The prognostic factors of in-hospital death among patients with pneumonic COPD acute exacerbation

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Abstract

Purpose: Pneumonic acute exacerbation of chronic obstructive pulmonary disease (COPD-AE) is associated with worse outcomes compared with non-pneumonic COPD-AE. Currently, only one study has been evaluated the prognostic factors of pneumonic COPD-AE; the study is limited by sample size, and ignoring heterogeneity of the treatment strategy. Thus, we aimed to include more patients and explore the more focused prognostic factors of patients with pneumonic COPD-AE who were treated with systemic steroids.

Patients and methods: This multicentered retrospective cohort study was conducted across five acute hospitals in Japan. Hospitalized patients ≥ 40 years of age with pneumonic COPD-AE who were administered systemic corticosteroids during hospitalization were included. Patients with other causes of respiratory failure (heart failure, pneumothorax, asthma exacerbation, and obstructive pneumonia), daily systemic steroids users, and patients who were not treated with systemic steroids were excluded. The following potential prognostic factors were selected in advance based on the existing clinical prediction models: age (> 70 years), eosinophilic count ($\geq 0.05 \times 10^9 /L$), blood urea nitrogen (> 7 mmol/L), respiratory rate ($\geq 30/\text{min}$), diastolic blood pressure (≤ 60 mmHg), and altered mental status. Multivariate logistic regression was conducted to determine whether the potential prognostic factors were associated with in-hospital death.

Results: After excluding 897 patients based on the exclusion criteria, 669 patients with pneumonic COPD-AE who were administered systemic corticosteroids were included. The in-hospital mortality rate was 5.1 %; the median age was 78.0; 15 patients were intubated; and the median length of hospital was 12 days. Altered mental status was associated with mortality (odds ratio, 4.47; 95% confidence intervals, 2.00 to 10.00]) and a high eosinophil count was associated with a lower risk of mortality (odds ratio, 0.19; 95% confidence intervals: 0.06 to 0.56).

Conclusion: Altered mental status may be the prognostic factor of in-hospital death among patients with pneumonic COPD-AE who are receive systemic corticosteroids. Moreover, high eosinophilia may be a prognostic factor for lower in-hospital mortality in hospital among these patients.

Introduction

Chronic obstructive pulmonary disease (COPD) and pneumonia are leading causes of death worldwide.¹⁻³ Acute exacerbation of COPD (COPD-AE) is the major cause of impaired health status in patients with stable COPD, and COPD-AE is also the major cause of death. Prognostic factors of mortality have been evaluated for pneumonia^{4,5} and COPD-AE⁶⁻¹⁰; research shows that vital signs and laboratory results are potential prognostic factors.

Although these prognostic factors have been used in daily practice to predict prognosis, they have only been investigated in either pneumonia alone or COPD-AE alone. Sixteen percent of patients with COPD-AE were found to have pneumonia, and pneumonic COPD-AE was found to be associated with in-hospital

mortality.^{11,12} Moreover, pneumonic COPD-AE was associated with increased health care costs,¹³ length of hospital stay, and intensive care unit admission.¹² Therefore, it is important to investigate the prognostic factors in patients with pneumonic COPD-AE. To the best of our knowledge, only one study has described the prognostic factors in patients with pneumonic COPD-AE. Specifically, the single-centered prospective cohort study found that readmission within 30 days, serum hemoglobin concentration, and albumin level were associated with 180-days mortality.¹⁴ However, this study was limited by its small sample size and oversimplified study design, which ignored heterogeneity in the treatment strategy (differenced in treatment patterns, which types of drugs were administered [steroids, antibiotics], and steroid dose). Therefore, we conducted this multicenter retrospective cohort study to evaluate patients with pneumonic COPD-AE all of whom received the same treatment — systemic corticosteroids which are a recommended treatment according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for COPD.¹⁵

Material And Methods

Study design and ethical approval

This multicentered retrospective cohort study was conducted designed across five acute general hospitals in Japan including Kameda Medical Center, Hyogo Prefectural Amagasaki General Medical Center, Kobe City Medical Center General Hospital, Saiseikai Yokohamashi Tobu Hospital, and Ichinomiyaniishi Hospital. The study protocol was approved by the Institutional Review Board of Kobe City Medical Center General Hospital (approval number: 200811). The requirement for Informed consent was waived by the Institutional Review Board of Kobe City Medical Center General Hospital because of the retrospective nature of the study. We followed the STROBE statement (Supplemental Table 1) in reporting this study.¹⁶

Study participants

Patients from each hospital were enrolled from different time periods of April 1, 2008 and July 31, 2020 because the hospitals had different storage terms for their electronic medical records. The inclusion criteria were as follows: (1) hospitalized patients with pneumonic COPD-AE who were aged ≥ 40 years of age (2) patients who were administered systemic corticosteroids during hospitalization regardless of the dose and timing. To select the patients with pneumonic COPD-AE, we used a validated selection algorithm based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) in another study.¹⁷ Specifically, we used the following criteria: (1) the admission precipitating the diagnosis of pneumonia (ICD-10 codes: J12, J13, J14, J15, J16, J18, J69, and P23) with comorbidity of COPD or COPD-AE (ICD-10 codes: J44.1 and J44.9) and (2) the admission precipitating diagnosis of COPD exacerbation (ICD-10 code; J44.1) with comorbidity of pneumonia (ICD-10 codes: J12, J13, J14, J15, J18, J69, and P23). We excluded the following other causes of respiratory

failure: heart failure (ICD-10 code: I50), pneumothorax (ICD-10 code: J93), asthma exacerbation (ICD-10 code: J45), obstructive pneumonia (ICD-10 code: J188). In addition, we excluded patients who required daily systemic steroid use as well as patients who were not administered systemic steroids during the hospitalization.

Exposures and outcome

We selected the potential prognostic factors and the cut-off points in advance; these included age (> 70 years), eosinophilic count ($\geq 0.05 \times 10^9 /L$), blood urea nitrogen (> 7 mmol/L), respiratory rate ($\geq 30/\text{min}$), systolic blood pressure (< 60 mmHg), and altered mental status. These variables were extracted from the electronic medical records. In-hospital death. Was the primary outcome of the study.

Statistical analysis

Participants' baseline characteristics are summarized as proportions for categorical variables and as means and standard deviations for continuous variables. For the main analysis, multiple imputation and multivariate logistic regression analysis were conducted. To impute missing values, we used multiple imputation by chained equations under missing at random assumption creating 100 multiply imputed datasets.¹⁸ Multivariate logistic regression was conducted as the outcome analysis within each imputed dataset; next, we combined the estimates using Rubin's rules.¹⁹ As a sensitivity analysis, we conducted multivariate logistic regression among patients without missing data under the missing completely at random assumption. In addition, as explanatory analyses, we estimated the univariate associations of the following explanatory variables: blood urea nitrogen, eosinophil count, respiratory rate, age, systolic blood pressure, and mortality using a logistic regression model. All analyses were conducted using a statistical software package (R version 4.0.0), including packages: "mice" (version 3.8.0) for multiple imputation, and "mitools" (version 2.4) for combining the results.

Results

Participant characteristics

In total, 1566 hospitalized patients with pneumonic COPD exacerbation were selected based on the ICD-10 algorithm (Figure 1). After excluding 897 patients based on the exclusion criteria, we included 669 patients with pneumonic COPD-AE who were administered systemic corticosteroids. The patient characteristics are summarized in Table 1. Among 669 patients, 34 patients (5.1%) died during the hospitalization and 15 patients (2.2%) were intubated. The median length of hospital stay was 12 days (interquartile range, 8.0–18.0 days).

Statistical analyses results

Multiple imputation and multivariate logistic regression analyses revealed that altered mental status was associated with higher mortality and that a higher eosinophil count was associated with lower mortality in patients with pneumonic COPD-AE. The odds ratio for altered mental status was 4.47 (95% confidence interval: 2.00 to 10.00) and the odds ratio for the eosinophil count was 0.19 (95% confidence interval: 0.06 to 0.56). These statistically significant results were consistent with those of the complete case analysis (Table 2). The univariate logistic regression (conducted among patients without missing data) showed that only altered mental status was associated with in-hospital death (4.51; 95% confidence interval: 2.12 to 9.30; Table 3).

Discussion

This multicentered retrospective study showed that (1) altered mental status was associated with higher mortality of patients hospitalized for pneumonic COPD-AE and (2) high eosinophilia was associated with a lower risk of mortality in these patients. This information allows for stratification of patients according to risk of hospital mortality, and may contribute to physicians' decision-making in daily practice.

This study has some remarkable strengths. First, the prognostic factors focused on the specific population of patients with pneumonic COPD-AE who were administered systemic corticosteroids. Systemic corticosteroids could be a standard therapy for pneumonic COPD-AE based on the guideline statement of COPD-AE alone.¹⁵ However, in this study, approximately half of the selected COPD-AE patients did not receive systemic corticosteroid treatment. Although we could not elucidate the treatment effect of systemic corticosteroids in patients with pneumonic COPD-AE, we focused on the population concordance with the guideline. Moreover, this study presents clinically meaningful prognostic factors in the setting of administering systemic corticosteroid among patients with pneumonic COPD-AE. Second, more patients were included in this study compared to the previous study. Here, we recruited patients from five acute general hospitals and imputed missing values to avoid losing information. Thus, the prognostic factors may have been elucidated more precisely. Third, the prognostic factors included in our study are easily accessible; they were routinely available from medical examinations and invasive testing and expensive data collection were not required.

Altered mental status was found to be associated with the mortality in patients with pneumonic COPD-AE. This result is consistent with the previous studies which evaluated prognostic factors of either pneumonia alone or COPD-AE alone. The validated clinical prediction rules of community-acquired pneumonia (CURB-65 and BAP-65) contain altered mental status.²⁰ Those prognostic scores for pneumonia were applied to the mortality of patients with COPD-AE.^{7,9} Previous studies which included hospitalized patients with COPD-AE alone showed that altered mental status was associated with mortality.^{6,21} Thus, it is unsurprising that our study revealed that altered mental status was associated with mortality in patients with pneumonic COPD-AE.

In addition, we found that high eosinophilia was associated with a lower risk of mortality in patients with pneumonic COPD-AE. The main analysis showed that high eosinophilia was associated with a lower risk

of mortality in patients with pneumonic COPD-AE, although the sensitivity analysis did not show a statistically significant difference. However, eosinophilic COPD-AE was found to be sensitive to systemic corticosteroids from both in-vitro and in-vivo studies.^{22,23} Considering the mechanism of systemic corticosteroid treatment for eosinophils, it is plausible that high eosinophilia in patients with pneumonic COPD-AE is associated with a low risk of in-hospital death.

This study has several limitations. First, due to the observational nature of the study, it is possible that we missed other potential prognostic factors such as pulmonary function test results.²⁴ A previous study showed that a low forced expiratory volume in the first second was associated with a higher admission rate for acute exacerbation of COPD.²⁵ However, in daily practice, pulmonary function test results might be missing, especially from the patients' first visit.¹⁷ Our study selected easily accessible variables that physicians can use in various clinical settings. Second, in our dataset, the eosinophil count was missing in 44.7% of cases. Although we coped with this problem using multiple imputation, the assumption of missing at random may be violated because the exploratory analyses and sensitivity analysis showed inconsistent results.

Conclusion

In conclusion, we found that altered mental status was associated with in-hospital death and that high eosinophilia was associated with a lower risk of mortality. These prognostic factors can be used to detect patients with pneumonic COPD-AE who were administered systemic corticosteroid treatment who are at high risk of mortality. Moreover, these prognostic factors may be utilized for decision-making among physicians who administer systemic corticosteroids to patients with pneumonic COPD-AE.

Abbreviations

COPD: chronic obstructive pulmonary disease

COPD-AE: acute exacerbation of chronic obstructive pulmonary disease

ICD-10: International Classification of Diseases and Related Health Problems

Declarations

Disclosure

The authors declare that they have no competing interests.

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None.

Ethics Approval and Informed Consent

This project was approved by the institutional review board of each hospital, and the need for written informed consent was waived by the institutional review board of Kobe City Medical Center General Hospital (approval number, 200811)

Consent for publication

All authors agree to the publish statements.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Tables

Please see the supplementary files section to view the tables.

Figures

Figure 1

Patient flowchart

Supplementary Files

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- [GURAK3Q1Supplement.docx](#)
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