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Improved survival of critically ill cancer patients with septic shock

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Abstract *Objective:* To identify predictors of 30-day mortality in critically ill cancer patients with septic shock. *Design:* Retrospective study over a 6-year period. *Setting:* Twelve-bed medical intensive care unit (ICU). *Patients:* Eighty-eight patients (55 men, 33 women) aged 55 (43.5–63) years admitted to the ICU for septic shock. *Interventions:* None. *Measurements and main results:* Eighty (90.9%) patients had hematological malignancies and eight (9.1%) had solid tumors; 47 patients (53.4%) were neutropenic, 19 (21.6%) were hematopoietic stem cell transplantation (HSCT) recipients, and 27 (30.7%) were in remission. Microbiologically documented infections were found in 60 (68.2%) patients. The Simplified Acute Physiologic Score II (SAPS II) and Logistic Organ Dysfunction (LOD) scores at ICU admission were 66 (47–89) and 7 (5–10), respectively, and the LOD score on day 3 was 8 (4–10). Sixty-eight (78.1%) patients received invasive mechanical ventilation (MV), 12 (13.6%) noninvasive MV, 22 (25%) dialysis. Thirty-day mortality was 65.5% (57/88). By multivariable analysis, mortality was higher when time to antibiotic treatment was >2 h [odds ratio (OR), 7.05; 95% confidence interval (95% CI), 1.17–42.21] and when DLOD (day 3–day 1 LOD score/day 3 LOD score) was high (OR, 3.47; 95% CI, 1.44–8.39); mortality was lower when admission occurred between 1998 and 2000 (OR, 0.23; 95% CI, 0.05–0.98) and when initial antibiotics were adapted (OR, 0.24; 95% CI, 0.06–0.09). *Conclusions:* Earlier ICU admission and antibiotic treatment of critically ill cancer patients with septic shock is associated with higher 30-day survival. The LOD score change on day 3 as compared to admission is useful for predicting survival.

Keywords Critically ill cancer patients · Septic shock · LOD score · Mortality · Treatment delays · Antibiotics

Introduction

Over the past few decades, the nature of cancer treatment has changed, with the introduction of new and intensified treatment protocols used in combination with advanced support therapy. This has led to longer survival at the expense of an increasing number of disease- and therapy-associated complications, which often warrant intensive care. Severe infectious complications requiring admission to the intensive care unit (ICU) are common in cancer patients and cause major morbidity and mortality [1].

Critically ill cancer patients have an overall 30-day mortality of about 50% [2, 3, 4, 5, 6]. Rather than neutropenia and bone marrow transplantation, predictors of death in recent studies were mainly related to the importance of organ failure as reflected by the need for mechanical ventilation [7, 8, 9] and vasopressors [3]. The

prognosis of cancer patients requiring mechanical ventilation has been specifically studied, and the lower mortality with noninvasive mechanical ventilation has been underlined [10, 11]. However, no studies have been specifically designed to identify predictors of death in critically ill cancer patients with septic shock.

We described critically ill cancer patients admitted to the ICU for septic shock and looked for determinants of 30-day mortality, with particular attention to outcome changes over the 6-year study period.

Patients and methods

We retrospectively studied patients with leukemia, lymphoma, myeloma, or solid tumors admitted for severe sepsis with septic shock between 1 January 1995, and 31 December 2000, to the medical ICU of the Saint Louis Teaching Hospital, a 630-bed university hospital in Paris, France. Patients recipients of allogenic bone marrow transplantation were excluded. The hospital has 230 hematology beds, including units managing only patients with acute leukemia, lymphoma, myeloma, or solid tumors. The medical ICU is a closed unit that admits 500–600 patients per year, including 20% with hematological disorders. One of the senior and one of the junior intensivists are on duty 24 h a day, each day.

Septic shock was defined on the basis of the five following criteria, according to the consensus conference [12, 13]: a) clinical evidence of infection; b) tachycardia (>90 beats/min); c) tachypnea (>20 breaths/min) or need for mechanical ventilation; d) refractory hypotension defined by a sustained decrease in systolic blood pressure <90 mmHg despite fluid replacement (500 ml), or use of vasopressor to maintain systolic blood pressure >90 mm Hg; and e) evidence of inadequate organ function or perfusion within 12 h of enrollment, as manifested by at least one of the following syndromes: acute alteration of mental status, arterial hypoxemia (PaO_2/FiO_2<280), plasma lactate concentrations above the normal range or metabolic acidosis, oliguria defined by urine output <0.5 ml·kg–1·h–1, and disseminated intravascular coagulation.

The following information was abstracted from the medical charts of the patients: age and sex; chronic health status as evaluated using the Knaus scale [14] and comorbidities; characteristics of the malignancy including number of previous courses of chemotherapy and current status (complete or partial remission); neutropenia (white blood cells <1,000 leukocytes per mm^3) [15]; infection category (fever of unknown origin, clinically documented infection, or microbiologically documented infection) [16]; severity-of-illness scores (Simplified Acute Physiology Score II, SAPS II [17]; and Logistic Organ Dysfunction, LOD [18]); therapeutic interventions and times from ICU admission to the initiation of these interventions, including antibiotics, volume repletion, vasopressor use, mechanical ventilation, renal replacement therapy, stress-dose steroids, and granulocyte-colony-stimulating-factor (G-CSF) to hasten neutropenia recovery; length of ICU stay; and 30-day mortality.

Management of the septic shock

All patients with septic shock were admitted to the medical ICU, once the diagnosis was performed. They came either directly from the emergency department, or from the hematology or oncology ward. Criteria for ICU admission and triage were not different during the study period.

Standard medical treatment included broad-spectrum antibiotics (betalactamin plus an aminoside plus a glycopeptide) immediately after initial clinical evaluation. Initial appropriate antibiotic treatment was a treatment covering all the retrieved pathogens, or in absence of available microbiological results, a treatment associated with an improvement of patient's status. Time to antibiotic administration was calculated from ICU-admission to first administration of antibiotics. Beside antibiotics, all patients also received intensive treatment for the shock once they had been managed by the intensivist (either at ICU-admission for direct admission or when the intensivist was called in the wards). Fluid expansion (using either crystalloid or colloids) was the first therapeutic used to increase blood pressure. Then, the use of either dopamine, epinephrine or norepinephrine was decided by the intensivist in charge of the patient. Stress-dose steroids were not routinely administrated in our patients at this time. Hemodynamic exploration, using echocardiography or Swan Ganz catheter, were routinely performed in patients with no response to high-dose vasopressors (dopamine 15 μg kg min or epinephrine/norepinephrine 1 mg/h). Similarly, the choice between noninvasive and invasive mechanical ventilation was let at the discretion of the intensivist in charge of the patient. Noninvasive mechanical ventilation was not performed in comatose patients and rarely performed in patients with high-dose vasopressors.

Statistical analysis

Results are reported as medians (25th–75th percentiles) or numbers (%). Patient characteristics were compared using the chi-square test or Fisher exact test, as appropriate, for categorical variables and the Wilcoxon test for continuous variables. Vital status on day 30, a date on which all the patients either had died from their acute illness or had been discharged from the hospital, was available for all patients.

Because changes in organ failure over time are associated with outcome [19], and to assess the impact of the LOD score change between day 1 and day 3, we constructed a continuous variable by computing the ratio (LOD day 3–LOD day 1/LOD day 3). This variable, which we designated DLOD, was constructed as a ratio rather than a difference to avoid grouping together patients with the same absolute LOD change but with widely differing severities at admission [e.g., (LOD3–LOD1)=1 in patients with LOD1=3 and LOD3=4 but also in patients with LOD1=12 and LOD3=13]. Since the distribution of DLOD was linear in our patient population, we introduced DLOD as a continuous variable in the model.

To investigate the association between patient characteristics and death, we first performed bivariable analyses to look for a significant influence of each variable on 30-day mortality according to logistic regression. Multivariable analysis was performed using a stepwise forward selection procedure. Since DLOD was entered in the model, we did not introduce any other severity score (i.e., SAPS II score) nor other markers related to organ dysfunction (mechanical ventilation, dialysis, vasopressors, and inotropes). In the first step, all variables associated with mortality in the univariate analysis were entered into the model. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Odds ratios (OR) and their 95% confidence intervals (CI) were computed. Goodness-of-fit (Hosmer-Lemeshow) was computed to assess the relevance of the logistic regression model. Thirty-day mortality was the outcome variable of interest. All tests were two-sided, and P values of less than 0.05 were considered statistically significant. Analyses were done using the SAS 6.12 software package (SAS Institute, Cary, Calif., USA).

Table 1 Patient characteristics. {*SAPS II* Simplified Acute Physiologic Score, *LOD* logistic organ dysfunction, *DLOD* [(LOD score on day 3–day 1)/ LOD score on day 3], *ICU* intensive care unit}

	Patients, *n* (%) or median (25th–75th centiles)
Comorbidities	
Previous chemotherapy	76 (86.4)
Chronic renal failure (baseline creatinine serum level >250 μg/l)	10 (11.3)
Radiotherapy	10 (11.3)
Steroid treatment	9 (10.2)
Chronic health status (Knaus scale)	24 (27.3)
Underlying malignancy	
Leukemia	30 (34.4)
Lymphoma	21 (24.1)
Myeloma	22 (25.3)
Solid tumors	7 (8)
Other malignancies	7 (8)
Complete or partial remission	27 (31.8)
Autologous hematopoietic stem cell transplantation (HSCT)	19 (21.6)
Neutropenia at ICU admission (leukocytes <1,000)	47 (53.4)
Deep neutropenia at ICU-admission (neutrophils <100)	31 (35.4)
Severity scores	
SAPS II score at ICU admission	66 (47–89)
LOD score at ICU admission	7 (5–10)
LOD score on ICU day 3	8 (4–10)
DLOD	0 (–0.75–0.25)
Management in the ICU	
Time from hospital to ICU admission >2 days	75 (86.2)
Volume repletion on the first ICU day	
Colloid (ml)	1000 (0–2000)
Crystalloid (ml)	500 (0–1000)
Vasopressors	
Time to administration of vasopressors (h)	1 (1–5)
Median dose of epinephrine (mg/ h)	4 (3–8)
Median dose of norepinephrine (mg/h)	4 (3–8)
Median dose of dopamine (μg kg min)	10 (10–15)
Median dose of dobutamine (μg kg min)	7.5 (5–10)
Mechanical ventilation	68 (78.1)
Noninvasive ventilation	12 (13.8)
Dialysis	22 (25)
Granulocyte-colony-stimulating-factor	24 (28.6)
Stress dose steroids	9 (10.2)
Length of ICU stay (days)	5 (2–13.75)
ICU mortality	57 (65.5)

Results

Patient characteristics

Our study included 88 patients, 55 men (62.5%) and 33 women (37.5%), aged 55 (43.5–63) years. ICU admission occurred between 1 January 1995 and 31 December 1997, in 34 patients (38.6%), and between 1 January 1998, and 31 December 2000, in 54 (61.4%) patients. The characteristics of the patients and malignancies are reported in Table 1. More than half (53.4%) the patients were neutropenic and seven patients were at the phase of neutropenia recovery. Nineteen (21.6%) patients had received autologous bone marrow transplantation, consisting in hematopoietic stem cell transplantation in all but one patient.

ICU admission and management

Time between hospital and ICU admission was 7 (0–40) days. All patients received vasopressors and 72 (81.8%) received volume repletion with crystalloid or colloid (Table 1). Durations of treatment with epineph-

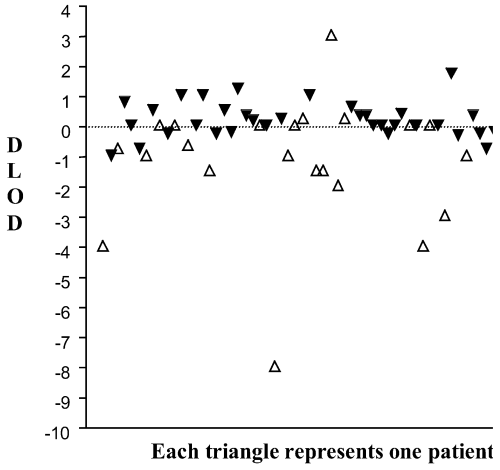

Fig. 1 DLOD ratio distribution in survivors (*open triangles*) and decedents (*solid triangles*)

rine, norepinephrine, dobutamine, and dopamine were 22 (10–72) h, 72 (11–144) h, 72 (24–186) h, and 48 (14–96) h, respectively. Metabolic acidosis was found in 41 (46.6%) patients. Median arterial bicarbonate level was 21 (13–25), mainly related to a lactic acidosis [median arterial lactate levels was 3.7 (2.1–7)]. Durations of conventional and noninvasive mechanical ventilation were 4 (1–13) days and 2 (1–4.75) days, respectively. Duration of mechanical ventilation was 3 (1–7) days in non-survivors and 11.5 (7–15) days in survivors. PaO_2/FiO_2 ratio was 111 (81–160). Among the 22 patients requiring dialysis, 12 needed sequential dialysis and ten continuous venovenous hemofiltration. Duration of dialysis was 3 (2–4) days.

Severity-of-illness scores and management in the ICU are described in Table 1. The LOD score increased between ICU admission and day 3 in the overall population. Among the 20 patients who received vasopressors, mechanical ventilation, and dialysis at any time during their ICU stay, only two survived, and there were no survivors among the eight patients who still needed epinephrine or norepinephrine, mechanical ventilation, and dialysis on day 3. Among the 11 patients receiving epinephrine and the 21 patients receiving norepinephrine on day 3, one and 16 survived, respectively. Among the 43 patients still requiring mechanical ventilation on day 3, 14 were discharged alive from the hospital. Finally, among the 15 patients still needing dialysis on day 3, only three were discharged alive from the hospital. The distribution of DLOD values is displayed in Fig. 1.

Table 2 displays the data on infections in our patient population. Thirteen (14.7%) patients had sepsis of unknown origin, 75 (85.2%) had clinically documented infection, and 60 (68.2%) had microbiologically documented infection. The organ most often involved by clinically documented infection was the lung (48 patients).

Table 2 Infections and antibiotic treatments

	Patients (*n*, %)
Sepsis from unknown origin	13 (14.7)
Clinically documented infections	75 (85.2)
Pulmonary	48 (54.5)
Cellulitis and necrotizing fasciitis	20 (22.7)
Abdominal	12 (13.6)
ENT	3 (3.4)
Urinary	4 (4.5)
Cerebral	2 (2.3)
Microbiologically documented infections	60 (68.2)
Location	
Respiratory samples	22 (24.7)
Urine	8 (9)
Bacteremia	49 (55.1)
CSF	3 (3.4)
Gastrointestinal	3 (3.4)
Intravenous catheter	3 (3.4)
Other	1 (1.1)
Type of organisms	
Gram-negative cocci	48 (51.2)
Escherichia coli	16 (18.4)
Pseudomonas aeruginosa	14 (16.1)
Enterobacter sp.	10 (11.5)
Others	9 (9.2)
Gram-positive bacteria	25 (28.7)
Staphylococcus aureus	17 (19.5)
Coagulase-negative staphylococcus	2 (2.3
Others	6 (6.8)
Fungi	14 (16.1)
Candida albicans	2 (2.3)
Other candida	2 (2.3)
Aspergillus sp.	5 (5.7)
Others	1 (1.1)
Other bacteria	4 (4.6)
Antibiotics used	
Penicillin	21 (23.9)
Third-generation cephalosporin	35 (39.8)
Broad-spectrum 3rd-generation cephalosporin	3 (3.4)
Imipenem	19 (21.6)
Aminoglycoside	50 (56.8)
Glycopeptide	35 (39.8)
Fluoroquinolone	23 (26.1)
Amphotericin B (standard or lipid formulations)	12 (13.6)
Fluconazole	1 (1.1)
Antiviral drug	7 (7.9)
Sulfamethoprime-Cotrimoxazole	10 (11.4)
Imidazole	18 (20.4)
Antibiotic adaptation	47 (53.4)

Gram-negative bacilli were the main pathogens identified by microbiological studies (48 patients), followed by gram-positive cocci (25 patients), and fungi (14 patients). In 47 (53.4%) patients, the initial antibiotic treatment was adapted, either because susceptibility testing showed that it was ineffective on the identified pathogens (*n*=8) or produced an unnecessarily broad spectrum

Table 3 Univariable analysis: risk factors for 30-day mortality. {*SAPS II* Simplified Acute Physiologic Score, *LOD* logistic organ dysfunction, *DLOD* [(LOD score on day 3−day 1)/LOD score on day 3], *ICU* Intensive care unit}

	Odds ratio	95% CI	*P* value
Lymphoma	4.154	1.113–15.506	0.03
ICU admission between 1998 and 2000	0.278	0.099–0.782	0.0153
LOD (day 1)	1.316	1.116–1.552	0.0011
LOD (day 3)	1.644	1.336–2.023	<0.0001
DLOD	2.872	1.417–5.820	0.0034
SAPS II score at ICU admission	1.045	1.021–1.070	0.0002
Time to antibiotic administration 2 h	6.5	1.386–30.492	0.0176
Antibiotic adaptation	0.303	0.115–0.798	0.0156
Use of imipenem	3.512	0.933–13.220	0.0632
Use of colloids on day 1	1.001	1–1.001	0.0075
Colloids >1,000 cc on the first ICU day	3.172	1.175–8.562	0.0226
Crystalloid on day 1	0.359	0.13–0.96	0.0401
Dose of norepinephrine (per mg/h)	2.113	1.127–3.963	0.0197
Need for mechanical ventilation	20.571	5.247–80.648	<0.0001
Renal replacement therapy	4.105	1.096–15.372	0.036

Table 4 Multivariable analysis to identify independent risk factors of 30-day mortality. Goodness-of-fit chi-square *P* value >0.05. {*DLOD* [(LOD score on day 3−day 1)/LOD score on day 3]}

	Odds ratio	95% CI	*P* value
ICU admission between 1998 and 2000	0.231	0.054–0.988	0.04
Lymphoma	5.6	0.40–16.60	0.07
Time to antibiotic administration >2 h	7.05	1.17–42.21	0.03
DLOD ratio	3.47	1.44–8.39	0.005
Colloid on day 1	3.43	0.63–18–69	0.15
Antibiotic adaptation	0.245	0.06–0.95	0.04

Table 5 Comparison between the first half (1995–1997) and second half (1998–2000) of the study period. {*SAPS II* Simplified Acute Physiologic Score, *LOD* logistic organ dysfunction, *DLOD* [(LOD score on day 3−day 1)/LOD score on day 3], *ICU* intensive care unit}

	ICU admission between 1995 and 1997 (*n*=34)	ICU admission between 1998 and 2000 (*n*=54)	*P* value
Patient age (years)	53 (40–63)	56 (50–63)	0.39
Remission of the malignancy	21 (61.8)	31 (57.4)	0.79
Autologous HSCT	6 (17.6)	13 (24)	0.59
Neutropenia	18 (52.9)	30 (55.5)	0.82
Duration of neutropenia	6 (3-8)	4 (2–6)	0.16
Poor chronic health status (Knaus scale C or D)	11 (32.3)	9 (16.6)	0.05
Hospitalization >48 h before ICU admission	31 (91.1)	40 (74)	0.03
LOD Day 1	8 (6–11)	7 (4–9)	0.49
LOD Day 3	8 (5–11)	8 (5–10)	0.19
DLOD	0 (−0.25–0.25)	0 (−0.75–0.25)	0.20
SAPS II score at ICU admission	72 (53–86)	65 (45–93)	0.33
Multiple organ failure	7 (20.6)	13 (24)	0.79
Mechanical ventilation	31 (93.9%)	37 (68.5%)	0.005
Mechanical ventilation >4 days	16 (47)	21 (38.9)	0.13
Noninvasive ventilation	4 (11.8)	8 (14.8)	0.12
Renal replacement therapy	8 (23.5)	13 (24)	0.93
Complete remission	8 (23.5)	11 (20.4)	0.73
Time to antibiotic administration >2 h	10 (29.4)	10 (18.5)	0.24
Administration of norepinephrine >24 h	7 (20.6)	11 (20.4)	0.32
Administration of epinephrine >24 h	2 (5.9)	6 (11.1)	0.08
Administration of dobutamine >24 h	6 (17.6)	18 (33.3)	0.11
Administration of colloids >1,000 ml	17 (50)	18 (33.3)	0.11
Volume crystalloid infused on day 1 (ml)	141 (0–500)	444 (0–1200)	0.03
End-of-life decisions	6 (17.6)	11 (20)	0.54
30-day mortality	27 (79.4)	30 (55.5)	0.01

(*n*=12) or because persistent fever or other clinical evidence of inadequate effectiveness made a broader spectrum desirable (*n*=27).

Survival and prognostic factors

The overall 30-day mortality rate was 65.5% (57 deaths). Among the 57 deaths, 31 (54.4%) occurred within 3 days of ICU admission. Mortality was significantly higher in the first half of the study period (1995–1997, 79.4%) than in the second half (1998–2000, 55.5%).

Table 3 displays the results of the univariable analysis. Among the characteristics of the malignancies, lymphoma was the only parameter associated with 30-day mortality. Period of ICU admission, time to antibiotic therapy, and antibiotic adaptation were also associated with the outcome. Other predictors of 30-day mortality were related to the nature, severity, and persistence of organ failure. Table 4 reports the results of the multivariable analysis. Four parameters were independently associated with 30-day mortality. Two were protective, namely, ICU admission between 1998 and 2000 (OR, 0.231; 95% CI, 0.054–0.988) and antibiotic adaptation (OR, 0.245; 95% CI, 0.06–0.095). Two were aggravating, namely, time to antibiotic administration >2 h (OR, 7.05; 95% CI, 1.17–42.21) and DLOD ratio (OR, 3.47 per point; 95% CI, 1.44–8.39). Parameters reflecting the characteristics of the malignancy (diagnosis, remission, neutropenia, and bone marrow transplantation) were not associated with 30-day mortality.

Comparison of the two periods of ICU admission (1995–1997 and 1998–2000)

As shown in Table 5, although severity at ICU admission and on day 3 were not different, the number of patients who received invasive mechanical ventilation decreased over time, and there was a trend toward greater use of noninvasive mechanical ventilation. In the more recent period, patients were less likely to have a poor chronic health status, to receive crystalloid, and to be admitted directly from the emergency department or mobile emergency unit. The use of vasopressors was the same between the two periods.

Discussion

Critically ill cancer patients have a high risk of severe infection related to immunosuppression induced by the malignancy and its treatment [20, 21, 22]. This susceptibility to infection is greatest in neutropenic patients and in bone marrow transplant recipients [16, 23, 24, 25]. To the best of our knowledge, this is the first study conducted specifically in critically ill cancer patients with septic shock to identify predictors of mortality. The results show an improvement in survival over recent years. Also striking is that mortality was more closely associated with persistent organ failure during the first ICU days than with the characteristics of the malignancy, in keeping with earlier data [3, 4].

Improved survival of critically ill cancer patients has been reported [2, 5, 6, 10, 26] and the fact that classic predictors of mortality (i.e., autologous bone marrow transplantation and neutropenia) have been stripped of much of their value has been acknowledged [5, 10, 15]. In this six-year study, survival was better in the second half of the study period. The comparison of the early and late study periods indicates that the most likely explanations are use of crystalloid rather than colloid, more frequent direct admission from the emergency room to the ICU, changes in patient selection with fewer ICU admissions of patients with poor chronic health status, and a trend toward greater use of noninvasive mechanical ventilation. Volume repletion is of central importance because it contributes to the aggressive hemodynamic optimization needed to reverse the exaggerated systemic inflammatory response characteristic of septic shock [27]. Preferences in the substance used for volume repletion are changing in response to evidence that crystalloid is as hemodynamically effective as colloid but causes less toxicity [28]. Because of recent changes in the prognosis of critically ill cancer patients, the hematologists, oncologists, and emergency room physicians of our hospital send patients directly to the ICU from the emergency room more often than before. As previously reported, earlier admission requires more effective collaboration between intensivists and hematologists or oncologists, as well as training of physicians to identify criteria for ICU admission before organ failure becomes irreversible [2]. Finally, noninvasive mechanical ventilation has been shown to improve survival in critically ill cancer patients [10, 11]. In the present study, the lack of a significant association between noninvasive mechanical ventilation and mortality may be ascribable to low statistical power related to the limited sample size. Our finding that use of noninvasive mechanical ventilation has increased in recent years indicates that the classic contraindication to noninvasive mechanical ventilation in septic shock is being reappraised. This growing use of noninvasive mechanical ventilation in critically ill cancer patients with septic shock deserves attention for further studies.

In the general ICU population, changes in organ failure scores within the first few days after ICU admission have been shown to predict survival more accurately than do scores on the day of ICU admission [29, 30]. This not only fits in with the clinical intuition that organ dysfunction severity does not predict the response to

treatments, but also is in keeping with the recommendation that a trial of intensive care should be offered to patients in whom the potential benefits of ICU admission seem unclear at presentation [31]. Consistent with the better predictive value of score changes, we found that a higher DLOD ratio was an independent predictor of death. This score is conceptually in agreement with the need to reevaluate the reversibility of acute organ failure after 3 or 4 days of ICU trial. Among the patients who needed vasopressors, mechanical ventilation, and dialysis on day 3, none survived, whereas one-third of the patients needing only mechanical ventilation on day 3 (i.e., who were weaned from vasopressors by day 3) were discharged alive from the hospital. These findings may support a policy of broad ICU admission of critically ill cancer patients with septic shock, followed by reappraisal of the benefits of intensive care after 3–4 days in the ICU.

A striking finding from this study is that a longer time to antibiotic administration was associated with higher mortality. Similar data have been reported by Natsch et al. in the emergency department and used to develop guidelines and educational programs [32, 33]. Reevaluation of the antibiotic strategy was protective against mortality in our study. Elting et al. reported higher mortality in neutropenic cancer patients with bacteremia caused by a pathogen resistant to the initial antibiotics, a fact more marked in patients with septic shock [21]. These data on antibiotic therapy indicate that prompt management of critically ill cancer patients with septic shock is associated with a higher survival rate. They are also in agreement with our finding that improved survival in the second half of the study period was associated with earlier ICU admission.

Taken together, our results highlight the need for immediate and aggressive management of critically ill cancer patients with septic shock, thus supporting recent findings [27]. Beyond a more selective ICU admission process, the information that—in a subset of patients (no allogeneic BMT, more likely to be receiving curative cancer treatment, less likely to have extensive malignant disease or poor chronic health status) [2, 10]—critically ill cancer patients with septic shock now have a nearly 50% chance of survival to hospital discharge should be disseminated in the medical community and to patients and surrogates in order to avoid losing a chance with these patients. Additional work is needed to further improve the prognosis by evaluating treatments such as stress-dose steroids [35], human recombinant-activated protein C [34], and early goal-directed therapy [27], and to develop new treatments for critically ill cancer patients with septic shock.

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