Outcomes and Predictors of 28-Day Mortality in Patients With Hematologic Malignancies and Septic Shock Defined by Sepsis-3 Criteria

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ABSTRACT

Background: To describe short-term outcomes and independent predictors of 28-day mortality in adult patients with hematologic malignancies and septic shock defined by the new Third International Consensus Definitions (Sepsis-3) criteria. **Methods:** We performed a retrospective cohort study of patients admitted to the medical ICU with septic shock from April 2016 to March 2019. Demographic and clinical features and short-term outcomes were collected. We used descriptive statistics to summarize patient characteristics, logistic regression to identify predictors of 28-day mortality, and Kaplan-Meier plots to assess survival. **Results:** Among the 459 hematologic patients with septic shock admitted to the ICU, 109 (23.7%) had received hematopoietic stem cell transplant. The median age was 63 years (range, 18–89 years), and 179 (39%) were women. Nonsurvivors had a higher Charlson comorbidity index ($P=.007$), longer length of stay before ICU admission ($P=.01$), and greater illness severity at diagnosis and throughout the hospital course ($P<.001$). The mortality rate at 28 days was 67.8% and increased with increasing sequential organ failure assessment score on admission (odds ratio [OR], 1.11; 95% CI, 1.03–1.20), respiratory failure (OR, 3.12; 95% CI, 1.49–6.51), and maximum lactate level (OR, 1.16; 95% CI, 1.10–1.22). Aminoglycosides administration (OR, 0.42; 95% CI, 0.26–0.69), serum albumin (OR, 0.51; 95% CI, 0.31–0.86), and granulocyte colony-stimulating factor (G-CSF) (OR, 0.40; 95% CI, 0.24–0.65) were associated with lower 28-day mortality. Life support limitations were present in 81.6% of patients at death. At 90 days, 19.4% of the patients were alive. **Conclusions:** Despite efforts to enhance survival, septic shock in patients with hematologic malignancies is still associated with high mortality rates and poor 90-day survival. These results demonstrate the need for an urgent call to action with higher awareness, including the further evaluation of interventions such as earlier ICU admission, aminoglycosides administration, and G-CSF treatment.

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Background

Cancer survival rates have improved significantly over the past 3 decades.¹ As cancer mortality decreases and the cancer population grows older, the burden of cancer continues to increase.^{2,3} This progressively larger population of patients with cancer, especially those with hematologic malignancies, have a significantly higher risk of developing sepsis compared with the noncancer population.^{4,5} Recent epidemiologic reports indicate that 1 in 5 patients with sepsis has cancer⁶ and 8.5% of all cancer deaths are associated with severe sepsis.⁴

Between 2009 and 2014, sepsis incidence in the United States increased by 10.3% (95% CI, 7.2%–13.3%).⁶ In 2017, 11 million deaths related to sepsis were reported worldwide, comprising 19.7% of all deaths that year.⁷ In the United States, it is estimated that one-third of hospitalized patients' deaths are related to sepsis.^{6,8} Overall, the sepsis mortality rate ranges between 12.5% and 17%.^{6,9,10} However, based on the severity of the sepsis, mortality can be as low as 5.6% in sepsis without organ dysfunction or can increase to 34.2% for septic shock.¹⁰ In a cohort of patients with solid tumors and hematologic malignancies from 1994 to 2015, those with sepsis and septic shock had a 30-day mortality of 42.6%.⁵

Most large epidemiologic studies report sepsis in combination with septic shock and do not address patients with cancer.^{6–9} Some studies address critically ill patients with hematologic malignancies but not sepsis or septic shock,^{11,12} whereas other reports that addressed septic shock in this population predated the latest 2016 international consensus definitions for sepsis and septic shock and thus used Sepsis-2 definitions.^{13,14} Some studies included small cohorts or were spread over long periods, leading to time bias.^{5,15,16} In other studies, severe sepsis and septic shock are reported together.^{5,14} This article reports on the short-term outcomes and the independent predictors of 28-day mortality in adult patients with

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hematologic malignancies and septic shock using the new Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) clinical criteria in a high-volume comprehensive cancer center.¹⁷ We hypothesized that the mortality rates of septic shock in patients with hematologic malignancies remain unacceptably high.

Methods

Design, Setting, and Participants

This retrospective longitudinal study was conducted with the approval of The University of Texas MD Anderson Institutional Review Board. The hospital ICU is a 52-bed facility, with a well-delineated and open admission policy, as previously described.^{18,19} Other features include an ICU admission triage service, a rapid response system, an outreach program, multidisciplinary rounds, evidence-based protocols, and a historical average of 3,500 annual admissions.¹⁹ The study population was identified from all adult patients with cancer (age ≥ 18 years) admitted to the medical ICU from April 1, 2016, to March 31, 2019, who had an ICD-10 diagnosis code for sepsis or diagnostic-related group (DRG 870, 871, or 872) as described by Paoli et al.⁹

To this population, we applied inclusion criteria of having a diagnosis of hematologic malignancy and septic shock meeting Sepsis-3 criteria (suspected infection, persistent hypotension requiring vasopressors to maintain a mean arterial pressure of ≥ 65 mm Hg despite adequate volume resuscitation, and a serum lactate level of >2 mmol/L).¹³ Patients with a lactate level of ≤ 2 mmol/L after resuscitation prior to ICU admission, those without septic shock, and those with sepsis concomitant with other types of shock, such as cardiogenic, hemorrhagic, or neurologic shock, were excluded to reduce bias. We also excluded all postsurgical patients.

Data Sources and Measurements

Demographic and clinical information such as age, sex, comorbidities, Charlson comorbidity index (CCI), and characteristics of cancer, such as cancer diagnosis, histologic type, and current status (remission, relapse, or progression), were extracted from patients' electronic medical records. We also collected relevant information on cancer therapy, including the recent history of chemotherapy and characteristics of stem cell transplants (SCTs). We determined the source of admission to the ICU (emergency department or hospital ward), the main reason for ICU admission, presence of sepsis on admission, the sequential organ failure assessment (SOFA) score at the time of septic shock diagnosis, maximum SOFA score during the ICU stay, length of stay (pre-ICU, ICU, hospital), neutropenia (absolute neutrophil count [ANC] $\leq 1,500/\text{mm}^3$), severe neutropenia (ANC $< 500/\text{mm}^3$), therapeutic interventions during the ICU stay (use of vasopressors,

mechanical ventilation, dialysis, chemotherapy), use of noninvasive mechanical ventilation, renal replacement therapy, and additional laboratory values. Outcomes included 28-day mortality, ICU mortality, hospital mortality, 90-day mortality, and ICU resource utilization such as ICU length of stay, days on ventilator, and days on vasopressors. The change in code status during ICU stay (do-not-resuscitate [DNR] order), life support limitations or withdrawal, survival status at the time of hospital discharge, and the discharge destination were captured up to 90 days after ICU admission. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²⁰

Statistical Analysis

Descriptive statistics were used to summarize the demographic, clinical, and treatment-related patient features. Bivariate analyses were conducted to explore associations with 28-day ICU mortality for all candidate predictors. Predictors were screened using logistic regression in a univariable setting. Continuous predictors were assessed for linearity in functional form. All potential predictors whose relationship with 28-day mortality met a threshold of $P < .10$ were considered for full model inclusion. After we established a full model of all candidate predictors, backward elimination was used to isolate independent predictors where the probability of covariate retention was $P < .05$. Odds ratio (OR) estimates and 95% confidence intervals summarized study findings. The multivariable logistic regression model was critically assessed using the Hosmer-Lemeshow goodness-of-fit test.²¹ Also calculated was the concordance index, which specifies the area under the receiver operating characteristic curve.²² To assess model discrimination visually, probability estimates of 28-day mortality emanating from the multivariable model used terciles to categorize patients as low, moderate, and high risk for early mortality after ICU admission. Survival was computed from the date of ICU admission to the patient's date of death or date of the last follow-up, at which time patients were censored. Kaplan-Meier plots were generated to assess survival distributions based on patient characteristics of interest. Survival was artificially censored at 90 days because of the high rate of mortality experienced at day 28. P values of $< .05$ were considered statistically significant. Statistical analyses were conducted using STATA, version 15 (StataCorp LP).

Results

During the 3-year study period, 86,231 patients were admitted, of whom 6,486 (7.5%) were admitted to the ICU. Among them, 2,242 (34.6%) had sepsis, and of those, 809 (36%) met Sepsis-3 criteria for septic shock (Figure 1). Of these patients with septic shock, 459 also had hematologic

Figure 1. Flowchart of included participants by the Sepsis-3 definition.

malignancies: 284 (61.9%) had leukemia, 97 (21.1%) had lymphoma, and 78 (17%) had other hematologic malignancies (supplemental eFigure 1, available with this article at JNCCN.org). By day 28 after ICU admission, 311 patients (67.7%) died and 148 (32.2%) survived. Of the nonsurvivors, 147 (47.2%) had relapsed/refractory disease at ICU admission. A total of 109 patients (23.7%) had a history of SCT, 20% autologous and 80% allogeneic, with no mortality difference between the transplant types at 28 days ($P=.165$); nor was there a difference in 28-day mortality rate between patients with and without a SCT (67% [73/109] vs 68% [238/350], respectively; $P=.83$). There were more men (61%) than women, and most patients were White (61.4%). The median age was 63 years (range, 18–89 years), and the median body mass index was 27 kg/m² (range, 15–57 kg/m²). The primary source of admission was the hospital ward (71.4%), 35 patients (7.6%) had pre-ICU cardiac arrests, and 7.6% were later readmitted to the ICU. Approximately half of the patients had <3 comorbidities (51.6%), and one-third had a history of diabetes (31%). The demographic characteristics according to 28-day survival status are summarized in Table 1, and comorbidities are summarized in supplemental eTable 1.

Respiratory failure was present during the ICU stay in 88.8% of patients, and of those, 293 (71.8%) died ($P<.001$).

Of the 277 patients who required intubation, 174 (62.8%) were intubated within 24 hours of admission, and 199 (71.8%) died, whereas among the 45 patients who required only high-flow oxygen or noninvasive ventilation, 26 (57.8%) died ($P=.011$).

Characteristics and outcomes are compared between survivors and nonsurvivors in Tables 1 and 2. Patients who died within 28 days had significantly higher lactate levels at the time of septic shock diagnosis (mean [SD], 7.8 [6.4] vs 4.7 [3.0] mmol/L) and at ICU admission (mean [SD], 10 [6.9] vs 5.7 [3.9] mmol/L; $P<.0001$) but significantly lower serum albumin levels (mean [SD], 2.5 [0.5] vs 2.6 [0.5] g/dL; $P<.0001$) (supplemental eTable 2). All the patients were treated with at least one antibiotic. Most patients received antifungals (81.2%), followed in frequency by antivirals (61.4%) and aminoglycosides (60.7%). Microbial organisms were isolated in 66.6% of patients (supplemental eTable 3). Among them, the patients with fungal isolates had the highest mortality rate (72.7%). Mortality was significantly lower for patients with gram-negative organisms compared with the remainder of the cohort (61% vs 71%; $P=.029$), and in patients who received meropenem, aminoglycosides, or cefepime ($P<.0001$), as well as those who received hydrocortisone ($P=.044$) (supplemental eTable 4).

Table 1. Study Cohort Characteristics

Variable	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
Total, n	459	148	311	
Age, median (range), y	63 (18–89)	60 (19–84)	64 (18–89)	.002
Female	179 (39.0)	61 (41.2)	118 (37.9)	.501
Race/Ethnicity				.038
White	282 (61.4)	79 (53.3)	203 (65.2)	
African American	57 (12.4)	18 (12.1)	39 (12.5)	
Hispanic	41 (8.9)	17 (11.4)	24 (7.7)	
Asian American	25 (5.4)	8 (5.4)	17 (5.4)	
Other ^a	54 (11.7)	26 (17.5)	28 (9)	
BMI, median (range), kg/m ²	27 (15–57)	27 (15–50)	27 (15–57)	.498
Underlying malignancy				.007
ALL	54 (11.7)	26 (17.5)	28 (9)	
AML	198 (43.1)	47 (31.7)	151 (48.5)	
CLL	17 (3.7)	7 (4.7)	10 (3.2)	
CML	12 (2.6)	4 (2.7)	8 (2.5)	
APL	3 (0.6)	2 (1.3)	1 (0.3)	
MDS	30 (6.5)	7 (4.7)	23 (7.3)	
Myelofibrosis	6 (1.3)	1 (0.6)	5 (1.6)	
Hodgkin lymphoma	10 (2.1)	6 (4)	4 (1.2)	
Non-Hodgkin lymphoma	87 (18.9)	29 (19.5)	58 (18.6)	
Multiple myeloma	37 (8)	16 (10.8)	21 (6.7)	
Other	5 (1)	3 (2)	2 (0.6)	
Disease status				.076
Relapsed/Refractory	217 (47.2)	70 (47.2)	147 (47.2)	
Remission	43 (9.3)	21 (14.1)	22 (7)	
Newly diagnosed	20 (4.3)	5 (3.3)	15 (4.8)	
Active	177 (38.5)	51 (34.4)	126 (40.5)	
BMT/HSCT	109 (23.7)	36 (24.3)	73 (23.4)	.841
Autologous	22 (4.7)	10 (6.7)	12 (3.8)	.165
Allogeneic	87 (18.9)	26 (17.5)	61 (19.6)	
GVHD	33 (7.1)	10 (6.7)	23 (7.3)	.806
Neutropenia	298 (64.9)	93 (62.8)	205 (65.9)	.49
Severe neutropenia ^b	247 (53.8)	83 (56.5)	164 (53.2)	.52
CCI, median (range)				
Score	5 (1–18)	4 (1–11)	5 (2–18)	.007
10-y survival estimate	21 (0–96)	37 (0–96)	21 (0–90)	.018
ECOG performance status				.003
0	55 (11.9)	19 (12.8)	36 (11.5)	
1	163 (35.5)	69 (46.6)	94 (30.2)	
2	97 (21.1)	28 (18.9)	69 (22.1)	
3	90 (19.6)	19 (12.8)	71 (22.8)	
4	36 (7.8)	7 (4.7)	29 (9.3)	
Information not available ^c	18	6	12	

(continued on next page)

Table 1. Study Cohort Characteristics (cont.)

Variable	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
ICU admission source				<.001
Emergency	131 (28.5)	58 (39.1)	73 (23.4)	
Hospital ward	328 (71.4)	90 (60.8)	238 (76.5)	
Reason for ICU admission				.005
Sepsis/Shock	323 (70.3)	117 (79)	206 (66.2)	
Other ^d	136 (29.6)	31 (20.9)	105 (33.7)	
CPR before ICU admission	35 (7.6)	8 (5.4)	27 (8.6)	.216
SOFA at SS diagnosis, median (range)	11 (4–21)	10 (4–18)	12 (4–21)	<.001
Maximum SOFA, median (range)	14 (4–22)	12 (4–22)	14 (6–21)	<.001
Respiratory failure	408 (88.8)	115 (77.7)	293 (94.2)	<.001
Acute kidney injury	369 (80.3)	111 (75)	258 (82.9)	.045
Atrial fibrillation	147 (32)	34 (22.9)	113 (36.3)	.004
Recent chemotherapy	65 (14.1)	24 (16.2)	41 (13.1)	.313
Checkpoint inhibitors	11 (2.3)	2 (1.3)	9 (2.8)	.312

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BMI, body mass index; BMT, bone marrow transplant; CCI, Charlson comorbidity index; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CPR, cardiopulmonary resuscitation; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndromes; SOFA, sequential organ failure assessment score; SS, septic shock.

^aOne patient with missing race/ethnicity was classified as "other."

^bAbsolute neutrophil count <500/mm³.

^cPatients with unavailable information were not included for statistical comparison.

^dIncludes respiratory failure; cardiac, neurologic, renal, multiorgan causes; coagulopathy.

ICU mortality was 63.8%, 28-day mortality was 67.7%, hospital mortality was 73.9%, and the 90-day mortality was 80.6%. Patients who had an allogeneic SCT with graft-versus-host disease had the lowest survival rates at 90 days (4%). A subanalysis of septic shock patients not meeting Sepsis-3 criteria demonstrated significantly lower ICU (34.3%; $P<.0001$), 28-day (38.9%; $P<.0001$), hospital (44.9%; $P<.0001$), and 90-day (58.3%; $P<.0001$) mortality rates than patients meeting Sepsis-3 criteria (Figure 1; supplemental eTable 5). Two-thirds of patients (67.5%) had life supportive measures withheld (DNR) after ICU admission. At 90 days, 370 patients (80.6%) had died. Of those patients, 302 (81.6%) had a DNR order in place and 209 (56.4%) had life support withdrawn at the time of death (supplemental eTable 6). The 1-year survival of the Sepsis-3 cohort was 10% ($n=46$). The patient distribution by SOFA score and survival at 28 days is shown in supplemental eFigure 2.

Kaplan-Meier plots were used to visually assess survival distributions of patients by hematologic malignancy, leukemia subtype, SCT type, and severe neutropenic status at 90 days (Figure 2). The reduced logistic regression model derived using backward elimination resulted in a 6-covariate model containing: admission SOFA score, respiratory failure, aminoglycoside use, highest lactate level, serum albumin level, and G-CSF use. Multivariable analysis showed that higher serum albumin level (OR, 0.51; 95% CI, 0.31–0.86; $P=.011$), G-CSF (OR, 0.4; 95% CI, 0.24–0.65; $P<.001$), and therapy with aminoglycosides (OR, 0.42; 95%

CI, 0.26–0.69; $P=.001$) were associated with lower mortality, whereas respiratory failure (OR, 3.12; 95% CI, 1.49–6.51; $P=.003$), higher lactate level (OR, 1.16; 95% CI, 1.10–1.22; $P<.001$), and higher admission SOFA score (OR, 1.11; 95% CI, 1.03–1.20; $P=.005$) were associated with higher mortality (Figure 3). There was no mortality difference between patients with severe versus nonsevere neutropenic septic shock ($P=.36$) (supplemental eTable 7). Patients who received G-CSF had a lower hospital and 28-day mortality, but the difference disappeared at 90 days (supplemental eTable 8). The Hosmer-Lemeshow goodness-of-fit test suggested adequate model fit (chi-square, 7.03; $df=8$; $P=.533$). The prediction model discrimination is visually represented in supplemental eFigure 3. The C-index associated with this clinical prediction model was 0.795, suggesting moderate to good discrimination.^{21,22}

Discussion

In this study of a large cohort of adult patients with hematologic malignancies and septic shock by Sepsis-3 criteria, two-thirds of the patients died within 28 days, and only 1 in 5 were alive at 90 days. Multivariable analysis showed a survival benefit among those receiving aminoglycosides, those given G-CSF, and those with higher albumin levels, whereas respiratory failure, higher lactic acid levels, and higher SOFA scores were associated with increased mortality. The highest mortality was in transplant patients who had graft-versus-host disease.

Table 2. Resource Utilization

Variable	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
Total, n	459	148	311	
Pre-ICU LoS, median (range)	6 (0–30)	2 (0–141)	8 (0–230)	.010
ICU LoS, median (range)	5 (0–104)	8 (0–104)	5 (0–28)	<.001
Hospital LoS, median (range)	22 (1–245)	33 (3–242)	19 (1–245)	<.001
Type of respiratory support				.011
NIV/HFOT	45 (9.8)	19 (12.8)	26 (8.3)	
IMV	127 (27.6)	27 (18.2)	100 (32.1)	
Both	150 (32.6)	51 (34.4)	99 (31.8)	
Intubation time				.269
<24 h	174 (37.9)	45 (30.4)	129 (41.4)	
≥24 h	103 (22.4)	33 (22.2)	70 (22.5)	
Ventilator days, median (range)	7 (0–77)	11 (1–77)	5 (0–28)	<.001
Vasopressor days, median (range)	1.5 (0–41.5)	1.3 (0–41.5)	1.5 (0–19.3)	.006
RRT	97 (21.1)	38 (25.6)	59 (18.9)	.100
Transfusions	394 (85.8)	132 (89.1)	262 (84.2)	.156
ICU readmission	35 (7.6)	21 (14.1)	14 (4.5)	<.001
Number of ICU readmissions				.009
1	28 (6.1)	15 (10.1)	13 (4.1)	
2	4 (0.8)	3 (2)	1 (0.3)	
3	3 (0.6)	3 (2)	0 (0)	
Discharge destination				<.001
Acute care hospital	17 (3.7)	13 (8.7)	4 (1.2)	
Expired	339 (73.8)	38 (25.6)	301 (96.7)	
Home/Self-care	69 (15)	3 (2)	66 (21.2)	
Hospice	10 (2.1)	7 (4.7)	3 (0.9)	
LTAC	5 (1)	5 (3.3)	0 (0)	
Rehabilitation	5 (1)	5 (3.3)	0 (0)	
Skilled nursing facilities	6 (1.3)	6 (4)	0 (0)	
Home health service	8 (1.7)	8 (5.4)	0 (0)	

Patients with unavailable information were not included for statistical comparison.

Abbreviations: HFOT, high-flow oxygen therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; LoS, length of stay; LTAC, long-term acute care facility; NIV, noninvasive ventilation; RRT, renal replacement therapy.

Life support limitations were present in 8 of every 10 patients at the time of death.

The survival of patients with cancer^{1,19} and of those with sepsis has improved during the past 2 decades, especially after outstanding international efforts in sepsis education and development of therapeutic strategies to reduce sepsis mortality²³; nevertheless, this study demonstrates poor outcomes in patients with hematologic malignancies meeting Sepsis-3 criteria. This cohort included a population with high SOFA and CCI scores, high need for ventilatory support, and high incidence of acute kidney injury. In contrast, patients with septic shock not meeting Sepsis-3 criteria demonstrated high but significantly lower mortality. These differences highlight the impact of the Sepsis-3 definition.^{24,25} This

correlation has been described previously.^{26,27} In a cohort of 241 patients with solid tumors and 112 with hematologic malignancies, Nathan et al²⁸ compared hospital mortality from septic shock between the Sepsis-2 and Sepsis-3 definitions. Although the use of invasive mechanical ventilation in their cohort was only 19%, they found a mortality of 60% with the Sepsis-2 definition in contrast to 68% with the Sepsis-3 definition.

Most large studies in this area analyze sepsis in general and do not detail the outcomes of septic shock in cancer independently. Williams et al⁴ showed an overall sepsis incidence of 4.9%, with 2.4% needing the ICU in 1999, similar to the 2.6% incidence of cancer hospitalizations experiencing sepsis and ICU admission we found in our

Figure 2. Survival curves by (A) hematologic malignancy type, (B) leukemia type, (C) hematopoietic stem cell transplant type, and (D) severe neutropenia status (absolute neutrophil count $<500/\text{mm}^3$). Differences between the curves were assessed using the log-rank test. Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; MM, multiple myeloma.

study. Williams et al⁴ reported a 36.1% combined (severe sepsis/septic shock) mortality in patients with hematologic malignancies. Similarly, Cooper et al²⁹ recently reported a cohort of 20,975 patient with and without cancer hospitalized with sepsis during a period of 12 years (2003–2014); of the 7,489 patients with cancer, 2,866 had hematologic malignancies (only 38.1% required vasopressors) and an overall sepsis in-hospital mortality rate of 28.8%. Hensley et al³⁰ reported 27.9% in-hospital mortality in patients with cancer with sepsis during 2013 to 2014, but no details about septic shock were provided. Lemiale et al⁵ reported a 30-day mortality of 39.9% in a cohort of patients with sepsis/septic shock and cancer, 82% of whom had hematologic malignancies, over a period of 21 years (1994–2015); mortality of the patients with hematologic malignancies and septic shock was not reported.

The decrease in the reported historical sepsis mortality rates over the past 20 years can be misleading, and many practitioners may underestimate the prognosis of septic shock. An Australian study of ICU patients found 18.4% in-hospital mortality for those with sepsis and 22% for those with septic shock in 2012.³¹ In a recent

systematic review (2005–2018) of the frequency and mortality of septic shock in Europe and North America, Vincent et al³² reported an ICU mortality of 37.3% (95% CI, 31.5%–43.5%) and a hospital mortality of 39.0% (95% CI, 34.4%–43.9%) in patients with septic shock defined using the Sepsis-2 criteria. When septic shock was defined using the Sepsis-3 criteria, the ICU mortality increased to 51.9% (95% CI, 43.9%–59.8%) and the hospital mortality to 52.1% (95% CI, 51.6%–52.6%). Azoulay et al¹¹ also reported a high hospital mortality in a large general cohort (including patients without sepsis or shock) of ICU patients with hematologic malignancies, of whom 51% required vasopressors, 26% required renal replacement therapy, and 48% required invasive mechanical ventilation; mortality rates were 57.5%, 59.2%, and 60.5%, respectively.

The increased risks of developing sepsis with organ dysfunction and the higher mortality of allogeneic SCT patients with graft-versus-host disease have been described.³³ Patients admitted to the ICU within 100 days of allogeneic transplant have a hospital mortality of 64% and a 1-year survival rate of 15%.³⁴ Therefore, given that

Figure 3. Multivariable analysis of risk factors associated with 28-day mortality (n=456; Hosmer-Lemeshow goodness-of-fit test, 7.03, $df=8$; $P=.533$; C-index = 0.795).

Abbreviations: G-CSF, granulocyte colony-stimulating factor; OR, odds ratio; SOFA, sequential organ failure assessment score.

80% of transplants in our cohort were allogeneic, the low survival rate seen in our study is not surprising.

We also observed that patients with acute myeloid leukemia (AML) had a lower 90-day survival rate compared with those with other types of acute leukemias (12% vs 28% in acute lymphocytic leukemia) (Figure 2). In a cohort of 2,173,776 adults discharged from hospitals in Texas, those with AML had an increased incidence of sepsis (16% vs 4%) and higher sepsis-associated hospital mortality (30% vs 21%) compared with patients with non-AML cancer.³⁵ In addition, when patients with AML develop renal failure, their 8-week mortality is as high as 65% regardless of dialysis.³⁶

Although our study showed no difference in mortality between patients with and without neutropenia, we did find that those who received G-CSF had a reduced risk of death at 28 days. A recent meta-analysis found an association between neutropenia and mortality, and this association disappeared after the analysis was adjusted for the use of G-CSF therapy.³⁷ The association we observed between the use of aminoglycosides and improved outcomes has also been previously reported, thus giving strength to this association.³⁸ The timing of antibiotics has also been proposed as a significant factor in the reduction of mortality among patients with sepsis.^{39,40} A recent publication of 162 ambulatory patients with cancer suspected of developing sepsis/septic shock treated with early fluid resuscitation and aggressive antibiotic treatment (meropenem, tobramycin, and linezolid) reported an overall mortality rate of 4%.⁴¹

Our study was conducted in a high-volume, quaternary comprehensive cancer center specialized in treating all types of cancers and experimental therapies. Overall, our findings

are consistent with the existing literature. At the same time, it is a retrospective cohort and single-center study, which may limit the generalizability of the results. However, we implemented strategies to diminish selection bias, such as data validation by an ICU physician. Another limitation is that we excluded patients with sepsis and a concomitant cardiogenic shock. Despite efforts to validate our findings, there is a possibility that a fraction of the patients with septic shock and sepsis-induced cardiomyopathy could have been omitted. Additionally, given our institution's nature, we manage large volumes of patients with advanced cancer, which may have skewed the patient population toward higher percentages of multiorgan dysfunction/failure and less organ reserve to respond during critical illness.

Conclusions

This study is the first to report comprehensively on the short-term mortality rates of adult patients with hematologic malignancies admitted to the ICU and meeting Sepsis-3 criteria for septic shock. Despite the survival improvements in patients with cancer and sepsis overall reported in the literature over the past 2 decades, as well as the impact of the Sepsis-3 definition, septic shock in patients with hematologic malignancies is still associated with high mortality rates and poor 90-day survival. These results are an urgent call to action with higher awareness, including the further evaluation of interventions such as earlier ICU admission, aminoglycosides administration, and G-CSF treatment.

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Supplemental online content for:

Outcomes and Predictors of 28-Day Mortality in Patients With Hematologic Malignancies and Septic Shock Defined by Sepsis-3 Criteria

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eFigure 1: Flowchart of Included Participants by Hematologic Malignancies

eFigure 2: Patient Distribution Based on SOFA Score and Survival Status at 28 Days

eFigure 3: Risk Stratification Plot

eTable 1: Comorbidities

eTable 2: Laboratory Parameters

eTable 3: Microbiologic Isolates

eTable 4: Interventions

eTable 5: Mortality Rates in Patients With Hematologic Malignancies by Septic Shock Definition

eTable 6: Advance Care Planning

eTable 7: Mortality by Neutropenia Status

eTable 8: Study Cohort by G-CSF Administration

eFigure 1. Flowchart of included participants by hematologic malignancies.

Abbreviations: GVHD, graft-versus-host disease; MDS, myelodysplastic syndromes; MM, multiple myeloma; SCT, stem cell transplant.

eFigure 2. Patient distribution based on SOFA score and survival status at 28 days.
Abbreviation: SOFA, sequential organ failure assessment score.

eFigure 3. Risk stratification plot.

This plot illustrates a clear separation of survival distributions based on risk groups derived using the tertiles of the estimated probability of 28-day mortality emanating from the 6-covariate multivariable model developed in our study.

Comorbidity	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
Total, n	459	148	311	
Myocardial infarction	38 (8.2)	10 (6.7)	28 (9)	.414
Congestive heart failure	56 (12.2)	18 (12.1)	38 (12.2)	.986
Peripheral vascular disease	11 (2.3)	2 (1.3)	9 (2.8)	.312
Cerebrovascular disease	26 (5.6)	7 (4.7)	19 (6.1)	.550
Dementia	2 (0.4)	1 (0.6)	1 (0.3)	.590
Chronic pulmonary disease	34 (7.4)	10 (6.7)	24 (7.7)	.713
Connective tissue disease	8 (1.7)	3 (2)	5 (1.6)	.748
Peptic ulcer disease	10 (2.1)	144 (97.2)	6 (1.9)	.596
Diabetes mellitus	142 (31.0)	98 (66.2)	92 (29.5)	.363
Moderate/Severe CKD	58 (12.6)	131 (88.5)	41 (13.1)	.609
Hemiplegia	2 (0.4)	147 (99.3)	1 (0.3)	.590
Liver disease	22 (4.7)	7 (4.7)	15 (4.8)	.965
AIDS	5 (1)	2 (1.3)	3 (0.9)	.709
Immunosuppression	237 (51.6)	85 (57.4)	152 (48.8)	.086
Steroid therapy	96 (20.9)	37 (25)	59 (18.9)	.138

Categorical variables differences were calculated with chi-square test. Continuous data differences were calculated with t test.
Abbreviation: CKD, chronic kidney disease.

eTable 2. Laboratory Parameters

Variable	Overall	Survivors	Nonsurvivors	P Value
Total, n	459	148	311	
Hemoglobin, ^a g/dL				.268
Mean [SD]	8.9 [1.6]	8.8 [1.6]	9 [1.6]	
Median (range)	9 (4–14)	9 (4–14)	9 (4–14)	
Hemoglobin ICU, ^b g/dL				.321
Mean [SD]	9 [0.8]	8.9 [0.7]	9 [0.9]	
Median (range)	9 (7–13)	9 (7–11)	9 (7–13)	
ANC value, cells $\times 10^9/L$				.309
Mean [SD]	3.3 [7.1]	2.8 [4.9]	3.5 [7.9]	
Median (range)	0 (0–50)	0 (0–22)	0 (0–50)	
Highest lactate, ICU admission, mmol/L				<.0001
Mean [SD]	8.6 [6.4]	5.7 [3.9]	10 [6.9]	
Median (range)	6 (2–38)	4 (2–24)	8 (2–38)	
Lactate at SS diagnosis, mmol/L				<.0001
Mean [SD]	6.8 [5.7]	4.7 [3]	7.8 [6.4]	
Median (range)	5 (2–38)	4 (2–24)	5 (2–38)	
BNP, n (%)	228 (49.6)	69 (46.6)	159 (51.1)	.948
NT-ProBNP, n (%)	87 (18.9)	26 (17.5)	61 (19.6)	
BNP value, pg/mL				.663
Mean [SD]	1,152.6 [1,166.6]	1,203.9 [1,080.8]	1,130.3 [1,204.5]	
Median (range)	710 (0–4,902)	809 (65–4,700)	643 (0–4,902)	
Platelet count, K/ μ L				.487
Mean [SD]	34.3 [56.9]	37 [61.9]	33.1 [54.4]	
Median (range)	14 (0–437)	14 (0–437)	14 (0–385)	
Serum albumin, mg/dL				<.0001
Mean [SD]	2.5 [0.5]	2.6 [0.5]	2.5 [0.5]	
Median (range)	2 (1–4)	3 (2–4)	2 (1–4)	

Categorical variables differences were calculated with chi-square test. Continuous data differences were calculated with t test.

Abbreviations: ANC, absolute neutrophil count; BNP, B-type natriuretic peptide; ICU, intensive care unit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SS, septic shock.

^aHemoglobin at septic shock diagnosis.

^bMean hemoglobin during the ICU stay.

eTable 3. Microbiologic Isolates				
Isolate	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
Total, n	459	148	311	
Microbial organism isolated	306 (66.6)	108 (72.9)	198 (63.6)	.048
Gram-positive	111 (24.1)	38 (25.6)	73 (23.4)	.606
Gram-negative	163 (35.5)	63 (42.5)	100 (32.1)	.029
Anaerobes	12 (2.6)	7 (4.7)	5 (1.6)	.05
Fungi	55 (11.9)	15 (10.1)	40 (12.8)	.4
Virus	52 (11.3)	22 (14.8)	30 (9.6)	.099

Categorical variables differences were calculated with chi-square test. Continuous data differences were calculated with t test.

eTable 4. Interventions

Intervention	Overall n (%)	Survivors n (%)	Nonsurvivors n (%)	P Value
Total, n	459	148	311	
Antibiotics				
Aminoglycosides	281 (61.2)	110 (74.3)	171 (54.9)	<.0001
Vancomycin	186 (40.5)	69 (46.6)	117 (37.6)	.066
Piperacillin-tazobactam	134 (29.1)	49 (33.1)	85 (27.3)	.203
Linezolid	309 (67.3)	102 (68.9)	207 (66.5)	.614
Meropenem	343 (74.7)	126 (85.1)	217 (69.7)	<.0001
Metronidazole	109 (23.7)	36 (24.3)	73 (23.4)	.841
Daptomycin	119 (25.9)	46 (31)	73 (23.4)	.082
Cefepime	200 (43.5)	83 (56)	117 (37.6)	<.0001
Aztreonam	21 (4.5)	8 (5.4)	13 (4.1)	.557
Clindamycin	27 (5.8)	9 (6)	18 (5.7)	.901
Minocycline	66 (14.3)	17 (11.4)	49 (15.7)	.223
Ceftazidime	118 (25.7)	28 (18.9)	90 (28.9)	.022
Tigecycline	134 (29.1)	39 (26.3)	95 (30.5)	.355
Ciprofloxacin	33 (7.1)	19 (12.8)	14 (4.5)	.001
Sulfamethoxazole	139 (30.2)	43 (29)	96 (30.8)	.693
Vasoactive agents				
Norepinephrine	453 (98.6)	143 (96.6)	310 (99.6)	.007
Epinephrine	111 (24.1)	35 (23.6)	76 (24.4)	.854
Vasopressin	258 (56.2)	63 (42.5)	195 (62.7)	<.0001
Angiotensin II	3 (0.6)	1 (0.6)	2 (0.6)	.968
Phenylephrine	92 (20)	17 (11.4)	75 (24.1)	.002
Dobutamine	2 (0.4)	1 (0.6)	1 (0.3)	.59
Steroids				
Any steroid	414 (90.1)	137 (92.5)	277 (89)	.239
Hydrocortisone	383 (83.4)	131 (88.5)	252 (81)	.044
Methylprednisolone	185 (40.3)	58 (39.1)	127 (40.8)	.737
Prednisolone	14 (3)	8 (5.4)	6 (1.9)	.043
Dexamethasone	48 (10.4)	16 (10.8)	32 (10.2)	.865
Fludrocortisone	14 (3)	7 (4.7)	7 (2.2)	.149
Other				
Thiamine	228 (49.6)	75 (50.6)	153 (49.1)	.767
Vitamin C	44 (9.5)	16 (10.8)	28 (9)	.539
Antiviral	281 (61.2)	92 (62.1)	189 (60.7)	.775
Antifungals	375 (81.6)	118 (79.7)	257 (82.6)	.452
G-CSF	125 (27.2)	55 (37.1)	70 (22.5)	.001

Categorical variables differences were calculated with chi-square test. Continuous data differences were calculated with t test.
Abbreviation: G-CSF, granulocyte colony-stimulating factor

eTable 5. Mortality Rates in Patients With Hematologic Malignancies by Septic Shock Definition

Outcome	Sepsis + Vasopressors n (%)	Did Not Meet Sepsis-3 Criteria for Septic Shock n (%)	Met Sepsis-3 Criteria for Septic Shock n (%)	P Value
Total, n	826	367	459	
ICU mortality	419 (50.7)	126 (34.3)	293 (63.8)	<.0001
Hospital mortality	504 (61)	165 (44.9)	339 (73.9)	<.0001
28-day mortality	454 (54.9)	143 (38.9)	311 (67.8)	<.0001
90-day mortality	584 (70.7)	214 (58.3)	370 (80.6)	<.0001

Categorical variables differences were calculated with chi-square test.

eTable 6. Advance Care Planning

Point of Death	Full Code + DNR n	Full Code at Time of Death n (%)	DNR at Time of Death n (%)	Comfort Care n (%)
ICU discharge	293	22 (7.5)	271 (92.4)	191 (65.1)
Hospital discharge	339	42 (12.3)	297 (87.6)	209 (61.6)
28 days	311	40 (12.8)	271 (87.1)	192 (61.7)
90 days	370	68 (18.3)	302 (81.6)	209 (56.4)

Abbreviations: DNR, do-not-resuscitate order; ICU, intensive care unit.

eTable 7. Mortality by Neutropenia Status

Variable	Severe Neutropenia ^a n (%)	No Neutropenia ^b n (%)	P Value
Total, n	247	208	
G-CSF	90 (36.4)	34 (16.3)	<.0001
ICU mortality	155 (62.8)	134 (64.4)	.712
Hospital mortality	175 (70.9)	160 (76.9)	.143
28-day mortality	164 (66.4)	144 (69.2)	.520
90-day mortality	191 (77.3)	175 (84.1)	.068

Categorical variables differences were calculated with chi-square test.

Abbreviations: ANC, absolute neutrophil count; G-CSF: granulocyte colony-stimulating factor; ICU, intensive care unit.

^aANC ≤500/mm³.

^bANC >500/mm³.

eTable 8. Study Cohort by G-CSF Administration

Variable	G-CSF n (%)	No G-CSF n (%)	P Value
Total, n	125	334	
Age, median (range), y	56.4 (22–89)	60.2 (18–86)	.017
Male sex	76 (60.8)	204 (61.1)	.957
BMI, median (range), kg/m ²	28.5 (14.6–57.5)	27.8 (15.09–50.14)	.357
Underlying malignancy			<.0001
ALL	32 (18.4)	31 (9.3)	
AML	40 (32)	158 (47.3)	
CLL	3 (2.4)	14 (4.2)	
CML	1 (0.8)	111 (3.3)	
APL	1 (0.8)	2 (0.6)	
MDS	4 (3.2)	26 (7.8)	
Myelofibrosis	1 (0.8)	5 (1.5)	
Hodgkin lymphoma	3 (2.4)	7 (2.1)	
Non-Hodgkin lymphoma	26 (16)	61 (18.3)	
Multiple myeloma	20 (16)	17 (5.7)	
Other	3 (2.4)	2 (0.6)	
Disease status			.06
Active	40 (32)	137 (41.3)	
Relapsed/Refractory	62 (50.4)	154 (46.4)	
Newly diagnosed	4 (3.2)	16 (4.8)	
Remission	18 (14.4)	25 (7.5)	
BMT/HSCT	48 (38.4)	61 (18.3)	<.0001
CCI, median (range)	4.7 (2–12)	5.3 (1–18)	.014
SOFA at SS diagnosis, median (range)	11.6 (4–19)	11.2 (4–21)	.279
Maximum SOFA, median (range)	14.3 (6–21)	13.3 (4–22)	.020
Severe neutropenia ^a	90 (72.6)	157 (47.4)	<.0001
Microbial isolates			
Gram-positive	37 (29.6)	74 (22.2)	.097
Gram-negative	49 (39.2)	114 (34.1)	.312
Anaerobes	4 (3.2)	8 (2.4)	.630
Fungi	14 (11.2)	41 (12.3)	.752
Virus	17 (13.6)	35 (10.5)	.348
ICU mortality	71 (56.8)	222 (66.5)	.055
Hospital mortality	82 (65.6)	257 (76.9)	.014
28-day mortality	70 (56)	241 (72.2)	.001
90-day mortality	95 (76)	275 (82.3)	.126

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BMI, body mass index; BMT, bone marrow transplant; CCI, Charlson comorbidity index; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; MDS, myelodysplastic syndromes; SOFA, sequential organ failure assessment score; SS, septic shock.

^aAbsolute neutrophil count <500/mm³.