ORIGINAL RESEARCH

Effect of outpatient therapy with inhaled corticosteroids on decreasing in-hospital mortality from pneumonia in patients with COPD

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Background and objectives: Inhaled corticosteroids (ICS) and long-acting inhaled bronchodilators (IBD) are beneficial for the management of COPD. Although ICS has been reported to increase the risk of pneumonia in patients with COPD, it remains controversial whether it influences mortality. Using a Japanese national database, we examined the association between preadmission ICS therapy and in-hospital mortality from pneumonia in patients with COPD.

Methods: We retrospectively collected data from 1,165 hospitals in Japan on patients with COPD who received outpatient inhalation therapy and were admitted with pneumonia. Patients were categorized into those who received ICS with IBD and those who received IBD alone. We performed multivariate logistic regression analysis to examine the association between outpatient ICS therapy and in-hospital mortality, adjusting for the patients' backgrounds.

Results: Of the 7,033 eligible patients, the IBD alone group (n=3,331) was more likely to be older, have lower body mass index, poorer general conditions, and more severe pneumonia than the ICS with IBD group (n=3,702). In-hospital mortality was 13.2% and 8.1% in the IBD alone and the ICS with IBD groups, respectively. After adjustment for patients' backgrounds, the ICS with IBD group had significantly lower mortality than the IBD alone group (adjusted odds ratio, 0.80; 95% confidence interval, 0.68–0.94). Higher mortality was associated with older age, being male, lower body mass index, poorer general status, and more severe pneumonia.

Conclusion: Outpatient inhaled ICS and IBD therapy was significantly associated with lower mortality from pneumonia in patients with COPD than treatment with IBD alone.

Keywords: inhaled corticosteroids, bronchodilators, in-hospital mortality, pneumonia, COPD

Introduction

COPD is the third leading cause of death in the world.[1] COPD is characterized by persistent airflow restriction, which is associated with chronic airway inflammation.[2] Mainstream treatments for COPD, as recommended by international guidelines,[3] are mainly inhaled bronchodilators (IBD), including long-acting β stimulants and long-acting muscarinic antagonists, to improve respiratory function and reduce respiratory symptoms,[4–6] and inhaled corticosteroids (ICS) to reduce the frequency of exacerbations and improve the quality of life in patients with severe COPD.[5,7,8] However, regular treatment with ICS does not modify the long-term decline of respiratory functions and mortality in COPD.[9,10] Combination therapy with ICS and IBD is recommended for patients with severe COPD symptoms and frequent exacerbations.[3]

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Recently, combination treatment with more than one long-acting IBD, consisting of long-acting β stimulants and long-acting muscarinic antagonists without ICS, has been reported to be more effective in improving respiratory function and symptoms,[11–13] and preventing exacerbations in severe COPD[14] than use of IBD alone. In addition, withdrawal of ICS from treatment with triple combination therapy, consisting of long-acting β stimulants, long-acting muscarinic antagonists, and ICS, does not change the risk of exacerbations.[15] This suggests that combined IBD treatment would be as effective in preventing exacerbations as triple combination therapy. Thus, the benefits of ICS in the treatment of COPD have been questioned, particularly because of the adverse side effect of ICS-caused pneumonia.

Lower respiratory infections, such as pneumonia, often occur in COPD and are known to cause COPD exacerbations, increasing the risk of mortality.[16,17] In addition, recent clinical studies and meta-analyses have reported that ICS use increases the occurrence of pneumonia.[18–21] Other studies have produced conflicting results regarding the rate of mortality from pneumonia in patients with COPD using ICS as outpatients.[18,22–24] Thus, it is important and useful for the management of COPD to clarify the association between ICS and mortality from pneumonia in patients with COPD.

This study aimed to examine the association between ICS and mortality from pneumonia in patients with COPD by comparing in-hospital mortality between those who received ICS with IBD and those who received IBD alone.

Methods
Database
We used the Japanese diagnosis procedure combination database, which contains administrative claims data and discharge abstract data from approximately 7,000,000 inpatients per year from around 1,100 hospitals across Japan. The database also includes the outpatient data of patients admitted to 426 hospitals. The database does not include data about those patients who only received outpatient treatment.

The inpatient database contains details of the primary diagnosis on admission, comorbidities present on admission, and complications occurring during hospitalization. These are recorded with the appropriate International Classification of Disease and Related Health Problems, 10th revision (ICD-10) codes accompanied by text in Japanese. This database also contains the following information on admission: dates of admission and discharge; intensive care unit admission during hospitalization; discharge status; the patient's age, sex, body height, and weight; severity of dyspnea based on

the Hugh-Jones dyspnea scale;[25,26] levels of consciousness based on the Japan Coma Scale;[27,28] activities of daily life on admission converted to the Barthel index;[29] and severity of pneumonia based on age, dehydration, respiratory failure, orientation disturbance, and low blood pressure (A-DROP) score.[30] Details of the Hugh-Jones dyspnea scale, the Japan Coma Scale, the Barthel index, and the A-DROP score are described in the "Supplementary materials". The database also includes data on the medication and procedures the patients received during hospitalization, for example, the administration of systemic corticosteroids and intubation/mechanical ventilation. The outpatient data contain information that includes prescription dates and the names of the drugs prescribed.

This study was approved by the Institutional Review Board of The University of Tokyo. The board waived the requirement for the patients' written informed consent because of the anonymous nature of the data.

Patient selection
Inclusion criteria for this study were as follows: 1) patients aged over 40 years, 2) those who were admitted to hospital for pneumonia (ICD-10 codes, J10–J18, J69) as the primary diagnosis between July 1, 2010 and March 31, 2013, 3) those who had a secondary diagnosis of COPD (J41–44); and 4) those who received IBD.

We excluded 1) patients who received ICS alone; 2) those who had other obstructive ventilatory impairments, including bronchiectasis (J47) and diffuse panbronchiolitis (J21); and 3) those who had pneumonia recorded as a complication during hospitalization, to preclude hospital-acquired and ventilator-associated pneumonia (J95).

Categorization by inhaled therapy
The IBD administered included tiotropium, glycopyrronium, acridinium, umeclidinium, salmeterol, formoterol, indacaterol, and vilanterol. The ICS administered included fluticasone, budesonide, mometasone, and beclomethasone. Patients who received any ICS with any IBD were defined as the ICS with IBD group. Patients who received one or more IBD but did not receive any ICS were defined as the IBD alone group.

A-DROP score
We used the A-DROP scoring system to evaluate the severity of pneumonia. This system was established by the Japanese Respiratory Society and is similar to the CURB-65 system used by the British Thoracic Society.[30] The severity of

pneumonia was classified into four classes using the A-DROP score: mild, 0 points; moderate, 1–2 points; severe, 3 points; and extremely severe, 4–5 points.

Outcomes

The primary outcome of this study was all-cause in-hospital mortality. The secondary outcomes were length of stay, length of intensive care unit stay, requirement for intubation/mechanical ventilation, duration of mechanical ventilation, and mortality in patients who underwent mechanical ventilation during their hospital stay.

Analysis

We used the chi-square test to compare proportional data, the two-sample t-test to compare average values, and the Mann–Whitney U-test to compare the median values between groups. We performed multivariate logistic regression analyses to assess the association between ICS use and in-hospital mortality with adjustment for patients' backgrounds, while also adjusting for within-hospital clustering by means of generalized estimation equations. The threshold for significance was $P<0.05$. We performed all statistical analysis using SPSS statistics for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

We identified 7,033 patients with COPD (aged ≥40 years) who were treated with outpatient inhaled therapy and were admitted to the hospital with pneumonia. Of them, 3,702 patients were treated with ICS and IBD, and 3,331 patients were treated with IBD alone. The patients' characteristics are shown in Table 1. A-DROP scores in the ICS and IBD group

Table 1 Clinical characteristics of patients on admission

	Total	ICS with IBD	IBD alone	*P*-value
	(n=7,033) (%)	(n=3,702) (%)	(n=3,331) (%)	
Age (years)[a]	76.3 (8.4)	75.7 (8.4)	77.0 (8.4)	<0.001
Sex (male)	6,315 (89.8)	3,281 (88.6)	3,034 (91.1)	0.001
BMI (kg/m²)				<0.001
<18.5	3,316 (47.1)	1,831 (49.5)	1,485 (44.6)	
18.5–24.9	2,499 (35.5)	1,247 (33.7)	1,252 (37.6)	
25.0–29.9	492 (7.0)	266 (7.2)	226 (6.8)	
≥30.0	51 (0.7)	18 (0.5)	33 (1.0)	
Missing	675 (9.6)	340 (9.2)	335 (10.1)	
Dyspnea scale by Hugh-Jones classification				<0.001
I	607 (8.6)	301 (8.1)	306 (9.2)	
II	897 (12.8)	460 (12.4)	437 (13.1)	
III	1,071 (15.2)	574 (15.5)	497 (14.9)	
IV	1,913 (27.2)	1,095 (29.6)	818 (24.6)	
V	1,754 (4.9)	922 (24.9)	832 (25.0)	
Unclassified	791 (11.2)	350 (9.5)	441 (13.2)	
Activity of daily living by Barthel index				<0.001
Completely independent	2,275 (32.3)	1,247 (33.7)	1,028 (30.9)	
Partially independent	1,064 (15.1)	604 (16.3)	460 (13.8)	
Partially dependent	1,295 (18.4)	681 (18.4)	614 (18.4)	
Completely dependent	1,163 (16.5)	534 (14.4)	629 (18.9)	
Missing	1,263 (17.6)	636 (17.2)	600 (18.0)	
Level of consciousness by Japan Coma Scale				<0.001
Clear	6,338 (90.1)	3,398 (91.8)	2,940 (88.3)	
Dull	541 (7.7)	240 (6.5)	301 (9.0)	
Somnolence	100 (1.4)	41 (1.1)	59 (1.8)	
Coma	53 (0.8)	23 (0.6)	30 (0.9)	
Pneumonia severity by A-DROP score				<0.001
Mild	416 (5.9)	222 (6.0)	194 (5.8)	
Moderate	3,349 (47.6)	1,808 (48.8)	1,541 (46.3)	
Severe	978 (13.9)	501 (13.5)	477 (14.3)	
Extremely severe	301 (4.3)	122 (3.3)	179 (5.4)	
Missing	1,989 (28.3)	1,049 (28.3)	940 (28.2)	

Notes: [a]Mean (SD). The two-sample t-test was used to compare average values between groups. The chi-square test was used to compare proportional data between groups. The threshold for significance was a value of $P<0.05$.
Abbreviations: A-DROP, age, dehydration, respiratory failure, orientation disturbance, and low blood pressure; BMI, body mass index; IBD, inhaled bronchodilators; ICS, inhaled corticosteroids; SD, standard deviation.

Table 2 Patient comorbidities on admission

	Total	ICS with IBD	IBD alone	*P*-value
	(n=7,033) (%)	(n=3,702) (%)	(n=3,331) (%)	
Asthma	1,872 (26.6)	1,379 (37.3)	493 (14.8)	<0.001
Interstitial pneumonia	323 (4.6)	125 (3.4)	198 (5.9)	<0.001
Lung cancer	719 (10.2)	261 (7.1)	458 (13.7)	<0.001
Congestive heart failure	1,223 (17.4)	597 (16.1)	626 (18.8)	0.003
Arrhythmia	331 (4.7)	157 (4.2)	174 (5.2)	0.052
Cerebrovascular disease	299 (4.3)	151 (4.1)	148 (4.4)	0.450
Chronic liver disease	86 (1.2)	38 (1.0)	4 (1.4)	0.114
Chronic renal failure	133 (1.9)	61 (1.6)	72 (2.2)	0.114

Notes: The chi-square test was used to compare proportional data between groups. The threshold for significance was a value of *P*<0.05.
Abbreviations: IBD, inhaled bronchodilators; ICS, inhaled corticosteroids.

were significantly lower, and therefore their pneumonia was less severe, than in the IBD alone group.

Comorbidities on admission are presented in Table 2. The percentage of asthma was higher in the ICS and IBD group than in the IBD alone group. The percentages of interstitial pneumonia, lung cancer, and congestive heart failure were lower in the ICS and IBD group.

The outcomes are shown in Table 3. All-cause in-hospital mortality in the ICS and IBD group was 8.1%, which was significantly lower than that in the IBD alone group (13.2%). Length of stay in the ICS and IBD group was shorter than that in the IBD alone group. The difference in the results for intensive care unit admission or requirement for mechanical ventilation was not significant between the groups. In-hospital mortality in patients who required mechanical ventilation was significantly lower in the ICS and IBD group (31.9%, n=100/313) than in the IBD alone group (39.7%, n=129/325).

The results of multivariate logistic regression analysis for all-cause in-hospital mortality associated with pneumonia in patients with COPD are shown in Table 4. Outpatient treatment with ICS and IBD was significantly associated with lower mortality than IBD treatment alone, even after adjustment for the patients' backgrounds. Higher mortality

was associated with being male, lower body mass index (BMI), severe dyspnea, poorer activities of daily living scores, and more severe pneumonia. Higher mortality was also associated with having interstitial pneumonia and lung cancer, whereas lower mortality was associated with having asthma.

Discussion

We demonstrated that in-hospital mortality associated with pneumonia in patients with COPD was significantly lower in patients treated with combined ICS and IBD therapy than IBD alone.

Previous studies have reported that the use of ICS in patients with COPD increased the occurrence of serious pneumonia requiring hospitalization.[18–21] However, the association between ICS use and mortality from pneumonia in patients with COPD has remained controversial. One study demonstrated that the use of ICS was associated with an increased risk of hospitalization for pneumonia and subsequent death.[18] Several studies have reported that the use of ICS had no impact on outcomes in patients with COPD admitted with pneumonia.[19,21,22] Other studies have demonstrated that ICS use was associated with a decreased risk of mortality, after adjusting for potential confounders, including age, sex,

Table 3 Clinical course and outcomes

	Total	ICS with IBD	IBD alone	*P*-value
	(n=7,033) (%)	(n=3,702) (%)	(n=3,331) (%)	
Death, n (%)	742 (10.6)	301 (8.1)	441 (13.2)	<0.001
Length of stay (days), median (IQR)	15 (10–25)	14 (10–23)	15 (10–26)	<0.001
Systemic corticosteroids, n (%)	20 (0.3)	12 (0.3)	8 (0.2)	0.509
ICU admission, n (%)	151 (2.1)	81 (2.2)	70 (2.1)	0.803
ICU stay (days), median (IQR)	5 (2–10)	5 (1.5–10)	4.5 (2–12)	0.577
Mechanical ventilation, n (%)	638 (9.1)	313 (8.5)	325 (9.8)	0.058
Length of MV (days), median (IQR)	8 (2–23)	7 (2–20.5)	8 (2.5–25)	0.202
Deaths among patients under MV (n=638); n (%)	229 (35.9)	100 (31.9)	129 (39.7)	0.042

Notes: The chi-square test was used to compare proportional data between groups. The Mann–Whitney U-test was used to compare the median values between groups. The threshold for significance was a value of *P*<0.05.
Abbreviations: IBD, inhaled bronchodilators; ICS, inhaled corticosteroids; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation.

Table 4 Multivariate logistic regression analysis for in-hospital mortality

	Adjusted odds ratio	95% Confidence interval		P-value
IBD alone	Reference			
ICS and IBD	0.80	0.68	0.94	0.007
Age (years)				
40–64	Reference			
65–74	1.51	1.04	2.20	0.033
75–84	1.36	0.93	1.99	0.116
>85	2.12	1.40	3.24	<0.001
Sex				
Male	Reference			
Female	0.66	0.48	0.90	0.008
BMI (kg/m²)				
<18.5	2.26	1.84	3.46	<0.001
18.5–24.9	Reference			
25–29.9	0.75	0.47	1.18	0.216
≥30	1.26	0.38	4.18	0.749
Missing	2.49	1.93	3.22	<0.001
Dyspnea classification				
I	Reference			
II	0.72	0.34	1.54	0.394
III	1.21	0.70	2.09	0.290
IV	1.86	1.08	3.20	0.026
V	4.08	2.42	6.86	<0.001
Unspecified	4.55	2.68	7.71	<0.001
Level of consciousness				
Clear	Reference			
Dull	1.29	0.98	1.70	0.073
Somnolence	2.28	1.50	3.48	<0.001
Coma	2.96	1.57	5.59	0.001
Activity of daily living				
Completely independent	Reference			
Partially independent	0.97	0.67	1.40	0.871
Partially dependent	1.55	1.12	2.14	0.009
Completely dependent	3.03	2.21	4.16	<0.001
Missing	1.44	1.03	2.01	0.033
Severity of pneumonia				
Mild	Reference			
Moderate	1.52	0.72	3.19	0.270
Severe	2.83	1.29	6.20	0.010
Very severe	7.41	3.24	16.95	<0.001
Missing	3.10	1.48	6.49	0.003
Systemic corticosteroids	0.96	0.24	3.84	0.948
Comorbidities				
Asthma	0.57	0.45	0.73	<0.001
Interstitial pneumonia	1.92	1.29	2.86	0.001
Lung cancer	3.57	2.74	4.65	<0.001
Chronic heart failure	1.24	1.00	1.54	0.047
Arrhythmia	1.10	0.74	1.63	0.639
Cerebrovascular disease	0.72	0.48	1.10	0.128
Chronic liver disease	0.95	0.39	2.33	0.918
Chronic renal failure	1.37	0.77	2.43	0.292

Notes: The multivariate logistic regression analyses were used to assess the association between ICS use and in-hospital mortality. The threshold for significance was a value of $P<0.05$.
Abbreviations: BMI, body mass index; IBD, inhaled bronchodilators; ICS, inhaled corticosteroids.

and comorbidities.[23,24] Furthermore, some of the previous studies[18,19] subjected the COPD patients who were taking inhaled therapy and evaluated the mortality of pneumonia, and the others[22–24] subjected the COPD patients who were admitted with pneumonia and evaluated the effects of prior use of

ICS on mortality; these latter studies were compatible with our study. However, these studies were limited because they did not adjust for the severity of pneumonia.[23,24] Our study confirmed that the outpatient usage of ICS was associated with lower mortality than nonusage of ICS, even after adjusting

for several confounders, including pneumonia severity. This indicates that treatment with ICS has protective effects against pneumonia-related mortality in patients with COPD.

A possible explanation for the association between ICS and decreased mortality is that corticosteroids produce anti-inflammatory effects by modulating inflammatory mediators. ICS may suppress the inflammatory response in the airway, which spreads to cause systemic inflammation.[31] It may reduce systemic inflammation by blocking excessive inflammation and the harmful effects this causes during infections.[32]

Our study demonstrated that A-DROP scores in patients receiving outpatient ICS treatment were lower than those not receiving ICS. A previous study with a relatively small sample size (n=490) demonstrated that ICS use was not associated with pneumonia severity.[22] Another previous study demonstrated that the use of ICS was associated with a lower degree of pleural inflammatory effusion,[33] suggesting that ICS has a protective effect against the progression of pneumonia and related complications. Because ICS has been reported to reduce bacterial invasion into the airway epithelium in an experimental model[34] and has the potential to reduce inflammation, prior use of ICS may lead to less severe pneumonia. Our study suggests that ICS may have protective effects against the progression of pneumonia in patients with COPD.

The association between ICS and mechanical ventilation has also been controversial.[22,24] Our study demonstrated that the percentage of patients requiring mechanical ventilation was lower in the ICS and IBD group than in the IBD alone group, although this result was not significant. Furthermore, the mortality from pneumonia in patients with COPD requiring mechanical ventilation was significantly lower in the ICS and IBD group than in the IBD alone group. These results also suggest that ICS may have protective effects against pneumonia and pneumonia-related mortality in patients with COPD.

Comorbidity of asthma was associated with decreased mortality in this study. Recently, comorbid asthma and COPD have been recognized as asthma–COPD overlap (ACO).[35] As patients with ACO have lower health-related quality of life, frequent exacerbations, and often require hospitalization,[36,37] patients with ACO have been suggested to have a poorer long-term prognosis, when compared with patients having asthma or COPD alone. However, recent studies have demonstrated that ACO patients have better short-term mortality, compared with COPD alone.[38,39] Our present study is consistent with the previous reports that comorbid asthma and COPD were associated with better prognosis.

Higher mortality was associated with worse general conditions at admission, including lower BMI, more severe dyspnea grade, lower level of consciousness, and poorer activities of daily life. The findings of this study were compatible with the previous study demonstrating the mortality of pneumonia in patients with COPD.[26] Further, missing data in the covariants, such as BMI and activities of daily life at admission, were also associated with higher mortality in this study. Because patients with severe conditions might not be able to get their body height and weight measured or their physical activities evaluated at admission, missing data of BMI and activities of daily life might indicate the more severe general conditions.

This study has several limitations. First, the database did not contain information on the degree of airflow limitation, such as details of pulmonary function tests and COPD severity. However, the grade of dyspnea was used as a covariant of respiratory condition in this study, as a previous study had shown that dyspnea grade reflects respiratory function.[40] Second, the database did not contain information related to the dosages of the medications used. Thus, we cannot evaluate the association between mortality and the dose of ICS.

Conclusion

Outpatient inhaled therapy with ICS and IBD was associated with lower mortality from pneumonia in patients with COPD than IBD treatment alone. ICS may have protective effects against pneumonia and help prevent pneumonia-related mortality in patients with COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials
Methods
Hugh-Jones dyspnea scale

The Hugh-Jones dyspnea scale is a system for grading dyspnea severity, established by Hugh-Jones and Lambert in 1952.[1] It is similar to the Medical Research Council's breathlessness scale, and is widely used in Japan.[2] The dyspnea scale is defined as follows: 1) the patient's breathing is as good as that of other people of their age and build when working, walking, and climbing hills or stairs; 2) the patient is able to walk on level ground at the pace of normal people of their age and build but is unable to maintain that pace when climbing hills or stairs; 3) the patient is unable to keep up with normal people of their age and build on level ground but is able to walk ~1.6 km or more at their own speed; 4) the patient is unable to walk more than ~50 m on level ground without resting; 5) the patient is breathless when talking or undressing or is unable to leave home because of breathlessness; (unspecified) the patient is unable to be classified into the above grades because of bedridden status.

Japan Coma Scale

The Japan Coma Scale is a system widely used in Japan[3] for assessing patients' levels of consciousness and is reported to correlate well with the Glasgow coma scale.[4] The Japan Coma Scale is defined as follows: one-digit codes (1–3) are given to patients who are conscious without any stimuli; two-digit codes (10–30) are assigned to patients who could be aroused by some stimuli; and three-digit codes (100–300) are given to patients in coma.

Barthel index

The Barthel index is a system for grading the activities of daily life, assessing functional status and the ability to perform daily activities.[5] It consists of ten factors: feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer, mobility, and stairs. Scores range from 0 to 20, with a score of 20 indicating total independence, lower scores indicating increasing dependence, and 0 signifying complete dependence. It should be noted that changes of more than two points (10%) in the total score accurately reflect changes in functional status.[6] We categorized patients into four groups according to their score: completely independent (20); partially independent; (19–14); partially dependent (13–7); and completely dependent (6–0).

BMI categories

BMI categories were assigned based on the World Health Organization classifications of underweight ($<$18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese ($\geq$30.0 kg/m^2).

A-DROP scores

The severity of pneumonia was evaluated using A-DROP scores, which use a six-point scale (0–5) to assess the clinical severity of community-acquired pneumonia. This scale was established by the Japanese Respiratory Society and is reportedly similar to the CURB-65 system of the British Thoracic Society.[7] The A-DROP score consists of the following parameters: 1) age (male $\geq$70 years, female $\geq$75 years), 2) dehydration (blood urea nitrogen $\geq$21 mg/dL), 3) respiratory failure (SaO$_2$ $\leq$90% or PaO$_2$ $\leq$60 mmHg), 4) orientation disturbance (confusion), and 5) low blood pressure (systolic blood pressure $\leq$90 mmHg). The severity of pneumonia was classified into four categories using the A-DROP score: mild, 0 points; moderate, 1–2 points; severe, 3 points; and extremely severe, 4–5 points.

ICD-10 codes of comorbidities

Comorbidities on admission were identified using ICD-10 codes: asthma (J45 and J46), interstitial pneumonia (J84), lung cancer (C34), congestive heart failure (I50), cardiac arrhythmia (I44 and I45, I47–I49), cerebrovascular disease (I60–I69), chronic liver disease (K70 and 71, K73 and 74, K76), and chronic renal failure (N18).

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