

Survival of Critically Ill Oncologic Patients Requiring Invasive Ventilatory Support: A Prospective Comparative Cohort Study With Nononcologic Patients

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PURPOSE Cancer is in the process of changing to become a chronic disease; therefore, an increasing number of oncologic patients (OPs) are being admitted to intensive care units (ICUs) for supportive care of disease or therapy-related complications. We compare the short- and long-term outcomes of critically ill mechanically ventilated OPs with those of their nononcologic counterparts.

PATIENTS AND METHODS We performed a prospective study of patients admitted to our ICU between October 2017 and February 2019. Demographic, physiologic, laboratory, clinical, and treatment data were obtained. The primary outcome was survival at 28 days and at the end of the follow-up period. Secondary outcomes were survival according to acute severity scoring (Acute Physiology and Chronic Health Evaluation II score), Eastern Cooperative Oncology Group (ECOG) performance status, and Charlson comorbidity index.

RESULTS A total of 1,490 patients were admitted during the study period; 358 patients (24%) were OPs, and 100 of these OPs were supported with mechanical ventilation. Seventy-three percent of OPs had an ECOG performance status of 0 or 1, and 90% had solid tumors. Reason for admission to the ICU was postoperative admission in 44 patients and neutropenic infection in 10 patients. The follow-up period was 148 days (range, 42 to 363 days). Survival at 28 days was similar between OPs and nononcologic patients and associated with the Acute Physiology and Chronic Health Evaluation II score. However, long-term survival was lower in OPs compared with nononcologic patients (52% v 76%, respectively; $P < .001$) and associated with poor ECOG performance status.

CONCLUSION Short-term survival of critically ill, mechanically ventilated OPs is similar to that of their nononcologic counterparts and is determined by the severity of the critical illness.

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INTRODUCTION

Cancer is a leading cause of death in the general population.¹ However, major advances in the knowledge regarding cancer biology and in cancer therapy have contributed to improved survival in patients with cancer. The continuous decline in cancer death rates coupled with an overall stable cancer incidence has resulted in a growing number of patients receiving oncologic treatment.¹⁻³ As a result, cancer is in the process of changing to become a chronic disease.

Traditionally, in Chile, oncologic patients (OPs) were considered poor candidates for intensive care unit (ICU) admission, and exclusion of these patients from ICU care was a common practice.^{4,5} Currently, up to 20% of ICU admissions are OPs.⁶⁻⁸ Over the past decade, both management and survival of critically ill OPs have improved significantly.⁹⁻¹¹ Major changes in the field of critical care of OPs have occurred.

Classic predictors of mortality have lost much of their prognostic value,¹⁰ noninvasive diagnostic and therapeutic strategies have allowed new clinical approaches for high-risk OPs,¹² and new strategies for ICU admission that have affected outcomes have been developed.¹³ In fact, early ICU admission has been associated with better survival rates in OPs.¹⁴ Moreover, many OPs who survive their ICU stay achieve cancer remission and a good quality of life.^{14,15} However, survival of OPs remains worse than that of patients without cancer.¹⁶

As in many countries in the world, cancer in Chile is currently the second leading cause of death, resulting in 25.6% of total annual deaths, and recent projections indicate it will become the leading cause of death by 2030. In Chile, cancer is also the main cause of disease burden, as measured by disability-adjusted life-years.^{17,18} Data on the characteristics and outcomes of critically ill OPs in South America are limited.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 29, 2019 and published at ascopubs.org/journal/jgo on September 3, 2019; DOI <https://doi.org/10.1200/JGO.19.00184>

CONTEXT

Key Objective

Do oncologic patients (OPs) admitted to intensive care unit (ICU) and supported with mechanical ventilation have lower survival compared with their nononcologic counterparts?

Knowledge Generated

In 1999, the Society of Critical Care Medicine guidelines recognized OPs as poor candidates for ICU admission. Since that time, both critical support and oncologic therapies have improved. Currently, data suggest improved outcomes in OPs admitted to the ICU. We found no difference in short- and long-term survival between OPs and nononcologic patients when severity of disease and comorbidities are considered. Poor performance status remains an important variable to consider for ICU admission.

Relevance

OPs who do not have a poor performance status should be considered for full ICU support.

Such data would help to inform decisions about ICU admission in the context of limited ICU bed availability.

The purpose of this study was to compare overall short- and long-term survival between oncologic and nononcologic critically ill patients requiring invasive ventilator support. In addition, the role of acute severity scoring and performance status as prognostic factors in this population was addressed.

PATIENTS AND METHODS

This was an observational analytic study of a prospective single-center cohort. Our institution is a private academic center with a 60-bed critical care department consisting of 12 ICU beds with invasive mechanical ventilation (IMV) availability and 48 intermediate care unit beds with non-invasive ventilatory support capability.

Our ICU has intensivist coverage 24 hours a day, 7 days a week. Multidisciplinary rounds are performed each morning and include an oncologist (when cancer has been diagnosed), clinical pharmacologist, physiotherapist, nutritionist, speech therapist, and occupational therapist. The nurse-to-patient ratio for IMV patients is 1:2, whereas the intensivist-to-patient ratio for these patients is 1:6. The local ethical board approved this study, and informed consent was provided by patients' relatives.

Patients

All patients consecutively admitted to the ICU between October 2017 and February 2019 were considered for this study. However, certain inclusion criteria were defined, which were as follows: age older than 18 years, need for IMV, and approved informed consent. For patients who were admitted more than once to the ICU during the study, only the first admission was considered. Patients were categorized as OPs and nononcologic patients. OPs included those with either solid or hematologic neoplasms. Patients were required to have histologically confirmed cancer. In addition, in OPs, baseline Eastern Cooperative Oncology Group (ECOG) performance status was assessed

at hospital admission (performance status range, 0 to 4), and admission criteria were recorded (see next section).

ICU Admission Criteria in OPs

The ICU admission decision for any patient was made by two or more intensivists. For each OP, the ICU plan was as follows.¹³ Patients who were candidates for receiving active cancer treatment with a reasonable chance of disease control were admitted to the full code plan; for this plan, unlimited interventions were considered, such as for other critical care patients without an oncologic diagnosis. Patients who had an intermediate prognosis who did not meet criteria for full code or palliative or end-of-life care were admitted to the ICU trial plan, which involved a limited time of advanced intervention that include periodic reassessment according to the patient's failure of systems.

Data Collection

Demographic, physiologic, and laboratory data; major reasons for ICU admission; and clinical and treatment data were extracted prospectively in a database that was updated daily. For each patient, the date of death was obtained from the national death registry database until March 2019.

The data were obtained and recorded by a research-trained therapist independent of the attending team (R.P.). The care providers were blinded to this prospective record.

Outcomes

The primary outcome of this study was survival at 28 days and at the end of the follow-up period. Secondary outcomes were survival according to ECOG performance status, ICU admission criteria, length of IMV, and ICU length of stay (ICU-LOS). Survival analyses adjusted by significant covariables were also performed.

Statistical Analysis

The characteristics of this cohort are provided as means with standard deviations (SDs) for continuous variables and as percentages with numbers of patients for dichotomous

variables. We used the *t* test for quantitative variables and the χ^2 or Fisher's exact test for qualitative variables.

Survival analysis according to oncologic or nononcologic status was performed at day 28 and at the end of the follow-up period. In addition, survival analyses according to ECOG performance status and ICU admission criteria categories in OPs versus nononcologic patients were performed at day 28 and at the end of the follow-up period. All survival comparisons were performed using adjusted Cox proportional hazards regression and adjusted hazard ratios (HRs) with 95% CIs. Both demographic and physiologic variables and clinical scoring were considered to adjust the survival analysis when these were associated with the probability of survival. A two-tailed *P* = .05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 20 (SPSS, Chicago, IL).

RESULTS

Patients

All patients considered for this study were successfully enrolled. A total of 1,490 patients were admitted to the ICU

between October 2017 and February 2019. A total of 358 patients (24%) had oncologic diagnosis, and 100 of these patients were supported with IMV. During the same period, 201 nononcologic patients were support with IMV.

According to ICU admission criteria, 76 OPs were admitted as full code, and 24 OPs were admitted under ICU trial criteria. Major reasons for admission to the ICU were post-operative admission in 44 patients and febrile neutropenia in 10 patients; 39 ICU admissions were categorized as other.

Baseline characteristics are listed in Table 1. Among all IMV patients, 57% were male, and the mean age was 59 years. OPs were older and presented with a higher Charlson comorbidity index (CCI) compared with nononcologic patients, whereas mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score and first-day Sequential Organ Failure Assessment score were not statistically different between the groups. No statistic differences were noted in the clinical or physiologic variables between OPs and nononcologic patients. In general, the main causes of IMV were acute respiratory failure and circulatory failure, whereas 46% of patients had postsurgical organ failure.

TABLE 1. Patient Characteristics

Characteristic	Total	Oncologic Patients	Nononcologic Patients	<i>P</i> (oncologic v nononcologic patients)
No. of Patients	301	100	201	
Demographic				
Male, % (No.)	57 (170)	51 (51)	59 (119)	.110
Mean age, years (SD)	59 (19)	64 (15)	57 (21)	.001
Mean ICU acuity assessment (SD)				
APACHE II score	15 (8)	15 (8)	16 (9)	.419
SOFA day 1 score	7 (3)	6 (3)	7 (3)	.083
SOFA day 3 score	5 (4)	5 (4)	5 (4)	.893
SOFA day 5 score	5 (4)	5 (4)	5 (4)	.728
P/F ratio	263 (205)	249 (109)	269 (232)	.525
Lactate, mg/dL	32 (40)	29 (28)	33 (44)	.481
Comorbidities, % (No.)				
Arterial hypertension	35 (108)	32 (32)	37 (75)	.372
Diabetes mellitus	20 (60)	21 (21)	19 (39)	.760
COPD	15 (45)	14 (14)	15 (31)	.864
Chronic kidney disease	6 (18)	4 (4)	8 (16)	.792
Cirrhosis	7 (21)	6 (6)	7 (15)	.796
Other	13 (39)	11 (11)	14 (28)	.586
Mean Charlson comorbidity index (SD)	4 (3)	7 (3)	3 (2)	< .001
Admission syndromes, % (No.)				
Acute respiratory failure	47 (141)	53 (53)	47 (94)	.533
Circulatory shock	41 (122)	39 (39)	42 (83)	.400
Surgical	46 (139)	44 (44)	47 (95)	.625

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; P/F ratio, ratio of arterial partial oxygen pressure to inspired oxygen; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Among OPs, 73% of patients had an ECOG performance status of 0 or 1, and solids tumors were more common than hematologic malignancies (90% v 10%, respectively). Lung and digestive cancers were the most frequent malignancies. Among patients with solid tumors, 4%, 31%, 14%, and 51% had stage I, II, III, and IV disease, respectively. Full code management was the most frequent strategy at ICU admission (76% v 24% with ICU trial management; Table 2).

Outcomes

Considering all patients, the mean duration of IMV was 4 days (SD, 5 days), and the mean ICU-LOS was 8 days (SD, 10 days). The mean follow-up time was 200 days (SD, 174 days). The survival rates at day 28 and at the end of the study were 85% and 68%, respectively.

Observed overall survival at day 28 was similar between OPs and nononcologic patients (Table 3). However, when we compare OPs and nononcologic patients, observed

overall survival at the end of the follow-up period was lower for OPs (52% v 76%, respectively; $P < .001$). A similar length of IMV was observed in both groups, whereas a significantly shorter ICU-LOS was observed in OPs compared with nononcologic patients (mean \pm SD, 6 ± 8 v 9 ± 11 days, respectively; $P = .009$).

Adjusted Survival Analysis

At day 28, the APACHE II score was the only variable associated with low survival (HR, 1.10; 95% CI, 1.07 to 1.12; $P < .001$). At the end of the follow-up period, both APACHE II score and CCI were associated with low survival, with HRs of 1.06 (95% CI, 1.04 to 1.09; $P < .001$) and 1.20 (95% CI, 1.12 to 1.28; $P < .001$), respectively. Therefore, all survival analyses at day 28 were performed using Cox proportional hazards regression adjusted by APACHE II score, whereas all survival analyses at the end of follow-up were performed using Cox regression adjusted by APACHE II and CCI.

TABLE 2. Oncologic Patient Characteristics and Mortality

Characteristic	No. of Oncologic Patients (%; n = 100)	Mortality, No. of Patients (%)		
		In ICU	At 28 Days	At End of Follow-Up
Cancer type				
Hematologic	10 (10)	4 (40)	5 (50)	8 (80)
Lung	11 (11)	3 (27)	3 (27)	4 (36)
Breast	6 (6)	0 (0)	0 (0)	3 (50)
Colon	8 (8)	0 (0)	0 (0)	1 (13)
Gastric	2 (2)	0 (0)	0 (0)	2 (100)
Other	63 (63)	5 (8)	11 (18)	25 (40)
Solid tumor stage				
All stages	90 (90)	10 (11)	14 (16)	36 (40)
I	4 (4)	0 (0)	0 (0)	0 (0)
II	31 (31)	1 (3)	2 (7)	5 (16)
III	14 (14)	0 (0)	1 (7)	4 (29)
IV	51 (51)	9 (18)	11 (22)	27 (53)
ECOG PS				
0	3 (3)	1 (33)	1 (33)	1 (33)
1	70 (70)	7 (10)	9 (13)	27 (39)
2	22 (22)	4 (18)	8 (36)	13 (59)
3	5 (5)	3 (60)	3 (60)	4 (80)
4	0 (0)	NA	NA	NA
ICU criterion of admission				
Full code	76 (76)	10 (13)	15 (20)	30 (40)
ICU trial	24 (24)	6 (25)	8 (33)	17 (71)
ICU admission reason				
Febrile neutropenia or neutropenic infections	10 (10)	3 (30)	4 (40)	6 (60)
Other postchemotherapy admission	7 (7)	1 (14)	2 (29)	6 (86)
Postoperative admission	44 (44)	2 (5)	3 (7)	12 (27)
Other ICU admission	39 (39)	10 (26)	14 (36)	23 (59)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICU, intensive care unit; NA, not applicable.

TABLE 3. Outcomes Data

Outcome	All Patients	Oncologic Patients	Nononcologic Patients	P (oncologic v nononcologic patients)
Mean length of IMV, days (SD)	4 (5)	5 (5)	4 (4)	.260
Mean ICU LOS, days (SD)	8 (10)	6 (8)	9 (11)	.009
ICU mortality, %	15	16	14	.375
Mortality at 28 days, %	22	23	21	.345
Mortality at end of follow-up, %	31	48	24	< .001
Median long-term follow-up, days (IQR)	148 (42-363)	135 (36-277)	171 (47-406)	.004

Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

No statistic difference in terms of mortality was observed between OPs and nononcologic patients at day 28 or at the end of the follow-up period (Figs 1A and 1B). Mortality rate according to stratification by ECOG performance status demonstrated that patients with an ECOG performance status of 2 or 3 had a significantly higher risk of death at day 28 and at the end of the follow-up period (Figs 2A and 2B). The ICU admission criteria were not associated with differences in overall survival (Figs 2C and 2D).

DISCUSSION

Cancer is an important worldwide health problem, and as described in the literature, patients with cancer constitute a significant portion of patients admitted to ICUs around the world.¹⁶ In this prospective cohort of patients who required IMV, interesting data were observed. Thirty percent of patients who required IMV had an oncologic diagnosis, and 90% of these OPs had a solid tumor. In terms of severity score (APACHE II), no difference was observed between OPs and nononcologic patients. Adjusted survival rates at 28 days and at the end of the follow-up period were not statistically different between OPs and nononcologic patients. A factor predicting adverse outcomes in OPs observed in our study was poor ECOG performance status. However, interestingly, 45% of patients with an ECOG performance status of 2 or 3 were alive at the end of the follow-up period. The policy of ICU admission (ICU trial v full code) was not associated with a difference in probability of survival.

In this prospective cohort, OPs composed 24% of overall ICU admissions, which is similar to previously reported data.¹⁹ Of the total cohort of patients supported with IMV, 30% were OPs. The proportion of OPs with solid tumors was 90% (v 10% with hematologic malignancies), similar to the proportion observed by Soares et al¹⁹ in a Brazilian retrospective cohort of patients with cancer admitted to 70 Brazilian ICUs. In addition, the significant increase in risk of death observed in OPs with an ECOG performance status of 2 or 3 in this study is in agreement with data previously reported in a large retrospective cohort,²⁰ suggesting a strong association between poor ECOG performance status and low survival. However, our data differ from data previously reported from Chile. In fact, in the study by

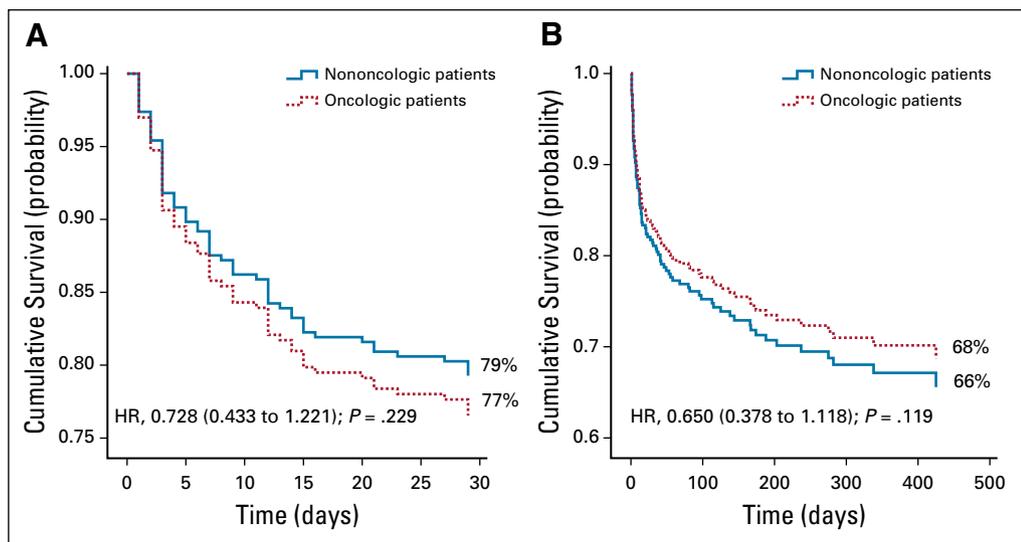


FIG 1. (A) Survival at day 28 between oncologic and nononcologic patients adjusted by Acute Physiology and Chronic Health Evaluation II (APACHE II) score. (B) Survival at end of follow-up between oncologic and nononcologic patients adjusted by APACHE II score and Charlson comorbidity index.

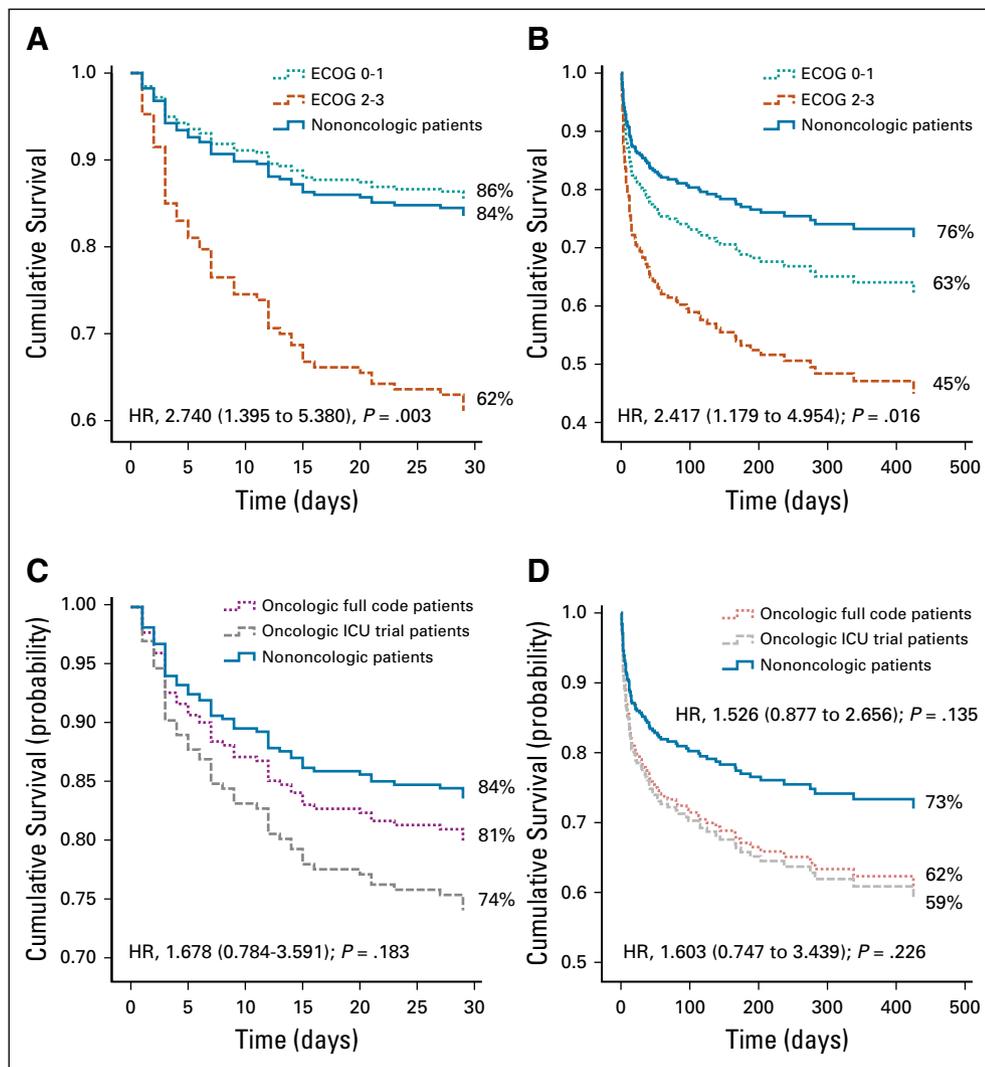


FIG 2. (A) Survival at day 28 in nononcologic patients and oncologic patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or an ECOG performance status of 2 or 3, adjusted by Acute Physiology and Chronic Health Evaluation II (APACHE II) score. (B) Survival at the end of follow-up in nononcologic patients and oncologic patients with an ECOG performance status of 0 or 1 or an ECOG performance status of 2 or 3, adjusted by APACHE II score and Charlson comorbidity index. (C) Survival at day 28 between nononcologic patients and oncologic patients on intensive care unit (ICU) trial and oncologic patients on full code, adjusted by APACHE II score. (D) Survival at end of follow-up between nononcologic patients and oncologic patients on ICU trial and oncologic patients on full code, adjusted by APACHE II score and Charlson comorbidity index. Hazard ratios were calculated with respect to the group with better survival.

Panay et al,²¹ hematologic malignancies were over-represented, and 62% of the overall cohort was supported by IMV. Therefore, these Chilean studies are not comparable, but may be complementary.

Limitations of our study include that it was conducted in a single academic center and that a relatively low number of OPs were evaluated. In addition, particular risk groupings, such as neutropenic infections, could not be performed in our cohort of patients.

Quality of life and functionality of patients are variables that should also be considered in future studies because they

have been recognized as relevant outcomes in OPs and critical care patients.²² The characteristics of OPs and nononcologic patients differed; however, our data are from patients supported with IMV in the real-world setting. Among the strengths of our study is the prospective design and the successful enrollment of all patients considered for this study. Multidisciplinary evaluation of ICU patients with participation of different specialists in daily rounds could lead to reduced delay in initiation of specific therapy, which could result in improved mortality rates. In our study, survival analysis allowed a specific mortality characterization according to severity scores. Survival comparison

between different ECOG performance status groups in OPs and nononcologic patients could be used as an approach to identify OPs who would benefit from ICU support. Challenges to consider in the near future are adding quality-of-life indicators and considering toxicities and adverse effects of targeted cancer therapy that require intensive care support.²²

In conclusion, our data suggest that in OPs the short-term survival is determined by the severity of the critical illness and that long-term survival is lower in OPs

compared with nononcologic patients only if poor performance status is documented. In patients with cancer admitted under ICU trial criteria and supported with IMV, a long-term survival rate of almost 60% was observed. Similar to previous studies,^{19,23} our study emphasizes that ICU admission should not be determined only on the basis of whether a patient has a neoplastic disease and that different variables should be considered from patient to patient.

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Manuscript writing: All authors

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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Travel, Accommodations, Expenses: Roche, MSD Oncology

No other potential conflicts of interest were reported.

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