Doctor of Medicine

Prognostic Analysis of Cancer Patients with Septic Shock In Emergency Department from 2009 to 2017 : A Retrospective Cohort Study

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Prognostic Analysis of Cancer Patients with Septic Shock In Emergency Department from 2009 to 2017 : A Retrospective Cohort Study

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Abstract

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Background

The increasing incidence of cancer significantly strains global healthcare finances, particularly among individuals aged 75 and older, leading to more frequent emergency department (ED) visits and treatments for cancer patients. Despite advancements in cancer diagnosis and treatment, prolonged treatment and associated complications contribute to various organ dysfunctions, with septic shock being as a common life-threatening complication among cancer patients. Although recent studies show improved survival outcomes for cancer patients with septic shock, managing their ED care remains challenging due to extensive resource demands and costs. Neutropenia is prevalent among cancer patients with septic shock; however, its prognostic impact remains unclear. Furthermore, septic shock often leads to acute kidney injury (AKI), a complication associated with increased mortality rates and medical expenses in cancer patients. Our population-based study aims to assess trends in mortality rates among cancer patients experiencing septic shock, evaluate the impact of neutropenia, and explore factors associated with sepsis-related AKI to provide insights for improved treatment strategies.

Method

This population-based cohort study utilized data from the Korean National Health Information Database (NHID) spanning from 2009 to 2017. Patients presenting with

septic shock through the emergency department were identified using clinical surveillance criteria. Cancer patients within this cohort were identified by diagnosis codes within 90 days before admission. Descriptive analyses assessed characteristics and mortality rates among survivors and non-survivors at 30 days and 1 year. Adjusted hazard ratios (HR) for 30-day mortality were calculated, controlling for age, sex, Charlson Comorbidity Index (CCI) and hospitalization year. Additional analyses explored neutropenia presence among cancer patients and its association with mortality rates. In another AKI cohort, baseline characteristics were compared between groups based on dialysis need for septic AKI and 2-year survival status. Independent predictors for septic AKI were identified through multivariate logistic regression analyses, and Cox-proportional hazards models compared survivors and non-survivors at 30 days and 2 years. All analyses used two-sided P values < 0.05 and were conducted using SAS Enterprise Guide version 7.1.

Results

From 2009 to 2017, 322,526 patients were admitted to South Korean EDs with septic shock, 43,850 (13.6%) had a cancer diagnosis within the preceding 90 days. After excluding patients under 18 years old or with incomplete data, 43,466 patients were analyzed, among whom 22,639 (52.1%) died within 30 days and 35,325 (81.3%) died within 1 year. From 2010 to 2015, there was a slight decrease in cancer patients with septic shock, followed by an increase in 2016. Mortality rates at 30 days and 1 year showed a decline since 2011. Adjusted HRs for 30-day mortality indicated higher risk with increasing age, presence of comorbidities, and specific cancer types. Notably, admissions in 2016 and 2017 showed improved 30-day mortality rates compared to 2009. Among cancer patients with septic shock, 14.7% had neutropenia, which was

associated with a 30-day mortality rate of 44.5%. Patients without neutropenia were older and had higher comorbidity burdens. Neutropenic patients had better survival rates at both 30 days and 1 year. Among cancer patients with septic shock, 12.8% experienced AKI requiring dialysis, with 77.9% of these patients recovering within 30 days. Those needing dialysis were younger and had lower comorbidity scores. Female sex, younger age, and absence of hypertension, diabetes, heart failure, or liver cirrhosis reduced the likelihood of developing septic AKI. The occurrence of AKI requiring dialysis was associated with higher 1-month mortality rates. The overall 2-year mortality rate was 85.1%. More non-survivors required dialysis during hospitalization. Higher age, male gender, liver cirrhosis, and higher comorbidity scores were associated with higher 2-year mortality rates.

Conclusions

Recently, mortality rates of septic shock among cancer patients have decreased across all cancer types. Even with neutropenia, mortality rates did not worsen, suggesting that intensive care should not be withheld solely on neutropenia status. In septic AKI patients requiring dialysis, mortality rates were notably high, especially among males, hematologic cancer patients, and those with multiple comorbidities.

Key words

Cancer patients with septic shock; Mortality; Neutropenia; Acute Kidney Injury

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List of Abbreviations

ANC = absolute neutrophil count;

AKI = acute kidney injury;

CCI = Charlson Comorbidity Index;

CLD = chronic lung disease

CI = confidence Interval;

CHF = congestive heart failure;

CRRT = continuous renal replacement therapy;

DM = diabetes mellitus;

ED = emergency department;

FRS = female reproductive system;

G-CSF = granulocyte colony-stimulating factor;

HR = hazard ratio;

HIRA = Health Insurance Review and Assessment Service;

HD = hemodialysis;

HTN = hypertension;

ICU = intensive care unit;

ICD - 10 = International Classification of Diseases 10th edition;

IQR = interquartile ranges;

LC = liver cirrhosis;

MRS = male reproductive system;

NHID = National Health Information Database;

NHIS = National Health Insurance Service;

NHL = Non-Hodgkin Lymphoma;

RRT = renal replacement therapy;

SS = septic shock

Introduction

Cancer presents a significant global health burden, with a 20% increase in incidence among individuals aged 75 and older.[1] Emergency department (ED) visits and treatments for cancer patients are also on the rise.[2] Over the past two decades, significant advancements in cancer diagnosis and treatment have led to improved survival outcomes.[3-7] However, the prolonged duration of cancer morbidity and significant complications due to treatments such as chemotherapy, radiotherapy, and surgery lead to an increased incidence of organ dysfunction.[8-10] Septic shock, in particular, stands out as one of the most common life-threatening complications among cancer patients, with a high mortality rate.[7,11-14]

Among patients admitted to the intensive care unit (ICU) with septic shock, the presence of cancer and treatment history have been identified as a risk factor for in-hospital mortality.[15,16] Recent research indicates that the survival outcomes of cancer patients with septic shock have improved over time.[7,17,18] However, managing ED care and treatment for cancer patients with septic shock is challenging due to extensive medical resource utilization and associated costs.[17] There is insufficient reliable data available to guide medical decisions, and more comprehensive information is required in this regard.[17,18]

Neutropenia is common among cancer patients with septic shock. It is one of the major side effects of chemotherapy drugs, defined as an absolute neutrophil count (ANC) of less than 500/mm³. However, the prognostic impact of neutropenia in sepsis and septic shock has not been thoroughly evaluated. ICU physicians often associate neutropenia with higher mortality rates in critically ill patients.[19] Nevertheless,

advancements in the management of sepsis and cancer, such as the empirical use of broad-spectrum antibiotics and antifungals based on experience-driven guidelines, have led to an overall improvement in survival rates.[20,21] Previous studies of neutropenic patients suggested that the timing of ICU admissions is crucial for improving the survival rates. These studies showed that neutropenia does not significantly affect mortality rates among cancer patients admitted to the ICU.[20,22-24] Therefore, neutropenia cannot be used as a criterion for admitting cancer patients to the ICU, nor does it necessarily warrant withdrawal of life-sustaining treatments in this population. There is limited data on neutropenic patients with septic shock, one of the most critical complications in cancer patients. Current guidelines for the management of neutropenic septic shock in cancer patients advocate for further research without excluding specific patient populations.[25]

Another significant complication of septic shock is acute kidney injury (AKI). Septic shock itself is one of the most common causes of AKI, associated not only with in-hospital mortality but also with the development of chronic kidney disease and end-stage renal failure. Additionally, it is related to increased long-term medical costs and mortality risk.[26] These adverse effects are particularly prominent in patients requiring dialysis for severe AKI.[27,28] Cancer patients are more likely to require dialysis for severe AKI compared to non-cancer patients.[29,30] The high incidence of AKI in cancer patients may be associated with exposure to nephrotoxic drugs and radiation, advancing age, cardiovascular diseases, and the increasing prevalence of chronic kidney conditions.[27,28,31] There have been studies evaluating the relationship between sepsis-related AKI and mortality, but less is known about the epidemiology and course of AKI in cancer patients. Most studies include small sample sizes and focus on

individual types of cancer. Additionally, the relationship between sepsis-related AKI and long-term mortality is particularly unclear.[29]

Our population-based study aims to evaluate the trends in short-term and long-term mortality rates among cancer patients who visited the ED with septic shock from 2009 to 2017 in Korea, stratified by cancer types. Second, we aim to determine whether neutropenia is associated with increased short-term and long-term mortality rates in cancer patients with septic shock. Third, we assessed factors associated with the occurrence of sepsis-related AKI among cancer patients experiencing septic shock and evaluated the impact of AKI requiring dialysis on long-term mortality.

Recent advancements in cancer treatment and the introduction of early protocol-driven resuscitation therapy for septic shock are presumed to result in more favorable outcomes for cancer patients with septic shock. This study could assist in devising improved treatment strategies by ensuring proper patient selection and allocation of clinical resources.

Subjects and methods

I. Study design and data collection

This study was a population-based cohort study using data from the Korean National Health Information Database (NHID), collected from 2009 to 2017 and released in 2021. NHID is a public database covering healthcare usage, health screening, socio-demographic variables, and mortality for the entire South Korean population (approximately 50 million people), established and maintained by the National Health Insurance Service (NHIS).[32] Following the enactment of South Korea's Medical Insurance Act in 1963, NHIS was established as the exclusive insurer. Every South Korean citizen is obligated to register with the NHIS.[32]

The data we extracted include demographic information, detailed medical cost information, medical treatments, disease history, and prescription information, which was converted into insurance claim information for the first day of medical treatment. The prescription information in the National Health Information Database (NHID) includes prescribed drugs (according to the NHIS drug list code), prescription dates, dosage, supply days, and administration routes. However, laboratory and radiologic data were not available.

II. Study Patients and Data Definitions

We identified patients who presented through the ED between 2009 and 2017 and met the clinical surveillance criteria for septic shock. According to The Third International Consensus Definitions for Sepsis and Septic Shock, sepsis and septic shock are defined as life-threatening conditions resulting from organ dysfunction caused by a dysregulated host response to infection, necessitating vasopressor therapy and characterized by elevated lactate levels.[33] We employed a clinical surveillance definition for septic shock, based on the simultaneous administration of vasopressors, antibiotics, and blood cultures.[34] Patients who had blood culture orders and received intravenous antibiotics (indicative of suspected infection) concurrently were categorized as septic shock patients if they received any form of vasopressor, including dopamine, norepinephrine, epinephrine, vasopressin, or phenylephrine.

Cancer patients were identified within the initial cohort of screened subjects as those individuals who had a cancer diagnosis code within the 90 days preceding their admission for septic shock. The accuracy of patient identification using a combination of diagnosis codes from NHID was estimated to be 98.2%, similar to that in the Korean National Cancer Incidence Database.[35,36] This identification method involved the use of International Classification of Diseases 10th edition (ICD-10) codes and rare incurable disease registration codes (V193, V027) to minimize misclassification, simultaneously considering patients diagnosed with cancer within 90 days before admission for septic shock, whether admitted as inpatients or received outpatient care.

Since 2005, the Korean NHIS has reimbursed 95% of all medical expenses related to cancer treatment for a period of 5 years after diagnosis. The Health Insurance Review and Assessment Service (HIRA) of South Korea evaluates the appropriateness of healthcare services and medical fee claims. If HIRA identifies insufficient medical charges related to healthcare services, NHIS either cancels the payment or demands reimbursement from healthcare providers. The cancer registration program by NHIS has strengthened the registration of cancer diagnosis codes as either primary or secondary diagnoses for Korean cancer patients.[37] The data cover almost all Koreans (approximately 50 million individuals) and the clinical data from all healthcare facilities in Korea.[38]

The primary cancer sites in the current research cohort were categorized into 21 types according to the classification provided by the Korean Cancer Association.[36] Underlying comorbidities were identified by recording patients who had two or more hospital visits with relevant diagnostic codes within a year prior to the septic shock date and calculating the Charlson comorbidity index (CCI).[39] Patients who were less than 18 years old at the time of their septic shock hospitalization or who had incomplete data were excluded. In cases of patients admitted multiple times due to septic shock, data collected at the first admission were utilized.

To identify patients with neutropenia, we used the ICD-10 diagnosis code for neutropenia (D70) or prescription information for granulocyte colony-stimulating factor (G-CSF) at the time of admission.

We defined AKI requiring dialysis among cancer patients with septic shock based on the admission diagnostic codes due to a lack of laboratory data on

creatinine levels and glomerular filtration rate in the NHID. Specifically, we considered continuous renal replacement therapy (CRRT) or hemodialysis (HD). Patients diagnosed with end-stage renal disease within 1 year or those who received renal replacement therapy (RRT) were excluded.[40] Recovery within one month from AKI-related dialysis was determined using diagnostic codes for RRT, HD, and peritoneal dialysis.

This study was approved by the Asan Medical Center Institutional Review Board (Study Number: 2019-0743) and the NHIS Inquiry Committee. To protect the personal privacy of study participants, the NHID from the NHIS were subjected to de-identification processes.

III. Statistical analysis

We conducted separate analyses for the overall patient cohort, the group divided based on the presence of neutropenia, and the group categorized by the occurrence of AKI.

Descriptive analyses were conducted to evaluate the characteristics of the 30-day and 1-year survivors and non-survivors among the total study patients. Categorical variables are presented as numbers and percentages and compared using Chi-square tests, whereas non-normally distributed continuous variables are presented as medians and interquartile ranges (IQR) and compared using Mann–Whitney U tests. Adjusted hazard ratios (HRs) for 30-day mortality was calculated after controlling for age, sex, and CCI in relation to the year of hospitalization. The composition ratio of cancer types and the mortality rates of the top 7 major cancers were also described by year.

Further descriptive analyses were conducted to characterize cohort stratified by the presence of neutropenia. We investigated the 30day and 1-year mortality rates regarding neutropenia occurrence across the top 7 prevalent cancers. Moreover, we calculated the percentage of patients receiving chemotherapy within 30 days preceding the onset of septic shock among the top 5 solid tumor patients. Adjusting for age, sex, and CCI, HRs were calculated to assess the association between neutropenia occurrence and the 30-day and 1-year mortality rates.

Additional descriptive analyses were conducted to compare the baseline characteristics between the group divided based on the need for dialysis for septic AKI and the group divided based on the status of 2-year survival. Independent

predictors for septic AKI development were identified through backward stepwise multivariate logistic regression analyses, incorporating variables with statistically significant differences (P values < 0.1) from univariate analysis. A Cox proportional hazards model with multivariable adjustment was utilized to compare survivors and non-survivors within 30 days and 2 years.

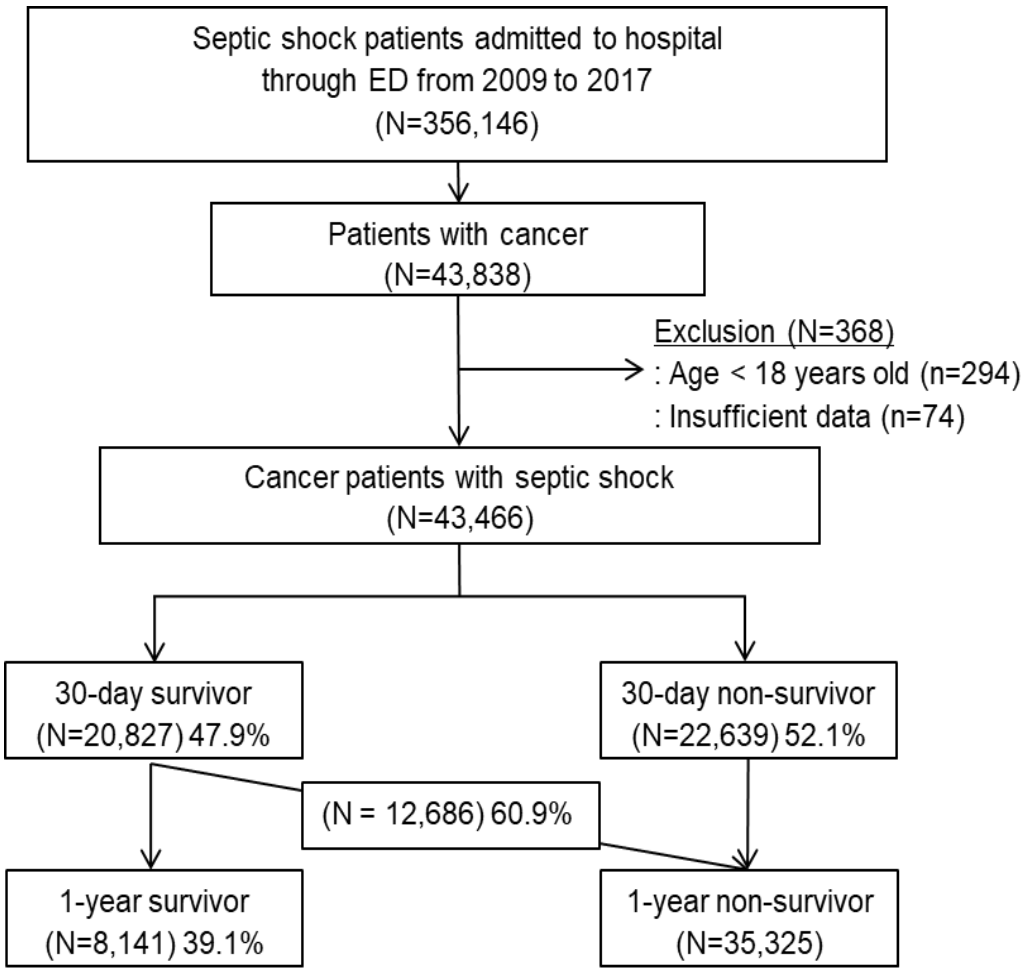
All tests of significance used two-sided P values < 0.05. These analyses were conducted using Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA).

Results

I. Patient enrollment and inclusion

From 2009 to 2017, there were 322,526 patients in South Korea who were admitted through the ED and met the clinical criteria for septic shock. 43,850 (13.6%) of these patients had ICD-10 codes (C00-C97) and cancer registration codes (V193, V027) for cancer within 90 days of the admission date. Patients under 18 years of age at the time of admission (290 individuals) or those with incomplete data (94 individuals) were excluded. Ultimately, the analysis in this study included 43,466 patients, among whom 22,639 (52.1%) died within 30 days of admission, and 35,325 patients (81.3%) died within 1 year (Figure 1).

Figure 1. Patients flow diagram for the study cohort



ED, emergency department.

II. Analysis of mortality rates and factors among cancer patients with septic shock.

Between 2010 and 2015, there was a small drop in the number of cancer patients experiencing septic shock, followed by a resurgence in enrollments from 2016. Mortality rates at both 30 days and 1 year showed a slight rise until 2011 but steadily declined since then until 2019. Despite fluctuations in total patient numbers, there is a consistent trend of decreasing mortality rates (Figure 2).

Figure 2. The annual total number of cancer patients and 30-day and 1-year the mortality rates

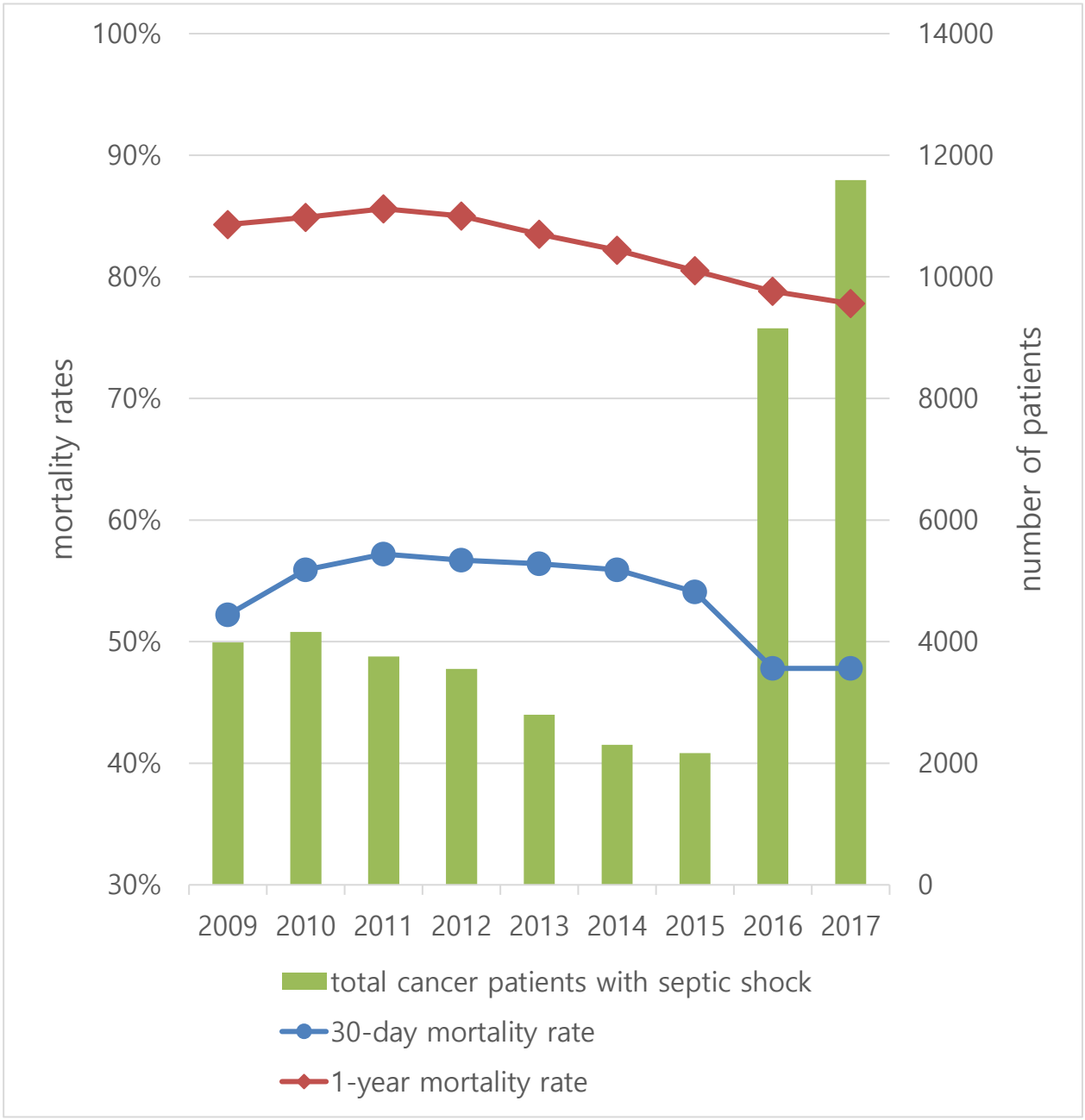


Table 1 presents the characteristics of the study population and the risk estimates for 30-day mortality. Female patients accounted for 35.4% of the total, with a lower HR compared to males (HR, 0.909; 95% CI, 0.884–0.934; P < 0.001). As age categories increased, the risk of 30-day mortality also increased, with the highest HR observed in the group aged 80 years and older compared to the reference group of 18 to 29 years (HR, 1.909; 95% CI, 1.614–2.259; P < 0.001).

The presence of multiple comorbidities was also correlated with the risk of 30-day mortality. Among the comorbidities, liver cirrhosis (11.4%) showed the highest HR (HR, 1.364; 95% CI, 1.313–1.417; P < 0.001), followed by chronic lung disease (HR, 1.212; 95% CI, 1.166–1.260; P < 0.001) and heart failure (HR, 1.123; 95% CI, 1.082–1.166; P < 0.001). With increasing grades according to the CCI, there was a corresponding increase in the risk of 30-day mortality. Specifically, compared to the group with a CCI score of less than 2, the group with a score of 8 or higher exhibited an observed HR of 1.822 (95% CI, 1.750–1.896; P < 0.001) (Table 1).

Table 1. Characteristics and hazard ratios for 30-day mortality based on demographics and comorbidities

Characteristic	Total (n = 43,466)	Survivor (n = 20,857)	Non-Survivor (n = 22,639)	Univariate Analysis		
				Hazard Ratios	95% CI	P value
Female	15,399 (35.4%)	7,736 (37.1%)	7,663 (33.9%)	0.909	0.884–0.934	<0.001
Age (years)						
18–29	397 (0.9%)	256 (1.2%)	141 (0.6%)	Reference		<0.001
30–39	828 (1.9%)	463 (2.2%)	365 (1.6%)	1.344	1.106–1.632	0.003
40–49	2,786 (6.4%)	1,408 (6.8%)	1,378 (6.1%)	1.576	1.325–1.874	<0.001
50–59	7,300 (16.8%)	3,633 (17.4%)	3,667 (16.2%)	1.630	1.378–1.929	<0.001
60–69	11,772 (27.1%)	5,875 (28.2%)	5,897 (26.1%)	1.634	1.382–1.931	<0.001
70–79	13,576 (31.2%)	6,187 (29.7%)	7,389 (32.6%)	1.841	1.559–2.175	<0.001
≥80	6,807 (15.7%)	3,005 (14.4%)	3,802 (16.8%)	1.909	1.614–2.259	<0.001

Table 1. Cont'd

Comorbidities						
Hypertension	23,136 (53.2%)	10,790 (51.8%)	12,346 (54.5%)	1.078	1.050–1.107	<0.001
Diabetes	16,977 (39.1%)	7,828 (37.6%)	9,149 (40.4%)	1.079	1.051–1.108	<0.001
CHF	5,745 (13.2%)	2,540 (12.2%)	3,205 (14.2%)	1.123	1.082–1.166	<0.001
CLD	5,008 (11.5%)	2,084 (10.0%)	2,924 (12.9%)	1.212	1.166–1.260	<0.001
Renal failure	2,783 (6.4%)	1,262 (6.1%)	1,521 (6.7%)	1.071	1.017–1.129	0.009
LC	4,974 (11.4%)	1,900 (9.1%)	3,074 (13.6%)	1.364	1.313–1.417	<0.001
CCI						
0–2	7,816 (18.0%)	4,731 (22.7%)	3,085 (13.6%)	Reference		<0.001
3–4	9,652 (22.2%)	4,922 (23.6%)	4,730 (20.9%)	1.366	1.306–1.430	<0.001
5–7	8,256 (19.0%)	3,986 (19.1%)	4,270 (18.9%)	1.469	1.402–1.538	<0.001
≥8	17,742 (40.8%)	7188 (34.5%)	10,554 (46.6%)	1.822	1.750–1.896	<0.001

Variables are expressed as number (%).

CCI, Charlson comorbidity index; CI, Confidence Interval; CLD, Chronic lung disease; CHF, Congestive heart failure; LC, Liver cirrhosis

The prevalence and the 30-day mortality rate varied by cancer type. Four major types, lung cancer (n = 6,657, 15.3%), liver cancer (n = 6,238, 14.4%), colorectal cancer (n = 4,494, 10.3%), and stomach cancer (n = 3,684, 8.5%), accounted for nearly half of all patients in the study. The highest HR for 30-day mortality was observed in lung cancer (HR, 2.292; 95% CI, 2.028–2.591; P < 0.001) and liver cancer (HR, 2.160; 95% CI, 1.909–2.442; P < 0.001) (Table 2).

Table 2. Characteristics and hazard ratios for 30-day mortality by cancer type

Cancer type	Total (n = 43,466)	Survivor (n = 20,857)	Non-Survivor (n = 22,639)	Univariate Analysis		
				HR	95% CI	P value
Brain	772 (1.8%)	500 (2.4%)	272 (1.2%)	Reference		<0.001
Lung	6,657 (15.3%)	2,469 (11.9%)	4,188 (18.5%)	2.292	2.028–2.591	<0.001
Liver	6,238 (14.4%)	2,506 (12.0%)	3,732 (16.5%)	2.160	1.909–2.442	<0.001
Colon	4,494 (10.3%)	2,611 (12.5%)	1,883 (8.3%)	1.310	1.154–1.488	<0.001
Stomach	3,684 (8.5%)	1,819 (8.7%)	1,865 (8.2%)	1.677	1.477–1.905	<0.001
Gall bladder	1,981 (4.6%)	1,117 (5.4%)	864 (3.8%)	1.336	1.166–1.532	<0.001
Pancreas	1,943 (4.5%)	913 (4.4%)	1,030 (4.6%)	1.782	1.559–2.037	<0.001
Leukemia	1,917 (4.4%)	864 (4.2%)	1,053 (4.7%)	1.822	1.594–2.082	<0.001
Non-Hodgkin’s lymphoma	1,475 (3.4%)	742 (3.6%)	733 (3.2%)	1.583	1.378–1.820	<0.001
Female reproductive system	1,249 (2.9%)	740 (3.6%)	509 (2.3%)	1.281	1.106–1.485	0.001

Table 2. Cont'd

Breast	1,112 (2.6%)	574 (2.8%)	538 (2.4%)	1.623	1.402–1.877	<0.001
Kidney/bladder	1,095 (2.5%)	567 (2.7%)	528 (2.3%)	1.556	1.344–1.801	<0.001
Multiple myeloma	923 (2.1%)	446 (2.1%)	477 (2.1%)	1.712	1.475–1.987	<0.001
Male reproductive system	754 (1.7%)	356 (1.7%)	398 (1.8%)	1.817	1.558–2.120	<0.001
Oropharynx	439 (1.0%)	242 (1.2%)	197 (0.9%)	1.458	1.214–1.751	<0.001
Esophagus	391 (0.9%)	190 (0.9%)	201 (0.9%)	1.681	1.401–2.017	<0.001
Thyroid	169 (0.4%)	101 (0.5%)	68 (0.3%)	1.220	0.936–1.592	0.140
Larynx	149 (0.3%)	82 (0.4%)	67 (0.3%)	1.399	1.071–1.827	0.010
Hodgkin lymphoma	50 (0.1%)	23 (0.1%)	27 (0.1%)	1.642	1.106–2.439	0.010
Other, unspecified	2,995 (6.9%)	1,622 (7.8%)	1,373 (6.1%)	1.442	1.266–1.642	<0.001

Variables are expressed as number (%).

CI, Confidence Interval; HR, Hazard Ratio

Adjusted for age, sex, and CCI, the comparison of 30-day mortality rates by year revealed significant improvements. Notably, patients admitted in 2016 (adjusted HR, 0.793; 95% CI, 0.754–0.835; P < 0.001) and 2017 (adjusted HR, 0.788; 95% CI, 0.750–0.828; P < 0.001) experienced significantly better 30-day mortality rates compared to those admitted in 2009 (Table 3).

Table 3. Hazard ratios for the year of hospitalization on 30-day mortality rate among cancer patients with septic shock; multivariate Cox proportional hazards analysis adjusted for age, sex, and Charlson Comorbidity Index

Characteristics	Adjusted HR	95% CI	P value
Year			
2009	Reference		<0.001
2010	0.995	0.938–1.054	0.860
2011	1.029	0.970–1.092	0.340
2012	1.011	0.952–1.074	0.720
2013	1.026	0.962–1.095	0.440
2014	1.026	0.958–1.099	0.460
2015	0.964	0.898–1.035	0.310
2016	0.793	0.754–0.835	<0.001
2017	0.788	0.750–0.828	<0.001
Female	0.910	0.885–0.935	<0.001
Age (years)			
18–29	Reference		<0.001
30–39	1.245	1.025–1.512	0.030
40–49	1.406	1.182–1.672	<0.001
50–59	1.437	1.214–1.701	<0.001
60–69	1.418	1.200–1.677	<0.001

Table 3. Cont'd

70–79	1.640	1.388–1.938	<0.001
≥80	1.845	1.560–2.184	<0.001
CCI			
0–2	Reference		<0.001
3–4	1.373	1.312–1.437	<0.001
5–7	1.455	1.389–1.524	<0.001
≥8	1.861	1.787–1.938	<0.001

CCI, Charlson comorbidity index; CI, Confidence Interval; HR, Hazard Ratio

The proportions of the cancer types did not change significantly over the study period (Figure 3).

Figure 3. Annual distribution of cancer types among patients with septic shock presenting to the emergency department

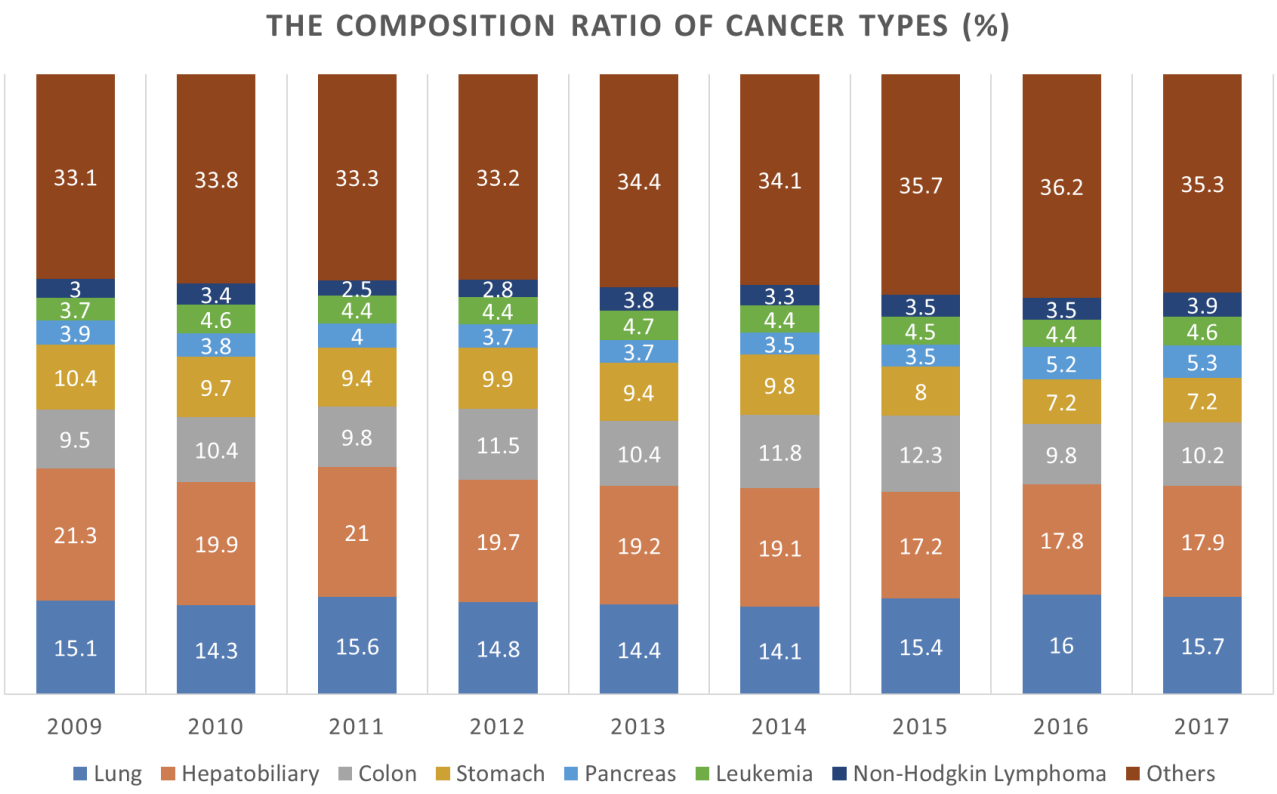
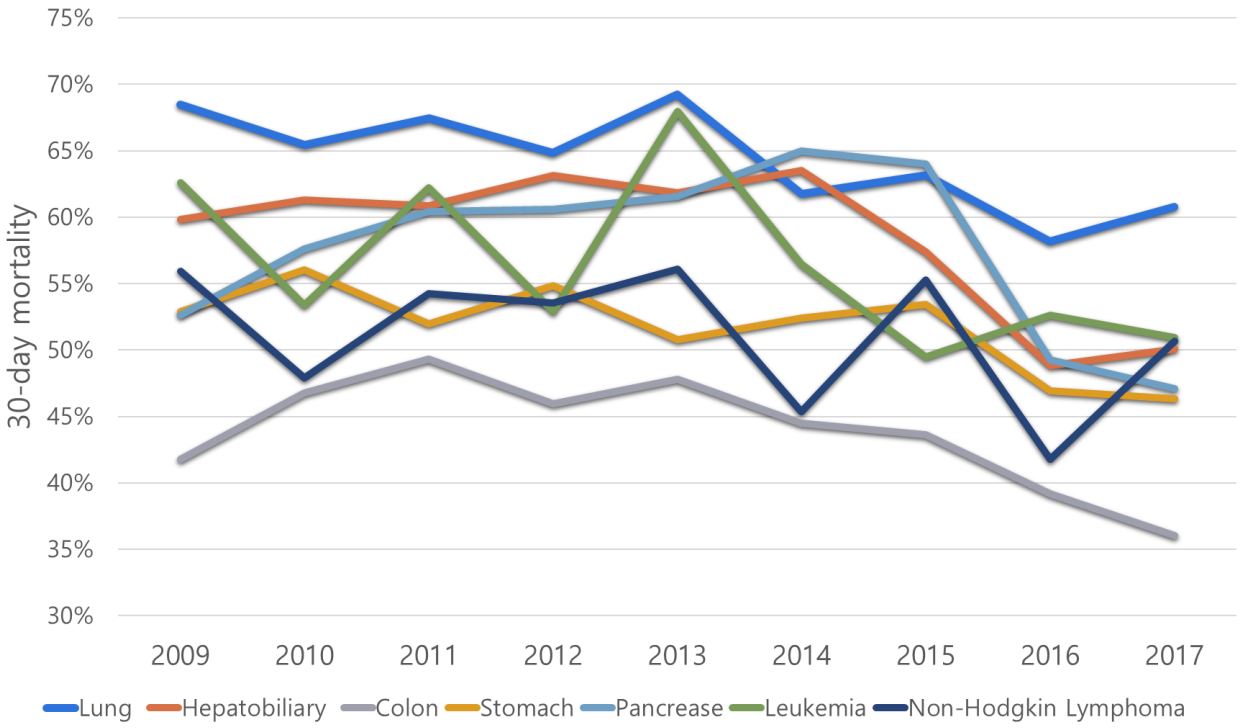


Figure 4 illustrates the annual mortality rates for seven major cancer types (five solid cancers and two hematologic cancers) from 2009 to 2017. While fluctuations were observed until 2013, a consistent decline in mortality rates has been noted since 2016.

Figure 4. The Annual mortality rates for 7 major cancer types among patients with septic shock in the emergency department



III. The influence of neutropenia on mortality rates and factors in cancer patients with septic shock

From 2009 to 2017, 43,466 cancer patients with septic shock were identified. Among these, neutropenia was confirmed in 6,391 patients (14.7%) who had diagnosis codes for neutropenia and information on G-CSF prescription. The 30-day mortality rate was 44.5% in patients with neutropenia-associated septic shock compared to 53.4% in patients without neutropenia (Figure 5).

Figure 5. Patient flow based on the presence of neutropenia and associated mortality rate

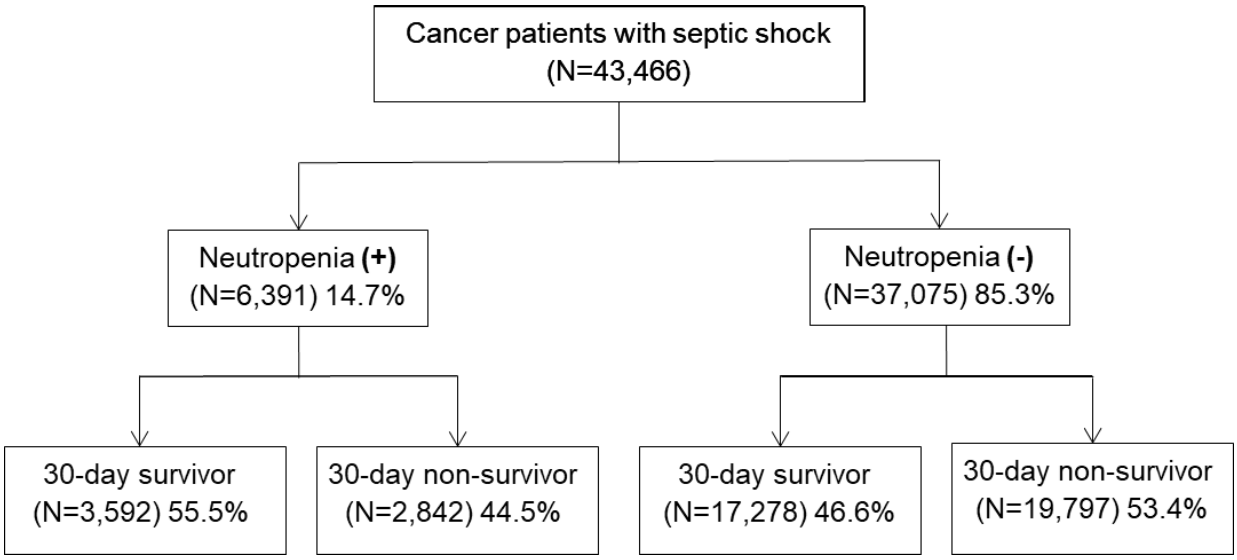


Table 4 presents the characteristics of the study patients according to the presence or absence of neutropenia. Patients without neutropenia had a lower proportion of females (34.8% vs. 39.0%; $P < 0.001$) and a higher mean age compared to those with neutropenia (67.8 ± 12.6 vs. 62.6 ± 12.9; $P < 0.001$). Underlying conditions such as hypertension, diabetes mellitus, congestive heart failure, and cirrhosis were significantly more frequent in patients without neutropenia compared to those with neutropenia, although the mean CCI did not significantly differ between the groups. Among solid tumors, hepatocellular carcinoma, colorectal cancer, gallbladder cancer, and pancreatic cancer were more common in patients without neutropenia. Conversely, hematologic malignancies such as leukemia, non-Hodgkin lymphoma, and multiple myeloma were more common in patients with neutropenia compared to those without neutropenia.

Chemotherapy and radiotherapy were administered more frequently to patients with neutropenia compared to those without neutropenia at both the 30 days and 90 days. The overall 30-day and 1-year mortality rates were 52.1% and 81.3%, respectively. Patients with neutropenia had better survival rates at both the 30 days and 1 year compared to those without neutropenia.

Table 4. Baseline and clinical characteristics of patients with septic shock, categorized by the presence or absence of neutropenia.

Characteristics	All Patients (n = 43,466)	Non-Neutropenic Septic Shock (n = 37,075)	Neutropenic Septic Shock (n = 6391)	P value
Female	15,399 (35.4)	12,909 (34.8)	2,490 (39.0)	<0.001
Age (years)	67.0 ± 12.7	67.8 ± 12.6	62.6 ± 12.9	<0.001
Comorbidities				
HTN	23,136 (53.2)	20,091 (54.2)	3,045 (47.7)	<0.001
DM	16,977 (39.1)	14,758 (39.8)	2,219 (34.7)	<0.001
CHF	5,745 (13.2)	5,008 (13.5)	737 (11.5)	<0.001
CLD	5,008 (11.5)	4,301 (11.6)	707 (11.1)	0.213
Renal failure	2,783 (6.4)	2,397 (6.5)	386 (6.0)	0.199
Liver cirrhosis	4,974 (11.4)	4,705 (12.7)	269 (4.2)	<0.001
CCI				
0–2	7,816 (18.0)	6,709 (18.1)	1,107 (17.3)	
3–4	9,652 (22.2)	8,160 (22.0)	1,492 (23.4)	
5–7	8,256 (19.0)	7,231 (19.5)	1,025 (16.0)	
8+	17,742 (40.8)	14,975 (40.4)	2,767 (43.3)	
Cancer type				<0.001
Brain	772 (1.8)	736 (2.0)	36 (0.6)	

Table 4. Cont'd

Lung	6,657 (15.3)	5,646 (15.2)	1,011 (15.8)
Liver	6,238 (14.4)	6,074 (16.4)	164 (2.6)
Colon	4,494 (10.3)	4,122 (11.1)	372 (5.8)
Stomach	3,684 (8.5)	3,284 (8.9)	400 (6.3)
Gall bladder	1,981 (4.6)	1,911 (5.2)	70 (1.1)
Pancreas	1,943 (4.5)	1,799 (4.9)	144 (2.3)
Leukemia	1,917 (4.4)	1,053 (2.8)	864 (13.5)
NHL	1,475 (3.4)	724 (2.0)	751 (11.8)
FRS	1,249 (2.9)	862 (2.3)	387 (6.0)
Breast	1,112 (2.6)	752 (2.0)	360 (5.6)
Kidney/bladder	1,095 (2.5)	1,010 (2.7)	85 (1.3)
Multiple myeloma	923 (2.1)	635 (1.7)	288 (4.5)
MRS	754 (1.7)	641 (1.7)	113 (1.8)
Oropharynx	439 (1.0)	364 (1.0)	75 (1.2)
Esophagus	391 (0.9)	324 (0.9)	67 (1.0)
Thyroid	169 (0.4)	160 (0.4)	9 (0.1)
Larynx	149 (0.3)	131 (0.4)	18 (0.3)
Hodgkin lymphoma	50 (0.1)	28 (0.1)	22 (0.3)
Other, unspecified	2,995 (6.9)	2,564 (6.9)	431 (6.7)
Multiple	4,979 (11.5)	4,255 (11.5)	724 (11.3)

Table 4. Cont'd

Treatment				
Radiotherapy within 30 days	1,607 (3.7)	1,272 (3.4)	335 (5.2)	<0.001
Chemotherapy within 30 days	8,310 (19.1)	4,693 (12.7)	3,617 (56.6)	<0.001
Radiotherapy within 90 days	3,723 (8.6)	3,019 (8.1)	704 (11.0)	<0.001
Chemotherapy within 90 days	13,831 (31.8)	9,425 (25.4)	4,406 (68.9)	<0.001
Outcome				
30-day mortality	22,639 (52.1)	19,797 (53.4)	2,842 (44.5)	<0.001
1-year mortality	35,325 (81.3)	30,369 (81.9)	4,956 (77.5)	<0.001

Variables are expressed as mean number ± standard deviation, number (%) as appropriate.

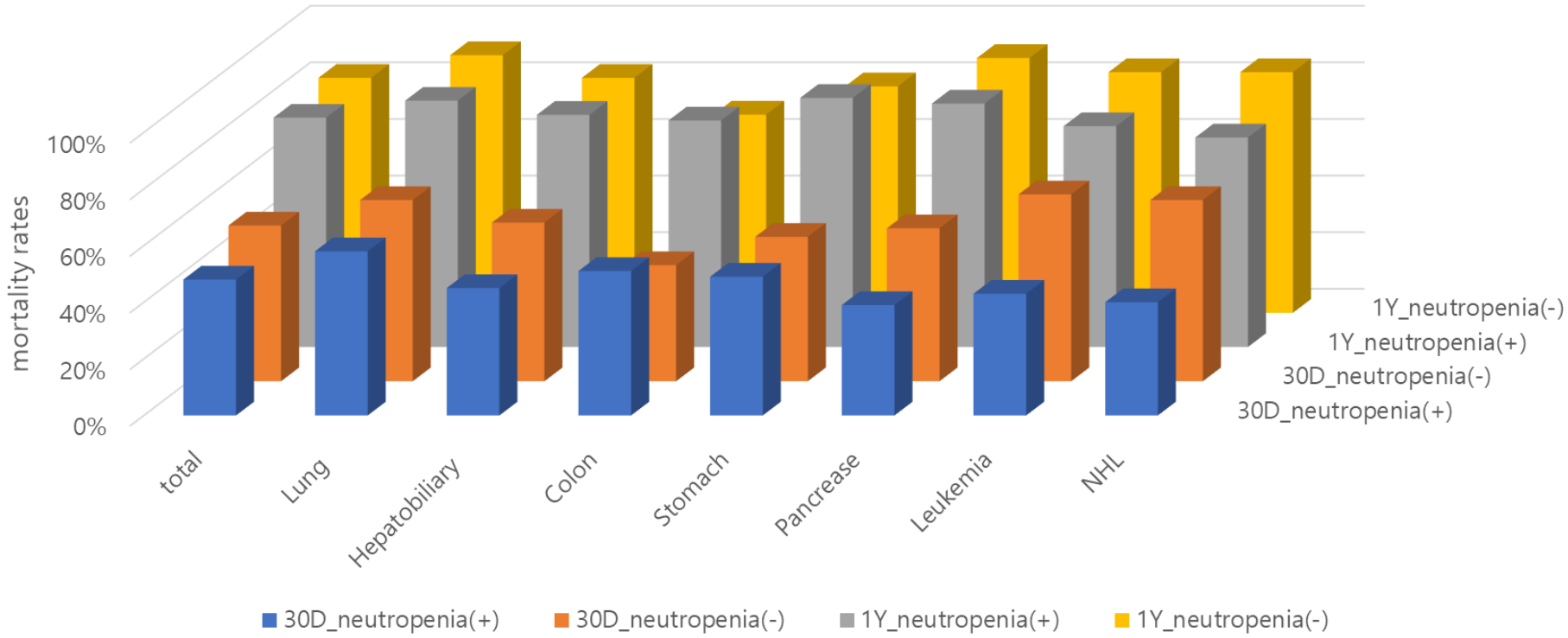
CCI, Charlson comorbidity index; CHF, Congestive heart failure; CLD, Chronic lung disease; DM, Diabetes Mellitus; FRS, Female reproductive system; HTN, Hypertension; MRS, Male reproductive system; NHL, Non-Hodgkin Lymphoma; SS, Septic shock

Figure 6 illustrates the mortality rates of septic shock among different cancer subtypes. For all cancer subtypes, except colorectal cancer, the overall 30-day mortality rate was significantly higher in patients without neutropenic septic shock compared to those with neutropenia (55% vs. 48%).

The 1-year mortality rate was significantly higher in patients without neutropenia compared to those with neutropenic septic shock for lung cancer (91% vs 87%), leukemia (85% vs 78%), and non-Hodgkin lymphoma (85% vs 74%). In hepatobiliary (83% vs. 82%) and pancreatic cancer (90% vs. 86%), the 1-year mortality rate was higher in patients without neutropenia compared to those with neutropenic septic shock, although this difference was not statistically significant.

However, in colorectal (70% vs 80%) and gastric cancer (80% vs 88%), patients with neutropenic septic shock had a higher 1-year mortality rate compared to those without neutropenia.

Figure 6. The 30-day and 1-year mortality rates for 7 major types of cancer patients with septic shock, grouped and stratified by neutropenia status

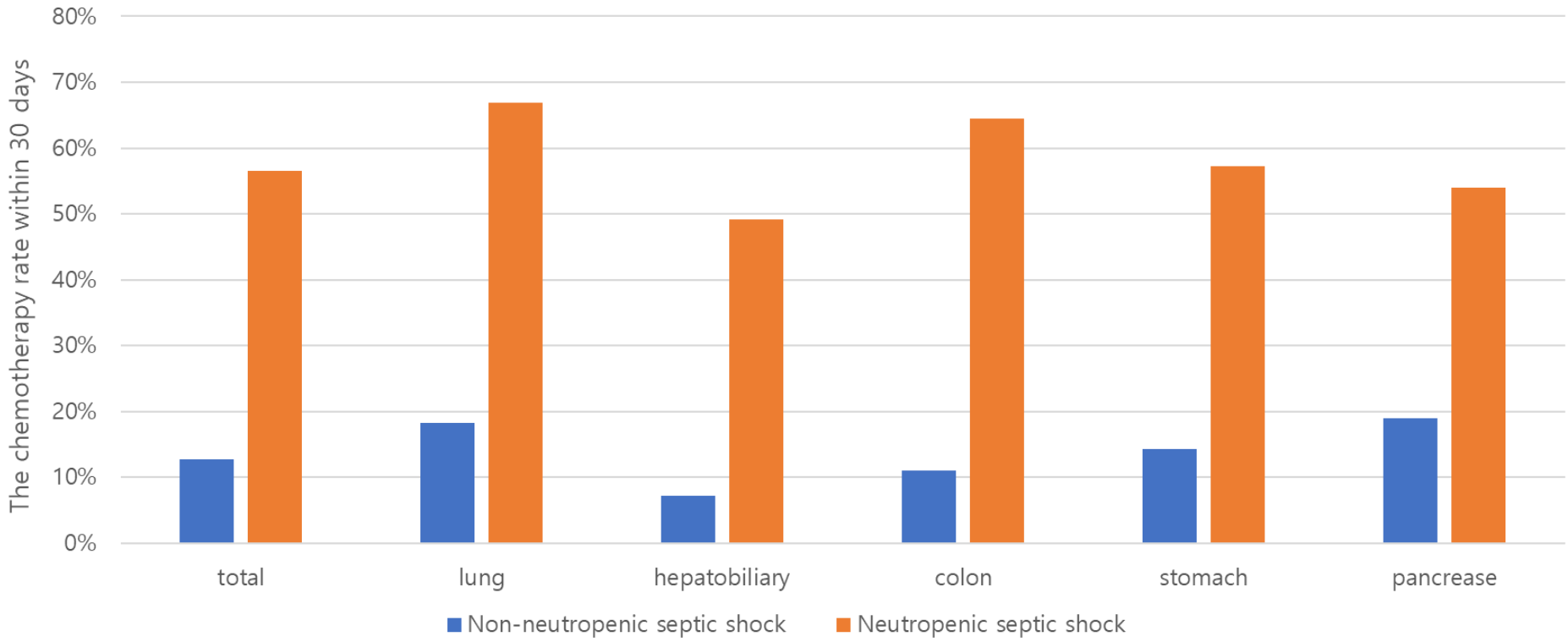


NHL, Non-Hodgkin Lymphoma

Figure 7 shows the proportion of patients receiving chemotherapy within 30 days among the top five solid tumor types. Across all cancer subtypes, patients receiving chemotherapy had a higher incidence of neutropenic septic shock, compared to those not receiving chemotherapy. Among all patients, 57% of those with neutropenic septic shock received chemotherapy within 30 days, compared to 13% of those without neutropenia.

The highest rates of chemotherapy administration among patients who developed neutropenia were observed in lung cancer (67%) and colon cancer (64%). Conversely, the lowest rates of chemotherapy were noted in hepatobiliary cancer (7%) and colon cancer (11%) among patients without neutropenia.

Figure 7. The proportion of patients receiving chemotherapy within 30 days in 5 major types of solid cancer



We conducted Cox proportional hazards regression analyses to identify potential risk factors associated with 30-day and 1-year mortality rates, including variables such as age, sex, CCI, and neutropenia. Even after adjusting for other confounding variables, neutropenia was independently associated with both the 30-day (HR 0.811, 95% CI 0.779–0.844; P < 0.001) and 1-year (HR 0.861, 95% CI 0.836–0.888; P < 0.001) mortality rates (Table 5).

Table 5. Multivariate Cox proportional hazards regression analysis of neutropenia-associated 30-day and 1-year mortality

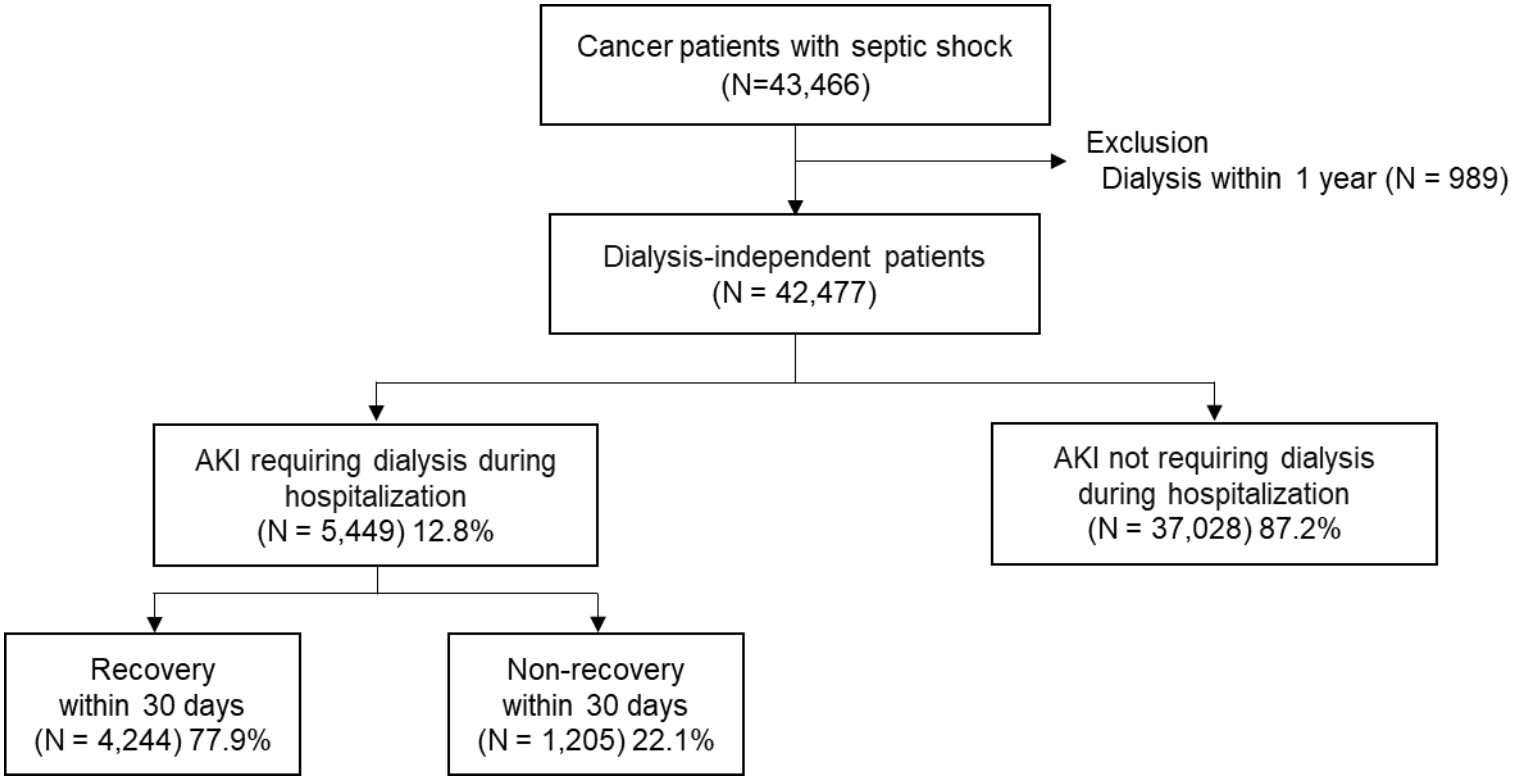
Characteristics	30-day mortality			1-year mortality		
	Adjusted HR	**95% CI**	**P value**	**Adjusted HR**	**95% CI**	**P value**
Neutropenia	0.811	0.779–0.844	<0.001	0.861	0.836–0.888	<0.001
Female	0.919	0.894–0.945	<0.001	0.919	0.899–0.939	<0.001
Age	1.007	1.006–1.008	<0.001	1.009	1.008–1.010	<0.001
CCI						
0–2	Reference			Reference		
3–4	1.356	1.296–1.419	<0.001	1.312	1.267–1.359	<0.001
5–7	1.431	1.366–1.499	<0.001	1.405	1.355–1.456	<0.001
8+	1.840	1.767–1.915	<0.001	1.862	1.805–1.921	<0.001

CCI, Charlson comorbidity index; CI, Confidence Interval; HR, Hazard Ratio

IV. The effect of dialysis-requiring acute kidney injury on the prognosis of cancer patients with septic shock

From 2009 to 2017, 43,466 cancer patients with septic shock were identified. Among them, 989 patients who received blood or peritoneal dialysis within 1 year of their ED visit date were excluded from the analysis. Ultimately, 42,477 cancer patients with septic shock were included. Of these, 5,449 (12.8%) experienced acute kidney injury (AKI) requiring dialysis during their hospitalization, with a recovery rate of 77.9% within 30 days of dialysis (Figure 8).

Figure 8. Patient flow based on the occurrence of AKI requiring dialysis



AKI, acute kidney injury

Table 6 presents the baseline characteristics of the study population according to the development of septic AKI requiring dialysis. Females accounted for 35.5% of the patients, and the median age was 69.0 years. Patients with septic AKI requiring dialysis were younger (median age: 68.0 years vs. 69.0 years) and had lower CCI scores (median CCI: 5.0 vs. 6.0) compared to those not requiring dialysis. Underlying conditions such as hypertension, diabetes, and liver cirrhosis were more frequently observed in the dialysis-requiring group. Patients with solid tumors were more common in the non-dialysis group (85.9% vs. 94.9%), while those with hematologic malignancies were more common in the dialysis group (14.1% vs. 5.1%).

Table 6. Comparison of demographic and clinical characteristics between cancer patients with septic shock, with and without dialysis-requiring acute kidney injury

Characteristics	Total (N = 42,477)	non dialysis requiring AKI (N = 37,028)	dialysis requiring AKI (N = 5,449)	P value
Female	15,058 (35.5)	13,282 (35.9)	1,776 (32.6)	< 0.001
Age (years)	69.0 (59.0–76.0)	69.0 (59.0–77.0)	68.0 (58.0–75.0)	< 0.001
CCI (mean)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	5.0 (3.0–8.0)	< 0.001
Comorbidities				
Hypertension	22,338 (52.6)	19,191 (51.8)	3,147 (57.8)	< 0.001
Diabetes mellitus	16,321 (38.4)	13,993 (37.8)	2,328 (42.7)	< 0.001
Congestive heart failure	5,475 (12.9)	4,663 (15.6)	812 (14.9)	< 0.001
CLD	4,903 (11.5)	4,397 (11.9)	506 (9.3)	< 0.001

Table 6. Cont'd

Liver cirrhosis	4,823 (11.4)	4,030 (10.9)	793 (14.6)	< 0.001
Cancer type				
Solid*	39,811 (93.7)	35,129 (94.9)	4,682 (85.9)	< 0.001
Hematologic**	2,666 (6.3)	1,899 (5.13)	767 (14.1)	< 0.001

Variables are expressed as median (interquartile ranges) and number (%) as appropriate.

* Solid cancer comprised lung, hepatobiliary, colon, stomach, pancreas, and brain.

** Hematologic cancer comprised leukemia, lymphoma, and multiple myeloma.

AKI, acute kidney injury; CCI, Charlson Comorbidity Index; CLD, chronic lung disease.

Table 7 presents the analysis of univariate and multivariate logistic regression models to predict the occurrence of septic AKI requiring dialysis. Females (adjusted OR 0.848, 95% CI 0.797–0.903) and older patients (adjusted OR 0.989, 95% CI 0.987–0.991) had a lower likelihood of developing septic AKI. Among underlying conditions, hypertension (adjusted OR 0.848, 95% CI 0.797–0.903), diabetes (adjusted OR 1.359, 95% CI 1.274–1.449), heart failure (adjusted OR 1.229, 95% CI 1.127–1.340), and liver cirrhosis (adjusted OR 1.382, 95% CI 1.382–1.640) were independent risk factors for the development of septic AKI requiring dialysis. Hematologic cancers, compared to solid tumors, significantly increased the risk of septic AKI (adjusted OR 2.652, 95% CI 2.414–2.911).

Table 7. Univariate and multivariate logistic regression analysis for predicting the development of septic acute kidney injury requiring dialysis

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	Adjusted OR	95% CI	P value
Female	0.864	0.814–0.918	< 0.001	0.848	0.797–0.903	< 0.001
Age	0.991	0.988–0.993	< 0.001	0.989	0.987–0.991	< 0.001
Comorbidities						
Hypertension	1.271	1.200–1.346	< 0.001	1.390	1.302–1.484	< 0.001
Diabetes	1.228	1.200–1.611	< 0.001	1.359	1.274–1.449	< 0.001
CHF	1.215	1.121–1.317	< 0.001	1.229	1.127–1.340	< 0.001
CLD	0.760	0.689–0.836	< 0.001	0.840	0.759–0.928	< 0.001
LC	1.395	1.284–1.513	< 0.001	1.506	1.382–1.640	< 0.001
CCI (mean)	0.949	0.942–0.957	< 0.001	0.935	0.927–0.944	< 0.001

Table 7. Cont'd

Cancer type						
Solid*	Reference			Reference		
Hematologic**	3.030	2.771–3.312	< 0.001	2.652	2.414–2.911	< 0.001

* Solid cancer comprised lung, hepatobiliary, colon, stomach, pancreas, and brain.

** Hematologic cancer comprised leukemia, lymphoma, and multiple myeloma

CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CLD, chronic lung disease; LC, liver cirrhosis; OR; odds ratio

Table 8 presents the univariate and multivariate Cox proportional hazards models related to 30-day mortality rates. The occurrence of AKI requiring dialysis (HR = 1.353, 95% CI 1.313–1.395, P < 0.001), presence of liver cirrhosis (HR = 1.335, 95% CI 1.283–1.389, P < 0.001), and diagnosis of hematologic cancer (HR = 1.214, 95% CI 1.149–1.283, P < 0.001) were associated with higher 30-day mortality rates.

Table 8. Univariate and multivariate Cox proportional hazards analysis for predicting 30-day mortality, considering the requirement of dialysis, demographic, and clinical characteristics

Characteristics	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Dialysis	1.295	1.248–1.344	< 0.001	1.338	1.288–1.389	< 0.001
Female	0.907	0.882–0.933	< 0.001	0.946	0.920–0.973	< 0.001
Age	1.007	1.006–1.008	< 0.001	1.010	1.009–1.011	< 0.001
Comorbidities						
Hypertension	1.073	1.044–1.101	< 0.001	0.948	0.921–0.977	< 0.001
Diabetes	1.079	1.050–1.109	< 0.001	0.884	0.859–0.911	< 0.001
CHF	1.122	1.080–1.165	< 0.001	0.999	0.959–1.040	0.955
CLD	1.216	1.170–1.265	< 0.001	1.094	1.050–1.139	< 0.001
LC	1.372	1.320–1.426	< 0.001	1.335	1.283–1.389	< 0.001

Table 8. Cont'd

CCI (mean)	1.054	1.051–1.058	< 0.001	1.061	1.057–1.065	< 0.001
Cancer type						
Solid*	Reference			Reference		
Hematologic**	1.025	0.971–1.081	0.373	1.214	1.149–1.283	< 0.001

* Solid cancer comprised lung, hepatobiliary, colon, stomach, pancreas, and brain.

** Hematologic cancer comprised leukemia, lymphoma, and multiple myeloma

CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CLD, chronic lung disease; HR, Hazard ratio; LC, liver cirrhosis

Table 9 presents the characteristics of the study population according to the 2-year mortality rate. The 2-year mortality rate was 85.1% (n = 36,161). Patients requiring dialysis during hospitalization were more prevalent in the non-survivor group than in the survivor group. Among the 2-year survivors, there were more females (39.7% vs. 34.7%), younger individuals (mean age 64.0 vs. 69.0 years), and lower CCI scores (mean CCI 4.0 vs. 6.0) compared to non-survivors. The prevalence of all comorbidities was lower in the survivor group. There was no significant difference in mortality rates between the groups with solid and hematologic malignancies.

Table 9. Characteristics of the study population based on 2-year mortality

Characteristics	Total (N = 42,477)	2-year survivors (N = 6,316)	2-year non-survivors (N = 36,161)	P value
Dialysis	5,449 (12.8)	504 (8.0)	4,945 (13.7)	< 0.001
Female	15,058 (35.5)	2,505 (39.7)	12,553 (34.7)	< 0.001
Age (years)	69.0 (59.0 – 76.0)	64.0 (55.0 – 73.0)	69.0 (60.0 – 77.0)	< 0.001
CCI (mean)	6.0 (3.0 – 9.0)	4.0 (2.0 – 7.0)	6.0 (3.0 – 10.0)	< 0.001
Comorbidities				
Hypertension	22,338 (52.6)	2,989 (47.3)	19,349 (53.5)	< 0.001
Diabetes mellitus	16,321 (38.4)	2,041 (32.3)	14,280 (39.5)	< 0.001
Congestive heart failure	5,475 (12.9)	645 (10.2)	4,830 (13.4)	< 0.001
CLD	4,903 (11.5)	458 (7.3)	4,445 (12.3)	< 0.001
Chronic kidney disease	2,083 (4.9)	278 (4.4)	1,805 (5.0)	< 0.001

Table 9. Cont'd

Liver cirrhosis	4,823 (11.4)	598 (9.5)	4,225 (11.7)	< 0.001
Cancer type				
Solid*	39,811 (93.7)	5,912 (93.6)	33,899 (93.7)	0.670
Hematologic**	2,666 (6.3)	404 (6.4)	2,262 (6.3)	0.670

Variables are expressed as median (interquartile ranges) and number (%) as appropriate.

* Solid cancer comprised lung, hepatobiliary, colon, stomach, pancreas, brain, and lymphoma.

** Hematologic cancer comprised multiple myeloma and leukemia.

CCI, Charlson Comorbidity Index; CLD, chronic lung disease

The univariate and multivariate Cox proportional hazards models related to the 2-year mortality rate are presented in Table 10. The occurrence of AKI requiring dialysis showed the highest relative HR among independent risk factors for the 2-year mortality rate (HR = 1.353, 95% CI 1.313–1.395, P < 0.001). Additionally, advanced age, male sex, liver cirrhosis, and higher CCI were associated with higher two-year mortality rates. Compared to solid tumors, hematologic malignancies exhibited worse 2-year mortality rates (Table 10).

Table 10. Analysis of univariate and multivariate Cox proportional hazards models predicting 2-year mortality based on demographic and clinical characteristics, including the requirement for dialysis

Characteristics	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Dialysis	1.308	1.269–1.348	< 0.001	1.353	1.313–1.395	< 0.001
Female	0.906	0.887–0.926	< 0.001	0.940	0.919–0.961	< 0.001
Age	1.009	1.008–1.010	< 0.001	1.012	1.011–1.013	< 0.001
Comorbidities						
Hypertension	1.094	1.071–1.116	< 0.001	0.943	0.921–0.965	< 0.001
Diabetes	1.114	1.091–1.138	< 0.001	0.904	0.884–0.926	< 0.001
CHF	1.129	1.095–1.164	< 0.001	0.981	0.950–1.013	0.237
CLD	1.246	1.208–1.286	< 0.001	1.090	1.055–1.126	< 0.001
LC	1.225	1.186–1.265	< 0.001	1.178	1.139–1.217	< 0.001

Table 10. Cont'd

CCI (mean)	1.058	1.056–1.061	< 0.001	1.065	1.062–1.068	< 0.001
Cancer type						
Solid*	Reference			Reference		
Hematologic**	1.008	0.966–1.052	0.701	1.193	1.142–1.247	< 0.001

*Solid cancer included brain, lung, liver, colon, stomach, gall bladder, pancreas

**Hematologic cancer included multiple myeloma, leukemia and lymphoma

CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CLD, chronic lung disease; HR, Hazard ratio; LC, liver cirrhosis

Discussion

Our nationwide population-based cohort study revealed significant improvements in 30-day and 1-year mortality rates among cancer patients with septic shock from 2009 to 2017. The 30-day mortality rate decreased from 56.4% in 2013 to 47.8% in 2017, an absolute decrease of 8.6%. Continuous annual reductions in 30-day mortality were observed for lung and stomach cancers, while pancreatic cancer exhibited the most substantial improvement from 2014 to 2019.

Previous studies have reported an increasing incidence of sepsis and septic shock alongside a decreasing mortality trend.[41] Consistent with previous studies, our analysis found that the number of cancer patients experiencing septic shock more than doubled from 3,987 in 2009 to 11,592 in 2017. A recent study of sepsis statistics in Korea, using sepsis diagnosis codes, indicated that between 2007 and 2016, the incidence of sepsis increased from 173.8 to 233.6 per 100,000 persons, while in-hospital mortality decreased from 30.9% to 22.6%, with the incidence nearly doubling since 2016.[42] This increase may partly be due to the actual rise in sepsis prevalence.

The implementation of Sepsis-3 in 2016, with its new definition of septic shock, may have altered the findings of previous studies. In Sepsis-3, the use of quick SOFA (Sequential Organ Failure Assessment) has led to more proactive sepsis recognition and earlier use of vasopressors, resulting in more patients being enrolled than before 2016.[33] Additionally, errors are likely to occur when using diagnostic code data to identify trends in sepsis and septic shock.[34,43] Kadri et al. used clinical surveillance data (showing an average increase of 4.9% per year, from 12.8 to 18.6 per 1,000 persons) and claims data (showing an average increase of 19.8% per year, from 6.7

to 19.3 per 1,000 persons) from 2005 to 2014 across 27 academic hospitals in the United States to demonstrate different incidence rates of septic shock and suggested that clinical surveillance definitions are superior for identifying septic shock patients by review of clinical medical records.[41]

Data from other studies on the incidence and prevalence of cancer in Korea indicate that the incidence of cancer remained similar to previous levels until 2016. However, the prevalence of cancer has markedly increased due to improved survival rates. Notably, between 2013 and 2017, the 5-year survival rate for all cancer patients exceeded 70%, resulting in a significant rise in prevalence. Consequently, this increase helps to explain the substantial rise in the number of patients included in this study since 2016.[36]

In our study, more than half (52.1%) of cancer patients who experienced septic shock died within 30 days of admission to the ED. Interestingly, the trend in 30-day mortality rates in our current cohort has shown a significant decrease since 2013, declining from 56.4% in 2013 to 47.8% in 2017. There was no significant difference between 2009 and 2013 (55.2% in 2009 and 56.4% in 2013). Furthermore, there was a substantial improvement in 30-day mortality rates from 54.1% in 2015 to 47.8% in 2016. In 2013, the Korean Ministry of Health and Welfare announced a focus on improving the treatment of critically ill patients, and hospital quality evaluations, including the ratio of ICU beds to patients and nurse-to-patient ratios, were implemented biennially starting in 2014. Additionally, the Emergency Medical Services Act was amended in 2015 to require 1st and 2nd grade emergency centers to expand their facilities and medical personnel to enhance the treatment capacity and quality of care for critically ill patients, along with the implementation of emergency center

quality assessments. Moreover, in 2013, the Korean Shock Society was established with emergency medicine physicians and critical care medicine specialists to research and improve shock treatment. As a result of these policy changes, hospitals and emergency centers in Korea may have increased the number of critical care specialists. Our study findings from 2013 to 2017 demonstrated improvements in short-term and long-term mortality rates, and a significant decrease in the 30-day mortality rate among cancer patients with septic shock between 2015 and 2016, are consistent with previous research on the incidence rates and clinical outcomes of hospitalized patients with sepsis using NHID data in Korea. This study showed a decline in hospital mortality trends, with a substantial improvement in in-hospital mortality from 26.1% in 2015 to 22.6% in 2016.[42]

Until the early 2000s, admission of cancer patients with septic shock to the ICU was perceived as futile. However, this perception has evolved over time, showing that with appropriate patient selection, similar treatment outcomes for septic shock can be achieved in patients with and without cancer.[18,44,45] This encouraged a more proactive approach to ICU management for cancer patients and contributed to improving treatment outcomes. Our current study found a continuous decrease in the 1-year mortality rate over time, indicating improved survival after recovery from septic shock. The improvement in 1-year mortality rates can be attributed to advancements in cancer therapies, enhanced detection of early-stage cancer patients through national cancer screening programs, and improvements in sepsis management.[36,46-48]

During our investigation, we examined the 30-day and 1-year mortality rates

for various types of cancer. These trends suggest that advancements in both sepsis and cancer treatments have improved patient outcomes. Notably, pancreatic cancer patients who experienced septic shock showed a remarkable 11% annual decrease in 30-day mortality rates from 2014 to 2019. However, there were no significant changes in the 1-year mortality rates over time. This finding is consistent with Korean cancer statistics, which report the slowest improvement in survival rates for pancreatic cancer from 1993 to 2017.[36] In contrast, patients with lung and stomach cancers showed continuous improvement in both 30-day and 1-year mortality rates during the study period, indicating significant improvements in survival rates for these cancer types in Korea.[36] However, the mortality rates associated with hematologic cancers showed a decreasing trend but were not statistically significant.

When considering the trend patterns across various cancer types in this study, it is anticipated that continued advancements in cancer treatment will lead to improved outcomes for cancer patients experiencing septic shock. The progress in sepsis management is expected to have a positive impact on short-term results, and it is believed that early and aggressive intensive care should be considered for septic shock patients of all cancer types.[7,49-51]

In this study, we found that approximately 15% of cancer patients experiencing septic shock had neutropenia. After adjusting for other confounding factors such as age, sex, and CCI, neutropenia was associated with decreased 30-day and 1-year mortality rates.

Neutropenia is a common feature of several diseases affecting hematopoietic stem cells, such as leukemia, aplastic anemia, and myelodysplastic syndromes.

Additionally, it can be observed in many congenital conditions, as well as in cases of vitamin B12 or folate deficiency, copper deficiency, and autoimmune diseases such as systemic lupus erythematosus and Sjögren's syndrome. However, chemotherapy and radiotherapy are the most common causes of neutropenia in cancer patients. [52,53]

We used operational definitions of neutropenic septic shock based on diagnostic codes for neutropenia or G-CSF administration after admission in our study. Previous studies identified neutropenic patients using diagnostic codes for neutropenia or agranulocytosis.[54-57] Weycker et al. reported that using diagnostic codes, they could identify patients with neutropenic fever in claims data with over 80% positive predictive value.[58] However, because many patients may not have neutropenia recorded as a primary diagnosis code, there is a possibility that only a limited number of cases are identified. In Korea, insurance coverage for G-CSF therapy is provided only when patients receiving chemotherapy have either severe neutropenia (ANC < 500 cells/mm3) or fever accompanied by mild neutropenia (ANC < 1000 cells/mm3). Previous studies used G-CSF prescription data from the Korean NHIS to identify patients with fever accompanied by neutropenia.[59] We also included patients who received G-CSF therapy for therapeutic purposes to identify patients those with neutropenic septic shock, which is considered practical due to the strict validation process of the NHIS for insurance coverage.

The prevalence of neutropenic sepsis among cancer patients ranges widely from 7% to 45%, depending on the patient selection criteria used in previous investigations.[60-62] In this study, 14.7% of septic shock patients had neutropenia. However, the prognostic significance of neutropenia in cancer patients with septic shock remains debated. Reilly et al. reported that neutropenic sepsis independently

increased the risk of AKI but was not associated with 30-day mortality.[63] Another previous study investigating 464 septic shock patients admitted to the ICU found no difference in mortality rates between neutropenic and non-neutropenic patients.[64]

To our knowledge, this study is the first to investigate the prognostic impact of neutropenia in septic shock cancer patients using population-based claims data. The discrepancy in prognoses and neutropenia incidence rates from previous reports may stem from differences in admission policies and patient selection. Thus, a strength of this study is its inclusion of claims data from all cancer patients without excluding them based on specific criteria. This may provide valuable evidence for evaluating neutropenia as a prognostic factor in septic shock cancer patients.

This study indicates an improvement in survival rates among patients with neutropenic septic shock. However, it does not imply superior outcomes for those receiving G-CSF therapy. Instead, it suggests that neutropenia, typically considered an adverse prognostic factor, does not significantly influence mortality rates in cancer patients with septic shock. The reduced mortality rates observed among neutropenic patients may vary based on underlying patient conditions, such as their relatively younger age and lower comorbidity burden. Additionally, individuals in earlier cancer stages may undergo more frequent chemotherapy, contributing to neutropenia. Prior investigations have demonstrated that cancer patients admitted to the ICU with chemotherapy-induced neutropenia have a more favorable survival outlook compared to those without this condition.[65]

Considering treatment modalities such as chemotherapy and radiation therapy, the disease status of patients with neutropenia may not necessarily be more advanced than those without neutropenia. Previous studies have identified underlying

patient conditions and associated organ dysfunction as key determinants of outcomes in critically ill cancer patients.[7,66] Vincent et al. suggested factors such as tumor type, systemic spread of disease, and the need for invasive mechanical ventilation, vasoconstrictors, or RRT as risk factors for 120-day survival rates among solid tumor patients.[67] In patients with colorectal and gastric cancer who experienced neutropenic septic shock, the 1-year survival rate was higher compared to those without neutropenia. Neutropenic enterocolitis, a rare but life-threatening complication, can impact prognosis and is particularly relevant in these types of cancers.[68,69] Hence, the susceptibility to infections in these cancer types, coupled with the critical nature of neutropenia, can be fatal for patients with neutropenia.

The role of G-CSF administration in neutropenia remains contentious. G-CSF can augment the leukocyte and lymphocyte counts in the bloodstream.[70] Present guidelines recommend preemptive G-CSF use in chemotherapy patients prone to febrile neutropenia.[71,72] However, there is insufficient evidence to support the administration of G-CSF in cases of neutropenic sepsis.[73] The primary aim of G-CSF therapy in chemotherapy recipients is to prevent neutropenia and maintain chemotherapy intensity.

As mentioned earlier, the appropriate selection of patients for ICU admission is expected to contribute to better outcomes.[7,17] Recent guidelines for ICU admission of cancer patients suggest that traditional mortality predictors are irrelevant and commonly used priority criteria may be unreliable.[74] In the case of neutropenia, mixed results have been reported due to potential selection bias when physicians provide

treatment. The findings of this study suggest that including neutropenia as a priority criterion for ICU admission and predicting mortality in cancer patients with septic shock may not be appropriate due to potential selection bias.

Among 42,477 adult cancer patients with septic shock, around 13% developed AKI requiring dialysis. Risk factors for AKI included hypertension, diabetes, congestive heart failure, liver cirrhosis, and a history of hematologic cancer. AKI requiring dialysis was linked to the highest adjusted risk of 2-year mortality in these patients.

The rising occurrence of AKI is likely due to aggressive cancer treatments and effective intensive care management. Recent nationwide studies have reported AKI rates requiring RRT among cancer patients ranging from 10% to 50%.[75,76] These variations can be explained by factors such as study size, AKI definition, disease severity, cancer stage, and patient ethnicity. Incidence rates were notably higher in severely ill cancer patients compared to those without similarly severe illnesses.[77,78] The exact epidemiology of septic AKI remains poorly understood. Our data indicate that approximately 13% of cancer patients experiencing septic shock developed AKI requiring RRT during hospitalization. The relatively lower incidence rate observed in our study compared to previous research may be due to excluding patients who had undergone RRT before arriving at the ED.[79] Our study represents the largest population-based investigation of septic AKI in cancer patients in our country and may contribute to updating our understanding of the epidemiology of critically ill cancer patients requiring dialysis dependence.

In our study, male sex, comorbidities, and hematologic malignancies were

more frequently associated with RRT. Age is commonly recognized as a risk factor for the occurrence of AKI. Our study found that the median age of patients requiring RRT was lower than those not requiring RRT.[80] This may suggest that older patients could potentially refuse treatment including RRT. Although we were unable to ascertain the number of patients with do-not-resuscitate orders, older patients tend to refuse aggressive interventions such as mechanical ventilation, ICU admission, and RRT.

Furthermore, this study found a higher incidence rate of AKI in patients with hematologic malignancy patients such as leukemia, lymphoma, and multiple myeloma compared to those with solid tumor.[81] This suggests that hematologic malignancy patients may be more susceptible to infections, have more severe diseases, receive nephrotoxic treatments more frequently, and experience metabolic abnormalities more often than solid tumor patients.[82]

Our data revealed that the overall 2-year mortality rate for cancer patients who developed septic AKI requiring RRT was 85.1%. While several retrospective studies have assessed the association between septic AKI requiring RRT and short-term outcomes, determining the contribution of septic AKI requiring RRT to long-term mortality can be difficult due to cancer itself being a challenge as an underlying condition. Utilizing nationwide population-based data excluding life-sustaining therapies, our study found RRT-dependent septic AKI to be an independent risk factor for long-term mortality even after adjusting for known confounders.

The 2-year mortality rate among cancer patients who developed AKI requiring dialysis was higher than that of patients with other chronic conditions.[83] In a clinical trial involving ICU patients with AKI requiring dialysis, infection-related factors such as sepsis were identified as the most frequent cause of death.[84] The occurrence of

septic AKI in cancer patients can alter the pharmacokinetics and pharmacodynamics of cancer treatment drugs, leading to adverse effects and potentially excluding eligible patients from beneficial clinical trials.

Our study has several distinct strengths and limitations. A major strength of our study design is the high coverage (97%) of the national population analysis using recent national databases, incorporating objective clinical surveillance criteria to confirm the included study population with the latest definition of septic shock. This will help provide a more comprehensive understanding of cancer patients experiencing septic shock.

However, limitations of this study include the NHIS database lacking specific clinical and laboratory data, precise cancer stages, performance statuses, and treatments. Specifically, detailed data such as serum lactate levels or ANC necessary to define septic shock and neutropenia were not provided. Therefore, although we utilized diagnostic codes proven to be effective in identifying neutropenia patients and defined neutropenia more broadly using G-CSF prescription information compared to previous studies, potential misclassification cannot be avoided. Information regarding specific types and timing of treatments such as surgery, chemotherapy, and radiotherapy, as well as changes and advancements in various treatments during the study period, was not considered in the analysis. Other causes of neutropenia, excluding chemotherapy and radiotherapy, were not considered in this analysis. Additionally, the study population consisted almost entirely of Asians.

Conclusion

The mortality rate associated with septic shock in cancer patients has decreased across almost all cancer types in recent years. Even in cases of neutropenia, which is common in septic shock, neutropenia itself does not increase the mortality rate in patients with septic shock. This suggests that withholding intensive care treatment for cancer patients with septic shock just because they have neutropenia should be avoided.

Dialysis-requiring septic AKI occurred in 13% of adult cancer patients with septic shock and was associated with male sex, hematologic cancers, and comorbidities. Furthermore, it was significantly associated with increased long-term mortality in these patients. Prospective studies are needed to investigate methods to prevent and properly manage dialysis-requiring septic AKI in adult cancer patients with septic shock.

Physicians should prioritize sepsis management over traditional or isolated cancer patient indicators, potentially leading to improved prognoses for cancer patients.

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국문요약

배경

발달하고 있는 암 진단과 치료 기술에 암 발생률과 치료기간이 증가되고 있으며 이에 따른 응급실 방문 및 처치 또한 늘어나고 있다. 장기간의 항암치료와 그에 따른 합병증은 다양한 장기 손상으로 발현될 수 있다. 그 중 패혈증 쇼크는 암 환자 사이에서 생명을 위협하는 가장 흔한 합병증이다. 최근 연구에 따르면, 패혈증을 겪는 암 환자의 생존 결과가 개선되고 있지만, 이들 환자의 응급실 치료는 방대한 자원 소모와 관련 비용으로 인해 어려움을 겪고 있다. 또한 패혈증 쇼크를 겪는 암 환자 중 적지 않는 수에서 호중구 감소증이 발생하지만, 이에 따른 패혈성 쇼크 암환자의 예후에 미치는 영향은 아직까지 명확하게 규명되지 않았다. 또한, 패혈성 쇼크는 흔하게 신부전 장애를 동반할 수 있고, 이는 환자의 의료비 상승 및 사망률과 관련이 있다고 알려져 있다. 이에 저자들은 암 환자들 중 치료과정 중 패혈성 쇼크로 응급실로 내원한 국내 환자들 자료를 분석하여, 패혈성 쇼크를 겪는 암 환자의 사망 추이를 평가하고, 이들에서 호중구 감소증 동반 시 예후에 미치는 영향을 평가하며, 급성신부전의의 동반 요인을 탐구하여 치료 전략을 개선하기 위해 국가보건정보 데이터베이스를 기반으로 한 인구 기반 코호트 연구를 진행하였다.

방법

본 연구는 2009년부터 2017년까지의 데이터를 활용한 대한민국 국가보건정보 데이터베이스를 기반으로 한 인구 기반 코호트 연구로 응급실을 통해 패혈성 쇼크로 내원한 환자들을 임상 감시 기준을 사용하여 식별하였고, 이 중 암 환자는 입원 90일 전에 암 진단 코드가 등록된 것으로 정의하였다. 생존자와 비생존자 사이의 특성을 30일과 1년 사망률을 통해 평가하였고, 단 변량 분석에서 유의하였던 변수들, 나이, 성별, 찰슨 동반 질병 지수(Charlson Comorbidity Index)들

을 보정하여 다변량 분석을 진행하였다. 또한 호중구 감소증의 존재와 사망률 간의 관련성을 확인하였다. 패혈성 쇼크로 인한 신장 손상에 대한 투석 필요성을 확인하였고 투석 필요성 및 2년 생존률과 관련된 변수를 확인하기 위해 다변량 회귀 분석과 Cox 비례 위험 모형을 사용하였다. 모든 분석은 양측 P 값 < 0.05를 사용하였으며, SAS Enterprise Guide 버전 7.1을 사용하였다.

결과

2009년부터 2017년까지 대한민국 응급실을 내원한 322,526명의 패혈성 쇼크 환자 중, 90일 이내 암 진단 코드가 확인된 환자는 43,850명 (13.6%) 이었다. 이 중 18세 미만이거나 데이터 누락이 있는 환자를 제외한, 43,466명의 환자가 연구에 등록되었다. 패혈증 쇼크 암환자들의 30일 사망률은 22,639명 (52.1%), 1년 사망률은 35,325명 (81.3%)였다. 패혈증 쇼크 암환자들은 2016년부터 증가하는 추세이나, 이들의 30일 및 1년 사망률은 2011년 이후 꾸준히 감소 추세였다. 가장 높은 유병율을 보인 암은 순서대로 폐암 (15.5%), 간암 (14.4%), 대장암 (10.3%), 위암 (8.5%), 담낭암 (4.6%), 췌장암 (4.5%), 백혈병 (4.4%), 비호지킨 림프종(3.4%)이었으며, 30일 사망율이 가장 높은 순으로는 폐암 (62.9%), 간암 (59.8%), 백혈병 (54.9%), 췌장암 (53.0%), 위암 (50.6%), 비호지킨 림프종 (49.7%), 담낭암 (43.6%), 대장암 (41.9%)이었다. 패혈증 쇼크 암 환자 중 14.7%가 호중구 감소증이 동반되었으며, 이들의 30일 사망률은 44.5%였다. 호중구 감소증이 없는 환자들은 더 나이가 많으며, 동반 질환 부담이 더 컸다. 패혈증 쇼크 암 환자 중 호중구 감소증이 있는 환자들은 30일과 1년 생존률 모두 호중구 감소증이 동반되지 않는 패혈증 쇼크 암 환자들보다 높았다. 패혈증 쇼크 암 환자 중 12.8%는 투석을 필요로하는 급성 신장 손상을 겪었으며, 이 중 77.9%는 30일 이내에 회복되었다. 투석이 필요한 환자들은 더 어렸으며, 동반 질환 점수가 낮았다. 여성 성별, 젊은 나이, 고혈압, 당뇨병, 심부전 또는 간경변증의 부재는 감염성 신장 손상 발생 가능성을 낮추었다. 투석을 필요로 하는 감염성 신장 손상의 발생은 1개월 사망률을 높였고 이들의 2년 사망률은 85.1%였다. 입원

중 투석이 필요한 환자들은 비생존자들 사이에서 더 많았습니다. 높은 나이, 남성, 간경변증 및 높은 동반 질환 점수는 2년 사망률과 관련이 있는 변수들이었다.

결론

최근 몇 년 동안 암 환자들에서 패혈성 쇼크로 인한 사망률은 암의 종류에 관계없이 점차 감소하였다. 호중구 감소증이 있더라도 패혈성 쇼크의 사망률이 유의하게 악화되지 않았다. 이는 호중구 감소증 동반 여부만으로 패혈증 쇼크 암환자들의 추가적인 집중 치료등을 보류하는 것은 적절하지 않음을 시사한다. 패혈증 쇼크 암환자들에서 투석이 필요한 급성 신장 손상의 동반은 장기적인 사망률을 증가시켰다.

중심 단어

암 환자들과 감염성 쇼크; 사망률; 중성구 감소증; 급성 신장 손상