Mortality of Adult Critically Ill Subjects With Cancer

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BACKGROUND: Cancer patients may require intensive care support for postoperative care, complications associated with underlying malignancy, or toxicities related to cancer therapy. The higher mortality rates found in this population than in the population of ICU patients without cancer may be attributable to confounding due to a higher prevalence of multiple organic dysfunctions at ICU admission in patients with malignancy; however, data regarding this hypothesis are scarce. Accordingly, we performed the present study to compare the crude and propensity score-matched mortality rates between adult subjects with and without cancer admitted to a mixed medical-surgical ICU. METHODS: We conducted a retrospective analysis of a comprehensive longitudinal ICU database in a tertiary referral hospital in Southern Brazil. All adult subjects who were admitted to the ICU from January 2008 to December 2014 were evaluated. Crude and propensity score-matched all-cause 30-d mortality rates of critically ill subjects with cancer were compared with those of critically ill subjects without cancer. RESULTS: A total of 4,221 subjects were evaluated. The survival analysis revealed that the crude mortality rate was higher among subjects with cancer than among subjects without cancer (18.7% vs 10.2%, $P < .001$). However, after matching by propensity score, the 30-d mortality rates of subjects with and without cancer were similar (18.5% vs 15.2%, $P = .17$). CONCLUSIONS: The present study failed to show an association between malignancy and all-cause 30-d mortality rate in adult subjects admitted to a mixed medical-surgical ICU. The propensity score-matched analysis showed no evidence of excessive mortality due to cancer diagnosis. *Key words: critical illness; critical care; cancer; mortality; prognosis.* [Respir Care 2017;62(5):615–622. © 2017 Daedalus Enterprises]

Introduction

Patients with cancer are living longer nowadays.[1] With advancements in diagnosis and treatment, even for advanced cases, malignant neoplasms are being controlled and long-term remission is being achieved. Similarly, the admission of oncologic patients to ICUs has become increasingly common, given the chronic disease status that cancer has reached. Patients with malignant neoplasms may require admission to the ICU for various reasons, usually respiratory failure, renal failure requiring renal replacement therapy, severe sepsis or septic shock, drug tox-

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icities related to medical treatment, and postoperative care. Currently, it is estimated that these patients account for 15–18% of all ICU admissions, and this rate is expected to increase with increases in long-term survival in this population.[2,3]

Early studies have shown that the mortality rates for subjects with cancer were substantially higher than those for subjects without cancer, suggesting that the presence of malignancy could be classified as a gloomy prognostic factor in the critical care scenario.[4,5] This belief has long been used to support refusing ICU admission or withdrawing intensive support early in cancer patients, especially for those with advanced disease and in the context of reduced ICU bed availability. However, more recently published literature indicates that the mortality rate for critically ill subjects with cancer is decreasing[6] and that the mere diagnosis of malignancy may no longer represent a strong predictor of ICU mortality, with mortality rates similar to those of subjects without cancer or even lower than those of subjects with some specific diseases, such as advanced heart failure.[2,3,7] These studies showed that ICU mortality is more closely related to the number and severity of organ dysfunctions during ICU stay than to the cancer diagnosis per se, suggesting the existence of confounding in the relationship between cancer diagnosis and ICU mortality. To clarify the role of cancer mortality in critically ill subjects, we performed this study with the objective of comparing the crude and propensity score-matched mortality rates between subjects with and without cancer admitted to a single medical-surgical ICU in Southern Brazil.

QUICK LOOK

Current knowledge

The higher mortality rates found for cancer patients than for ICU patients without cancer may be attributable to confounding due to a higher prevalence of multiple organic dysfunctions at ICU admission in those patients with malignancy.

What this paper contributes to our knowledge

In the crude model analyses, cancer subjects had a higher rate of organ dysfunction and a greater need for intensive support (ventilatory, hemodynamic, and renal support). After one-to-one propensity score-matched analysis to address selection bias, we found no evidence of higher mortality in critically ill subjects due to cancer diagnosis. Therefore, the higher mortality of subjects with cancer admitted to the ICU is due to greater development of multi-organ dysfunction and not the cancer itself.

Methods

Study Design, Subjects, and Setting

A retrospective analysis of a comprehensive longitudinal ICU database was conducted at a single tertiary center. The present study followed all ICU subjects >18 y old who were consecutively admitted to the 31-bed mixed medical-surgical ICU of the Hospital Moinhos de Vento in Porto Alegre, Brazil from January 2008 to December 2014. Patients who were receiving palliative treatment only or had an ICU stay of <24 h were excluded. Subjects were not allowed to re-enter the study after their first ICU admission.

The ICU evaluated in the present study had the same policy for ICU admission of cancer subjects during the study period: first, all admissions of cancer subjects were determined jointly by the oncology and intensive care teams; second, subjects with poor performance status and no cancer treatment options were not considered for ICU admission; third, a broad policy of admission to the ICU was encouraged to avoid inappropriate ICU refusal.

Sample Size Calculation

To detect a 10% difference in all-cause 30-d mortality between subjects with and without cancer in the ICU with a power of 90% and a type-1 error rate of 0.05 by using a Pearson chi-square test, we calculated that 379 pairs of propensity score-matched subjects would be required. This calculation considered an all-cause 30-d mortality rate of 27% among cancer ICU subjects.[3] To avoid reduction of power due to follow-up losses, the present study protocol determined evaluation of at least 419 pairs of propensity score-matched subjects.

Definitions

Subjects admitted to the ICU were classified as cancer subjects depending on the diagnosis of solid or hematologic neoplasia before ICU admission. Subjects with a past history of cancer and with complete remission for >5 y were placed in the non-cancer group.

The type of ICU admission was classified into a dichotomous variable: admission due to a medical condition or surgery. Subjects were classified as admitted due to a surgery if they were admitted to the ICU immediately after a surgery (early postoperative period). Subjects admitted in the late postoperative period due to complications that did not require surgical interventions were classified as medical patients. We made this classification, because the outcomes of patients admitted to the ICU in the late postop-

erative period are more closely related to medical than to early postoperative surgical patients.[8]

Infection was defined as clinically suspected infection (pneumonia, bloodstream infections [including infective endocarditis], intravascular catheter-related infection, intra-abdominal infections, urinary tract infections, surgical wound infections, skin and soft tissue infections, and central nervous system infections) according to the international sepsis forum consensus conference on the definitions of infection in the ICU.[9] Severe sepsis and septic shock were defined according to the Surviving Sepsis Campaign guidelines.[10] Subjects were defined as having ARDS if the arterial oxygen pressure to inspiratory oxygen fraction was <300, bilateral infiltrates were observed on the chest radiograph, and there was no clinical evidence of heart failure.[11] The severity of the critical illness and the degree of organ failure were assessed within 24 h of ICU admission by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the sequential organ failure assessment (SOFA) score, respectively. The ICU interventions performed within the first 24 and 72 h of ICU admission were evaluated by the simplified therapeutic intervention scoring system (TISS 28). APACHE II is a common scoring system used to grade the severity of illness in critically ill subjects. It generates a score ranging from 0 to 71 based on 12 physiologic variables, including age and variables describing the patient's underlying health: The higher the score, the greater the acute illness severity.[12] The SOFA score is based on the extent of the patient's organic function determined by physiological parameters of the respiratory, neurologic, cardiovascular, hepatic, coagulation, and renal systems: The higher the score, the greater the number of organic dysfunctions.[13] The TISS 28 score is based on interventions related to basic activities, including ventilator support, cardiovascular support, renal support, neurologic support, metabolic support, and specific interventions: The higher the score, the greater the number of interventions the patient is receiving.[14]

Outcome, Follow-Up, and Data Management

The primary outcome of this study was all-cause mortality 30 d after ICU admission. During the ICU stay, subjects were followed through interviews and medical record reviews by researchers who were not associated with the attending physician's team. For subjects who were discharged from the hospital in <30 d, follow-up telephone calls were made on the 30th day after ICU admission to determine whether they were still alive; if a subject was deceased at the time of the telephone call, the survival time was calculated based on the date of death reported by the family. Data were collected using preprinted case report forms. The data collection on ICU admission included demographic data; number of comorbidities; type of ICU admission (medical vs surgical); and diagnoses of infection, severe sepsis, septic shock, and ARDS. The data collected during the ICU stay included APACHE II, SOFA, and TISS 28 scores and specific interventions, such as mechanical ventilation, vasopressors, inotropes, renal replacement therapy, corticosteroids, neuromuscular blocking agents, and urgent surgery.

Statistical Analysis

Observational studies are often limited by an imbalance in both known and unknown confounders, which cause some cancer subjects to be more likely to develop unfavorable outcomes during their ICU stay than subjects without cancer. Therefore, we applied propensity score matching to balance baseline characteristics and reduce the probability of selection bias.[15] The propensity score (probability of having cancer) was calculated using a multivariate logistic regression model in which the dependent variable was diagnosis of malignancy. Multi-collinearity was assessed according to the variance inflation factor of the multivariate model.[16] The variance inflation factor estimates how much the variance of a coefficient is inflated because of the linear dependence of other predictors. Indicators of multi-collinearity include individual variance inflation factors of >10 or an average variance inflation factor of >6. Matching was performed with the use of a 1:1 matching protocol without replacement (nearest neighbor algorithm).[17] Standardized differences were estimated for all of the baseline covariates before and after matching to assess prematch imbalance and postmatch balance. Standardized differences ≤10.0% for a given covariate indicated a small imbalance. Kaplan-Meier curves were used to calculate the time-dependent occurrence of death in both the unmatched and propensity score-matched cohorts; the log-rank test was used for comparisons between groups. The 30-d all-cause mortality rate was also evaluated with the Pearson chi-square test. A significance level of 0.05 was adopted for all statistical comparisons. The software used for the statistical analysis was STATA 12 (StataCorp, College Station, Texas).

Ethics

The Institutional Research Ethics Committee of the Hospital Moinhos de Vento, Porto Alegre, Brazil approved the study protocol and waived the requirement of informed consent.

Results

During the study period, 4,221 subjects (981 with cancer and 3,240 without cancer) were admitted to the ICU

Table 1. Comparison of Variables Between Intensive Care Subjects With Cancer and Those Without Cancer

Variables	Entire Cohort (N = 4,221)		Propensity Score-Matched Cohort (n = 842)	
	Cancer group (n = 981)	Non-Cancer Group (n = 3,240)	Cancer Group (n = 421)	Non-Cancer Group (n = 421)
Male sex, n (%)	562 (57.2)	1,688 (52.1)	216 (51.3)	224 (53.1)
Age, mean ± SD y	69.2 ± 14.2	67.8 ± 18.6	69.0 ± 14.5	70.1 ± 17.1
Number of comorbidities,* mean ± SD	3.0 ± 0.9	2.7 ± 1.1	2.9 ± 0.9	2.8 ± 1.1
Admission due to a medical condition, n (%)	527 (53.7)	2,115 (65.2)	253 (60.1)	275 (65.3)
APACHE II, mean ± SD	17.5 ± 8.1	15.6 ± 8.0	16.8 ± 7.8	17.8 ± 8.0
SOFA at ICU admission, mean ± SD	3.6 ± 3.4	3.1 ± 3.3	3.9 ± 3.3	3.9 ± 3.3
Infection at ICU admission, n (%)	407 (41.4)	1034 (31.9)	181 (42.9)	194 (46.0)
Severe sepsis at ICU admission, n (%)	94 (9.5)	204 (6.3)	41 (9.7)	50 (11.8)
Septic shock at ICU admission, n (%)	173 (17.6)	353 (10.9)	70 (16.6)	67 (15.9)
ARDS at ICU admission, n (%)	41 (1.2)	19 (1.9)	9 (2.1)	8 (1.9)
Mechanical ventilation, n (%)	451 (45.9)	1243 (38.3)	211 (50.0)	227 (53.9)
Vasopressor, n (%)	442 (45.0)	1167 (36.0)	191 (45.3)	190 (45.1)
Inotrope, n (%)	27 (2.7)	120 (3.7)	12 (2.8)	10 (2.3)
Corticosteroids, n (%)	353 (32.9)	697 (21.5)	133 (31.5)	151 (35.8)
Neuromuscular blocking agent, n (%)	31 (3.1)	80 (2.4)	14 (3.3)	16 (3.8)
Renal replacement therapy during ICU stay, n (%)	135 (13.7)	384 (11.8)	64 (15.2)	65 (15.4)
Urgent surgery during ICU stay, n (%)	57 (5.8)	194 (5.9)	29 (6.8)	24 (5.7)
TISS 28 after 24 h, mean ± SD	22.0 ± 8.5	20.0 ± 8.9	22.4 ± 8.0	22.3 ± 8.7
TISS 28 after 72 h, mean ± SD	18.4 ± 9.4	16.4 ± 9.9	18.3 ± 8.8	18.7 ± 9.2

* Heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus, COPD, cirrhosis, HIV infection, chronic renal failure.
APACHE II = Acute Physiology and Chronic Health Evaluation II score
SOFA = Sequential Organ Failure Assessment score
TISS 28 = simplified therapeutic intervention scoring system

and were included in this study; 62.6% (n = 2,642) were admitted due a medical condition, and 37.4% (n = 1,579) were admitted due to a surgery. Among the subjects with cancer admitted to the ICU, 85.9% (843 subjects) had solid neoplasms and 14.1% (138 subjects) had hematologic neoplasms. The rate of metastatic disease among subjects with solid neoplasms and the rate of relapsed disease among subjects with hematologic disease were 27.4% (231 subjects) and 53.6% (74 subjects), respectively. The baseline clinical characteristics of all subjects evaluated in the present study are shown in Table 1. As a result of the non-randomized design of this study, the baseline characteristics of the subjects with cancer were different from those of the subjects without cancer in the unmatched cohort. The differences that were particularly important were sex; admission due to a medical condition; APACHE II score; infection, severe sepsis and septic shock at ICU admission; TISS 28 score at 24 and 72 h after ICU admission; and some specific ICU interventions, such as mechanical ventilation, administration of vasopressors and corticosteroids, and renal replacement therapy.

Several clinical factors were significantly associated with cancer diagnosis (Table 2): male sex, higher number of comorbidities, higher APACHE II score, infection at ICU admission, and requirement of corticosteroids. In contrast, admission due to a medical condition and the need for an inotrope and renal replacement therapy were negatively associated with the diagnosis of malignant neoplasm. The multivariate logistic regression model of factors associated with cancer diagnosis among critical care subjects was used to determine the propensity score. The analysis of the variance inflation factor showed no evidence of important multi-collinearity: the maximum individual variance inflation factor was 2.5, and the average was 1.5. Subjects with similar propensity scores were matched at a 1:1 ratio; as a result, 421 pairs of subjects were identified. In the cohort of propensity score-matched subjects, the standardized differences of all covariates between subjects with and without cancer were <10%, which suggested that the propensity score matching appropriately adjusted for the initial selection bias (Fig. 1). No follow-up losses occurred in the propensity score-matched cohort.

The all-cause 30-d mortality rates in the overall study population were 12.2% (515 subjects) for the unmatched cohort and 16.8% (142 subjects) for the propensity score-matched cohort. The analysis of survival rates (Figs. 2 and 3) showed higher mortality rates for subjects with cancer than for those without cancer in the unmatched cohort (18.7% vs 10.2%, log-rank and chi-square $P < .001$); however, in the propensity score-matched cohort, subjects

Table 2. Multivariate Logistic Regression Model of Baseline Factors Associated With Cancer Among Intensive Care Subjects (Propensity Score Model)

Variable	Odds Ratio	95% CI	*P*
Male sex	1.19	1.00–1.42	.042
Age, per year	0.99	0.98–1.00	.09
Number of comorbidities*	1.41	1.29–1.54	<.001
Admission due to a medical condition	0.34	0.28–0.42	<.001
APACHE II, per point	1.04	1.02–1.05	<.001
SOFA at ICU admission, per point	0.96	0.93–1.00	.058
Infection at ICU admission	1.31	1.05–1.62	.01
Severe sepsis at ICU admission	1.18	0.86–1.60	.29
Septic shock at ICU admission	1.07	0.80–1.44	.61
ARDS at ICU admission	1.03	0.53–2.00	.91
Mechanical ventilation	0.93	0.73–1.18	.57
Vasopressor	1.00	0.79–1.27	.97
Inotrope	0.57	0.33–0.99	.045
Corticosteroids	1.47	1.19–1.82	<.001
Neuromuscular blocking agent	0.93	0.56–1.55	.80
Renal replacement therapy during ICU stay	0.70	0.53–0.92	.01
Urgent surgery during ICU stay	0.68	0.47–0.97	.034
TISS 28 after 24 h, per point	1.00	0.98–1.01	.77
TISS 28 after 72 h, per point	1.00	0.99–1.01	.40

* Heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus, COPD, cirrhosis, HIV infection, chronic renal failure.
APACHE II = Acute Physiology and Chronic Health Evaluation II score
SOFA = Sequential Organ Failure Assessment score
TISS 28 = simplified therapeutic intervention scoring system

with cancer had the same all-cause 30-d mortality as subjects without cancer (18.5% vs 15.2%, log-rank $P = .17$, chi-square $P = .19$). A post hoc power analysis showed that the present propensity score-matched cohort exhibited a power of 21% to detect a difference of 3.3% (18.5% vs 15.2%) for all-cause 30-d mortality, considering a 2-sided α of 0.05. To reach a power of 80% to detect a 3.3% difference for mortality, 2,078 propensity score-matched pairs of subjects would be necessary.

Discussion

In the present study, the higher crude 30-d mortality found in ICU subjects with cancer than in those without cancer was due to confounding. In the crude model, subjects with cancer had a higher rate of organ dysfunction and a greater need for intensive support (eg, mechanical ventilation, vasopressor administration, and renal replacement therapy). Using a one-to-one propensity score-matched analysis to address selection bias, we found no evidence of higher mortality in critically ill subjects due to cancer diagnosis.

In the 1980s and 1990s, some studies highlighted the role of the intensivist refusing admission of patients with cancer to ICUs. Data published in this context showed unacceptable mortality rates of subjects with cancer despite intensive life support.[5,18] At that time, the inclusion of some subjects with cancer, especially those with advanced disease, which underwent intensive therapeutic strategies, may have been disproportional, and those treatments may have been deleterious given the poor prognosis of that population. However, with the progressive advancements in the treatment of cancer and the supportive care provided to critically ill patients in recent decades, the long-term survival rates of both oncologic and critically ill patients have increased. This explains the current critical care background in which critically ill patients, both with and without cancer, can have comparable outcomes. Similar to our findings, several studies[2,3,19,20] have shown that the presence of malignancy may no longer be an independent risk factor for death in the context of critical care. For instance, a large multi-center European study reported a mortality rate for subjects with solid cancer similar to that of ICU subjects without cancer.[3] Moreover, the work of Tanvetyanon and Leighton[7] showed that the in-hospital mortality of critically ill subjects with cancer was not higher than that of subjects with other comorbidities.

Our results should be interpreted with caution, especially in ICUs with a high prevalence of hematological neoplasms, given that our sample of critically ill subjects with hematological malignancy was <15% of our total

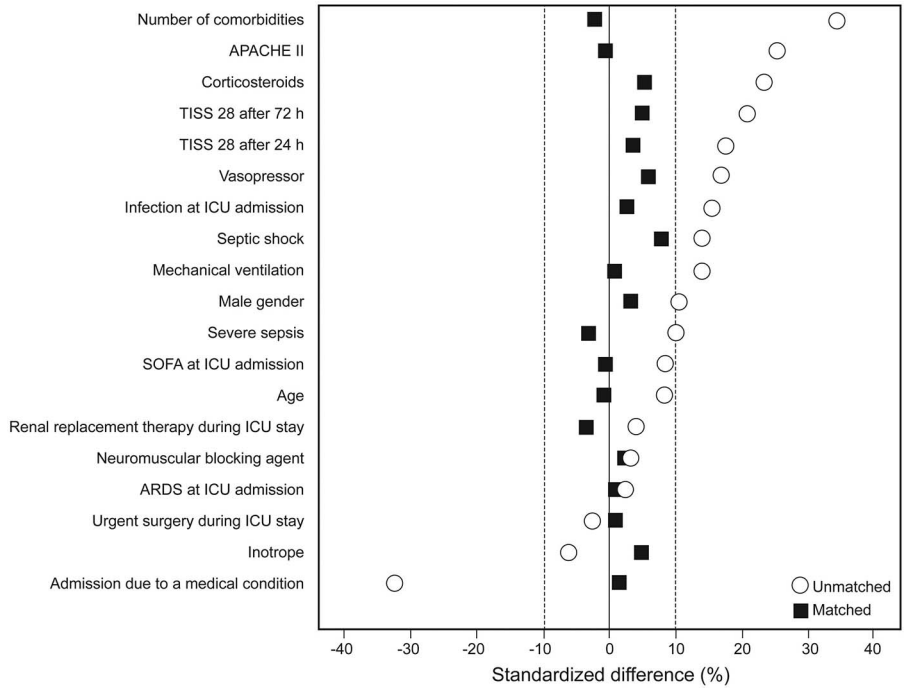
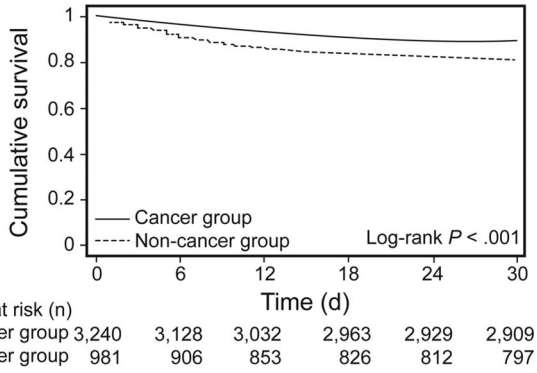


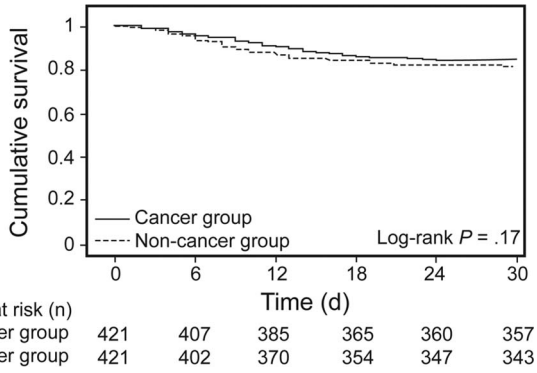
Fig. 1. Balance of covariates between critical care subjects with and without cancer and before and after propensity score matching. Note: After propensity score matching, 421 matched pairs were identified. The standardized differences are reported as percentages; a difference of ≤10.0% indicates a relatively small imbalance. APACHE II = acute physiology and chronic health evaluation II, TISS 28 = therapeutic intervention scoring system, SOFA = sequential organ failure assessment.



Subjects at risk (n)

Non-cancer group	3,240	3,128	3,032	2,963	2,929	2,909
Cancer group	981	906	853	826	812	797

Fig. 2. Comparison of Kaplan-Meier survival curves between critical care subjects with and without cancer; crude analysis.



Subjects at risk (n)

Non-cancer group	421	407	385	365	360	357
Cancer group	421	402	370	354	347	343

Fig. 3. Comparison of Kaplan-Meier survival curves between critical care subjects with and without cancer; propensity score-matched analysis.

ICU cancer population. However, conflicting data also exist regarding the higher mortality risk among the subpopulation of cancer subjects with hematological malignancies. Although some large studies have found higher mortality rates for subjects diagnosed with hematological malignancies than for subjects diagnosed with solid neoplasms,[3,21] some evidence suggests that the role of the type of malignancy in outcome determination in the setting of critical care illness is questionable. Accordingly, a prospective study by Soares et al[2] with >700,000 subjects with cancer showed that mortality was predicted by severity of organ failures and performance status and not by cancer-related characteristics, such as the type of malignancy and neutropenia. Moreover, a study by Massion et al[22] showed that the short-term prognosis of critically ill subjects with hematologic cancer is related to acute organ dysfunctions and pathogen aggressiveness; the severity of the underlying hematologic malignancy was not independently associated with mortality.

The strength of the present study includes the low risk of selection and confounding bias due to equivalence of important covariates between the 2 study groups in the propensity score-matched cohort. Previous studies evalu-

ating cancer subjects admitted to ICUs used heterogeneous statistical analysis methods.[2,3,5,15,20] Some statistical methods, such as standard multivariate regression, tend to inflate effects in observational studies, especially when the number of prognostic factors is high and when there is insufficient overlap of covariates between the 2 study arms.[23] In contrast, the propensity score method creates a model that reflects the effects of risk factors on the exposure. Matching using a single summary variable that predicts the probability of being exposed as a function of the confounders creates a statistical model with fewer assumptions and may lead to improved estimates of exposure effects in some settings.[24] Using a stringent and conservative matching analysis, we attempted to achieve causal inference of mortality.

Our study has limitations. Because of the one-to-one propensity score matching procedure with a narrow caliper, the sample size was reduced. Moreover, the mortality rate of our cohort was lower than expected, and the study was underpowered to detect differences $<10\%$ of all-cause 30-d mortality between subjects with and without cancer. In addition, our study evaluated only short-term mortality of ICU subjects; this outcome may underestimate the true mortality of ICU patients, given that the mortality in the first months after ICU discharge is high, and ICU cancer patients may be particularly susceptible to this long-term outcome.[25] Also, the lack of quality-of-life measurements among survivors represents a drawback: were survivors with and without cancer comparable with regard to quality of life? How did the ICU intervention impact dignity and distress among those cancer survivor subjects with reversible physiologic dysfunction but with a poor malignancy prognosis? Other important limitations of the present study were related to its single-center retrospective design; lack of control of important covariates associated with prognosis, such as delay between ICU referral and admission, type of malignancy, cancer progression, or previous allogeneic stem cell transplantation; and possible systematic errors related to observational studies, given that the propensity score can balance study groups with respect to measured covariates only, and we cannot be certain that we identified all potential confounding factors for mortality in the critical care scenario.

In conclusion, the diagnosis of cancer before ICU admission does not necessarily impact all-cause ICU mortality. ICU admission policies should be rationally enhanced to cover all potential beneficiaries of intensive care, taking into account the needs and perspectives of patients and their families. Currently, the best approach for critically ill cancer patients at ICU admission is to improve communication among the multidisciplinary oncology and critical care teams to offer early and complete vital support for those patients with a reasonable baseline prognosis (an ICU trial).[26] After this full-code approach, there should be a predefined revaluation in 3–5 d of the number of recovered organ dysfunctions and response to therapies in course. Ideally, the participation in decisions of withholding and withdrawing life support should be discussed with a consultant palliative care specialist, considering patient and family preferences.[27] After 2–3 weeks of stay in intensive care full support with ventilator, vasoactive drugs, and renal replacement therapy, a condition usually referred as chronic critical illness,[28] the short- and long-term prognoses in the general ICU population are dismal and are probably much worse in the oncologic patient. One of the intensivist's attributions and competences to communicate the new prognosis to the oncologist and the family, helping them to deescalate treatment in the patient's best interest. Future research in the field of intensive care of cancer patients should explore the impact of ICU admission on overall long-term and disease-free survival as well as quality of life among ICU survivors with cancer.

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