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Clinical Characteristics and Economic Burden of Asthma in China: A Multicenter Retrospective Study

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ABSTRACT

Asthma is a common chronic airway inflammation that produces a healthcare burden on the economy. We aim to obtain a better understanding of the clinical status and disease burden of patients with asthma in China.

A retrospective study was carried out based on the computerized medical records in the Jinan Health Medical Big Data Platform between 2011 and 2019 (available data from 38 hospitals). The asthma severity of each patient was assessed retrospectively and categorized as mild, moderate, or severe according to Global Initiative for Asthma 2020 (GINA 2020).

The results revealed that the majority (75.0%) of patients suffered from mild asthma. Patients treated with inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) at emergency department visits had lower frequencies of exacerbations compared with non-ICS/LABA-treated patients. The incidence rates for 1, 2, 3, and 4 exacerbation of the patients treated with ICS/LABA are lower than those treated without ICS/LABA (14.49 vs. 15.01%, 11.94% vs. 19.12%, 6.51% vs.

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12.92% and 4.10% vs. 9.35%). The difference got a statistical significance Chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease (GERD), two comorbidities related to asthma, were risk factors for asthma exacerbation. Finally, patients who suffered from exacerbations produced a heavier economic burden compared to the patients who never suffered exacerbations (mean costs are ¥ 3,339.67 vs. ¥ 968.45 separately).

These results provide a reference for clinicians and patients to obtain a better treatment and therapy strategy management for people living with asthma.

Keywords: Asthma; Economic burden; Retrospective study

INTRODUCTION

Asthma is a common chronic airway inflammation that presents in the clinic with symptoms such as shortness of breath, wheezing, tightness of the chest, and a persistent cough.[1-3] As a serious health problem worldwide, asthma affects about 300 million individuals globally.[4] It is estimated that 45.7 million individuals in China suffer from asthma.[5] Several studies investigated the prevalence of asthma (Supplementary Table 1). The results published indicated that the prevalence of Asthma in China is between 1.24% and 4.2%. Since asthma patients often have an associated reduced quality of life and an increased treatment burden,[6,7] it is a great public challenge to control asthma in China.

The trigger of asthma is driven by a complicated cascade of processes that include both genetic and environmental factors.[8] Regardless of its complex pathogenesis, asthma can be controlled effectively with proper treatment, especially when accompanied by monitoring during stable periods of the disease. Each patient is encouraged to construct a personalized action plan to reduce the risk of exacerbations.[2] Asthma exacerbation means an acute worsening of symptoms, which may need emergency treatment or hospitalization. Thus, asthma exacerbation might be the costliest problem for patients with asthma. Public education and proper self-management are essential for patients to reduce the risk of exacerbations.[1] For this purpose, clinicians should be aware of the risks of exacerbation in patients with different degrees of asthma severity. It is also necessary for clinicians to evaluate the risk of future exacerbations in their patients. Several studies have reported the relationship between asthma and some risk factors, but the extent to which the risk factors affect acute exacerbation is still under intensive study. Besides, evidence is accumulating that the development of asthma involves a variety of factors that can vary with time. Acting in concert these factors can affect a number of biochemical processes that can drive asthma exacerbation. Modern information technology methods and data processing techniques provide new ways to study this disease and involve the collection of available data provided globally and shared by many stakeholders.

As an asthma exacerbation is life-threatening, the patient will likely visit the emergency department for acute medical care.[9] Inhaled corticosteroids (ICS) combined with long-acting beta-agonists (LABA) are usually employed to treat asthma patients, either for the immediate relief of symptoms or asthma control.[1] Thus, an oral drug inhalation device combined with ICS plus LABA is preferable for the management of asthma.[10]

In this study, we used longitudinal data from an asthma cohort in 11 hospitals in Jinan to examine the prevalence of different subtypes and the economic burden. We also analyzed the potential risk factors for asthma exacerbation through local databases. This study will provide important information about the clinical status of asthma patients in Jinan, China.

MATERIALS AND METHODS

Sources Data and Cohort of Patients Studied

This retrospective study was based on the computerized medical records stored in the Jinan Health Medical Big Data Platform, which contains data extracted from 38 hospitals in Jinan, China (with more than 8.9 million inhabitants). We included adults aged ≥ 18 diagnosed at least once with asthma in the included hospitals. Individuals were excluded if their ages were missing or had undergone surgery, anesthesia, pathological tests, delivery, nuclear medicine, interventional therapy, oral therapy, vaccination, intrauterine device removal, transfusion, hemodialysis, or early education during the same visit. The screening process is indicated in Figure 1.

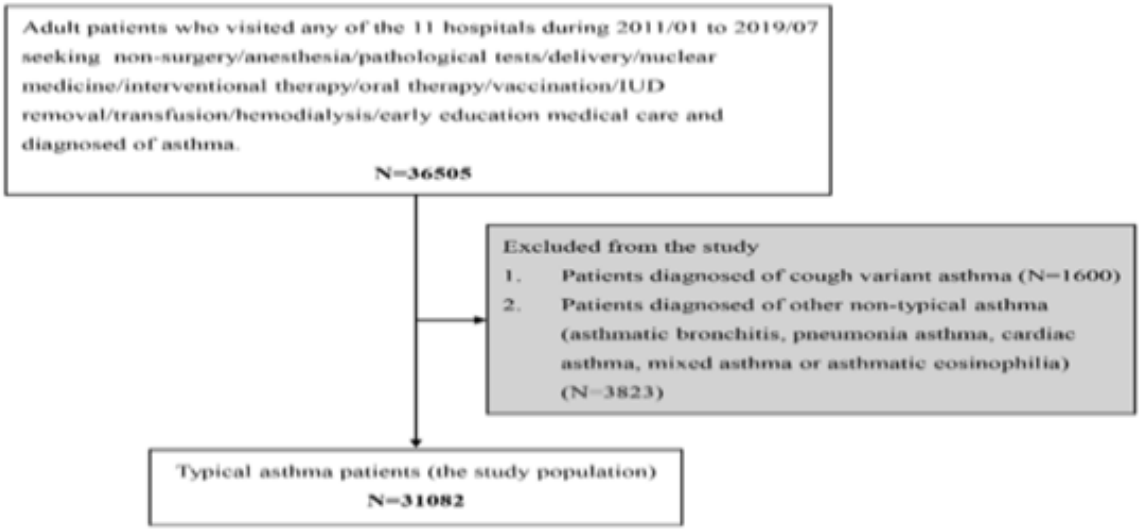

Figure 1. Screening scheme of patients enrolled

Different types of asthma were determined and screened. Asthma severity was categorized as mild, moderate, or severe, according to the Global Initiative for Asthma (GINA) 2020 guidelines. In brief, asthma severity was assessed retrospectively from the medication and dosage recorded at the last visit during a 6-month observation period (from 1 July to 30 December of the first year). Asthma exacerbations were evaluated during the measurement period (from 1 October of the first year to 30 September of the next year). In addition, the degree of asthma severity of the patients was reviewed by an asthma specialist. The primary endpoint included the proportion of patients with different degrees of asthma severity in each year of the study.

The secondary endpoints included The risk factors for asthma exacerbation, the effect of ICS/LABA usage during emergency department visits on asthma exacerbation, and the economic burdens on patients with different severities of asthma. An exacerbation was defined by the following criteria: if the patient was admitted to the emergency department or hospital ward or if they were referred to an outpatient clinic but received intravenous corticosteroids or theophylline for the asthma flare-up.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) for normally distributed continuous variables, the median and interquartile ranges for non-normally distributed continuous variables, and proportions for categorical variables. Potential differences between the two groups were assessed using a *t*-test for normally distributed continuous variables, the Wilcoxon test for non-normally distributed continuous variables, and the chi-square or Fisher's test for categorical variables. Logistic regression analysis was used to evaluate potential risk factors for asthma exacerbation. Potential risk factors with a p value ≤ 0.05 in the univariate analysis were considered and included in the multivariate analysis afterward. The odds ratio (OR) and the 95% confidence interval (CI) were also determined.

RESULTS

Patient Characteristics

The patients' characteristics are summarized in Supplementary Table 2. In total, 36,505 individuals were documented as having at least one diagnosis of asthma. Of these eligible patients, 31,082 were identified with typical asthma and 1,600 with cough variant asthma. In addition, 3,823 were diagnosed with asthmatic bronchitis, pneumonia-associated asthma, cardiac asthma, mixed asthma, or asthmatic eosinophilia. Of the asthmatic patients, 14,177 (45.6%) were males, and 16,900 (54.4%) were females. The gender of 5 individuals (<0.1%) was unknown. The asthmatics were generally middle-aged (50.7±16.5 years

old). The majority (71.0%) were between 18 and 60, and the remainder were >60. The total number of clinic visits for asthma patients was 78,103; thus, the average number of visits for each patient was 2.5±5.1 (mean ± SD). Among the total visits, 69,894 (88.3%) were outpatient, 4,164 (5.3%) were inpatient, and 5,068 (6.4%) were emergency cases.

Characteristics of Patients with Different Severities of Asthma

The characteristics of patients with different severities of asthma are shown in Table 1. Of the 36,505 patients, the data for severity was available for only 14,264. Most patients (10,691 [75.0%]) had mild asthma, with a mean age of 50.0±16.2 years. While 3,488 (24.5%) had moderate asthma with a mean age of 51.2±16.4 years, and 85 (0.6%) had severe asthma with a mean age of 58.3±15.0 years. The average age of patients with different degrees of asthma severity showed a statistically significant difference (p<0.001).

As shown in Table 2, the majority of patients with different severities of asthma did not experience asthma exacerbation during the measurement period. 1.9% of the patients with mild asthma had 1 exacerbation during the measurement period, and 1.2% had 2 or more. The average interval time between exacerbations was 33.0±54.5 days. Similarly, 2.8% of the patients with moderate asthma had 1 exacerbation during the investigation period, and 1.3% had more than two. The average interval time between exacerbations was 61.3±83.0 days. Of the patients, 3.5% with severe asthma had 1 exacerbation during the measurement period, and 2.4% had more than two. The average interval time between exacerbations was 91.1 ± 29.5 days.

Table 1. Characteristics of patients with different severities of asthma

	Total	Mild	Moderate	Severe
Patient Number	14,264 (100%)	10,691 (75.0%)	3,488 (24.5%)	85 (0.6%)
Gender				
Male	6,760 (47.4%)	4,956 (46.4%)	1,754 (50.3%)	50 (35.3%)
Female	7,502 (52.6%)	5,734 (53.6%)	1,733 (49.7%)	35 (41.2%)
Unknown	2 (< 0.1%)	1 (< 0.1%)	1 (< 0.1%)	0 (0.0%)
Age (Mean ± SD)	50.3 ± 16.3	50.0 ± 16.2	51.2 ± 16.4	58.3 ± 15.0

Table 2. Characteristics of asthma exacerbations in patients with different asthma severities

	Total	Mild	Moderate	Severe
Patient Number	14,264 (100%)	10,691 (75.0%)	3,488 (24.5%)	85 (0.6%)
Exacerbation Number				
Never	13,791 (96.7%)	10,366 (97.0%)	3,345 (95.9%)	80 (94.1%)
1	299 (2.1%)	200 (1.9%)	96 (2.8%)	3 (3.5%)
≥2	174 (1.2%)	125 (1.2%)	47 (1.3%)	2 (2.4%)
Average Interval of Exacerbation (days)*	41.3 ± 64.4	33.0 ± 54.5	61.3 ± 83.0	91.1 ± 29.5
Interval of Exacerbation [Median (Q1, Q3), (d)*]	13.1 (2, 52.6)	9.5 (2, 43.3)	27 (3, 76.2)	91.1 (80.7,101.6)

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ICS/LABA Use at Exacerbation Index Reduces the Frequency of Attacks in the Following Year.

The study reviewed treatment records to identify documented cases of asthma exacerbations among the 31,082 patients with asthma codes. A total of 12,566 exacerbations were documented, as presented in Table 3. Of these, 10,630 exacerbation records were analyzed more than one year prior to the end of the audit to investigate the incidence of recurrent exacerbations in the following year. Supplementary Table 3 shows that, out of the 10,630 patients, 2,195 received ICS/LABA treatment. Among the ICS/LABA treated patients, 1,615 (73.58%) did not experience any further attacks after the index exacerbation, while 318 (14.49%) experienced one recurrence and 262 (11.94%) were re-attached at least twice.

Of the non-ICS/LABA treated patients, 5,548 (66.77%) never experienced a recurrence in the year following the index date, 1,274 (15.10%) had 1 attack, and 1613 (19.12%) had at least 2 attacks. More importantly, the proportion of patients without recurrence in the next year was much higher in the ICS/LABA treated group than in the non-ICS/LABA treated group ($p < 0.001$). Furthermore, whether or not the index exacerbation was excluded, the ICS/LABA-treated patients experienced a significant longer mean interval between repeat attacks than the non-ICS/LABA-treated patients (index excluded: 69.0 ±63.2 days *vs* 41.3±57.4 days, $p < 0.001$; index included: 98.5±91.1 days *vs* 46.0 ± 67.2 days, $p < 0.001$). These results revealed a better control of asthma exacerbations following ICS/LABA treatment, which indicates that ICS/LABA therapy of the exacerbation is more effective than non-ICS/LABA for the prevention of exacerbation recurrences in the following year.

Table 3. Analysis of the exacerbation frequency after ICS/LABA or non-ICS/LABA treatment at the exacerbation index

	ICS/LABA	Non-ICS/LABA	*p*
Patient Numbers	2,195	8,435	
Exacerbation Number			
Never	1,615 (73.58%)	5,548 (65.77%)	< 0.001
Ever	580 (26.42%)	2,887 (34.23%)	
1	318 (14.49%)	1,274(15.10%)	
≥ 2	262 (11.94%)	1,613 (19.12%)	
≥ 3	143 (6.51%)	1,090 (12.92%)	
≥ 4	90 (4.10%)	789 (9.35%)	
Interval of exacerbation (excluding the asthma exacerbation index, days)*			
Mean ± SD	69.0 ± 63.2	41.3 ± 57.4	< 0.001
Median (Q1, Q3)	50.3 (30.7, 91.9)	22.6 (3, 51.5)	< 0.001
Interval of exacerbation (including the asthma exacerbation index, days)			
Mean ± SD	98.5 ± 91.1	46.0 ± 67.2	< 0.001
Median (Q1, Q3)	65.2 (34.2, 134.6)	21 (2.5, 58.0)	< 0.001

* patients suffered from exacerbations ≥ 2 times

ICS, Inhaled corticosteroids; LABA, Long-acting beta-agonists; SD, Standard deviation

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Risk Factors for Asthma Exacerbation

Since asthma is a common condition, the purpose of asthma management is to achieve asthma control and prevent exacerbation. It is important for clinicians to bear in mind the risk factors for exacerbation. Supplementary Table 3 presents the potential risk factors for asthma exacerbation.

In the present study, the demographic variables included gender, age, and age groups, and a strong association between age and exacerbation was found (OR, 1.012; 95% CI, 1.006–1.017, p<0.001). Next, the comorbidities that might have modified the exacerbations were evaluated. The comorbidities presented here were derived from existing variables, such as Chronic Obstrcutive Pulmonary Disease (COPD), rhinitis, nasosinusitis, nasal polyposis, Gastroesophageal Reflux Disease (GERD), anxiety, depression, and obesity. As a result, significant comorbidities associated with exacerbation were COPD (OR, 2.618; 95% CI, 1.945–3.459, p<0.001) and GERD (OR, 2.101; 95% CI, 1.131–3.57, p=0.016).

The Economic Burden of Asthma

The managesment of asthma undoubtedly increases the economic burden on healthcare systems, and any exacerbation will likely further amplify this burden. It is necessary to analyze the costs for patients who experience exacerbations or not. Table 4 summarizes the expenditure on asthma management of patients who experienced exacerbations or did not.

Table 4. Analysis of the costs of asthma management

		Total cost	Medicine fee	Testing fee	Fee for others
Asthma patients ever suffered an exacerbation	**Patients (N)**	468	468	468	468
	Patients with cost incurred（%）*	468 (100%)	365 (77.99%)	211 (45.09%)	358 (76.5%)
	Mean	3,339.67	2,052.12	451.93	835.62
	SD	6,232.47	4,258.97	1,155.03	1,809.68
	Q1	361.36	136.75	0	2
	Medium	1,074.34*	747.44*	0*	106.01*
	Q3	3,132.41	2,141.67	214	658.15
	Contribution to the total cost	100%	61.45%	13.53%	25.02%
Asthma patients never suffered an exacerbation	**Patient numbers**	8,012	8,012	8,012	8,012
	Patients with cost incurred（%）*	8,012 (100%)	6,730 (84%)	1,025 (12.79%)	4,969 (62.02%)
	Mean	968.45	1,320.25	515.26	38.79
	SD	1,932.38	1,983.20	1,305.81	150.93
	Q1	197.89	385.38	75.84	0
	Medium	433.52	747.9	221	0
	Q3	948.37	1,483.07	484.66	0
	Contribution to the total cost	100%	53.2%	4.01%	42.79%

*All costs, fees, and payments are presented as Renminbi (RMB) (1 RMB is approximately equal to 0.15 USD.)
SD: standard deviation

In our study, the analysis of the asthma economic burden included 468 patients who suffered exacerbations and 8,012 patients who never experienced a flare-up after filtering the patients with expense records. The total mean expenditure of the patients who suffered exacerbations was ￥3,339.67 ± ￥6,232.47, to which the fee for medicines made the most significant contribution (61.45%, ￥2,052.12 ± ￥4,258.97). To a

lesser extent, fees for testing (13.53%, ¥ 451.93± ¥ 1,155.03) and others (25.02%, ¥ 835.62 ± ¥ 1,809.68) were smaller fractions of total costs. However, the total expenditure of the patients who never suffered an exacerbation was ¥ 968.45± ¥ 1,932.38, which was much lower than that of the patients who experienced attacks. In another aspect, the medication fee accounted for the highest proportion of the total fee (53.2%, ¥ 1,320.25 ± ¥ 1,983.20), and the next was the fee for testing (4.01%, ¥ 515.26± ¥ 1,305.81) and others (42.79%, ¥ 38.79± ¥ 150.93). More importantly, patients who never suffered exacerbations had significantly lower expenditure for either item compared to patients who experienced attacks (p<0.05).

DISCUSSION

Asthma is a common condition that is usually managed by drugs. Our results provide important information on asthma exacerbations and the economic burden in Jinan, China.

Though a controllable disease, poor asthma management will increase exacerbations of asthma. According to the previous study, asthma severity is highly correlated with likely exacerbations.[11] Here, we show that patients with any severity may suffer an exacerbation. Patients with mild asthma experienced exacerbations less frequently than those with moderate or severe asthma. A previous survey reported that the exacerbation rate of patients in 6 cities in China with mild asthma was 17.8%,[12] which is much higher than 3.3% (Table 2) in this study. The different outcomes may be due to the different populations of the study cohort.

In recent years, due to the continuous improvement of medical insurance policies and the increase in income, the proportion of Chinese asthma patients with standardized treatment has increased significantly. As a result, more asthma patients can use ICS/LABA for long-term symptom control.[13]

On the other hand, the current survey population was asthma patients in the urban area of Jinan with a per capita economic income and education level higher than the Chinese average, which may also be an important reason for the significantly lower rate of asthma exacerbations in this study. Alternatively, the survey methods may have differed. For example, this study assessed asthma severity retrospectively according to the treatment. However, the previous study defined asthma severity based on self-reporting. Further, a study is required to investigate the factors associated with the change in the ratio of patients with different degrees of asthma severity. A previous report in the United States showed that the highest asthma death rate was for adults aged ≥65 years old.[14] Therefore, more attention should be paid to asthma management in elderly patients.

Comorbidity is a modifiable risk factor for asthma exacerbation and is linked with greater healthcare use and a lower quality of life.[15] Thus, much attention should be paid to comorbidities during asthma management. Previous studies have reported several comorbidities associated with asthma, such as obesity, GERD, anxiety, depression, rhinitis, sinusitis, and nasal polyps. In this regional population-based cohort study, we found that either GERD or COPD was highly correlated with asthma exacerbations. Both asthma and GERD are common causes of upper airway cough. As a chronic disease, GERD affects the upper gastrointestinal tract.[16,17] However, it also coexists with asthma in 80% of asthma patients without gastrointestinal symptoms.[18] Similar to asthma, COPD and airway inflammation are also treated with ICSs, long-acting muscarinic-antagonists (LAMA), and LABA.[19] Thus, these results prompt us to believe that COPD-asthma and GERD-asthma overlap during asthma management and should be seriously considered.

ICS-formoterol is a treatment of choice in the emergency department to relieve acute asthma bronchoconstriction, which is also recommended by GINA 2020.[11] One previous study has compared budesonide plus formoterol (LABA) with salbutamol (SABA) therapy for the treatment of exacerbations of asthma in the emergency room and found that a high dosage combination of budesonide and formoterol is effective.[20]

Furthermore, our study found a significantly lower frequency of re-exacerbations after ICS/LABA therapy in emergency visits compared to non-ICS/LABA. Due to the continuous improvement of China's health insurance policy, we found that the financial burden of asthma patients is significantly lower than that of developed countries such as the United States. Similar results were obtained from several related studies in mainland China.[21,22] A study found that the annual per-person incremental medical cost of asthma in the United States was $3,266, of which $1,830 was attributable to prescription medication, $640 to office visits, $529 to hospitalizations, $176 to hospital-based outpatient

visits, and $105 to emergency room visits in 2015.[23] In addition, we found that asthma patients who ever suffered exacerbation had higher medication costs and lower screening costs relative to patients without previous acute asthma exacerbations.

We speculate that this phenomenon may be more related to compliance. Patients with poorly controlled asthma tend to have poor compliance and are unable to complete the regular pulmonary function and nitric oxide tests and control their symptoms with medication alone. This result also suggests that we should focus on health education for asthma patients in the future and emphasize the need for pulmonary function and other tests so that more asthma patients can be effectively controlled in the long term.

This study also has some limitations. Since the clinical data of all patients were obtained from the outpatient electronic medical record system of 10 tertiary care hospitals, the vast majority of the hospitals could not directly connect the pulmonary function test results to the outpatient system. Hence, the investigators had some difficulties in the later data collection, resulting in missing pulmonary function results in more than 50% of the patients. Secondly, the classification of asthma was not reflected in the medical records of patients in eight of the hospitals, so the investigators were only able to make the corresponding judgments through the description of clinical information such as patient history, symptoms, and signs. Thus they may differ from the accurate classification of patients.

From the study findings, we first established a detailed overview of asthma in the Jinan province of China by analyzing the medical records of 31,082 asthma patients using real-world medication data. Patients with mild asthma exhibited the highest rate of asthma exacerbations. Age, COPD, and GERD were unequivocally identified as risk factors for asthma exacerbations, and ICS/LABA therapy at the exacerbation stage is more effective than non-ICS/LABA. This study provides more detailed and exact information about the clinical status of asthma patients in Jinan, China, that can be used for their further medical management and therapy strategy.

STATEMENT OF ETHICS

This study was approved by the Committee on Ethics of Jinan Central Hospital, affiliated with Shandong First Medical University, Shandong (No. JCH2020-136-01).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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