Impact of inhaled corticosteroid use on elderly chronic pulmonary disease patients with community acquired pneumonia

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To the Editor: With an aging global population, the incidences of community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) have significantly increased.[1] Previous studies have confirmed that COPD and asthma are independently associated with the prevalence of CAP. The use of inhaled corticosteroid (ICS), the cornerstone of treatment for asthma, COPD with frequent acute exacerbations, and asthma-COPD overlap (ACO) may induce changes in the local lung microbiome and abnormal lung immunity, ultimately, causing a significantly increased risk of pneumonia. However, in cases of pneumonia, the effect of the use of ICS on CAP mortality remains controversial. While data from one study favored the prior use of ICS, which was associated with a significantly lower short-term mortality rate,[2] other studies have identified no impact on mortality. To date, data on the impact of the use of ICS on mortality, prehospitalization or during hospitalization, are scarce, particularly in the older population. Therefore, this multicenter, retrospective study explored the association between the use of ICS during hospitalization and short-term mortality in older patients with CAP and those with chronic pulmonary disease (CPD).

A multicenter, retrospective study on hospitalized patients with CAP aged ≥65 years from the CAP-China network, between January 1, 2014 and December 31, 2014, was conducted (details are available in a study by Han *et al*[1]). The present study was approved by the Human Subject Protection Program Institutional Review Board of China-Japan Friendship Hospital (No. 2015-85). Additional approval was obtained from the local institutional review boards of each participating hospital. The requirement for patient consent was waived owing to the retrospective and observational study design. This study had been registed on Clinicaltrials.gov (https://register.clinicaltrials.

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CPD was defined as the presence of asthma, COPD, or ACO. ACO was characterized by persistent airflow limitation with several features typically associated with asthma and COPD. ICS exposure was defined as the use of fluticasone, budesonide, or beclomethasone alone or in combination with β-receptor agonists and/or adrenergic receptor blockers through dry powder inhalers, atomized inhalation metered-dose inhalers, or aerosol inhalation during hospitalization.

Categorical variables are presented as frequencies or percentages, and continuous variables are presented as mean ± standard deviation. The χ^2 test or Fisher's exact tests with Boferroni method was used for categorical variables, and the analysis of variance test for continuous variables with least significant difference (LSD) method for pairwise comparisons. Patients were divided into the following groups: without CPD, COPD, asthma, and ACO groups. We performed 1:1 propensity score matching (PSM) without replacement to match participants within a predefined propensity score radius (caliper width of 0.1) among patients with and without the use of ICS. The following covariates were matched: age, sex, hypertension, congestive heart failure, cerebral vascular disease, and diabetes mellitus. Variables with *P* value less than 0.10 in univariate logistic analyses were included in a multivariate logistic regression analysis model for 30-day mortality in PSM patients and all COPD patients, and a stepwise forward model was used to select independent risk factors. The 95% confidence intervals (CIs) and levels of significance are reported. The cumulative survival curve for 30-day mortality was stratified according to the use of ICS during hospitalization. All data were analyzed using SPSS (version 20, IBM Corp., New York, USA); a value of $P < 0.05$ was considered statistically significant.

A total of 2437 patients with CAP aged ≥65 years were finally enrolled in the study. Among them, 1997 (81.9%), 355 (14.6%), 64 (2.6%), and 21 (0.9%) patients were classified into the without CPD, COPD, asthma, and ACO groups, respectively. The mean age of asthmatic patients with CAP was significantly lower than that of the patients in COPD group or without CPD group ($P < 0.001$), as was the male proportion (asthma group *vs.* COPD group, $\chi^2 = 15.554$, $P < 0.001$; asthma group *vs.* without CPD group, $\chi^2 = 11.940$, $P = 0.001$). The proportion of patients using ICS during hospitalization was significantly lower in patients without CPD than in those with CPD. No significant differences were identified in the pneumonia severity index scores, clinical stability on admission, intensive care unit (ICU) admission, mechanical ventilation, treatment failure, in-hospital mortality, 30-day mortality, or length of stay among the four groups [Supplementary Table 1, http://links.lww.com/CM9/B809].

After PSM, 384 pairs of older patients [Supplementary Table 2, http://links.lww.com/CM9/B809] were included in the multivariate logistic analysis of 30-day mortality. Blood sodium level <130 mmol/L (odds ratio [OR] = 6.184; 95% CI: 1.821–20.993, $P = 0.003$), white blood cell count >10 × 10^9/L (OR = 4.975; 95% CI: 2.111–11.723, $P < 0.001$), and the CURB-65 (confusion, uremia >7 mmol/L, respiratory rate ≥30/minutes, hypotension, and aged 65 years or older) score (OR = 2.973; 95% CI: 1.754–5.041, $P < 0.001$) were independent risk factors for 30-day mortality, whereas use of ICS during hospitalization (OR = 0.408; 95% CI: 0.175–0.952, $P = 0.038$) was a protective factor [Supplementary Table 3, http://links.lww.com/CM9/B809]. The Kaplan–Meier (KM) curve demonstrated that older patients who used ICS during hospitalization in the matched cohort had significantly higher survival ($\chi^2 = 5.460$; $P = 0.019$) [Supplementary Figure 1A, http://links.lww.com/CM9/B809].

For the subgroup of patients with COPD ($n = 376$), the CURB-65 score (OR = 4.190; 95% CI: 1.684–10.427, $P = 0.002$), blood sodium level <130 mmol/L (OR = 5.779; 95% CI: 1.310–25.488, $P = 0.021$), and arterial oxygen saturation <90% (OR = 3.414; 95% CI: 1.033–11.284, $P = 0.044$) were independent risk factors for 30-day mortality, whereas use of ICS during hospitalization was not a protective factor (OR = 0.233; 95% CI: 0.048–1.119, $P = 0.069$) [Supplementary Table 4, http://links.lww.com/CM9/B809]. The KM curve indicated that use of ICS during hospitalization significantly reduced the 30-day mortality in the subgroup of patients with COPD ($\chi^2 = 5.264$; $P = 0.022$) [Supplementary Figure 1B, http://links.lww.com/CM9/B809].

This study aimed to evaluate the association between the use of ICS during hospitalization and short-term mortality in older CAP patients and those with CPD in China. We found that hyponatremia, leukocytosis, and the CURB-65 score were independent risk factors associated with 30-day mortality in matched 384 pairs of patients, whereas the use of ICS during hospitalization was a protective factor. The use of ICS during hospitalization in patients with COPD significantly decreased short-term mortality, but not independent risk factor.

A meta-analysis of the effect of COPD on mortality in patients with CAP showed no associations between the presence of COPD and in-hospital or 30-day mortality in CAP patients (OR = 0.93, 95% CI: 0.60–1.45 and OR = 1.06, 95% CI: 0.72–1.58, respectively).[3] Moreover, a prospective study on 4079 patients with CAP over a 12-year period identified no significant differences in ICU admission, mechanical ventilation, and 30-day mortality among patients with or without asthma,[4] consistent with our results. In our study, the mortality rate of patients with CAP and ACO is low.

The role of corticosteroids against the inflammatory response to infection in patients with CAP is debatable. Given the impact on clinical outcomes, patients with severe CAP may benefit from systemic corticosteroids. Some patients with CAP, even those without CPD, may experience wheezing, chest tightness, severe and frequent cough due to airway hyper-responsiveness, and airway mucus hypersecretion. Aerosol inhalation of ICS alone or that combined with β-receptor agonists and/or M-cholinergic receptor blockers may be appropriate for

such patients. In our study, approximately one-third of the patients without CPD experienced wheezing or chest tightness, and 11.2% of these patients were prescribed ICS during hospitalization; and the proportion of the use of ICS was 33.3%–37.5% in the patients with CPD. The KM curves in the current study indicate that the use of ICS during hospitalization significantly reduces 30-day mortality in the matched cohort and patients with COPD ($P = 0.019$ and 0.022, respectively). In addition, the use of ICS during hospitalization (OR = 0.408; 95% CI: 0.175–0.952, $P = 0.038$) was a protective factor in the matched cohort but not in the patients with COPD (OR = 0.233; 95% CI: 0.048–1.119, $P = 0.069$). A study analyzing the association of ICS exposure with mortality in 6353 older patients with CAP and COPD showed that prehospital use of ICS was significantly associated with lower 30-day mortality (adjusted OR = 0.76; 95% CI: 0.70–0.83), and the KM curve indicated that patients with ICS use had significantly higher survival over the first 90 days after admission.[2] Chen *et al*[5] also confirmed that the use of ICS decreased 30-day mortality in patients with CAP and COPD, generally concordant with our data.

In the present study, hyponatremia, leukocytosis, and the CURB-65 score were independent risk factors for short-term mortality in older patients with CAP, consistent with previous observations. The incidence of hyponatremia was 8%–31% in adult patients with CAP and was associated with increased mortality, more severe pulmonary inflammation with higher levels of leukocytes and C-reactive protein, more severe disease severity, more frequent ICU admission, and prolonged hospital stay. In patients with CAP and COPD, dyspnea occurred in 60.4% of cases. Data showed hypoxemia was associated with 30-day mortality in such population, consistent with the report from the Pneumonia Patient Outcomes Research Team cohort study.

The present study had several limitations. First, data regarding prehospitalization use of ICS, ICS dose, duration of treatment, and combination with long-acting β-agonists and/or M-cholinergic receptor blockers were not systematically documented. Second, the diagnoses of COPD and asthma were self-reported, and data on lung function related to CPD were lacking. Therefore, the relationship between ICS and/or bronchodilators, lung function, and mortality could not be evaluated. Third, some bias may have been introduced owing to the partial loss of laboratory data when performing the statistical analysis.

In conclusion, this study revealed that the use of ICS during hospitalization was associated with a significantly lower 30-day mortality in older patients with CAP. These findings provide new perspectives on the potential benefit of ICS use as an immunomodulatory therapy in older patients with CAP. Therefore, further multicenter prospective studies are warranted.

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Conflicts of interest

None.

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