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The outcome of cancer patients with acute respiratory distress syndrome

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ABSTRACT

Objective: The objective of the study is to determine the 28-day mortality of critically ill cancer patients with acute respiratory distress syndrome (ARDS).
Design: This is a retrospective cohort study of patients enrolled in the ARDS Network randomized controlled trials.
Results: A total of 2515 patients did not have cancer, and 116 patients had cancer. Patients with cancer were older (median, 61 vs 49 years; $P < .0001$), more critically ill (the median Acute Physiology and Chronic Health Evaluation III score without cancer comorbidity was 105 for the cancer group compared with 87 for those without cancer; $P < 0.0001$), and more likely to have pneumonia or sepsis as cause of acute lung injury (79.31% vs 62.70%; $P = .0011$). The overall mortality at day 28 was 25.7%. Patients with cancer had significantly higher mortality (55.2%) compared with those without cancer (24.3%) ($P < .0001$). The odds ratio for mortality from ARDS at 28 days for cancer patients was 2.54 (95% confidence interval [CI], 1.570-4.120). Acute Physiology and Chronic Health Evaluation III score and age were found to be significant predictors of outcome in cancer patients with odds ratio of 1.034 (95% CI, 1.007-1.062; $P = .0135$) and 1.075 (95% CI, 1.024-1.129, $P = .0036$), respectively.
Conclusions: Cancer patients with ARDS have a significantly higher risk of death compared with those without cancer. The increased risk appeared to be mediated by increased severity of illness at presentation, as well as by age.

1. Introduction

Over the past 2 decades, there have been significant advances in the management and outcome of critically ill cancer patients. Some studies suggest that mortality rates for critically ill cancer patients without comorbidities are not higher than critically ill patients with other comorbidities, such as congestive heart failure, liver cirrhosis, and other chronic illnesses [1]. Furthermore, cancer patients with acute respiratory failure requiring mechanical ventilation have better outcomes than previously reported [2-4]. These observations coincide with improved outcomes of patients with acute lung injury in general. A recent meta-analysis reviewing 72 published studies of acute lung injury (ALI) and acute respiratory distress syndrome between 1994 and 2005 found that there has been a reduction in mortality over time [5]. In a European study that analyzed all patients who had acute respiratory distress syndrome (ARDS) from 1988 to 2010, the overall hospital mortality was 37%. The mortality decreased by 1% per year during the study period, from 50% in 1988 to 1992 to 33% in 2006 to 2010 [6].

The ARDS Network conducted randomized controlled trials that enrolled patients with ALI to study several potential therapies. The large database includes cancer patients with ALI. The primary objective of our analysis is to determine the 28-day mortality of cancer patients enrolled in the ARDS Network randomized controlled trials.

2. Methods

The ARDS Network has conducted several randomized controlled trials to evaluate therapeutic interventions for the management of ALI. These trials have been previously published [7-11]. Table 1 summarizes the relevant features of these trials. Briefly, all patients fulfilled diagnostic criteria for ALI and were mechanically ventilated. Similar inclusion and exclusion criteria were used in all of the trials. The National Institute of Health and the local institutional review boards of each of the sites approved all studies.

We had authorized access to the original data for each of these studies to study the outcome of cancer patients with ARDS and compare them to those without cancer. This manuscript was prepared using KARMA, LASRS, LARMA, ALVEOLI, and FACTT research materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. The findings of this study do not necessarily reflect the opinions or views of the KARMA, LASRS,

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LARMA, ALVEOLI, and FACTT investigators or the NHLBI. Demographic and clinical data were collected and included age, sex, race, and body mass index. Baseline measurements immediately before randomization were also collected including Acute Physiology and Chronic Health Evaluation (APACHE) III score; vasopressor use; hemodynamic, respiratory, and ventilator parameters. We also obtained data on whether the patients had underlying cancer as reported by the original studies (hematologic malignancy—lymphoma or leukemia—and metastatic solid cancer). There were no further data available on type of underlying malignancy, treatment, or disease status.

3. Statistical analysis

We assessed the independent prognostic role of cancer comorbidity in this analysis. The primary end point for this analysis is the 28-day mortality. Patients who were discharged home and breathing without mechanical ventilation were assumed to be alive at day 28. The secondary end points are 60-day mortality, overall survival defined, and time from enrollment to death due to any reason.

Patient baseline characteristics across 5 studies were reported descriptively. The cancer and noncancer patients groups were compared using a χ^2 test for categorical variables and an analysis of variance (ANOVA). If the large sample assumption or normality does not hold, the Fisher exact test for categorical and the Kruskal-Wallis test for continuous variables were used. The APACHE III was calculated with or without cancer comorbidity.

Multivariable logistic regression was used as primary analysis to evaluate the potential independent prognostic role of cancer comorbidity. The model was adjusted for baseline covariates including APACHE III (without cancer), age, sex, ethnic (white, black, and other), body mass index (BMI), vasopressor use, tidal volume, plateau pressure, cause of lung injury (aspiration/trauma, pneumonia/sepsis, and multiple transfusions/others), positive end-expiratory pressure (PEEP), lung injury score, and study ID. The inclusion of these covariates was based on literature [12]. We also considered possible variation by the trial/study in which the patient was enrolled. Proportional hazard model was used for the time to event end point.

Subgroup analysis was carried out among the cancer patients only. The multivariable logistic regression for 28- and 60-day mortality and Cox model for overall survival were performed on the baseline patients characteristics APACHE III (without cancer comorbidity), age, sex, ethnicity (white, black, and other), BMI, vasopressor use, tidal volume, plateau pressure, cause of lung injury (aspiration/trauma, pneumonia/sepsis, and multitransfusions/others), PEEP, lung injury score, and study ID. The adjusted odds ratio (OR) was also evaluated with the same set of covariates and the stepwise variable selection process. The Kaplan-Meier analysis was used for plot and estimating median overall survival. Log-rank test was used for evaluating the difference of overall survival between cancer and noncancer patients.

Because of more than 10% missing values in our set of covariates, all the multivariable analyses were carried out in 2 parallel sets: one only with subjects that have complete data; the other with imputed missing values. The method of multiple imputations is the fully conditional specification method [13,14] that assumes the existence of a joint distribution for all variables, implemented in SAS PROC MI. The multiple imputation method was originally proposed by Rubin and Donald [15], and estimated SE is given by the formula of Rubin and Donald [16]. All P values are 2 sided with a significance level of .05. All calculations were performed with SAS 9.3 (Cary, NC, USA).

4. Results

A total of 2631 patients with ARDS were included in the cohort. A total of 2515 patients did not have cancer, and 116 patients had cancer. Of these, 78 had hematological malignancy—49 had leukemia and 29 had lymphoma—and 42 had metastatic solid cancer. Four patients had more than 1 malignancy. Table 2 provides the baseline characteristics of cancer patients compared with those without cancer. Patients with cancer were significantly older than patients without cancer (median, 61 vs 49 years, respectively; $P < .0001$). There were also significant differences in the etiology of ALI between patients with cancer and those without cancer. The former group was more likely to have pneumonia or sepsis as the cause of ALI (79.31% vs 62.70%; $P = .0011$). Patients with cancer were more critically ill at the time of enrollment in the studies. The median APACHE III score—without including cancer in the comorbidities—was the primary acuity score and was 105 for the cancer group compared with 87 for those without cancer; $P < .0001$. The median APACHE III score including cancer diagnosis showed similar trend (110 for the cancer patients compared with 87 for the noncancer group; $P < .0001$). In addition, patients in the former group were more likely to be on vasopressors upon enrollment in the studies. There were no differences in the baseline ventilator parameters between the 2 groups.

The overall mortality at day 28 for study participants was 25.7%. Patients with cancer had significantly higher mortality (55.2%) compared with those without cancer (24.3%) ($P < .0001$) (Table 3). There was no difference in 28-day mortality rate between patients with hematologic malignancy and those with metastatic solid cancer (55% [95% confidence interval [CI], 43%-65%) vs 55% [95% CI 40%-69%]). The overall 60-day mortality was also significantly higher for cancer patients compared with those without cancer (60.3% vs 27.9%, respectively; $P < .0001$). The OR for mortality from ARDS at 28 days for cancer patients was 2.54. Fig. 1 shows the Kaplan-Meier plot showing the cumulative proportion survival for patients by the presence and absence of cancer. The median overall survival for cancer patients was 18.3 days (95% CI, 14.3-25.3) compared with 145.6 days (95% CI, 103.6 to not available) for noncancer patients; $P < .0001$.

Table 1
Summary of the ARDS Network trials used for this analysis

	KARMA	LASRS	LARMA	ALVEOLI	FACTT
Years	1996-1998	1997-2003	1998-1999	1999-2002	2000-2005
No. of patients	667	180	235	550	1000
No. of cancer patients	30	3	14	20	49
Intervention	Low tidal volume ventilation/ketoconazole use in ARDS	Use of steroids in ARDS	Low tidal volume ventilation/lisofylline use early in ALI/ARDS	High PEEP/low F_{IO_2} vs low PEEP/high F_{IO_2} ventilation strategy	PA catheter vs central venous catheter, conservative vs liberal fluid strategy in management of patient's with ALI/ARD
Outcome	No effect of ketoconazole on mortality. Improved mortality with low tidal volume ventilation	No change in mortality	No effect of lisofyllline on mortality. Improved mortality with low tidal volume ventilation	No change in mortality	No change in mortality

KARMA and LARMA indicate Ketoconazole/Lisofylline and Respiratory Management in Acute Lung Injury/Acute Respiratory Distress Syndrome; LASRS, Late Steroid Rescue Study; ALVEOLI, Assessment of Low tidal Volume and increased End- expiratory volume to Obviate Lung Injury; FACTT, Fluid and Catheter Treatment Trials.