

Original Article



Hospitalization Due to Asthma Exacerbation: A China Asthma Research Network (CARN) Retrospective Study in 29 Provinces Across Mainland China

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Correspondence to

Jiangtao Lin, MD

Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, No. 2, Yinghua East Street, Chaoyang District, Beijing 100029, China.

Tel: +86-10-84206185

E-mail: jiangtao_l@263.net

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ORCID iDs

Jiangtao Lin

<https://orcid.org/0000-0002-1336-3922>

Bin Xing

<https://orcid.org/0000-0002-2700-9289>

Huaping Tang

<https://orcid.org/0000-0002-2464-5028>

Lan Yang

<https://orcid.org/0000-0003-3252-3300>

Yadong Yuan

<https://orcid.org/0000-0002-2417-1803>

Yuhai Gu

<https://orcid.org/0000-0001-5568-062X>

Ping Chen

<https://orcid.org/0000-0003-2126-9976>

Jiangtao Lin ¹, Bin Xing ¹, Huaping Tang ², Lan Yang ³, Yadong Yuan ⁴, Yuhai Gu ⁵, Ping Chen ⁶, Xiaoju Liu ⁷, Jie Zhang ⁸, Huiguo Liu ⁹, Changzheng Wang ¹⁰, Wei Zhou ¹¹, Dejun Sun ¹², Yiqiang Chen ¹³, Zhuochang Chen ¹⁴, Mao Huang ¹⁵, Qichang Lin ¹⁶, Chengping Hu ¹⁷, Xiaohong Yang ¹⁸, Jianmin Huo ¹⁹, Xianwei Ye ²⁰, Xin Zhou ²¹, Ping Jiang ²², Wei Zhang ²³, Yijiang Huang ²⁴, Luming Dai ²⁵, Rongyu Liu ²⁶, Shaoxi Cai ²⁷, Jianying Xu ²⁸, Jianying Zhou ²⁹ and on behalf of China Asthma Research Network

¹Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China

²Department of Respiration, Qingdao Municipal Hospital, Qingdao, Shandong, China

³Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

⁴Department of Respiration, The Second Hospital of Hebei Medical University, Shijiazhuang, China

⁵Department of Respiration, Qinghai People's Hospital, Xining, China

⁶Department of Respiratory Diseases, General Hospital of Shenyang Military Command, Shenyang, China

⁷Department of Respiration, The First Affiliated Hospital of Lanzhou University, Lanzhou, China

⁸Department of Pulmonary and Critical Care Medicine, The Second Hospital of Jilin University, Changchun, China

⁹Department of Respiration, Tongji Hospital, Wuhan, China

¹⁰Department of Respiration, Xinqiao Hospital, Third Military Medical University, Chongqing, China

¹¹Department of Respiration, General Hospital of Ningxia Medical University, Yinchuan, China

¹²Department of Pulmonary and Critical Care Medicine, Inner Mongolia People's Hospital, Hohhot, China

¹³Department of Respiration, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

¹⁴Department of Respiration, Henan Provincial People's Hospital, Zhengzhou, China

¹⁵Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

¹⁶Department of Respiration, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

¹⁷Department of Respiration, Xiangya Hospital, Changsha, China

¹⁸Department of Pulmonary and Critical Care Medicine, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

¹⁹Department of Respiration, The First Affiliated Hospital of Harbin Medical University, Harbin, China

²⁰Department of Respiration, Guizhou Provincial People's Hospital, Guiyang, China

²¹Department of Respiration, Shanghai Central Hospital, Shanghai, China

²²Department of Respiration, Tianjin First Central Hospital, Tianjin, China

²³Department of Respiration, The First Affiliated Hospital of Nanchang University, Nanchang, China

²⁴Department of Respiration, Hainan General Hospital, Haikou, China

²⁵Department of Respiration, Kunming General Hospital of the People's Liberation Army, Kunming, China

²⁶Department of Respiration, The First Affiliated Hospital of Anhui Medical University, Hefei, China

²⁷Department of Respiration, Nanfang Hospital, Guangzhou, China

²⁸Department of Respiration, Shanxi Bethune Hospital, Taiyuan, China

²⁹Department of Respiration, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Xiaoju Liu 
<https://orcid.org/0000-0002-8830-9429>

Jie Zhang 
<https://orcid.org/0000-0002-9888-5665>

Huiguo Liu 
<https://orcid.org/0000-0001-9229-4840>

Changzheng Wang 
<https://orcid.org/0000-0002-4728-1781>

Wei Zhou 
<https://orcid.org/0000-0001-9981-6437>

Dejun Sun 
<https://orcid.org/0000-0003-0841-1501>

Yiqiang Chen 
<https://orcid.org/0000-0001-6270-8600>

Zhuochang Chen 
<https://orcid.org/0000-0002-4172-0894>

Mao Huang 
<https://orcid.org/0000-0002-2743-1017>

Qichang Lin 
<https://orcid.org/0000-0003-3081-8084>

Chengping Hu 
<https://orcid.org/0000-0002-6185-5155>

Xiaohong Yang 
<https://orcid.org/0000-0002-0253-0051>

Jianmin Huo 
<https://orcid.org/0000-0002-1092-5352>

Xianwei Ye 
<https://orcid.org/0000-0002-2330-3907>

Xin Zhou 
<https://orcid.org/0000-0003-0629-1788>

Ping Jiang 
<https://orcid.org/0000-0002-6247-4477>

Wei Zhang 
<https://orcid.org/0000-0002-2756-459X>

Yijiang Huang 
<https://orcid.org/0000-0002-2484-7666>

Luming Dai 
<https://orcid.org/0000-0002-4110-4426>

Rongyu Liu 
<https://orcid.org/0000-0002-0483-0808>

Shaoxi Cai 
<https://orcid.org/0000-0002-3141-1457>

Jianying Xu 
<https://orcid.org/0000-0003-1016-3690>

Jianying Zhou 
<https://orcid.org/0000-0002-3150-5031>

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ABSTRACT

Purpose: Details of patients hospitalized for asthma exacerbation in mainland China are lacking. To improve disease control and reduce economic burden, a large sample survey among this patient population is indispensable. This study aimed to investigate the clinical characteristics and outcomes of such patients.

Methods: A retrospective study was conducted on patients hospitalized for asthma exacerbation in 29 hospitals of 29 regions in mainland China during the period 2013 to 2014. Demographic features, pre-admission conditions, exacerbation details, and outcomes were summarized. Risk factors for exacerbation severity were analyzed.

Results: There were 3,240 asthmatic patients included in this study (57.7% females, 42.3% males). Only 28.0% used daily controller medications; 1,287 (39.7%) patients were not currently on inhaled corticosteroids. Acute upper airway infection was the most common trigger of exacerbation (42.3%). Patients with severe to life-threatening exacerbation tended to have a longer disease course, a smoking history, and had comorbidities such as hypertension, chronic obstructive pulmonary disease (COPD), and food allergy. The multivariate analysis showed that smoking history, comorbidities of hypertension, COPD, and food allergy were independent risk factors for more severe exacerbation. The number of patients hospitalized for asthma exacerbation varied with seasons, peaking in March and September. Eight patients died during the study period (mortality 0.25%).

Conclusions: Despite enhanced education on asthma self-management in China during recent years, few patients were using daily controller medications before the onset of their exacerbation, indicating that more educational efforts and considerations are needed. The findings of this study may improve our understanding of hospital admission for asthma exacerbation in mainland China and provide evidence for decision-making.

Keywords: Asthma; disease progression; hospitalization; inpatients; risk factors; seasonal variation; medication adherence; mortality

INTRODUCTION

Asthma is a common heterogeneous disease characterized by chronic airway inflammation. The prevalence of asthma is increasing in many countries.¹⁻³ It is estimated that there are about 300 million asthma patients worldwide and that the number is still increasing.¹ Despite advances in prevention and treatment, asthma exacerbation remains a major threat to asthmatic patients. Hospitalization due to asthma exacerbation contributes largely to the healthcare expenses of asthmatic patients. According to research in the US, the costs of emergency department visits and hospitalization due to asthma exacerbation accounted for up to 80% of the direct costs of asthma patients.⁴

In China, little is known about the hospitalization of patients for asthma exacerbation. According to a domestic epidemiology study, the prevalence of asthma in mainland China is rapidly increasing in recent years,³ while risk factors of asthma exacerbation were not sufficiently investigated. This study aimed to investigate the clinical characteristics and outcomes of such patients in mainland China, with a view to improving control of the disease and lowering its economic burden.

MATERIALS AND METHODS

Study design

This is a retrospective study supervised by China Asthma Research Network (CARN) and conducted in 29 provincial hospitals in 29 provinces (autonomous regions/municipalities) across mainland China. The STROBE checklist was followed when this study was designed and conducted.⁵ The inclusion criteria were: 1) patients ≥ 14 years old; 2) hospitalized for asthma exacerbation; 3) diagnosed with asthma at least 3 months before admission according to the GINA criteria⁶; and 4) hospitalized between January 1, 2013 and December 31, 2014. If a patient was hospitalized more than once during the study period, only the last hospitalization was included. The criteria for the severity of asthma exacerbation was based on the Guidelines for the prevention and treatment of asthma published by the Chinese Medical Association of Respiratory Disease in 2008.⁷ An exemption from the informed consent of the study was approved by the Ethics Committee of China-Japan Friendship Hospital (ethics No. 2015-99).

Data collection

The flowchart of the study is shown in **Fig. 1**. Due to the lack of a commonly shared hospital information system in China so far, the investigators at each center searched the electronic medical record system for their hospital and enrolled patients who met the inclusion criteria. Information about the demographic features (age, sex), pre-admission conditions (history of smoking and hospitalization or emergency care due to asthma exacerbations during the previous year, and daily treatment), exacerbation details (triggering factor and severity), and outcomes were evaluated. The information on comorbidities was based on formal diagnoses extracted from the medical records, and the diagnosis of comorbidities, such as chronic obstructive pulmonary disease (COPD), was made by the doctors when the patients were hospitalized according to the international or domestic guidelines generally accepted. Non-adherence was defined as irregular use of the prescribed medications of asthma before the hospitalization.

A questionnaire was designed and distributed among all CARN members (experts, specialists, or healthcare professionals) for validation prior to the final version was CARN-approved for use in this study. Accordingly, an online electronic database was developed. Investigators at each participating center were trained on how to enroll the patients, extract the information, and complete the questionnaire, for standardization and quality control.

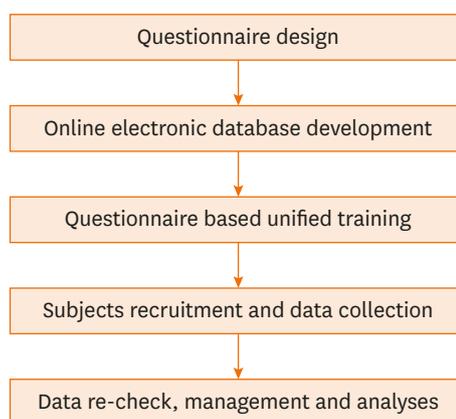


Fig. 1. Flowchart of the study.

They completed the questionnaire on paper for each case, after which the data were input into the online electronic database. The paper questionnaires at each site were then mailed to the steering institution of this nationwide study, where two independent investigators double-checked the data in the database to ensure accuracy.

The number of patients hospitalized for asthma exacerbation each month and the total number of monthly respiratory hospitalizations in each center over the study period were also recorded.

Data analysis

IBM SPSS Statistics 24.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) were utilized for analyses. For non-normally distributed data, median and quartiles were used for description. Numerical data with a non-normal distribution were compared using the Mann-Whitney *U* test. Differences between categorical variables were tested using the χ^2 test. Logistic regression was used to examine the effects of various factors on the severity of asthma exacerbation. *P* values < 0.05 were considered statistically significant.

RESULTS

Demographic characteristics

In all, 3,240 asthmatic patients were included (57.7% females; 42.3% males). According to the common geographic division of China, of all the patients enrolled, 396 were from Northeast China, 532 from North China, 426 from Central China, 648 from East China, 235 from South China, 725 from Northwest China, and 278 from Southwest China. Most patients were non-smokers. Current smokers and ex-smokers accounted for 10.4% and 13.4%, respectively (**Table 1**). Further analyses by age group showed that, in each age group, there were more females than males. The percentage of having a smoking history was higher in patients in older age groups; and for every age group, male patients were more likely to be smokers (**Table 2**).

History of treatment before hospitalization and comorbidities

About half of the patients had a history of hospitalization or emergency department visit for asthma in the previous year. Only 28.0% of the patients regularly used daily controller medications, including inhaled corticosteroid (ICS), long-acting β_2 -agonist (LABA), ICS/LABA, oral leukotriene receptor antagonists, oral corticosteroid (OCS), and theophylline. One thousand two hundred and eighty-seven patients (39.7%) were not using ICS currently, 161 patients (5.0%) were using OCS currently or until recently, and 1,067 (32.9%) patients had a history of non-adherence.

Comorbidities are summarized in **Table 1**. The prevalence of hypertension, diabetes mellitus, and coronary heart disease was 22.6%, 7.7%, and 7.7%, respectively. Of the patients, 13.0% had COPD, while 14.7%, 3.4%, and 1.1% had allergic rhinitis, sinusitis, and nasal polyps, respectively. Fifty-six (1.7%) of the patients had obstructive sleep apnea and hypoventilation syndrome, 49 (1.5%) had food allergy, 46 (1.4%) had gastro-esophageal reflux disease, and 24 (0.7%) had psychiatric problems such as depressive and anxiety disorders.

Details of the exacerbations

Factors triggering the exacerbation are summarized in **Table 1**. Acute upper airway infection triggered nearly half of all exacerbations. The first 6 leading triggering factors, in sequence, were acute upper airway infection, weather changes, noxious gas, allergen exposure,

Table 1. Demographic and clinical characteristics of the study patients

Factors	All (n = 3,240)	Mild and moderate asthma exacerbation (n = 2,577)	Severe and life-threatening asthma exacerbation (n = 652)	P
Age (yr)	57 (44–67)	57 (44–64)	59 (49.3–68)	0.40
Sex				
Male	1,369 (42.3)	1,067 (41.4)	299 (45.9)	0.04
Disease course (yr)	8 (2–20)	7 (2–20)	10 (3–20)	< 0.01
Smoking status (n = 3,230)				
Current smokers	337 (10.4)	252 (9.8)	84 (12.9)	0.02
Ex-smokers	433 (13.4)	319 (12.4)	114 (17.5)	< 0.01
Non-smokers	2,470 (76.2)	2,006 (77.8)	454 (69.6)	< 0.01
History of hospitalization or emergency care visit for asthma in the past year	1,359 (41.9)	1,061 (41.2)	294 (45.1)	0.07
Treatment before admission				
Using daily controllers regularly	907 (28.0)	711 (27.6)	194 (29.8)	0.27
Not currently using ICS	1,287 (39.7)	1,031 (40.0)	254 (39.0)	0.62
Currently using or having recently stopped using OCS	161 (5.0)	119 (4.6)	41 (6.3)	0.08
History of non-adherence	1,067 (32.9)	847 (32.9)	216 (33.1)	0.09
Comorbidities				
Hypertension	733 (22.6)	544 (21.1)	187 (28.7)	< 0.01
Diabetes mellitus	248 (7.7)	186 (7.2)	61 (9.4)	0.08
Coronary heart disease	248 (7.7)	196 (7.6)	51 (7.8)	0.80
COPD	421 (13.0)	298 (11.6)	123 (18.9)	< 0.01
Bronchiectasis	119 (3.7)	92 (3.6)	27 (4.1)	0.50
OSAHS	56 (1.7)	47 (1.8)	8 (1.2)	0.30
Allergic rhinitis	477 (14.7)	381 (14.8)	94 (14.4)	0.81
Sinusitis	109 (3.4)	81 (3.1)	28 (4.3)	0.15
Nasal polyps	37 (1.1)	26 (1.0)	11 (1.7)	0.15
Food allergy	49 (1.5)	32 (1.2)	17 (2.6)	0.01
GERD	46 (1.4)	42 (1.6)	4 (0.6)	0.08
Anxiety/depression	24 (0.7)	21 (0.8)	3 (0.5)	0.50
Triggering factor				
Acute upper airway infection	1,370 (42.3)	1,087 (42.2)	283 (43.4)	0.60
Weather changes	738 (22.8)	606 (23.5)	133 (20.4)	0.10
Noxious gas	140 (4.3)	111 (4.3)	29 (4.4)	0.90
Allergen exposure	115 (3.5)	100 (3.9)	15 (2.3)	0.07
Strenuous exercise	57 (1.8)	50 (1.9)	7 (1.1)	0.20
Air pollution	49 (1.5)	41 (1.6)	8 (1.2)	0.60

Values are presented as median with quartiles or number of patients (%).

ICS, inhaled corticosteroid; OCS, oral corticosteroid; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea and hypoventilation syndrome; GERD, gastroesophageal reflux disease.

Table 2. Sex and smoking history differences in different age groups

Age group (yr)	Sex		Smoking history	
	Male	Female	Male	Female
≤ 20	40 (42.6)	54 (57.4)	7 (17.5)	1 (1.9)
20–40	203 (40.5)	298 (59.5)	90 (44.3)	6 (2.0)
40–60	640 (40.2)	954 (59.8)	332 (51.9)	25 (2.6)
≥ 60	486 (46.2)	565 (53.8)	279 (57.4)	30 (5.3)

Values are presented as number of patients (%).

strenuous exercise, and air pollution. Most patients had mild to moderate exacerbations, with severe and life-threatening exacerbation accounting for about one-fifth of all cases.

Risk factors for severe asthma exacerbation

After excluding 11 patients who lacked complete information on severity, the remaining patients were categorized into 2 groups (mild-to-moderate and severe-to-life-threatening) based on the severity of exacerbation (Table 1). The characteristics of these 2 groups were compared using the Mann–Whitney *U* test (for age and disease course) or the χ^2 test (for

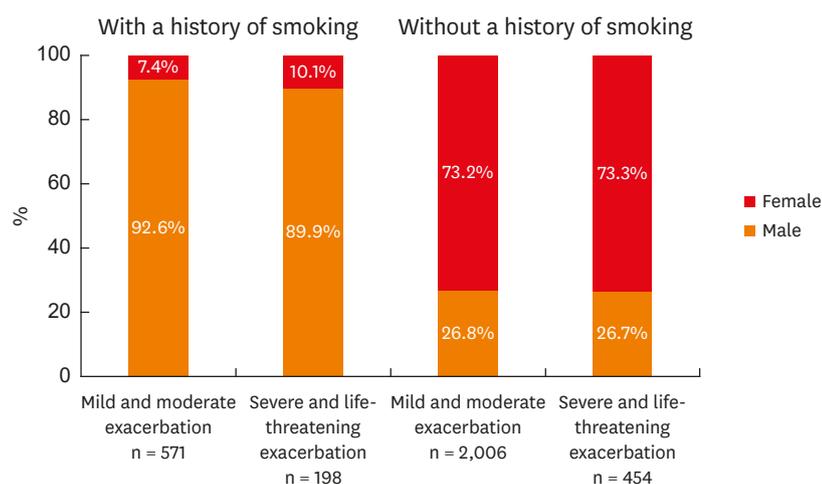


Fig. 2. Sex proportions in patients with mild-to-moderate exacerbation and severe-to-life-threatening exacerbation discriminated by the smoking history.

other factors). As shown in **Table 1**, patients in the more severe group had older median ages, although the difference was not significant. The disease course of patients in the more severe group was significantly longer ($P = 0.0003$). More patients in the severe group were male and had a smoking history (either current smokers or ex-smokers). Patients with more severe exacerbations were more likely to have hypertension, COPD, and food allergy (all $P < 0.05$). The differences in medication use before hospitalization and triggering factors between the 2 groups failed to reach statistical significance.

Although the severer group included more males than the less severe group, this difference may be related to the higher incidence of smoking history in male patients. Thus, we subdivided patients according to smoking history; this analysis showed that, in both patients with and without a smoking history, female patients were more likely to be in the severe group, but the differences were not significant (**Fig. 2**).

A multivariate analysis was performed to further evaluate the potential risk factors for the severity of asthma exacerbations. As shown in **Table 3**, a smoking history, comorbidities of hypertension, COPD, and food allergy were independent risk factors for severe exacerbation.

Seasonality of hospitalization

We calculated the number of patients hospitalized for asthma exacerbation each month and its proportion in the monthly respiratory hospitalizations over the study period (**Fig. 3**). The

Table 3. Multivariate analysis of risk factors for the severity of asthma exacerbation (mild or moderate vs. severe or life-threatening)

Factors	OR	95% CI	P value
Age (yr)	0.998	0.992–1.005	0.58
Sex	0.929	0.746–1.156	0.51
Disease course (yr)	1.006	1.000–1.012	0.07
Smoking history	1.538	1.205–1.962	< 0.01
History of hospitalization or emergency care visit for asthma in the past year	1.123	0.941–1.339	0.20
Hypertension	1.437	1.163–1.775	< 0.01
COPD	1.601	1.256–2.039	< 0.01
Food allergy	2.231	1.221–4.075	0.01

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 4. Details of patients who died during the study period

No.	Age (yr)	Sex	Month of admission	ICU admission	Mechanical ventilation	Cause of death	Comorbidities
1	94	F	January	Y	N	Acute myocardial infarction	COPD, CAD, CKD
2	69	M	January	Y	Y	Tension pneumothorax	TB
3	68	F	January	N	N	Not clear	IPA
4	75	M	March	N	N	Sudden death	AR
5	59	F	November	N	Y	Not clear	HTN, DM
6	81	F	November	N	N	Cardiac shock	HTN, DM, CAD
7	54	M	February	N	N	Not clear	Food allergy
8	64	F	November	N	N	Respiratory failure	N/A

ICU, intensive care unit; F, female; M, male; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, chronic kidney disease; TB, pulmonary tuberculosis; IPA, invasive pulmonary aspergillosis; AR, allergic rhinitis; DM, diabetes mellitus; N/A, not applicable.

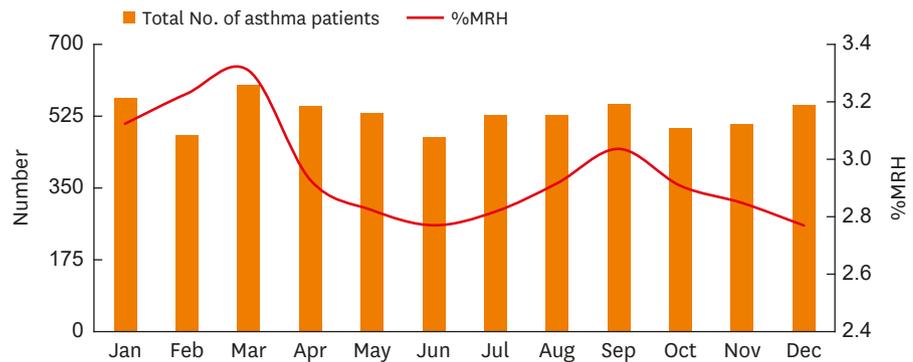


Fig. 3. Seasonality of hospital admission for asthma exacerbation. %MRH, % of monthly respiratory hospitalizations.

number of patients hospitalized for asthma exacerbation and its proportion in the monthly respiratory hospitalizations varied with seasonal changes; 2 peaks were obvious, one in March and the other in September. Further analysis showed that the proportion of hospitalization of asthma exacerbation in the monthly respiratory hospitalizations was higher in the northern cities, and that the seasonal fluctuations in the hospitalizations of asthma exacerbation in the northern cities were more obvious than in the southern cities (**Supplementary Fig. S1**).

Outcomes

The mean length of hospital stay was 8 (range, 6 to 11) days. Seventy-three (2.3%) patients were admitted to the intense care unit, and 73 (2.3%) patients underwent mechanical ventilation. Eight patients died during hospitalization, with an overall mortality of 0.25% (**Table 4**). These 8 patients were hospitalized during the period November to March; of these patients, 3 had metabolic or cardiovascular comorbidities, such as hypertension, diabetes mellitus, and coronary arterial disease. 2 had infectious diseases, such as tuberculosis and invasive pulmonary aspergillosis. And 2 died due to cardiac complications.

DISCUSSION

This retrospective study summarized the clinical characteristics and outcomes of patients hospitalized for asthma exacerbation in 29 provincial hospitals in 29 provinces, autonomous regions, or municipalities throughout mainland China. No previous multi-center large-scale study of asthma inpatients on the present study topic in mainland China has been reported.

The results of this study provide insights into this patient population, which may facilitate disease control and lower the economic burden of asthma exacerbation in the future.

For adults, the prevalence of asthma was higher in women than in men.⁶ Several previous studies that included inpatients hospitalized for asthma exacerbation also showed a similar tendency.^{8,9} The reasons for this sex-related difference are not clear, but may involve hormonal changes and genetic susceptibility.¹⁰ In this study, there were more female than male patients, but the male patients tended to have more severe exacerbations. This may be because male patients were more likely to have a smoking history. Further analyses that discriminated between patients with and without a smoking history showed that the differences between the sexes in terms of disease severity were not significant.

There is a close relationship between tobacco smoking and asthma. For asthmatic patients, smoking is related to poor asthma control,¹¹ an accelerated lung function decline,¹² and a poor response to inhaled or systemic corticosteroids.¹³ An epidemiological study performed in 8 provinces of China in the period 2010-2012 showed that, among asthmatic patients >14 years old, 34.5% were smokers. Compared to nonsmokers, asthma patients who had a smoking history had a lower control rate, and a higher rate of hospitalization and emergency department visits.¹⁴ The ratio of patients with a smoking history was 23.5% in this study, which was lower than in the previous study.¹⁴

In this study, the proportion of patients who used daily controller medications regularly before hospitalization was relatively low. It is recommended that all patients with persistent asthma use long-term control medications such as ICS daily.⁶ A meta-analysis showed that, even for patients with well-controlled asthma, the withdrawal of low-dose ICS was related to an increased risk of asthma exacerbation.¹⁵ More than one-third of patients overall and about half of the patients who had a history of hospitalization or emergency department visit for asthma exacerbation in the previous year were not using ICS before hospitalization, indicating that many of the patients were not using the recommended medications. This may have led to poor control of the disease and frequent exacerbations.

Asthma symptoms vary with seasons. This study showed that the number of patients hospitalized for asthma exacerbation had seasonal fluctuations, with 2 obvious peaks in March and September, similar to previous studies. Two studies that included patients hospitalized for asthma exacerbation in the US and Canada showed that, for elderly patients, hospitalization peaked during winter, while for younger patients, the peak occurred around September.^{16,17} A study in Korea showed that there were spring and autumn peaks of asthma exacerbation for children and adults, respectively, but only 1 winter peak for the elderly patients. The association between asthma exacerbation and influenza was greatest in patients aged over 60 years old.¹⁸ The increased hospitalization of the elderly asthma patients in winter may be caused by the increased prevalence of airway infection, which is a strong triggering factor of asthma exacerbation. The increased hospitalization rate of school-age children in September has been ascribed to epidemics of respiratory viral infection after school starts.¹⁹ However, several studies in China have reported that there was a strong relationship between asthma symptoms and airborne pollen levels. Yao and Zhang²⁰ revealed that the peak of the concentration of airborne autumn pollen in North China occurred between August and September, and that most outpatients with hay fever or asthma in that period were allergic to Mugwort or Humulus pollen. As autumn pollen allergens are the most important allergic pollen for asthmatic patients in China, the September hospitalization

peak may be explained by pollen allergy, but further studies are needed to prove it. Further analyses comparing the difference between the northern and southern cities showed that the seasonal fluctuations in hospitalization of asthmatics in the southern cities were less obvious than in the northern cities. The reasons for the results may be colder temperature, higher rates of respiratory infections, and more serious air pollution in the winter of northern cities.

The prevalence of asthma is increasing worldwide, but several studies have reported that asthma mortality is decreasing in some countries.^{21,22} Kaur *et al.*⁸ reported that the mortality of asthmatic inpatients during the period 2001-2010 in the US was 1%. In England, Watson *et al.*²³ reported that the mortality of adult asthmatic inpatients during the period 2000-2005 was 1.3%. In the present study, the mortality of asthmatic inpatients was 0.25%, which is lower than that reported in other countries. Higher levels of comorbidities have been associated with the increased mortality in elderly asthmatic patients.²⁴ Most of the 8 patients who died in our study had comorbidities, such as hypertension, diabetes mellitus, and coronary artery disease; of these, 2 died from cardiac complications. Two of the patients had infectious comorbidities: tuberculosis and invasive pulmonary aspergillosis, respectively. Asthma exacerbation was the primary cause of hospitalization of these patients, but the comorbidities may contribute to the worsening of the disease. As many patients received systemic glucocorticoids during hospitalization, they were at high risk of developing infections, such as tuberculosis or aspergillosis, which may further worsen the condition of the patients. All of the deceased patients had been admitted to the hospital from November to March, which are the coldest months in most of mainland China. Several studies have reported that the mortality of asthmatic patients increased during winter, perhaps due to the high prevalence of respiratory viral infections.⁸

The study had some limitations. First, this is a retrospective study, and the information was extracted from medical records, which may introduce some bias as medical records may not cover the complete history of the patients. Secondly, all the medical centers participating in this study were provincial hospitals located in the capitals of provinces, autonomous regions, or municipalities. There may be a regional imbalance, so that these centers may not comprehensively reflect the situation in some less-developed areas. More extensive studies are needed to obtain more detailed information about asthmatic patients.

This study involving 29 hospitals located in 29 regions that covered most parts of China improved our understanding of patients hospitalized for asthma exacerbations in this country and provided evidence for decision-making. In these Chinese patients, severe exacerbations of asthma were related to a history of smoking, comorbid hypertension, COPD, and food allergy; the exacerbations were mostly triggered by acute upper airway infection which peaked during March and September each year. We noted the underuse of daily controller medications among patients before hospitalized for asthma exacerbation. Regardless of rapid and wide-spreading patient education on self-management of asthma in China during recent years, the low patient adherence to daily controller medications as revealed in this study indicated more educational efforts and considerations should be needed.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. S1

Comparisons of the proportion of hospitalization due to asthma exacerbation in the monthly hospitalization rates between the northern and southern cities. The northern and southern cities are divided by the Qinling-Huaihe boundary.

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