Sepsis and Septic Shock in Patients With Malignancies: A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study

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Objectives: Cancer affects up to 20% of critically ill patients, and sepsis is one of the leading reasons for ICU admission in this setting. Early signals suggested that survival might be increasing in this population. However, confirmation studies have been lacking. The goal of this study was to assess trends in survival rates over time in cancer patients admitted to the ICU for sepsis or septic shock over the last 2 decades.

Data Source: Seven European ICUs.

Study Selection: A hierarchical model taking into account the year of admission and the source dataset as random variables was used to identify risk factors for day 30 mortality.

Data Extraction: Data from cancer patients admitted to ICUs for sepsis or septic shock were extracted from the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique database (1994–2015).

Data Synthesis: Overall, 2,062 patients (62% men, median [interquartile range] age 59 yr [48–67 yr]) were included in the study. Underlying malignancies were solid tumors (n = 362; 17.6%) or hematologic malignancies (n = 1,700; 82.4%), including acute leukemia (n = 591; 28.7%), non-Hodgkin lymphoma (n = 461; 22.3%), and myeloma (n = 244; 11.8%). Two-hundred fifty patients (12%) underwent allogeneic hematopoietic stem cell transplantation and 640 (31.0%) were neutropenic at ICU admission. Day 30 mortality was 39.9% (823 deaths). The year of ICU admission was associated with significant decrease in day 30 mortality over time (odds ratio, 0.96; 95% CI, 0.93–0.98; p = 0.001). Mechanical ventilation (odds ratio, 3.25; 95% CI, 2.52–4.19; $p < 0.01$) and vasopressors use (odds ratio, 1.42; 95% CI, 1.10–1.83; $p < 0.01$) were independently associated with day 30 mortality, whereas underlying malignancy, allogeneic hematopoietic stem cell transplantation, and neutropenia were not.

Conclusions: Survival in critically ill oncology and hematology patients with sepsis improved significantly over time. As outcomes improve, clinicians should consider updating admission policies and goals of care in this population. (*Crit Care Med* 2020; XX:00–00)

Key Words: acute kidney injury; hematology; neutropenia; oncology; outcomes; stem cell transplantation

Major advances have been reported in diagnostic and management strategies of patients with malignancies, resulting in survival improvements over the past 2 decades (1, 2). Furthermore, advances in cancer therapies, improvements in ICUs processes, and admission policies have contributed to improving overall survival (3–5). Consequently, the proportion of patients with malignancies admitted to the ICU has increased. Indeed, 5% of patients with solid tumors and up to 15% of patients with hematologic malignancies require ICU admissions due to life threatening conditions at the onset of the malignancy (6, 7). Furthermore, patients with malignancies account for approximately 20% of ICU admissions nowadays (5, 8), and sepsis is one of the leading reasons for ICU admission in this setting (9, 10). The prevalence of sepsis in patients with cancer is higher than in the noncancer population (8). Indeed, the immunosuppression caused by the

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underlying disease and owing to treatments increase their risk for severe infections. In comparison to general patients with sepsis, patients with malignancies are at high risk of intractable multiple organ failures, experience prolonged lengths of stay, and higher morbidity and mortality (11, 12). Furthermore, in this population, other clinical or biological factors such as allogeneic bone marrow transplantation are known to be risk factors for mortality (13, 14). However, updated data in this setting are lacking. Studies to appraise outcomes in critically ill cancer patients with sepsis are warranted. In the present study, we sought to assess trends in survival rates over time in cancer patients admitted to the ICU for sepsis or septic shock

PATIENTS AND METHODS

Patients and Data

The Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH) database comprises data from all cancer patients admitted in the seven participating ICUs and included in one of the 14 prospective or retrospective published studies of the research group, from 1994 to 2015. Data on cancer patients admitted in ICU for sepsis or septic shock were extracted from this database (3, 15–27). Appropriate institutional review board approved each study (3, 15–27). Sepsis and septic shock were defined according to the third international sepsis definitions conference (28). All studies included the data points reported in tables and figures. Multiple organ failure was defined as the association of three organ dysfunctions defined by their organ support (vasopressors, mechanical ventilation, and renal replacement therapy). Neutropenia at ICU admission was defined as grade 4 neutropenia with a neutrophils count less than 500/mm^3. Comorbidities included as follows: peripheral vascular disease, cirrhosis, chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and dementia. The Sequential Organ Failure Assessment (SOFA) score was computed at admission as previously defined (29); this score provides an estimate of the risk of death based on organ dysfunctions (3, 30, 31) (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F381). Outcome was defined as 30-day mortality or approximated using hospital mortality, and as last resort ICU mortality if the former were unavailable (32). This study was performed in a dataset which was independent from a recent meta-analysis performed by our group (33).

Statistical Analysis

All quantitative variables were described using medians (quartiles), whereas qualitative variables were described by frequencies (percentage). Day 30 (D-30) mortality was the variable of primary interest. Raw change in mortality according to ICU admission year was assessed using Wilcoxon test. Change in mortality over time, weighted for number of observations per year, was plotted for the whole population and for predefined subgroups using mean mortality for each admission year and change over time by linear regression with 95% CI. Independent predictors of mortality were assessed using logistic regression and mixed logistic models. Variables of interest were selected according to their relevance and statistical significance in univariate analysis. We used conditional stepwise regression with 0.2 as the critical *p* value for entry into the model, and 0.1 as the *p* value for removal. Variables with missing data rate above 10% were discarded from this analysis. The year of ICU admission was planned to be forced in the model in cases where the *p* value was greater than 0.2. Interactions and correlations between the explanatory variables were carefully checked. Continuous variables for which log-linearity was not confirmed were transformed into categorical variables according to median or interquartile range (IQR). The final models were assessed by calibration, discrimination, and relevance. Residuals were plotted and the distributions inspected. Then, mixed model was performed using variables previously selected as fixed effect. In order to investigate both study heterogeneity in the mortality rate and heterogeneity in the effect of the ICU admission year within studies, two random effects were introduced: respectively a random effect of study on the mean mortality rate (random intercept) and a random effect on the effect of the ICU admission year on within study mortality (random slope) (34). This model adjusting for clustering effect was planned a priori to be main result of the analysis. Same validation methods were used as previously and calibration was reported as calibration belt (35). Last sensitivity analysis in subgroup of patients with bacterial pneumonia as source of infection was performed following the same method. All tests were two-sided, and *p* values of less than 0.05 were considered statistically significant. Analyses were done using R software Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org), including lme4, lmerTest, and givitiR packages.

RESULTS

From 1994 to 2015, 4,636 critically ill cancer patients have been included in the GRRR-OH database, of which 2,062 patients with sepsis or septic shock (**Supplemental Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F382; **legend**, Supplemental Digital Content 7, http://links.lww.com/CCM/F387). In this cohort, patients were predominantly male (*n* = 1,275 [61.8%]) and the median age was 59 years (48–67 yr) (**Table 1**). Underlying malignancies were solid tumors in 362 patients (17.6%), mostly digestive tract cancers (*n* = 61; 16.9%) and breast cancers (*n* = 55; 15.2%) (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/F383). Metastatic cancers in solid tumor population were present in 174 patients (48.1%) and 211 patients (58.3%) received a systemic anti-cancer therapy within four weeks before ICU admission or during their ICU stay (Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/CCM/F383). Hematologic malignancies (*n* = 1,700 [82.4%]) included acute leukemia (*n* = 591; 28.7%), non-Hodgkin lymphoma (*n* = 461; 22.4%), and myeloma (*n* = 244; 11.8%). Two-hundred fifty patients (12.1%) underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) before ICU admission and 640 (31.0%) were neutropenic at ICU admission. The median

TABLE 1. Population Characteristics According to Day 30 Outcome

Variables	All (n = 2,062)	Survivors at Day 30 (n = 1,205)	Nonsurvivors at Day 30 (n = 823)	Univariate Analysis p
Gender, female, *n* (%)	787 (38.1)	465 (38.6)	322 (39.1)	1.00
Age, yr, median (IQR)	59 (48–67)	59 (47–67)	59 (49–68)	0.52
Year of inclusion, median (IQR)	2009 (2006–2010)	2010 (2007–2011)	2009 (2006–2010)	< 0.01
Sequential Organ Failure Assessment score at ICU admission, median (IQR)	6 (4–9)	6 (4–9)	8 (5–11)	< 0.01
Comorbidities, *n* (%)	1,043 (50.6)	645 (53.5)	398 (48.4)	0.41
Hematologic malignancies, *n* (%)	1,700 (82.4)	986 (81.8)	685 (83.2)	0.45
Allogeneic stem cell transplantation, *n* (%)	250 (12.1)	151 (12.5)	99 (12.0)	0.92
Neutropenia, *n* (%)	640 (31.0)	365 (30.3)	275 (33.4)	0.09
Acute respiratory failure, *n* (%)	927 (45.0)	578 (48.0)	349 (46.0)	0.50
Noninvasive ventilation, *n* (%)	635 (30.8)	357 (29.6)	278 (33.8)	0.05
Mechanical ventilation, *n* (%)	1,016 (49.3)	423 (35.1)	593 (72.0)	< 0.01
Vasopressor use, *n* (%)	1,172 (56.8)	577 (47.9)	595 (72.3)	< 0.01
Acute kidney injury, *n* (%)	291 (14.1)	173 (14.4)	118 (14.3)	0.31
Renal replacement therapy, *n* (%)	420 (20.4)	182 (15.1)	238 (28.9)	< 0.01

IQR = interquartile range.

(IQR) SOFA score at ICU admission was 6 (4–9) (Table 1). Data on D-30 mortality were available in 943 patients (45.7%), approximated using hospital mortality in 879 patients (42.6%) and as last resort ICU mortality if the former were unavailable. In this study, D-30 mortality rate was 39.9% (n = 823). By univariate analysis, variables associated with D-30 mortality were the year of ICU admission, SOFA score at ICU admission, mechanical ventilation, noninvasive ventilation, vasopressors use, and renal replacement therapy (Table 1).

After adjustment for the SOFA score at ICU admission, the year of ICU admission was significantly associated with D-30 mortality, decreasing over time (odds ratio [OR], 0.96; 95% CI, 0.93–0.98; p = 0.001). D-30 mortality probability according to the year of ICU admission predicted by the mixed-effect model and adjusted for the SOFA score at ICU admission is presented in **Figure 1**. Furthermore, this significant decrease of mortality over time was found in the subgroup of patients with solid tumors (OR, –2.63; 95% CI, 0.86–0.98; p = 0.03) and in the subgroup of patients with hematologic malignancies (OR, –2.72; 95% CI, 0.94–0.99; p < 0.01) (**Fig. 2**). Finally, a progressive decrease in mortality was observed in patients with (OR per year, 0.82; 95% CI, 0.82–0.95) and without (OR, 0.95; 95% CI, 0.92–0.98) multiple organ failure (**Fig. 3**). Numbers of withholding/withdrawing life-sustaining therapies did not evolve over time. After adjustment for withholding/withdrawing life-sustaining therapies, the year of ICU admission was still significantly associated with D-30 mortality (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/F384; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/F387).

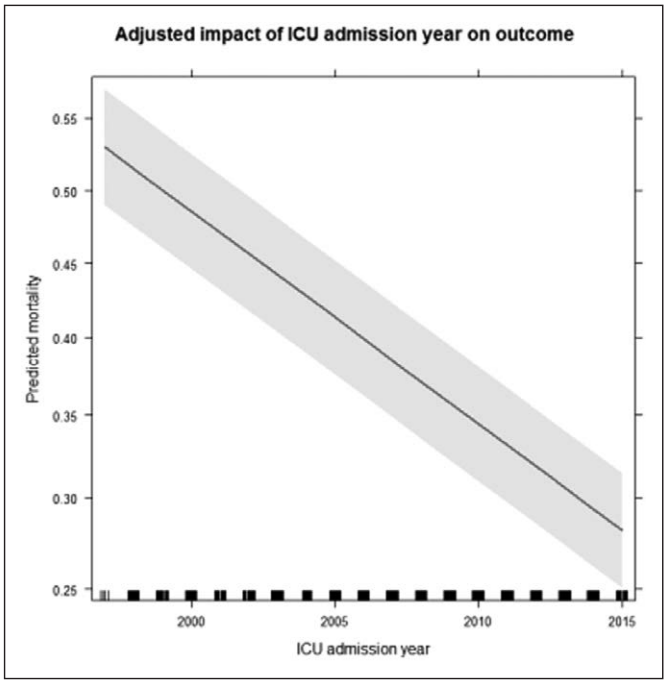

Figure 1. Thirty-day predicted mortality obtained by mixed-effect linear regression according to the year of ICU admission and adjusted on Sequential Organ Failure Assessment score at ICU admission.

By multivariable logistic regression at ICU admission, mechanical ventilation (OR, 3.21; 95% CI, 2.50–4.13; p < 0.01) and vasopressors use (OR, 1.42; 95% CI, 1.10–1.83; p = 0.006) were risk factors for D-30 mortality. A hierarchical model taking into account the year of ICU admission and the source dataset as

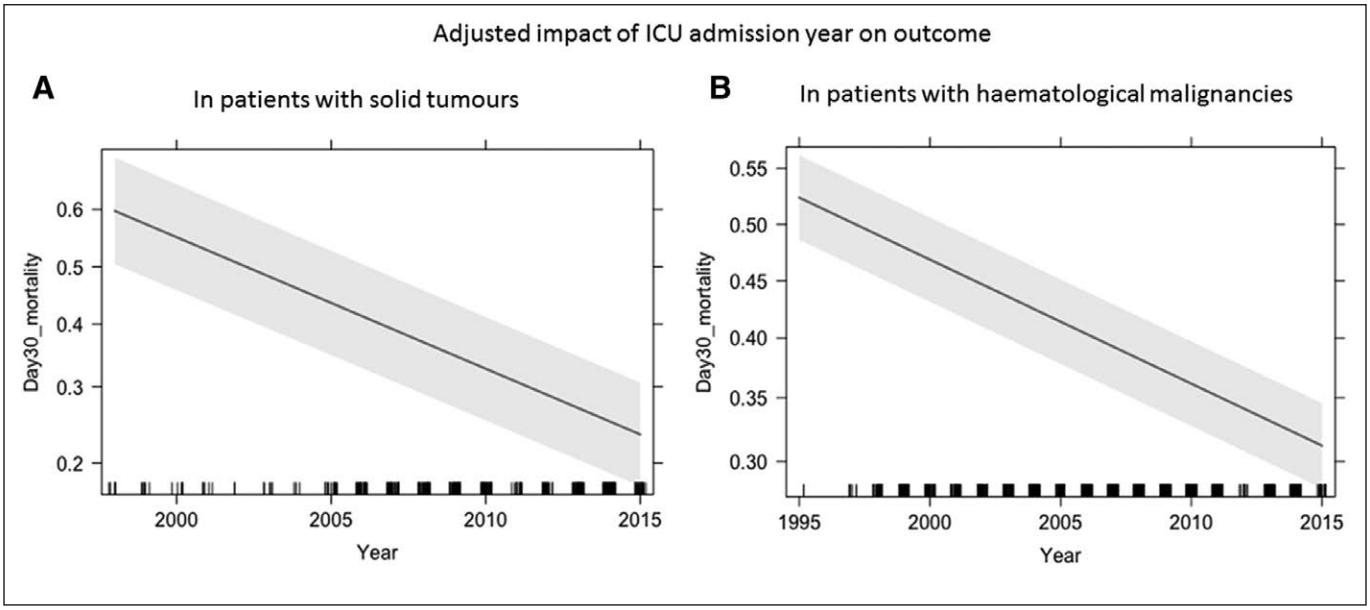

Figure 2. Thirty-day mortality over the years according the type of tumor. Thirty-day predicted mortality obtained by mixed-effect linear regression according to the year of ICU admission and adjusted on Sequential Organ Failure Assessment score at ICU admission in (**A**) patients with solid tumors (**B**) patients with hematologic malignancies.

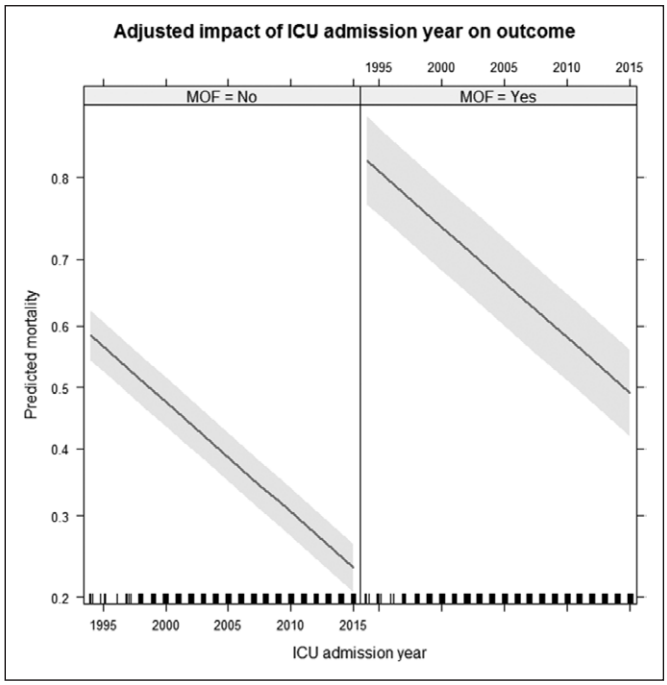

Figure 3. Thirty-day predicted mortality in patients with or without multiple organ failure obtained by mixed-effect linear regression according to the year of ICU admission. MOF = multiple organ failure.

random variables was used to identify risk factors for D-30 mortality. The calibration belt of the mixed-effect model is presented in **Supplemental Figure 3** (Supplemental Digital Content 5, http://links.lww.com/CCM/F385; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/F387). According to this model, mechanical ventilation (OR, 3.25; 95% CI, 2.52–4.19; $p < 0.01$) and vasopressors use (OR, 1.42; 95% CI, 1.10–1.83; $p < 0.01$) were significantly associated with D-30 mortality (**Fig. 4**). Neutropenia and allo-HSCT were not significantly associated with D-30 mortality.

Based on the linear mixed-effect model, sensitivity analysis in the subgroup of patients with clinically or microbiologically documented bacterial pneumonia found similar results: ICU admission year (OR, 0.90; 95% CI, 0.90–0.91; $p < 0.01$), mechanical ventilation (OR, 1.62; 95% CI, 1.06–2.50; $p < 0.01$), and renal replacement therapy (OR, 1.75; 95% CI, 1.14–2.70; $p < 0.01$) were significantly associated with D-30 mortality, whereas disease characteristics or previous stem cell transplantation were not (**Supplemental Fig. 4**, Supplemental Digital Content 6, http://links.lww.com/CCM/F386; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/F387).

DISCUSSION

This large multicenter study analyzing data from cancer patients admitted to the ICU for sepsis or septic shock put forward the continuing improved mortality in this high-risk patient population. To the best of our knowledge, this is the largest study assessing trends in survival rates over time in critically ill cancer patients with severe infections (11, 12).

With a D-30 mortality rate of 39.9%, this study suggests that mortality rates of cancer patients with sepsis is in line with those reported in patients with other severe comorbid conditions. Despite recent improvements and advances inpatient's management, mortality rates of sepsis in patients with malignancies remain higher than those in noncancer patients. However, earlier studies needed to be updated and the 60% mortality rate in cancer patients with severe sepsis and septic shock should be considered as not relevant anymore (10–12). Instead, cancer patients with severe infections exert survival rates that are in the ranges of those of patients with other severe comorbidities (9, 36, 37). Furthermore, in this study, almost a third of included patients had neutropenia secondary to recent

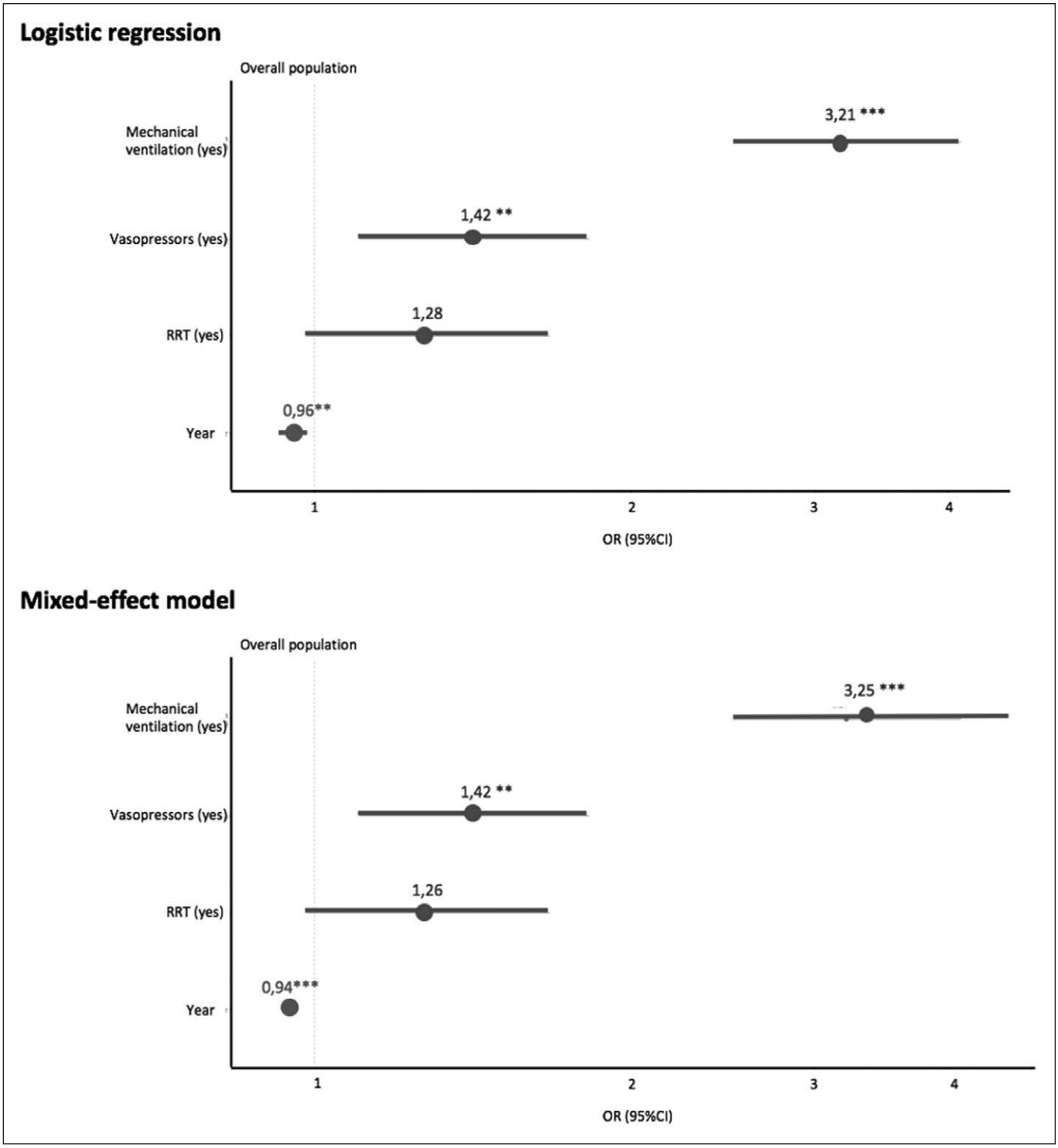

Figure 4. Risk factors for day 30 mortality determined by standard multivariate logistic regression and by mixed-effect linear regression at ICU admission. OR = odds ratio, RRT = renal replacement therapy.

intensive treatments such as auto-HSCT or allo-HSCT or intensive chemotherapy.

This study also generates hypotheses to explain why mortality decreased in cancer patients with severe infection. A better selection of patients, the increased awareness of sepsis diagnosis and management optimization may have contributed to improve outcomes over time. Indeed, various adjuvant therapies for both septic shock and general ICU care have arisen to form the basis of recommendations of the different Surviving Sepsis Campaigns (28, 38, 39). The compliance to the bundle of cares recommended by these international guidelines have been associated with increased survival of unselected ICU patients admitted for sepsis (37, 40). In critically ill cancer patients, Larché et al (41) followed by Pène et al (42)

also showed an improved outcome over time in patients with septic shock by comparing the mortality rates between two different time periods. Specific cares related to immunocompromised patients have also been developed in the past years, potentially explaining the decreased mortality in this population over time. For instance, Azoulay et al (21) reported that noninvasive diagnostic strategy for acute respiratory failure etiology was not inferior to invasive testing. Different ventilation strategies have also been specifically tested (19, 43). Furthermore, a better collaboration between oncologists/hematologists and intensive care doctors has dramatically improved the outcomes of patients with malignancies admitted to the ICU (5). In the ORCHESTRA study, Soares et al (5, 44) retrospectively reviewed onco-hematologic patients hospitalized in 51 ICUs from general hospitals and in 19 ICUs from cancer centers in Brazil. The authors found that presence of clinical pharmacists in the ICU, presence of ICU protocols, and daily meetings between oncologists and intensivists were associated with lower hospital mortality even after adjustment for hospital case volume. Finally, triage policies for ICU admission have evolved over time in cancer patients. Indeed, ICU triage criteria that are usually used are unreliable. An international expert consensus has issued ICU admission recommendations for critically ill patients with cancer (45). Different therapeutic strategies may be considered according to the patient and his disease; from full code management to 3 days ICU "trial" or no ICU admission/no intensified intensive care treatment. Furthermore, early ICU admission in case of acute physiologic disturbances or minor organ impairment in this specific population has been associated with improved survival, specifically in case of sepsis (20, 46–50). Thus, early ICU admission explains why almost half of the patients of our cohort admitted in ICU for sepsis had no need for vasopressor support. Interestingly, in the present study, allo-HSCT was not associated with D-30 mortality. Major advances have been made in the care of patients undergoing allo-HSCT over the last decade resulting in improved outcome (51, 52). ICU admission of allo-HSCT patients has been controversial. Studies from 1990s reported mortality rates over 90% (53). However, decrease in overall mortality, nonrelapse mortality, severe graft-versus-host disease, infections, and liver, kidney, and lung damages have been reported (54, 55). In a recent meta-analysis including 2,342 patients, ICU mortality rate was 51.7%. Furthermore, survival of critically ill adult allo-HSCT patients admitted to the ICU increased over time, supporting the usefulness of ICU management in well-selected patients (56). Thus, early admission of patients with only one organ failure can be beneficial in the allo-HSCT population, whereas attempt to resuscitate multiple organ failure mostly fails (3, 57).

According to these findings, neutropenia was not associated with D-30 mortality. Neutropenia is associated with complications like severe sepsis (20) or acute respiratory failure (58). Although these side effects are likely to influence the outcome of critically ill patients, several recent studies failed to demonstrate an impact of neutropenia on the outcome of critically ill patients (13) and showed a meaningful survival in this subgroup of patients (59). Conversely, a recent meta-analysis showed that neutropenia was independently associated with poor outcome in ICU patients (60). However, all these studies did not specifically address the issue of discrepancies in admission policies across studies, which might explain reported differences.

Last, we report in this analysis that the presence of organ failures remained the main determinant of outcome in critically ill cancer patients. In patients with solid tumor, Vincent et al (61) suggested that risk factors for 120 days mortality after ICU were the type of cancer, systemic extension of the disease, need for invasive mechanical ventilation, vasopressors, or renal replacement therapy. Furthermore, in a recent published study, de Vries et al (62) showed that 1-year mortality rate of patients with hematologic malignancies increased with the number of organ failure, with a survival rate among patients with two, three, and four failing organs of 27%, 22%, and 8%, respectively.

This study has several limitations. First, data on cancer patients admitted in seven participating ICUs and included in 14 different studies over a time period of 21 years were extracted from the GRRR-OH database and analyzed. Thus, these patients are representative of selected studies populations, which could limit generalizability of the data. This bias of selection may also explain the difference in numbers of patients with hematologic malignancies and those with solid tumors. Second, some data on patients with solid tumors are lacking, especially on the primary site of cancer and the metastatic status of the disease, restricting the external validity of the data on solid cancer patients. Furthermore, the date of the last inclusion was January 2015. Therefore, patients received chemotherapy regimens but none of them were treated by immunotherapy nor cancer targeted treatments. We acknowledge that these new treatments may have changed the prognosis of critically ill onco-hematologic patients (63). The study design does not allow us to ascribe reported survival benefits to specific targets. However, it is likely that more than single interventions, a global and comprehensive management has actually improved outcomes. Furthermore, anti-infectious agents have not been assessed in detail so that we are not in capacity to tackle the issue of appropriate antibiotics and source control, two tenets in the management of sepsis. The present study includes only patients who were considered eligible for ICU admission. This may have introduced a selection bias due to the triage process performed before ICU admission. Finally, as the data collection was retrospective for some studies, potential confounding factors may have been overlooked.

CONCLUSIONS

Survival in critically ill oncology and hematology patients with sepsis improved significantly over time. Given the high frequency of malignancy among patients with septic shock, studies are needed to identify targets to further improve survival in this growing subgroup of ICU patients.

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