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OUTCOMES IN CRITICALLY ILL CANCER PATIENTS WITH SEPTIC SHOCK OF PULMONARY ORIGIN

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ABSTRACT—Increased therapeutic intensity has translated into better survival at a price of infectious and toxic life-threatening complications, chiefly affecting the lungs. Yet, no study specifically evaluated outcomes in cancer patients admitted to the intensive care unit (ICU) for septic shock of pulmonary origin. This is a multicenter cohort study of cancer patients admitted to the ICU for septic shock and pneumonia between 1998 and 2008. Independent determinants of hospital mortality were assessed using a multivariate logistic regression model. Prognostic impact of persistence or acquisition of organ failures was evaluated by survival conditional probabilities. During the 10-year study period, 218 patients were included. Hematologic malignancy (mostly non–Hodgkin lymphoma and acute leukemia) affected 84%, and solid tumors (mostly lung cancer) affected 16% of patients. Chemotherapy was recently administered in 89% of patients, and 24.5% of patients were recipients of hematopoietic stem cell transplantation (35 autologous, 18 allogeneic). At the time of ICU admission, 60% of patients were in partial or complete remission. All patients received vasopressors; invasive mechanical ventilation (MV) was needed in 78.4% and dialysis in 30% of patients. Intensive care unit and hospital mortality rates were 56.4% and 62.4%, respectively. Independent risk factors for hospital mortality were age older than 60 years, time between first symptoms and ICU admission, use of invasive MV, need for invasive MV after use of noninvasive ventilation, and coma. Analysis of survival probability showed that there was no temporal threshold after which persistence or gain of organ dysfunction indicated no hope for survival. Survival in cancer patients with septic shock from pulmonary origin is substantial, even when organ dysfunctions are not rapidly reversible. Delayed ICU management is an independent predictor of death. Studies assessing survival benefits from early ICU management are warranted.

KEYWORDS—Septic shock, cancer, respiratory infection, neutropenia, mechanical ventilation, allogeneic bone marrow transplantation

INTRODUCTION

Despite constant therapeutic progress, severe sepsis remains the leading cause of death in patients admitted to the intensive care unit (ICU) (1). Its incidence is increasing over time—from 82.7 to 240.4 per 100,000 inhabitants per year between 1979 and 2000 in the United States (2). Cancer patients represent a specific category of critically ill patients because they are more prone to infection and septic shock. In a French epidemiologic survey conducted from 1993 to 2000, 15.4% of ICU patients admitted for septic shock had an underlying cancer or hematologic malignancy (3). Cancer patients have a nearly 10-fold risk of developing sepsis compared with patients without malignancy (4), and sepsis is the leading cause of ICU admission in cancer patients (5).

Cancer patients admitted for septic shock have an ICU mortality rate ranging from 40% to 60% in recent cohort studies (6–8). The characteristics of the underlying malignancy no longer predict outcomes (9), which mostly relies on the extent of organ dysfunction at ICU admission and throughout the ICU stay (10). Bacterial infection involving the lungs is the most frequent source of infection and accounts for 50% of septic shock in cancer patients (6, 11). Septic shock from pneumonia carries higher mortality rates than other sites of infection (12) mainly because of the fact that they present with acute respiratory failure and that invasive mechanical ventilation (MV) has been proven a major risk factor for death (13).

Because of high ICU mortality rates and poor long-term prognosis caused by the underlying malignancy, cancer patients requiring intensive care are still perceived as poor candidates for ICU admission. However, these beliefs are not relevant anymore because increased survival has been reported in cancer patients with septic shock (14, 15) or pneumonia (16). Moreover, classic predictors of mortality may have changed, suggesting that studies appraising both outcomes and determinants of death are warranted (17, 18). Previous studies reported that outcomes mostly relied on the first three ICU days (16) or on organ dysfunction assessment during the first week (19). However, whether these data are confirmed in more recently admitted patients still needs to be assessed. We performed this multicenter cohort study in cancer patients

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TABLE 1. **Patient characteristics (n = 218) at ICU admission**

Characteristics	n (%) or median (25th – 75th percentile)
Age, years	57 (46.3 – 66)
Male sex	156 (71.6)
Comorbidities	
Poor performance status	144 (66.1)
Diabetes mellitus	14 (6.6)
Cardiac insufficiency	10 (4.7)
Underlying malignancy	
Non-Hodgkin lymphoma	65 (29.8)
Acute leukemia	60 (27.5)
Solid tumors	34 (15.6)
Multiple myeloma	22 (10.1)
Hodgkin disease	11 (5)
Other hematologic malignancy	26 (11.9)
Hematopoietic stem cell transplantation	
Autologous	35 (16.2)
Allogeneic	18 (8.3)
Complete or partial remission	125 (59.5)
Treatment characteristics	
Ongoing chemotherapy	191 (88.8)
Anthracycline in chemotherapy regimen	70 (63.6)
Adjuvant radiotherapy	14 (6.4)
Long-term steroid therapy	61 (28.8)
Clinical and biological characteristics on admission	
Systolic arterial blood pressure, mmHg	91 (80 – 120)
Glasgow Coma Scale score	15 (14 – 15)
PaO_2/FiO_2 ratio	172 (109 – 273)
Neutropenia	191 (87.6)
Urea, mmol/L	9.7 (5.93 – 13.6)

Poor performance status indicated Knaus scale at C or D.

admitted to the ICU for septic shock of pulmonary origin with the aim to both identify determinants of death and to provide objective data to guide clinical decision making based on the evolution of organ dysfunction across the first ICU days.

METHODS

This multicenter retrospective cohort study recruited cancer patients from 16 ICUs in France. Patients were admitted after January 1, 1998. All ICUs participating in the studies included in the analysis are part of a clinical practice and research network, and patients were managed with similar protocols. The database includes patients who were previously published (14, 20, 21). The appropriate institutional review board approved the study. For the purpose of this study, we included all patients admitted to the ICU with respiratory infection associated with septic shock. Septic shock was defined as a need for vasopressor therapy (adrenalin, noradrenalin, or dopamine) within 72 h of ICU admission. Sepsis was considered of pulmonary origin based on clinical examination and imaging, as well as microbiological documentation when available.

Data that are presented in Tables 1 to 3 were collected. Hospital mortality was available for every patient. Performance status was reported according to the Knaus Scale, a functional status score where A stands for no functional limitation, B for limited functional limitation (e.g., chronic treatment), C for important limitation (e.g., chronic hemodialysis, chemotherapy, or radiotherapy), and D for bedridden patients (22). Patients were considered as having had anthracycline in their chemotherapy regimen if anthracycline was administered at any time in their medical history. Neutropenia was defined as a neutrophil count less than 500 cells/mL. To account for the extended period of inclusion and the improvement of intensive care management during that period, we defined two periods of inclusion: 1998 to 2003 and 2004 to 2009.

Statistical analysis

The primary outcome was vital status at hospital discharge. Results are described as medians (25th – 75th percentile) for quantitative variables or numbers (percentages) for qualitative variables. Characteristics of the patients were compared using Wilcoxon rank sum test or Fisher exact test. To identify independent predictors of hospital mortality, characteristics that were statistically significant or clinically relevant were included in a multivariable logistic regression model. Missing data were handled with multiple imputations by chained equations. Model of imputation included all variables used in the analysis, and five sets of data were imputed, leading to five imputed models that were pooled according to Rubin rule. Calibration of the model was checked using the le Cessie–van Houwelingen–Copas–Hosmer test for global goodness of fit, and the minimal P value over the five imputed models is provided.

A secondary objective was to assess whether maintaining life-sustaining therapies beyond a certain duration would still be beneficial. Conditional survival probability associated with organ failure was modeled among patients

TABLE 2. **Organ failure, therapeutic interventions in the ICU (n = 218), general outcome, and outcomes in selected subgroups of patients**

Characteristics	n (%) or median (25th – 75th percentile)
Time from first symptoms to ICU admission, days	2 (1 – 4)
Supportive therapy	
Use of vasopressor	218 (100)
Vasopressor treatment duration, days	3 (2 – 6)
Use of NIV	86 (39.4)
Use of invasive ventilation	171 (78.4)
Invasive ventilation duration, days	6 (2 – 11)
Time from admission to invasive ventilation, days	1 (0 – 1)
Use of RRT	65 (29.8)
Duration of RRT, days	0 (0 – 3.8)
Time from admission to dialysis, days	2 (1 – 3)
Length of ICU stay, days	7 (3 – 13)
Length of hospital stay, days	28 (12 – 44.5)
Global hospital survival (n = 218)	82 (37.6)
Hospital survival depending on ventilator management	
O_2 only (n = 31)	23 (74)
NIV only (n = 16)	12 (75)
MV only (n = 75)	26 (35)
MV after NIV (n = 96)	21 (22)
Hospital survival if persistence of shock after 3 days (n = 98)	30 (30.6)
Hospital survival if persistence of MV after 3 days (n = 122)	45 (36.9)
Hospital survival if persistence of 3 organ failures after 3 days (n = 28)	8 (28.6)
Hospital survival for inclusion period 1998 – 2003 (n = 58)	14 (24)
Hospital survival for inclusion period 2004 – 2009 (n = 160)	68 (43)

Three organ failures, shock + MV + RRT.

TABLE 3. **Multivariate analysis of in-hospital mortality risk factors**

Variable	OR (CI 95%)	*P*
Age >60 years	3.26 (1.55 – 6.82)	0.0019
Poor performance status	1.28 (0.53 – 3.1)	0.58
Allogeneic HSCT	3.74 (1 – 14.06)	0.051
Delay from first symptom onset (per day)	1.07 (1 – 1.15)	0.049
Ventilation strategy		
Use of O_2 only	1	
Use of NIV only	0.87 (0.2 – 3.85)	0.86
Use of MV only	6.53 (2.31 – 18.5)	<0.001
Use of MV after NIV	7.51 (2.60 – 2.73)	<0.001
Glasgow Coma Scale score (per point)	0.84 (0.73 – 0.98)	0.023
Inclusion period 2004 – 2009	0.31 (0.12 – 0.75)	0.01

le Cessie–van Houwelingen–Copas–Hosmer test for global goodness of fit: $P = 0.39$. 95% CI, confidence interval; OR, odds ratio.

requiring MV and/or renal replacement therapy (RRT) within the first 24 h of septic shock initiation. Conditional survival probability at day X represents the probability to be alive at ICU discharge for all patients still alive after X days of persistent organ failure.

All tests were two-sided, and values of $P < 0.05$ were considered statistically significant. Analyses were performed using R 2.10.1 (http://www.r-project.org).

RESULTS

Among the 795 cancer patients in the database, 218 (27.4%) presented with septic shock of pulmonary origin. Table 1 reports patient's characteristics on admission. Their functional status before ICU admission was altered, with Knaus scores C and D representing 66.1% of patients. Of the 218 patients, 15.6% had a solid tumor, and 84.4% had hematological malignancies. Among the 184 hematological patients, 28.8% had undergone hematopoietic stem cell transplantation (HSCT), of which 35 (19%) were autologous HSCT and 18 (9.8%) were allogeneic HSCT. Although 59.5% of the 218 patients were considered either in complete or partial remission, 88.8% had ongoing chemotherapy and 28.8% were on long-term steroid therapy.

On admission, patients were deeply hypoxemic with a median PaO_2/FiO_2 ratio of 172 (25th – 75th percentile, 109 – 273). The median time from first symptoms to ICU admission (Fig. 1) was 2 days (25th – 75th percentile, 1 – 4 days). As shown in Table 2, by definition, all patients received vasopressors for a median time of 3 days (25th – 75th percentile, 2 – 6 days). Noninvasive ventilation (NIV) was used in 39.4% of patients, avoiding intubation in 21.6%, and 78.4% ultimately required invasive MV for a median duration of 6 days (25th – 75th percentile, 2 – 11 days). Renal replacement therapy was initiated in 29.8% of patients. Median time from ICU admission to MV was 1 day (25th – 75th percentile, 0 – 1 day) and 2 days (25th – 75th percentile, 1 – 3 days) for RRT. Median stay was 7 days (25th – 75th percentile, 3 – 13 days) in the ICU and 28 days (12 – 44.5 days) in the hospital.

Intensive care unit mortality was 56.4% (123 deaths) and hospital mortality was 62.4% (136 deaths). Hospital survival was reduced from 37.6% to 28.6% in the subset of patients who had three organ failures for more than 3 days and to 30.6% in patients with shock for more than 3 days. However, hospital survival was not overtly decreased in patients with MV for more than 3 days. Univariate analysis for hospital mortality risk factors (see Supplemental Material, Supplemental Digital Content 1, at http://links.lww.com/SHK/A155) identified age at admission older than 60 years (survivors, 27% vs. deceased, 44%; $P = 0.014$), the delay between first symptoms and ICU admission (survivors, 2 days [25th – 75th percentile, 1 – 3 days] vs. deceased, 2 days [25th – 75th percentile, 1 – 5 days]; $P = 0.042$), the Glasgow Coma Scale score (survivors, 15 [25th – 75th percentile, 15 – 15] vs. deceased 15 [25th – 75th percentile, 12 – 15]; $P = 0.0005$), length of vasopressor treatment (survivors, 2 days [25th – 75th percentile, 1 – 4 days] vs. deceased, 3 days [25th – 75th percentile, 1 – 7]; $P = 0.031$), duration of NIV (survivors, 1 days [25th – 75th percentile, 0 – 3 days] vs. deceased, 0 days [25th – 75th percentile, 0 – 1]; $P = 0.009$), use of MV (survivors, 57.3% vs. deceased, 91.2%; $P < 0.0001$), duration of MV (survivors, 8 days [25th – 75th percentile, 5 – 13 days] vs. deceased, 5 days [25th – 75th percentile, 1 – 10 days]; $P= 0.009$), duration of RRT (survivors, 7 days [25th – 75th percentile, 4 – 15 days] vs. deceased, 4 days [25th – 75th percentile, 1 – 7]; $P = 0.038$), and the period of inclusion (76% mortality for the period 1998 – 2003 vs. 57% for the period 2004 – 2009; $P = 0.017$). Underlying malignancy was not a risk factor for hospital mortality nor was ongoing chemotherapy, long-term steroid therapy, or anthracycline use.

Multivariate analysis identified seven independent predictors of hospital mortality (Table 3). Namely, age older than 60 years (3.26 [25th – 75th percentile, 1.55 – 6.82]), time between respiratory symptoms onset and ICU admission (1.07 [25th – 75th percentile, 1 – 1.15]), use of MV (6.53 [25th – 75th percentile, 2.31 – 18.5]), use of MV after NIV (7.51 [25th – 75th percentile, 2.60 – 21.73]), coma at ICU admission (0.84 per point of Glasgow Coma Scale score [25th – 75th percentile, 0.73 – 0.98]), and inclusion during the period 2004 to 2009 (0.34 [25th – 75th percentile, 0.13 – 0.9]).

Conditional survival probabilities are presented in Figure 2. Although persistence of vasopressor treatment progressively altered hospital survival probability, persistence of MV for more than 14 days did not. Furthermore, persistence of three organ failures (MV, vasopressor treatment, and RRT) for 5 days did not dramatically alter hospital survival. Similarly, acquisition of organ failure after shock onset did not worsen hospital survival probability. Initiation of MV more than

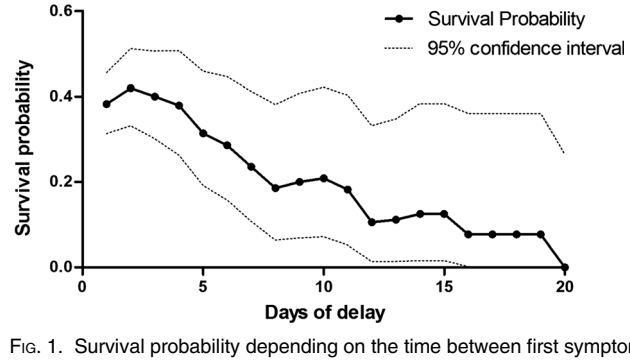

FIG. 1. Survival probability depending on the time between first symptoms and ICU admission.

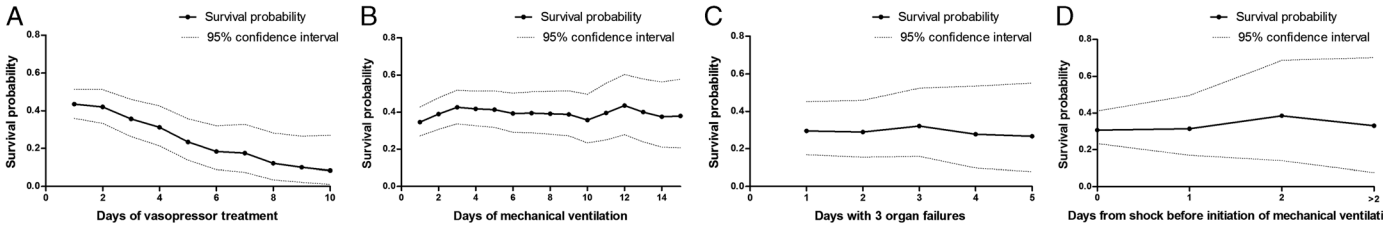

FIG. 2. **Conditional ICU survival probability associated with organ failures**. A, Intensive care unit survival probability depending on vasopressor duration. B, Intensive care unit survival probability depending on MV duration. C, Intensive care unit survival probability depending on time spent with three organ failures (defined as shock + MV + RRT). D, Intensive care unit survival probability depending on delay between shock onset and initiation of MV.

2 days after shock onset resulted in similar hospital survival compared with those of patients with earlier MV instauration. Hence, although hospital mortality decreases with the persistence of organ failure, conditional survival probability curves do not show a specific time threshold where persistence or gain of an organ failure would render intensive care futile.

DISCUSSION

Analysis of intensive care management of 218 cancer patients with septic shock of pulmonary origin showed a hospital mortality rate of 62.4%. Identified mortality risk factors were age older than 60 years, increased delay between the first symptom onset and ICU admission, use of MV, use of MV after NIV, altered Glasgow Coma Scale score, and being included in the study before 2004. Evaluation of the persistence or acquisition of organ dysfunction during ICU stay did not bring to light a particular temporal threshold after which survival probability becomes negligible and ICU management futile.

In our study, in-hospital mortality (62.4%) was higher than in a general ICU population with septic shock, currently evaluated as approximately 40% (23). It is, however, similar to those of previous studies specifically evaluating critically ill cancer patients in septic shock (6, 11). In fact, in-hospital mortality in our cohort is particularly low, regarding the high proportion of patients with hematological malignancy (84.5% vs. 55.5% in the study by Pène et al. [6]). Furthermore, we included in our study patients from 1998 to 2008 and, as expected, in-hospital mortality was lower in patients included from 2004 to 2008 because of improvement in management and outcome of septic shock patients during the last decade (6, 24). Finally, we hypothesized that our cohort, including only patients with septic shock of pulmonary origin with a higher proportion of respiratory distress and MV, would have a worse outcome than previously published cohorts. It is not the case, and pulmonary origin for a septic shock does not seem to influence prognosis.

Univariate and multivariate analyses of in-hospital risk factors at admission identified previously known risk factors such as age older than 60 years and use of MV (10).

Our study shows that allogeneic HSCT, although not statistically significant, could be a mortality risk factor. This was not the case in the study of 620 cancer patients in septic shock by Pène et al. (6). We believe that this difference is because our patients had exclusively septic shock of pulmonary origin, and that patients with allogeneic HSCT have dramatically decreased survival rates when MV is required (25). Multivariate analysis also showed that each day of delay between first symptom onset and ICU admission increased hospital mortality (odds ratio per day of delay, 1.2 [25th – 75th percentile, 1.07 – 1.17]; $P = 0.017$). Hence, early ICU admission of cancer patients with aggressive management of beginning organ dysfunction could prevent evolution to multiorgan failure and death. This strategy requires close collaboration between hematologists and intensivists and could improve management of this specific subset of patients. Unfortunately, because of the retrospective nature of our study, we could not identify precisely the nature of the first symptom.

We show in our study that patients who require invasive MV after NIV, that is, failure of NIV, have higher mortality rates than those of patients who undergo direct invasive MV. Use of NIV is a matter of controversy in cancer patients with acute respiratory distress. Use of invasive MV in critically ill cancer patients is often complicated with ventilator-acquired pneumonia and strongly impairs survival. Thus, NIV has been proposed to avoid endotracheal intubation and MV. Hilbert et al. have shown in a randomized controlled trial that use of intermittent NIV in immunosuppressed patients in acute respiratory failure could reduce endotracheal intubation incidence and reduce mortality (26). However, in a cohort of patients with hematologic malignancy, failure of NIV followed by endotracheal intubation and MV seemed to increase mortality compared with direct MV (16). Because the need for vasopressors is an independent predictor for NIV failure (16, 27), we believe that NIV use is associated with increased mortality because it delays endotracheal intubation and MV.

Acute organ failures in cancer patients are major mortality risk factors (10). However, organ failure scores such as SOFA (Sequential Organ Failure Assessment) and LODS (Logistic Organ Dysfunction Score) at admission do not discriminate survivors from nonsurvivors, but the evolution of those scores throughout ICU stay does. The delta of LODS between day 1 and day 3 was predictive of survival in cancer patients in septic shock (11) and between day 1 and day 6 in cancer patients admitted to the ICU for MV (19). Hence, the duration of full-code intensive care management before reassessment of eventual treatment limitations is not known. We have shown in our study, using conditional survival probabilities, that there is no clear-cut threshold for persistence of organ failure after which therapeutic limitation could be taken because of dramatic increase of hospital mortality. Of note, use of MV for up to 14 days did not significantly alter hospital survival. We found that cancer patients with three organ failures

for more than 3 days still have an in-hospital survival rate of 32.1%. Furthermore, initiation of MV three or more days after septic shock onset resulted in survival rates of 30%. Those data are in contradiction with the results of Lecuyer et al. (19) who showed a 100% mortality rate in cancer patients in whom either MV or RRT was initiated after 3 days of ICU stay.

The principal limitation of our study is its retrospective design, and because of the fusion of three databases, several data could not be retrieved. Microbiological documentation was missing, and organ dysfunction scores were not available. Nevertheless, it is the first study, to our knowledge, that specifically evaluates septic shock of pulmonary origin in critically ill cancer patients. It is furthermore a multicenter study with an important cohort of 218 patients.

CONCLUSION

This study provides new insights in the intensive care management of cancer patients with septic shock of pulmonary origin, which is the first primary source of infection in these patients. Mortality rates are higher than those of patients without cancer but do not justify initial therapeutic limitations. Early ICU admission of these patients seems warranted to continue to improve outcomes. Noninvasive ventilation is contraindicated in patients under vasopressors, and its use to prevent intubation must be carefully weighted in this context. Finally, there is no clear-cut temporal threshold for optimal clinical reevaluation of persistence or gain of organ failures, and therapeutic limitations must be taken on an individual case basis.

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