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# Outcomes and prognostic factors of patients with lung cancer and pneumonia-induced respiratory failure in a medical intensive care unit: A single-center study ☆

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ABSTRACT

*Purpose:* To evaluate the outcomes and prognostic factors of 28-day mortality following medical intensive care unit (MICU) admission of patients with lung cancer and pneumonia-induced respiratory failure.
*Materials and methods:* Patients admitted to the MICU of a tertiary referral hospital between 2000 and 2009 were retrospectively studied.
*Results:* In total, 143 patients were included. Their mean age was 65 ± 8 years and 94% were male. The 28-day mortality rate was 57%. Multivariate analysis was performed to identify variables associated with 28-day mortality. At 72 hours after admission, a history of radiotherapy (OR = 2.80, 95% CI: 1.15-6.78), $Pao_2/Fio_2$ (P/F) ratio at admission of <100 mmHg (OR = 5.62, 95% CI: 2.10-15.07), P/F ratio after 72 hours of <100 mmHg (OR = 4.61, 95% CI: 1.24-17.15), and arterial pH after 72 hours of <7.30 (OR = 5.78, 95% CI: 1.15-28.89) were associated with increased mortality.
*Conclusions:* The prognosis of patients with lung cancer and severe pneumonia after 72 hours of MICU management mainly depends on the severity of the underlying lung injury, which is reflected by a history of radiotherapy and a low P/F ratio, rather than on cancer stage or disease status.



## 1. Introduction

It is often difficult to determine when patients with lung cancer should be admitted to a medical intensive care unit (MICU) and how intensive their treatment should be. Although the mortality of such patients that are admitted to MICUs has gradually decreased in recent years, their in-hospital mortality remains high, especially if they require mechanical ventilation (MV) [1]. This has led to controversy because it has been suggested that intensive care is not just futile for these patients, but also causes them to suffer unnecessarily. The most common reason underlying MICU admission and MV for lung cancer patients is acute respiratory failure owing to pneumonia [2–7].

To determine whether these patients would benefit from MICU support, factors associated with high patient mortality before and immediately after intensive care need to be identified. Many reports have identified predictors of the outcomes of lung cancer patients who are admitted to MICUs [2–6,8,9]. However, although pneumonia is a leading cause of respiratory failure in lung cancer patients, the prognostic factors of patients who have pneumonia-induced respiratory failure as well as lung cancer remain poorly understood. The aim of this study was to evaluate the outcomes and prognostic factors of 28-day mortality of critically ill patients with lung cancer and pneumonia-induced respiratory failure who are admitted to MICUs.

## 2. Materials and methods

### 2.1. Study design

This retrospective study was conducted at Asan Medical Center, Seoul, Korea, a tertiary referral center. The 28-bed medical MICU is run as a closed unit by 4 full-time intensivists with 3 intensive care unit fellows, 7 medical residents, and 4 interns. Patients with cancer are generally admitted to the MICU if they were under chemotherapy or have other potentially lifespan-extending treatment plan. The data were collected by reviewing the medical records and the thoracic radiographic images of the patients. The Asan Medical Center Institutional Review Board approved this study (study number 2012-0198) and waived the need for informed consent. This study had no impact on patient treatment.

☆ Conflict of interest statement: None declared.

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### 2.2. Study subject

Patients were eligible if they had been admitted to the MICU between January 1, 2000, and December 31, 2009, and if they met all of the following criteria: (i) the patient had been newly diagnosed with pathologically confirmed primary lung cancer, or there was evidence of recurred lung cancer, 5 years before MICU admission; (ii) a new or progressive radiographic infiltrate was present together with at least 2 of 3 clinical features, namely, fever higher than 38°C, leukocytosis or leukopenia, and purulent secretions, or one of these 3 clinical features plus the proven presence of a pathogen; and (iii) the patient had respiratory failure, which was defined as a $Pao_2/Fio_2$ (P/F) ratio of less than 300 mmHg, or the need for MV to help with breathing. Patients who were admitted to the MICU for postoperative pneumonia, who stayed in the MICU for less than 24 hours, or who were transferred from other hospitals with endotracheal intubation or tracheostomy were excluded. With regard to those patients who were admitted to the MICU more than once during the same hospitalization, only data from their first admission were analyzed.

### 2.3. Data collection

The following demographic data were collected: age, gender, smoking history, pulmonary function test results, underlying lung disease, chronic underlying disease, the time interval between cancer diagnosis and MICU admission, cancer type, cancer stage (TNM classification) [10], resection of the lung cancer, cancer status, Eastern Cooperative Oncology Group performance status (ECOG-PS) [11], previous radiotherapy of the lung, chemotherapy within 30 days before MICU admission, and previous steroid use. The MICU admission route and the type of pneumonia were recorded. Laboratory data, presence of neutropenia, and physiological data such as vital signs, mental status, arterial pH, P/F ratio, and alveolar-arterial oxygen tension gradient ($AaDO_2$) at both MICU admission and 72 hours after admission were recorded. The poorest value for each variable was used in the analysis. Severity scores, including the Acute Physiology And Chronic Health Evaluation II (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) score, and the Clinical Pulmonary Infection Score (CPIS), were obtained within the first 24 hours after MICU admission and at the 72-hour follow-up. Organ failure during the initial 72 hours after MICU admission as well as the need for MV, vasopressors, or inotropes during the first 24 hours after MICU admission and at the 72-hour follow-up were recorded. The positivity of pathogen culture, the empirical use of susceptible antibiotics, and when empirical antibiotics were started were also recorded. The do-not-resuscitate (DNR) status records of the patients were also reviewed.

### 2.4. Definitions

The presence of pneumonia was defined as a new or progressive radiographic infiltrate with clinical evidence that it was of an infectious origin, as described above [12,13]. For the "MICU admission variables", the poorest values between 12 hours before and after MICU admission were used. For the "72-hour follow-up variables", the poorest values between 12 hours before and after the 72-hour follow-up were used. The pneumonia was classified according to the criteria that were established by the American Thoracic Society in 2007 [12,13]. Pulmonary function test values were determined close to when patients were admitted to the MICU. Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung disease, or post-pneumonectomy state. Chronic co-morbidities included diabetes mellitus, coronary artery disease, chronic liver disease, chronic kidney disease, neoplastic diseases apart from lung cancer but including hematological malignancy, cerebrovascular accident, neuromuscular disease, and chronic alcoholism. Organ failure was defined as outlined below [4]. Cardiovascular failure was defined as the presence of congestive heart failure; ventricular tachycardia, or fibrillation; or the need for intravenous dobutamine, norepinephrine, vasopressin, or epinephrine, or more than 5 $\mu g\ kg^{-1}\ min^{-1}$ dopamine for more than 4 hours. Renal failure was defined as a creatinine level higher than 3.4 mg/dL or the need for hemodialysis. Neurological failure was defined as a score of 6 or less on the Glasgow Coma Scale, a confused or decreased response state if the Glasgow Coma Scale was not measured, or an unconscious state when sedatives had not been administered. Hepatic failure was defined as a bilirubin level higher than 4 mg/dL. Sepsis, severe sepsis, and septic shock were defined in accordance with the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [14]. The primary outcome was 28-day mortality.

### 2.5. Statistical analysis

Continuous variables are reported as medians (25%-75% interquartile range [IQR]) or means (±SD), and categorical variables are reported as numbers (percentages). SPSS version 18.0 program (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Univariate analysis was performed with each variable using binary logistic regression. Multivariate analysis was performed with a backward, stepwise, logistic regression model. Variables that yielded $P$ values of $<0.1$ in univariate analyses were included in the multivariate analysis, along with clinically and historically important variables such as age, sex, and performance status. Survival curves were obtained using the Kaplan-Meier method with the log-rank test. With 2-tailed tests, $P < .05$ indicated statistical significance.

## 3. Results

### 3.1. Patient characteristics

In total, 143 patients who fulfilled the inclusion criteria were admitted to the MICU during the study period. Tables 1, E1, and E2 show the baseline and clinical characteristics of these patients at different time points. Most of the patients had non-small cell lung cancer (NSCLC). Of these, 24 (19%) had stage I, 12 (9%) had stage II, 25 (20%) had stage IIIA, 34 (27%) had stage IIIB, and 32 (25%) had stage IV disease. In the remaining patients, who had small cell lung cancer (SCLC), 4 (25%) had limited disease and 12 (75%) had extensive disease. We categorized the NSCLC patients into stage I-IIIA and stage IIIB-IV. This categorization was based on the operability of the patient following the initial evaluation of the lung cancer, in other words, the preoperative stage. We also investigated the postoperative stages of these patients. Most patients of stage I-IIIA (49/61 patients) underwent operations according to their preoperative stages. Their postoperative stages were consistent with their preoperative stages, with the exception of 2 patients. We also categorized the stage IIIB-IV of NSCLC and the extensive disease of SCLC as advanced stage. In 127 (89%) patients, the performance status was generally favorable (ECOG-PS 0-2). With regard to anticancer treatment, 80 patients (56%) had a history of radiotherapy of the lung and 57 patients (40%) had received chemotherapy within 30 days before MICU admission. Only 35 (24%) patients had a controlled cancer status. With regard to a history of radiotherapy of the lung, the median duration between irradiation and MICU admission was 6 months (IQR: 2-15). The mean total irradiation dose and median divided irradiation dose were 5270 and 200 cGy (IQR: 180-220), respectively.

With regard to the clinical characteristics of the patients at MICU admission, healthcare-associated pneumonia was the most common type of pneumonia (76%). The P/F ratio was 125 ± 56 mmHg, and 142 patients (99%) had a P/F ratio of less than 300 mmHg. MV was required in 133 patients (93%). APACHE II sand SOFA scores were 20 ±