups. After propensity score matching, hospital mortality was higher in patients with cancer than in those without cancer (hazard ratio, 1.25; 95% CI, 1.24-1.26). Of patients with sepsis and cancer, those with lung cancer had the lowest survival (hazard ratio, 1.65) compared with those with breast cancer, who had the highest survival.
Conclusions Cancer patients are at high risk for sepsis and associated mortality. Research is needed to guide sepsis monitoring and prevention in patients with cancer.
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Sepsis remains a major public health concern as a leading cause of hospitalizations, morbidity, and mortality within the United States and worldwide.[1-3] A recent study indicated that the cost of managing sepsis ranks the highest among all disease categories in hospitalized patients.[4] Patients with cancer often have immunosuppression caused by the cancer and by the corresponding treatments, increasing their susceptibility to sepsis.[5,6] Despite the burden of sepsis in patients with cancer, few studies of sepsis incidence and mortality in these patients have been published, and most of these are single-center studies.[7,8]

Much of the available epidemiologic data regarding sepsis in cancer patients is from studies of neutropenic patients with hematologic malignant neoplasms and stem cell transplant recipients, who tend to be more immunocompromised than patients with solid tumors.[9,10] Only limited data on sepsis in patients with solid cancers have been reported.[11] Although gram-positive bacteria were the leading agents responsible for sepsis in the 1990s, current data show that the trend is shifting from gram-positive to gram-negative bacteria.[12] The frequent use of invasive indwelling catheters was once believed to expose cancer patients, particularly those with neutropenia, to a greater risk of bloodstream infection.[13] However, with improvements in catheter management, new data suggest that up to 50% of sepsis cases among patients with cancer may result from damage to mucosal barriers.[14,15]

Whether sepsis is correlated with worse outcomes in patients with cancer than in those without cancer has not been documented in a national population-based study. Comparing trends of sepsis incidence, outcomes, and pathogens in patients with cancer and patients without cancer may inform public health and research resource allocation and may influence clinical decisions regarding antibiotics for patients with suspected sepsis. We conducted this retrospective study in a large, nationally representative cohort of patients to compare the following, with longitudinal evaluation of annual trends, in patients with cancer and patients without cancer: (1) sepsis incidence and hospitalizations by organism and (2) mortality rate and survival outcomes by organism and cancer type.

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Methods

Data Source

We obtained data for this analysis from the Healthcare Cost and Utilization Project National (Nationwide) Inpatient Sample (NIS), the largest publicly available all-payer inpatient health care database in the United States. The NIS is managed by the Agency for Healthcare Research and Quality and includes a 20% sample of patient records from 4378 hospitals.[16] The database provides information on patient demographics, diagnoses, and outcomes for each hospitalization. It includes data from more than 7 million hospital stays, weighted according to the survey's sampling design to estimate more than 35 million hospitalizations nationally. Weights are calculated by dividing the number of universe discharges (estimated from the American Hospital Association annual survey) by sampled discharges within each NIS stratum. Strata are defined by hospital characteristics including census division, location (rural or urban), bed size, teaching status, and ownership.

The board of the National Taiwan University Hospital approved this study. Because the study used a deidentified database for research and involved no patient interventions, registration was not required and institutional review board approval was waived.

Identification of Patients With Sepsis

We identified hospitalizations with a validated approach using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnostic codes defined by Martin et al.[17] We identified hospitalizations of adult patients (≥20 years of age) with sepsis from 2006 through 2014 by selecting all patients with an explicit *ICD-9, Clinical Modification* (*ICD-9-CM*) code for sepsis or systemic fungal infection (038, septicemia; 020.0, septicemic; 790.7, bacteremia; 117.9,

disseminated fungal infection; 112.5, disseminated *Candida* infection; or 112.81, disseminated fungal endocarditis) and a diagnosis of acute organ dysfunction. Acute organ or system dysfunctions identified for this study were cardiovascular, respiratory, central nervous, hematologic, hepatic, and renal system dysfunctions. Shock was included as a form of cardiovascular dysfunction. Sources of infection were categorized as lower respiratory tract, genitourinary tract, skin and skin structure, catheter-related bloodstream, intra-abdominal, biliary tract, or musculoskeletal infection. We excluded hospitalizations with missing values, transfers to short-term hospitals, and patients discharged against medical advice. We recorded sources of infection and microbiological profiles by using *ICD-9-CM* pathogen codes (Supplemental Table 1 and Supplemental Table 2). Eligible patients were classified as having or not having cancer on the basis of the presence or absence of *ICD-9-CM* cancer codes (Supplemental Table 3).

Classification of Cancer Types

We used diagnostic codes to identify admitted patients who had a diagnosis of lung, breast, gastrointestinal tract, hematologic, gynecologic, or unspecified site cancer (Supplemental Table 3). According to the Uniform Hospital Discharge Data Set guidelines, we used diagnostic codes to identify conditions that coexisted at the time of admission, that developed subsequently, or that affected the treatment received and/or the length of stay.

Outcome Measures

Annual incidence of sepsis events was presented as events per 100 000 hospitalizations, stratified by time periods (2006-2008, 2009-2011, and 2012-2014). For 13 specific pathogens, we assessed 2 longitudinal outcomes: mean annual change in incidence and change in hospital 30-day mortality. We stratified these outcomes according to the presence or absence of cancer. General mortality data for broad subgroups of pathogens (gram-positive bacteria, gram-negative bacteria, anaerobes, and fungi) included percentage changes in 30-day mortality rates and crude and propensity score–matched hazard ratios (HRs) to calculate overall death rates.

Statistical Analysis

We estimated the frequency of sepsis hospitalizations with infections due to specific pathogens following the recommendations of the Agency for Healthcare Research and Quality. By using survey-specific statements (SURVEYMEANS, SAS Institute Inc), we weighted the patient data using the weights provided in the NIS database. Continuous variables are presented as means and SEs. Categorical variables are reported as numbers and percentages. We calculated the overall and mean annual percentage changes in incidence and 30-day mortality for sepsis and specific sources of infection from 2006 through 2014. To examine the significance of incidence and mortality trends, we performed a generalized linear model analysis. We compared trends of sepsis incidence and mortality between patients with cancer and those without cancer by using the Cochran-Armitage test for trends.[18,19] We calculated adjusted and unadjusted HRs by using Cox regression models to estimate the mean mortality rate. To account for imbalanced covariates between patients with cancer and patients without cancer, we constructed a propensity score model[20] on the basis of age, sex, and combined Charlson score.[21] We then calculated a propensity score–adjusted HR to compare the mortality rates of patients with cancer and those without cancer. We also used Cox regression models to analyze propensity score–adjusted sepsis mortality rates in patients with different types of cancer. Two-sided *P* values of less than .05 were considered significant for all analyses. We conducted data management and statistical analyses with SAS software (SAS Institute Inc).

We calculated the overall and mean annual percentage changes in incidence and 30-day mortality for sepsis and specific sources of infection from 2006 through 2014.

Results

We identified 13 996 374 hospitalizations of patients with sepsis from 2006 through 2014 in the NIS database. Of these patients, 1 901 847 (13.6%) had cancer. The Figure shows the patient inclusion criteria, the proportion of cancer patients, and the 30-day mortality in both groups. The demographic characteristics of patients in the study are shown in Table 1. Compared with patients without cancer, patients with cancer were slightly older, were more likely to be female, and had a slightly higher burden of comorbidities. The lower respiratory and genitourinary tracts were the most common sources of infection in both groups. Patients with cancer had a significantly higher incidence of lower respiratory tract infection (35.0% vs 31.6%) and intra-abdominal infection (5.5% vs 4.6%) than did patients without cancer. Gram-positive and gram-negative bacteria were the most common pathogens in both groups.

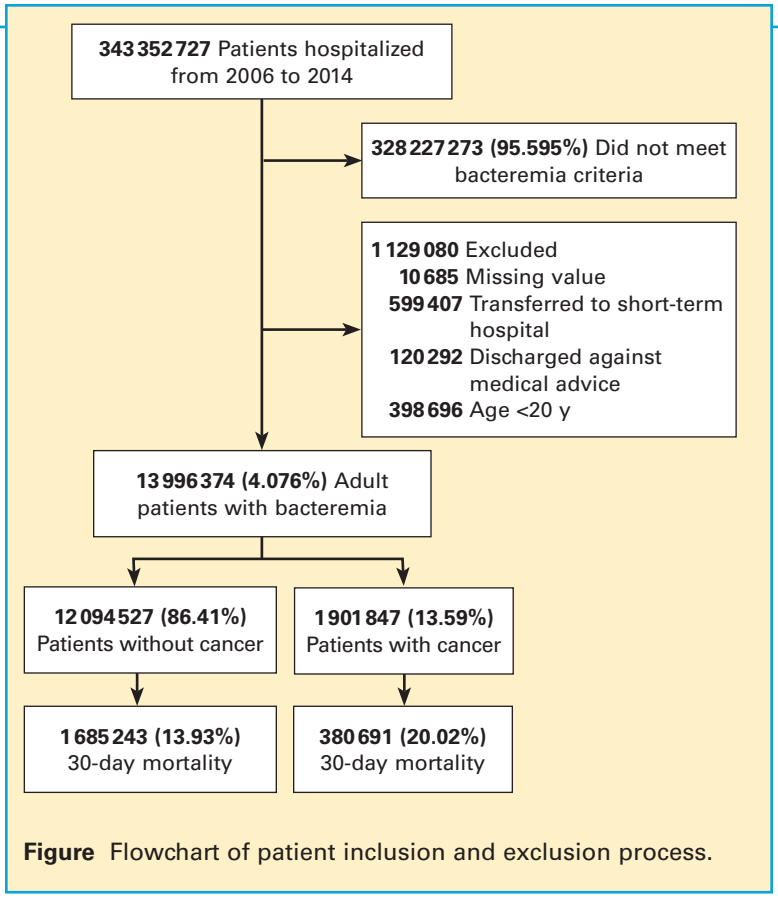

Figure Flowchart of patient inclusion and exclusion process.

Anaerobes (1.2% vs 0.9%) and fungi (4.8% vs 2.9%) were more common pathogens in patients with cancer than in patients without cancer (Table 1).

The trend analysis revealed a steady increase in sepsis incidence from 2006 through 2014 in patients with cancer and in those without cancer (Tables 2 and 3). *Escherichia coli* (77.1 cases per 100 000 hospitalizations), *Staphylococcus aureus* (56.2 cases per 100 000 hospitalizations), and *Streptococcus* species (53.9 cases per 100 000 hospitalizations) were the 3 most common microorganisms causing sepsis in patients with cancer from 2012 through 2014. Among these 3 organisms, the mean increase in annual incidence was highest for *E coli* (19.1%), followed by *Streptococcus* species (11.9%) and *S aureus* (6.4%). The incidence of anaerobic sepsis increased by 90.8% among patients with cancer during the study period, with an annual increase of 16.5%.

Compared with patients without cancer, patients with cancer had significantly increased rates of sepsis caused by gram-negative, gram-positive, and anaerobic organisms.

Compared with patients without cancer, patients with cancer had significantly increased rates of sepsis caused by gram-negative, gram-positive, and anaerobic organisms. The temporal incidence trends for the 2 groups are shown in Table 3 and Supplemental Figure 1. Despite the different trends of sepsis incidence in patients with cancer and those without cancer, the trends of sepsis mortality were similar in both groups of patients. The sepsis mortality rate decreased dramatically during the study period, particularly for infections caused by gram-positive bacteria, gram-negative bacteria, and anaerobes (Table 4, Supplemental Figure 2).

Patients with cancer had a higher crude 30-day mortality rate (20.0%) than did patients without cancer (13.9%). To evaluate the independent impact of cancer on sepsis mortality, we created a propensity score for matching. The standardized differences in baseline covariates after propensity score matching were minimal (Supplemental Table 4). In the propensity score–matched cohort, the mortality rate remained higher for patients with cancer than for patients without cancer overall (HR, 1.25; 95% CI, 1.24-1.26). The mortality rate differences in patients with cancer and patients without cancer were the most pronounced for sepsis caused by gram-negative organisms, followed by fungi, anaerobic organisms, and gram-positive organisms (Table 5). We further evaluated the independent impact of different cancer sites on survival of patients with sepsis by using a propensity score–adjusted Cox regression model. Compared with patients with breast cancer, who had the highest survival rate, patients with lung cancer had the lowest survival rate (HR, 1.65; 95% CI, 1.60-1.69), followed by those with gastrointestinal cancer (HR, 1.09; 95% CI, 1.06-1.12) and gynecologic cancer (HR, 1.06; 95% CI, 1.03-1.10). The mortality rate for patients with hematologic cancer was similar to that of patients with breast cancer (HR, 1.03; 95% CI, 1.00-1.06).

Discussion

Although several previous studies have focused on the epidemiology of sepsis at the population level,[22,23] few have specifically evaluated sepsis in patients with cancer. A prospective analysis of cancer survivors suggested that this population had a 2-fold increase in the risk of community-acquired sepsis, even after adjustments for common confounders.[6] The authors postulated that physiologic mechanisms to account for this association include cytokine release and the resulting chronic inflammatory state[6,24] and the destruction of healthy cells during cytotoxic treatments, all leading to compromised immunity.[6,24,25]

Table 1
Demographic characteristics of study cohort[a]

Characteristic	Patients without cancer (n = 12 094 527)	Patients with cancer (n = 1 901 847)	*P*
Age, mean (SE), y	66.4 (0.08)	67.7 (0.13)	<.001
Male sex	6 049 000 (50.0)	844 125 (44.4)	<.001
Comorbidity			
Combined comorbidity score, mean (SE)	11.0 (0.04)	11.5 (0.05)	<.001
Hypertension	6 458 354 (53.4)	912 422 (48.0)	<.001
Congestive heart failure	2 653 921 (21.9)	304 992 (16.0)	<.001
Valvular heart disease	767 509 (6.3)	99 949 (5.3)	<.001
Peripheral vascular disease	1 045 668 (8.6)	113 280 (6.0)	<.001
Chronic pulmonary disease	2 916 046 (24.1)	467 956 (24.6)	.003
Uncomplicated diabetes	2 816 584 (23.3)	377 530 (19.9)	<.001
Diabetes with complications	1 079 522 (8.9)	80 118 (4.2)	<.001
Chronic renal failure	3 058 712 (25.3)	327 970 (17.2)	<.001
Chronic liver disease	651 245 (5.4)	64 918 (3.4)	<.001
Rheumatic disease	423 519 (3.5)	51 290 (2.7)	<.001
Coagulopathy	1 464 986 (12.1)	318 449 (16.7)	<.001
Neurological disorders	1 759 941 (14.6)	166 476 (8.8)	<.001
Paralysis	839 019 (6.9)	53 535 (2.8)	<.001
AIDS	135 607 (1.1)	20 496 (1.1)	.08
Psychoses	619 188 (5.1)	65 416 (3.4)	<.001
Depression	1 147 515 (9.5)	181 680 (9.6)	.38
Obesity	1 279 919 (10.6)	129 793 (6.8)	<.001
Drug abuse	401 387 (3.3)	25 656 (1.3)	<.001
Alcohol abuse	521 300 (4.3)	35 588 (1.9)	<.001
Source of infection			
Lower respiratory tract	3 825 521 (31.6)	665 653 (35.0)	<.001
Genitourinary tract	4 541 396 (37.5)	531 214 (27.9)	<.001
Skin and skin structure	1 217 805 (10.1)	131 238 (6.9)	<.001
Bloodstream, catheter related	832 304 (6.9)	104 390 (5.5)	<.001
Intra-abdominal	558 476 (4.6)	104 605 (5.5)	<.001
Biliary tract	68 267 (0.6)	8109 (0.4)	<.001
Musculoskeletal	479 474 (4.0)	28 065 (1.5)	<.001
Causative microorganisms			
Gram-positive pathogens	3 548 623 (29.3)	520 736 (27.4)	<.001
Gram-negative pathogens	3 024 648 (25.0)	448 670 (23.6)	<.001
Anaerobes	112 687 (0.9)	22 969 (1.2)	<.001
Fungi	356 226 (2.9)	91 484 (4.8)	<.001

[a] Numbers are total episodes of sepsis hospitalizations in the subperiod; values are number (percentage) unless otherwise indicated in the first column.

A small retrospective study of patients with sepsis at a tertiary hospital emergency department suggested that patients with sepsis and cancer were younger, had fewer comorbidities, and had more hemodynamic instability during presentation than patients with sepsis and no cancer.[7] Our study, which used a larger, nationally representative sample, conversely showed that patients with sepsis and cancer were older, were more likely to be female, and had more comorbidities than patients with sepsis and no cancer.

Our trend analyses showed that the incidence of sepsis increased over time but that the sepsis mortality rate decreased in patients with cancer and in those without cancer. The general increase in sepsis incidence may be attributed partly to the aging population; older patients are at higher risk for infection because of frailty and a higher incidence of comorbidities.[26] However, changes in the coding of sepsis over the years may be a confounding factor.[27] Much of the improvement in sepsis mortality has been attributed to the Surviving Sepsis Campaign[28] and early goal-directed therapy. Early goal-directed therapy emphasizes the importance of early recognition and antibiotic administration to improve sepsis care in the emergency department.[29-32] Although this approach has become more controversial, with recent clinical trials questioning the need for every component of early goal-directed therapy,[33] following sepsis guidelines has been shown to improve mortality rates.[34] Many studies have shown improvements in sepsis mortality rates over the years. However, a large

Table 2
Number of sepsis hospitalizations by causative organism among patients with cancer

Organism	No. of events per 100 000 hospitalizations		
	2006-2008	2009-2011	2012-2014
Gram-positive pathogens	121.5	161.7	174.2
Staphylococcus aureus	40.0	52.6	56.2
Pneumococcus	8.5	11.3	11.6
Streptococcus species	31.1	47.8	53.9
Meningococcus	0.03	0.08	0.06
Gram-negative pathogens	89.6	137.9	168.2
Escherichia coli	36.6	59.6	77.1
Hemophilus influenzae	1.2	1.9	2.1
Proteus mirabilis	2.0	3.6	4.6
Pseudomonas species	16.0	23.6	24.4
Salmonella species	0.2	0.3	0.4
Serratia species	1.2	1.3	1.2
Anaerobes	4.6	6.9	8.8
Bacteroides fragilis	0.4	0.7	0.7
Clostridium perfringens	0.2	0.3	0.3
Fungi	21.1	29.3	29.9
Candida species	5.8	6.8	5.8

single-institution study found that sepsis mortality rates declined from 2003 to 2014 in patients with cancer but not in patients without cancer.[8] Unlike our study, that study used clinical criteria instead of administrative codes to define sepsis. This difference may be pertinent because the results of one study suggested that clinical data paint a different picture of sepsis trends than do claims-based analyses, showing that the sepsis-related mortality rate was stable from 2009 through 2014.[35] Cooper et al[8] theorized that cancer-specific reductions in sepsis-related mortality indicate that universal improvements in sepsis care may be overstated and that cancer-specific trends, such as the growing availability of targeted, less-toxic cancer treatments, should be examined instead.[8,36]

A systematic review by Montassier et al[12] revealed that gram-negative bacteria are now the most dominant pathogens in sepsis. Although sepsis caused by gram-positive bacteria was more common in our study, the differences have become smaller over time. This epidemiologic shift may have resulted from the decreased use of quinolone prophylaxis, the nature of chemotherapy (myeloablative vs nonmyeloablative chemotherapy), the decreased use of indwelling catheters, and the emergence of antibiotic-resistant pathogens. In our study, *E coli* was the most prevalent causative organism, although sepsis caused by anaerobes increased at the fastest rate (16.5% per year). Concern has been growing over the increase in extended-spectrum β-lactamase–producing *E coli* infections among immunocompromised patients with cancer.[37] This increase appears to have a strong link to prior antibiotic use. The use of quinolone prophylaxis in patients with cancer has decreased,[38] which may be one explanation for the trend of increased gram-negative over gram-positive bacteremia over the years. Another potential explanation is the emergence of more antibiotic-resistant organisms,

Table 3
Annual change in incidence of organisms causing sepsis in patients without cancer and patients with cancer

Organism	Patients without cancer		Patients with cancer		*P* (between groups)
	Annual change in incidence,%	*P*	Annual change in incidence,%	*P*	
Gram-positive pathogens	4.0	<.001	7.4	<.001	<.001
Staphylococcus aureus	3.2	<.001	6.4	<.001	<.001
Pneumococcus	2.2	.18	4.8	.01	.42
Streptococcus species	7.2	<.001	11.9	<.001	<.001
Meningococcus	6.9	.54	22.6	.35	.70
Gram-negative pathogens	9.8	<.001	15.8	<.001	<.001
Escherichia coli	11.2	<.001	19.1	<.001	<.001
Hemophilus influenzae	12.2	<.001	13.5	.001	<.001
Proteus mirabilis	9.2	<.001	15.8	<.001	<.001
Pseudomonas species	6.0	<.001	9.9	.002	<.001
Salmonella species	36.7	<.001	29.0	.004	<.001
Serratia species	2.8	.06	3.3	.43	.08
Anaerobes	13.4	<.001	16.5	<.001	<.001
Bacteroides fragilis	17.1	<.001	11.3	.005	<.001
Clostridium perfringens	4.9	.004	3.1	.26	.02
Fungi	4.2	.17	11.6	.007	.54
Candida species	-1.7	.06	2.5	.84	.04

Table 4
Annual change in hospital 30-day mortality according to organisms causing sepsis in patients without cancer and patients with cancer

Organism	Patients without cancer		Patients with cancer		*P* (between groups)
	Annual change in rate,%	*P*	Annual change in rate,%	*P*	
Gram-positive pathogens	−3.4	<.001	−2.5	<.001	.13
Staphylococcus aureus	−3.4	<.001	−2.9	<.001	.90
Pneumococcus	−3.6	<.001	−1.4	.11	.51
Streptococcus species	−3.7	<.001	−4.9	<.001	.03
Meningococcus	28.5	.32	−11.1	.12	.07
Gram-negative pathogens	−3.3	<.001	−2.5	<.001	.05
Escherichia coli	−3.7	<.001	−3.6	<.001	.01
Hemophilus influenzae	−3.8	.05	−1.5	.33	.71
Proteus mirabilis	−5.0	.003	−3.6	.02	.51
Pseudomonas species	−2.7	<.001	−1.9	.001	.24
Salmonella species	6.6	.68	−6.7	.44	.47
Serratia species	−3.5	.005	−2.8	.30	.65
Anaerobes	−4.4	<.001	−1.5	.04	.21
Bacteroides fragilis	−5.9	.31	−4.7	.47	.74
Clostridium perfringens	−7.0	.93	−1.3	.25	.29
Fungi	−0.5	.64	−0.5	.17	.29
Candida species	−1.0	.33	−0.3	.17	.43

Table 5
Crude mortality rates and hazard ratios for patients with sepsis without cancer and those with cancer according to type of pathogen

Type of pathogen	Crude mortality rate, % (No. of patients)		Hazard ratio (95% CI)[a]	
	Patients without cancer	Patients with cancer	Crude (reference: patients without cancer)	Propensity score–matched (95% CI)
Overall	13.9 (1 685 243/12 094 527)	20.0 (380 691/1 901 847)	1.48 (1.47-1.50)	1.25 (1.24-1.26)
Gram-positive	11.1 (393 012/3 548 623)	13.7 (71 105/520 736)	1.25 (1.22-1.27)	1.05 (1.04-1.06)
Gram-negative	7.8 (236 631/3 024 648)	12.1 (54 482/448 670)	1.59 (1.56-1.63)	1.29 (1.27-1.31)
Anaerobes	13.6 (15 272/112 687)	16.1 (3707/22 969)	1.20 (1.11-1.3)	1.12 (1.06-1.17)
Fungi	11.6 (41 461/356 226)	15.7 (14 375/91 484)	1.38 (1.32-1.45)	1.16 (1.13-1.19)

[a] *P*<.001 for all hazard ratios.

for example, the observed increase in bacteremia caused by extended-spectrum β-lactamase–producing *E coli* and vancomycin-resistant enterococci among cancer patients with neutropenia.[37,39] The use of quinolone prophylaxis has also been linked to the rise in antimicrobial-resistant gram-negative bacteria. In the future, careful antimicrobial stewardship must be tailored both to individual cancer patients and to the general population.

The sepsis mortality rate is higher in patients with underlying cancer than in patients without cancer.[6,34] One study demonstrated that in-hospital mortality caused by sepsis was 29% higher in patients with cancer than in patients without cancer.[7] The authors postulated that the higher sepsis-related mortality rate in patients with cancer may stem from a large tumor burden, cytokine release, and cytotoxic agents in patients with immunosuppression. In our study, we also found that patients with cancer had a higher mortality risk in both the crude analysis and in the propensity score–matched cohorts. One study of sepsis incidence and mortality

in patients with different cancer types showed that the incidence of sepsis was higher in patients with hematologic malignant neoplasms than in patients with solid tumors but that the mortality rate was similar in both groups.[40] Lung cancer was associated with the highest mortality rate in that study,[40] but gastrointestinal tumors were associated with the highest sepsis mortality rate in another.[7] Our findings were fairly consistent with the findings of these 2 studies, showing that lung cancer followed by gastrointestinal cancer had the highest rate of mortality resulting from sepsis.

The advantage of our study is the use of the largest administrative database of hospital admissions in the United States, with a nationally representative weighted sample, to examine incidence and mortality trends across time. These data are inherently subject to many limitations. Despite the robust propensity score matching that we performed, unmeasured confounders remain a potential issue given the observational nature of the study. All available data are from patients' hospitalizations, and the NIS does not include long-term outpatient data, so our analysis was limited to representing the short-term impact of cancer on event outcomes. Some data may be incomplete, misclassified, or omitted because of the reliance on medical coders. Changes in coding practices and quality over time may also affect the results. The codes from the NIS database used to define sepsis have been internally and externally validated[17] and did not change significantly during the study period. Nevertheless, the use of ICD data rather than clinical data for identifying sepsis is an increasing concern.[35]

The advantage of our study is the use of the largest administrative database of hospital admissions in the United States, with a nationally representative weighted sample, to examine incidence and mortality trends across time.

Conclusions

The epidemiology of sepsis has undergone substantial changes over the years in patients with cancer and in patients without cancer, so our study has widespread clinical and public health implications. Our study shows that patients with cancer are at high risk of sepsis incidence and sepsis mortality and provides pathogen-specific data relevant to clinicians. Guideline-based therapy may improve sepsis mortality rates. Antibiotic stewardship programs should identify patients with cancer as a high-risk group. Future studies are needed to tailor surveillance and antimicrobial prophylaxis appropriately according to the latest epidemiologic data.

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SEE ALSO

For more about sepsis, visit the *AACN Advances in Critical Care* website, **www.aacnacconline.org**, and read the article by Gilbert et al, "Strategies for the Management of Sepsis" (Spring 2019).

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Supplemental Table 1
ICD-9-CM codes for sources of infections associated with sepsis

Source of infection	*ICD-9-CM* codes
Lower respiratory tract	481, 482, 485, 486, 491.21, 494, 510, 513, 033, 484, 483
Genitourinary tract	590, 597, 599.0, 601, 098
Intra-abdominal	540, 541, 542, 566, 567, Peritonitis, 569.5, 569.83, 572.0
Skin and skin structure	682, 683, 686, 035
Musculoskeletal system	711.0, 730
Bloodstream, catheter related	996.6
Biliary tract	572.1, 575.0

Abbreviation: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*

Supplemental Table 2
ICD-9-CM codes used to identify specific organisms

Organism	*ICD-9-CM* codes
Gram-positive	
Staphylococcus aureus	038.11, 038.12, 041.11, 041.12, 482.41, 482.42
Other staphylococci	038.10, 038.19, 041.10, 041.19, 482.40, 482.49, 320.3, 008.41
Streptococcus species	038.0, 041.0, 041.00, 041.01, 041.02, 041.03, 041.04, 041.05, 041.09, 482.3, 482.30, 482.31, 482.32, 482.39, 320.2
Pneumococcus	038.2, 041.2, 481, 320.1
Meningococcus	036, 036.0, 036.1, 036.2, 036.3, 036.4, 036.40, 036.41, 036.42, 036.43, 036.8, 036.81, 036.82, 036.89, 036.9
Clostridium difficile	008.45
Bacillus anthracis (anthrax)	022.3, 022.8, 022.9, 484.5
Gram-negative	041.83
Salmonella	
Causing infection	003, 003.0, 003.1, 003.21, 003.22, 003.23, 003.24, 003.8, 003.9
Causing typhoid/paratyphoid fevers	002, 002.0, 002.1, 002.2, 002.3, 002.9
Hemophilus influenzae	038.41, 041.5, 482.2, 320.0
Escherichia coli	038.42, 041.4, 008.0, 008.00, 008.01, 008.02, 008.03, 008.04, 008.09, 482.82
Pseudomonas species	038.43, 482.1, 008.42, 041.7
Serratia species	038.44
Proteus mirabilis or *morganii*	041.6, 008.3
Legionella pneumophila	482.84
Others	038.4, 038.40, 038.49, 041.3, 041.85, 482.0, 482.83, 320.82, 008.1, 008.2, 008.43, 008.44, 008.47
Anaerobes	
Bacteroides fragilis	041.82
Clostridium perfringens	041.83
Others	038.3, 041.84, 482.81, 320.81, 008.46
Fungi	
Candida species	112.5, 112.81
Others	321.0, 321.1, 484.6, 484.7, 112.4, 112.83, 112.85, 115, 115.0, 115.01, 115.02, 115.03, 115.04, 115.05, 115.09, 115.1, 115.10, 115.11, 115.12, 115.13, 115.14, 115.15, 115.19, 115.9, 115.90, 115.91, 115.92, 115.93, 115.94, 115.95, 115.99, 117, 117.0, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.8, 117.9, 118

Abbreviation: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*

Supplemental Table 3
***ICD-9-CM* codes for types of cancer**

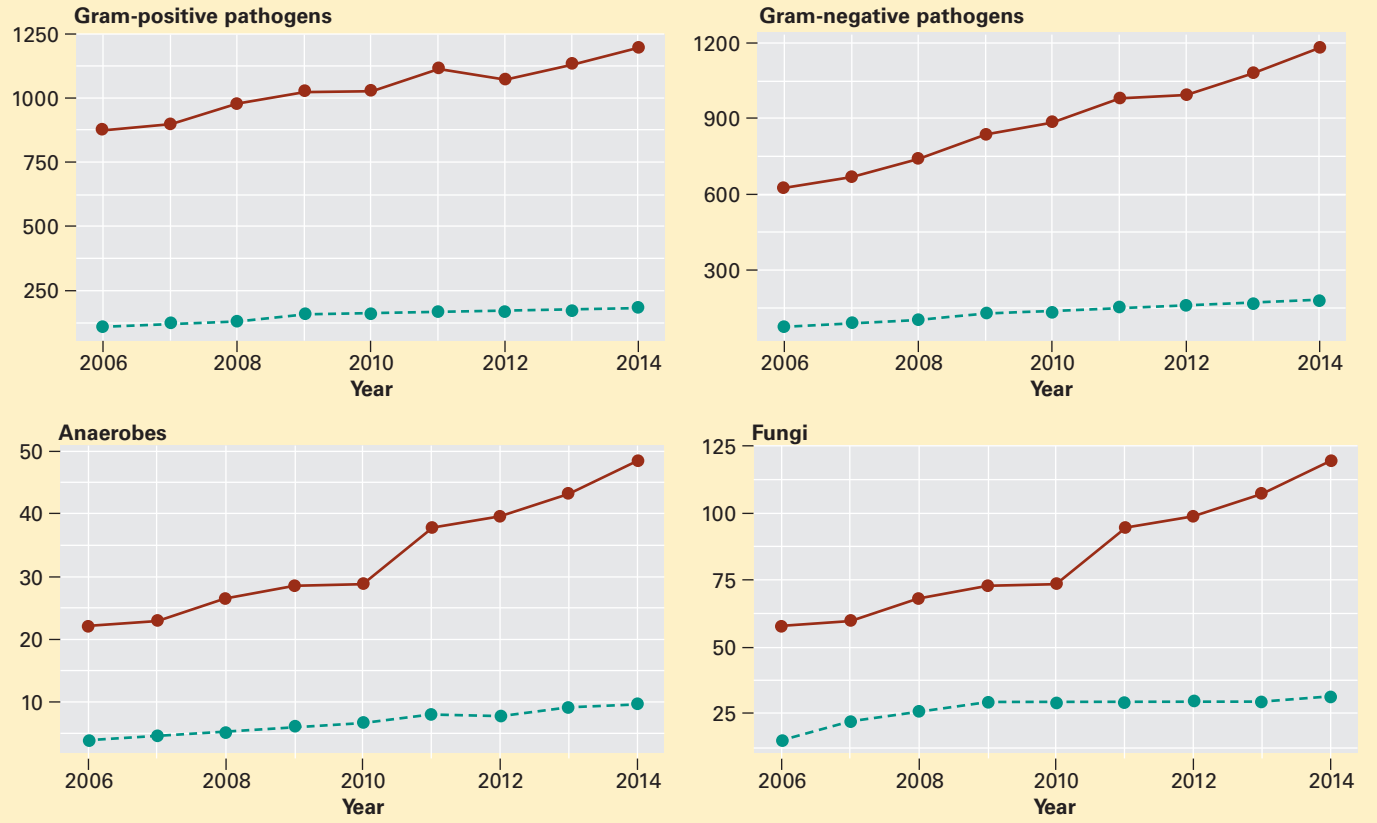
Primary type of cancer	*ICD-9-CM* codes
Cancer of bronchus; lung	(1622-1625), 1628, 1629, 20921, 2312, V1011, 1620, 1630, 1631, 1638, 1639, 1650, 1658, 1659, 2311, 2318, 2319, V1012, V1020, V1022
Malignant neoplasm of breast	(1740-1746), (1748-1750), 1759, 2330, V103
Malignant neoplasm of gastrointestinal tract	(1500-1505), 1508, 1509, 2301, V1003, (1510-1516), 1518, 1519, 20923, 2302, V1004, 1530, (1531-1539), 1590, 20910, (20911-20916), 2303, V1005, (1540-1543), 1548, 20917, (2304-2306), (79670-79674), 79676, V1006
Malignant neoplasm of the hematopoietic and lymphoid tissues (hematologic cancer)	(20100-20108), 20110, (20111-20118), 20120, (20121-20128), 20140, (20141-20148), 20150, (20151-20158), (20160-20168), (20170-20178), (20190-20198), V1072, (20000-20008), 20010, (20011-20018), 20020, (20021-20028), (20030-20038),(20040-20048), (20050-20058), (20060-20068), (20070-20078), (20080-20088), (20200-20208), (20210-20218), (20220-20228), (20270-20278), (20280-20288), (20290-20298), V1071, V1079, (20240-20248), 2031, (20310-20312), 2040, (20400-20402), 2041, (20410-20412), 2042, (20420-20422), 2048, (20480-20482), 2049, (20490-20492), 2050, (20500-20502), 2051, (20510-20512), 2052, (20520-20522), 2053, (20530-20532), 2058, (20580-20582), 2059, (20590-20592), 2060, (20600-20602), 2061, (20610-20612), 2062, (20620-20622), 2068, (20680-20682), 2069, (20690-20692), 2070, (20700-20702), 2071, (20710-20712), 2072, (20720-20722), 2078, (20780-20782), 2080, (20800-20802), 2081, (20810-20812), 2082, (20820-20822), 2088, (20880-20882), 2089, (20890-20892), (V1060-V1063), V1069, 2030, (20300-20302), 2038, (20380-20382)
Malignant neoplasm of genitourinary organs (gynecologic cancer)	179, 1820, 1821, 1828, 2332, V1042, 1800, 1801, 1808, 1809, 2331, 7950, 79506, V1041, (79501-79504), 1830, V1043, 181, (1832-1835), (1838-1844), 1848, 1849, 2333, (23330-23332), 23339, 79516, V1040, V1044
Malignant neoplasm of unspecified sites	(1640-1643), 1648, 1649, (1760-1765), 1768, 1769, (1900-1909), (1940-1949), (1951-1955), 1958, (20230-20238), (20250-20258), (20260 -20268), 20922, (20925-20927), 2340, 2348, 2349, 7951, (79510-79514), V1029, V1081, V1084, V1088, V1089, V109, V1090, V1091, V711, (1990-1992), 20920, 20929, 20930, 20970, 20975, 20979, 2350, (2351-2359), (2360-2367), 23690, 23691, 23699, (2370-2377), (23770-23773), 23779, 2379, 2380, 238

Abbreviation: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*

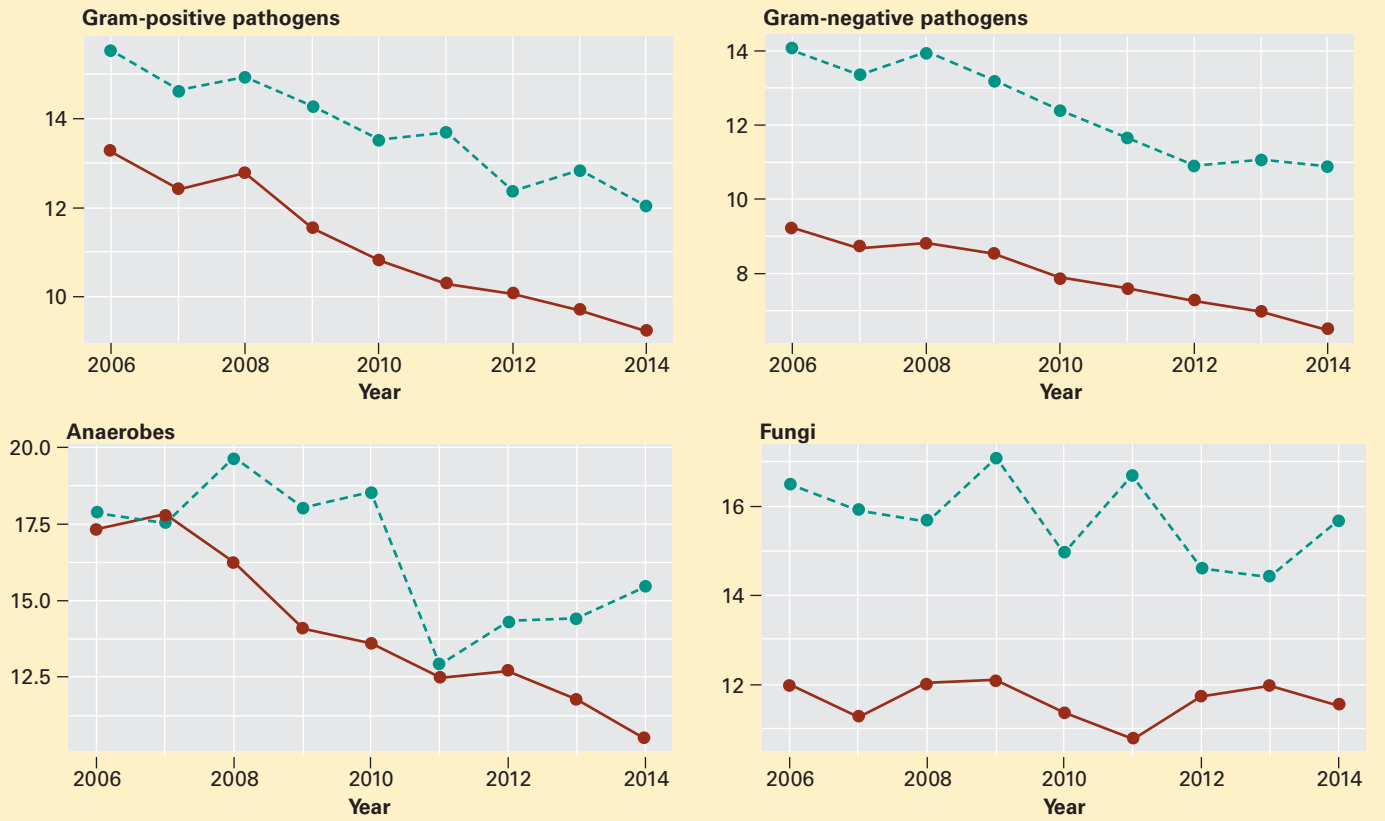
Supplemental Table 4

Standardized differences between patients with cancer and patients without cancer before and after propensity score matching

Variable	Standardized difference	
	Before matching	After matching
Age (years)	0.084	0.008
Male sex	0.113	0.016
Combined comorbidity score	0.052	0.022
Combined comorbidity score squared	0.034	0.019
Hypertension	0.109	0.005
Congestive heart failure	0.152	0.004
Valvular heart disease	0.047	0.002
Peripheral vascular disease	0.104	0.009
Chronic pulmonary disease	0.011	0.021
Uncomplicated diabetes	0.084	0.005
Diabetes with complications	0.192	0.005
Chronic renal failure	0.198	0.011
Chronic liver disease	0.096	0.000
Rheumatic disease	0.047	0.002
Coagulopathy	0.132	0.011
Neurological disorders	0.182	0.006
Paralysis	0.192	0.000
AIDS	0.004	0.010
Psychoses	0.083	0.001
Depression	0.003	0.004
Obesity	0.133	0.004
Drug abuse	0.131	0.001
Alcohol abuse	0.141	0.000
Lower respiratory tract infection	0.072	0.002
Genitourinary tract infection	0.206	0.013
Skin and skin structure infection	0.114	0.004
Catheter-related bloodstream infection	0.058	0.000
Intra-abdominal infection	0.041	0.010
Biliary tract infection	0.019	0.004
Musculoskeletal infection	0.153	0.005



Supplemental Figure 1 Number of sepsis hospitalizations according to type of pathogen in patients with cancer (green) and patients without cancer (red) from 2006 to 2014.



Supplemental Figure 2 Thirty-day mortality rate (%) according to type of pathogen in patients with cancer (green) and patients without cancer (red) from 2006 to 2014.