Severe and uncontrolled asthma in China: a cross-sectional survey from the Australasian Severe Asthma Network

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Background: Severe asthma is largely unexplored in the Chinese population. Patients with asthma underwent systematic evaluation, by investigating the characteristics of uncontrolled asthma and of asthma treated with three different controller therapies.

Methods: This multi-centre, real-world study was conducted from March 2014 to September 2015. Adults with stable asthma underwent assessment of medication use, asthma control, quality of life, psychological symptoms, work productivity and activity impairment, bronchodilator response and sputum induction.

Results: Participants (n=379) had a mean (SD) age of 47.4 (14.0) years, and 57.0% were female. There were 14.8% (n=56) of patients receiving treatment with Step 4/5 as severe asthma, but only 13 (3.4%) met ERS/ATS severe refractory asthma criteria. The patients with severe asthma usually used triple controller therapy: ICS/LABA, additional leukotriene modifier or theophylline, and reported better asthma control. Two fifths of patients (n=147) had uncontrolled asthma, with worse symptoms, psychological symptoms (both P<0.001), health-related work productivity and activity impairment, increased eosinophilic inflammation in sputum [1.68% (0.0, 17.1%) *vs.* 0.2% (0.0, 1.3%), P<0.0001] and more exacerbations (P<0.05). Multiple regression analysis indicated that triple controller therapy significantly reduced the risk of uncontrolled asthma [OR =0.32, 95% CI =(0.14, 0.75)].

Conclusions: Although there is a relatively low proportion of severe refractory asthma based on ERS/ATS criteria, two of five patients with asthma in China are uncontrolled, displaying more psychological symptoms and reduced work productivity. Substantial gain in asthma control is obtained by triple controller therapy and this may be a promising therapeutic option for persistent asthma.

Keywords: Severe asthma; uncontrolled asthma; controller therapy

Introduction

Asthma has an increasing prevalence in China (1,2). Severe asthma and poorly controlled asthma remain important global issues (2). Population-based studies found that control of asthma was not achieved in the majority of Chinese patients with asthma (2). Severe asthma is an important subset of asthma (about 5–10%). It is difficult-to-treat and accounts for a large proportion of resource expenditure (3). Severe asthma is largely unexplored in the Chinese population.

Controller medications, such as inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA) are recommended for asthma, with escalating doses of ICS and LABA added for poor asthma control. Second line controllers including leukotriene receptor antagonists (LTRA), theophylline, and long-acting muscarinic agents (LAMA) can be effective (4,5), and some guidelines provide triple controller therapy as an option (6,7). This is an important issue since triple combination inhalers are currently in development. While use of triple controller therapy is common in chronic obstructive pulmonary disease (COPD), there is little data on this approach in asthma. This real-life study systematically evaluates severe asthma in China, by investigating the characteristics of uncontrolled asthma and of asthma treated with triple controller therapies.

Methods

Study oversight and design

This study was as a part with Chinese population from the Severe Asthma Web-based Database (SAWD) via secure web site to facilitate data collection, which was manipulated by the Australasian Severe Asthma Network (ASAN). ASAN provided training to site staff regarding the study protocol, data collection requirements and sputum induction, performed quality control with selected source data verification and performed the analysis.

Data was collected from three sites in Sichuan and Jilin provinces, China from March 2014 to September 2015. Adult patients (≥18 years of age) with stable asthma, and confirmed by variable airflow obstruction, were recruited from the outpatient clinics of West China Hospital, Sichuan University, the People's Hospital of Jilin Province and No. 2 Affiliate Hospital, Jilin University. The subjects were excluded if they were pregnant, had cognitive impairment, current solid organ malignancy, or an inability to attend study visits. This study was conducted according to the

International Conference on Harmonisation Good Clinical Practice Guidelines and was approved by the Hunter New England and University of Newcastle human research ethics committees and local Institutional Review Boards from China. All participants gave informed written consent.

Data collection and assessments

Baseline data were collected during a period of stable asthma and included demographics, medications, asthma history, the 6-item Asthma Control Questionnaire (ACQ-6) (8) and Asthma Quality of Life Questionnaire (AQLQ) (9). Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards. Predicted FEV_1 and FVC were calculated using data from the Chinese population (10). Bronchodilator reversibility (BDR) was defined as a ≥12% or 200 mL improvement in FEV_1 at 15 minutes following inhaled salbutamol 200 mcg.

Sputum was induced using nebulised 4.5% saline as described (11), with salbutamol 400 mcg (GSK, Avda de Extremadura, Spain) pre-treatment. If the baseline pre or post FEV_1 was ≤40% of predicted, sputum induction was completed with 0.9% saline after it was deemed safe by the supervising physician. Selected sputum was dispersed using dithiothreitol, a total cell count performed, and cytospins prepared for differential cell count. Inflammatory phenotypes were classified as: eosinophilic (eosinophils ≥3%), neutrophilic (neutrophils >61%), paucigranulocytic (eosinophils <3% and neutrophils ≤61%) and mixed granulocytic (eosinophils ≥3% and neutrophils >61%).

Anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) (12). The effect of health problems on work productivity was assessed using the Work productivity and impairment: general health (WPAI:GH) questionnaire (13). The WPAI: GH questionnaire, as a validated and reliable tool, captures the work time lost due to absenteeism and presenteeism, with a recall period of 1 week. For presenteeism, the patients were asked about the extent to which patients' health problems affected their productivity while they were working. WPAI:GH outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (worse outcomes).

Atopy was assessed by skin prick testing with allergen extracts for house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), mold (*Alternaria tenuis*, *Aspergillus*), dog hair, cat hair, pollen (ragweed, birch,

Table 1 Patient characteristics

Variables	Data
N	379
Age[a]	47.4 (14.0)
Male/female (N=379)	163/216
Smoking[c] (N=344)	
Never	217 (63.1)
Current	57 (16.6)
Ex	70 (20.4)
Pack years (ex/current smokers)[b]	19.50 (7.50, 31.50)
BMI[b]	23.44 (21.12, 25.87)
Atopy[c]	78/127 (61.4)
Pre β_2 agonist spirometry[a] (N=375)	
FEV$_1$ % predicted	71.48 (23.30)
FVC % predicted	88.35 (20.22)
FEV$_1$/FVC	66.45 (14.38)
Post β_2 agonist spirometry[a] (N=340)	
FEV$_1$ % predicted	78.60 (23.47)
FVC % predicted	93.92 (19.66)
FEV$_1$/FVC	68.89 (14.25)
Sputum inflammatory phenotype[c] (N=236)	
Neutrophilic	27 (11.4)
Eosinophilic	63 (26.7)
Paucigranulocytic	143 (60.6)
Mixed	3 (1.3)

BMI, body mass index; Data given as [a]mean (SD), [b]median (Q1, Q2), [c]No. (%).

London plane) and cockroach, together with positive (histamine) and negative (saline) controls.

Definitions of severe asthma

This study used the ERS/ATS guideline (3) definition of severe refractory asthma, which required treatment with high dose ICS plus a second controller to prevent it from becoming uncontrolled or which remained uncontrolled despite this therapy. Furthermore, for the treatment based severe asthma classification, we had an alternative definition for severe asthma as patients receiving treatment with Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remaining uncontrolled despite this treatment (1). In addition, the triple controller therapy was defined as at least moderate dose ICS/LABA plus LTRA and/or theophylline or LAMA.

Statistical analysis

Comparisons were conducted using Chi-squared or Fisher's exact test for categorical data and Student's *t*-test or Wilcoxon rank sum test for continuous data as appropriate. Predictors of response were determined using single and multiple logistic regression adjusted for age, gender, smoking and site. All analyses were conducted using STATA 13 (College Station, Texas, USA). A P value ≤0.05 was considered significant.

Results

Characterisation of the participants

A total of 379 patients with asthma from Northeast and West China were included (*Table 1*). Participants were 57.0% female, had a mean (standard deviation, SD) age of 47.4 (14.0) years, a body mass index (BMI) of 23.4 (4), and 37% were current or ex-smokers. Most (61.4%) were atopic, with a mean (SD) asthma duration of 4.3 (7.0) years, and moderate impairment of lung function with mean (SD) 71.5% (23.3) of FEV$_1$% predicted. About one third had at least one exacerbation requiring oral corticosteroid (OCS) in the previous year. Asthma was objectively confirmed in all patients, by BDR in 201/233 (86.3%), airways hyperresponsiveness in 149/212 (70.3%), and peak flow variability in 5/11. According to sputum inflammatory counts, 26.7% of participants displayed an eosinophilic phenotype, 11.4% were neutrophilic, 1.3% were mixed granulocytic and 60.6% were paucigranulocytic.

Uncontrolled asthma

Based on ACQ cut-points, 39.4% (n=147) of patients had uncontrolled asthma (*Table 2*). In comparison with controlled asthma, the uncontrolled asthma group had worse eosinophilic inflammation in sputum [1.68% (0.0, 17.1%) *vs.* 0.2% (0.0, 1.3%), *P*<0.0001, *Figure 1*] (*Table 3*), and reduced lung function (FEV$_1$% pre 64.8±23.9 *vs.* 75.7±22.0, P<0.0001; FEV$_1$/FVC 65.0±13.6 *vs.* 71.6±14.1, P<0.0001) (*Table 2*). A greater proportion of patients with uncontrolled asthma reported ≥1 severe exacerbations in the

Table 2 Characteristics of patients with controlled and uncontrolled asthma

Variables	Controlled asthma (ACQ score <1.5)	Uncontrolled asthma (ACQ score ≥1.5)	P value
N	226	147	
Age[a]	46.8 (14.02)	48.0 (13.66)	0.425
Male/Female	93/133	66/81	0.475
Smoking[c]: never	135/201 (67.2)	82/141 (58.2)	0.085
Pack years (ex/current smokers)[b]	19.5 (8.0, 41.0)	19.5 (7.5, 30.0)	0.321
Atopy[c]	58/95 (61.1)	19/30 (63.3)	0.823
Pre-β_2 agonist spirometry[a] (N)	223	147	
FEV_1 % predicted	75.69 (22.04)	64.83 (23.90)	*<0.0001*
FVC % predicted	90.14 (18.30)	85.53 (22.84)	*0.045*
FEV_1/FVC	69.38 (13.97)	61.65 (13.76)	*<0.0001*
Post β_2 agonist spirometry[a] (N)	194	142	
FEV_1 % predicted	81.76 (22.13)	74.35 (24.87)	*0.004*
FVC % predicted	94.42 (17.67)	93.49 (22.33)	0.668
FEV_1/FVC	71.64 (14.14)	64.98 (13.55)	*<0.0001*
Asthma control			
ACQ6 score	0.5 (0.17, 1.0)	2.17 (1.83, 2.83)	*<0.0001*
Severe refractory asthma (ATS/ERS criteria)[c]	9/226 (4.0)	3/147 (2.0)	0.378
Severe asthma requiring Step 4/5[c]	47/226 (20.8)	9/147 (6.1)	*<0.0001*
Exacerbation history			
≥1 severe exacerbation in past year requiring OCS	71/225 (31.6)	61/146 (41.8)	*0.044*
Hospital admission	64/226 (28.3)	48/147 (32.7)	0.395
ICU admission	1/226 (0.4)	1/147 (0.7)	1.0
ER visit	28/224 (12.5)	19/145 (13.1)	0.865
Unscheduled doctor visit	49/225 (21.8)	50/146 (34.3)	*0.008*
Respiratory medications			
OCS use[c]	2/226 (0.9)	4/147 (2.7)	0.217
ICS/LABA use[c]	101/226 (44.7)	54/146 (37.0)	0.141
ICS dose (BDPmcg/day)[b]	400 (200, 1,000)	400 (400, 1,000)	0.609
Long Acting anticholinergic[c]	3/226 (1.3)	5/147 (3.4)	0.272
Leukotriene modifier[c]	56/226 (24.8)	14/146 (9.6)	*<0.0001*
Theophylline[c]	43/226 (19.0)	6/147 (4.0)	*<0.0001*

ACQ, Asthma Control Questionnaire; ATS, American Thoracic Society; BDP, beclomethasone dipropionate; ER, emergency room; ERS, European Respiratory Society; ICS, Inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting beta2-agonist; OCS, oral corticosteroid. Data given as [a]mean (SD), [b]median (Q1, Q2), [c]No. (%). Italic face indicates significant.
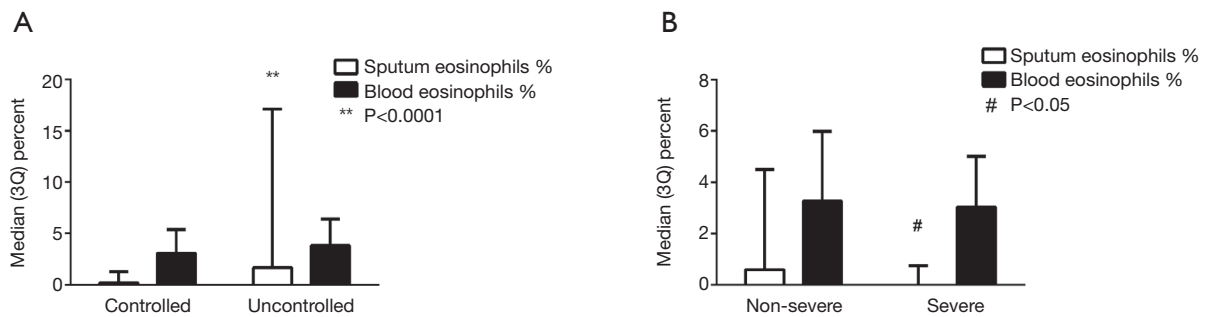
A

B

Figure 1 Blood and sputum eosinophils in (A) controlled and uncontrolled asthma and (B) non-severe and severe asthma. #, P<0.05, **, P<0.0001.

Table 3 Blood and sputum biomarkers in controlled and uncontrolled asthma

Variables	Controlled asthma	Uncontrolled asthma	P value
Sputum cell count			
Sputum[b] (N)	146	90	
Eosinophils (%)	0.2 (0, 1.3)	1.68 (0, 17.1)	*<0.0001*
Neutrophils (%)	8.75 (0.6, 39.25)	3.85 (0.2, 32.25)	0.215
Macrophage (%)	82.38 (55.0, 94.0)	71.63 (34.2, 91.0)	0.050
Lymphocyte (%)	0.95 (0.25, 2.300	0.88 (0.25, 1.900	0.619
Sputum inflammatory phenotype[c]			*<0.0001*
Eosinophilic	25 (17.1%)	38 (42.2%)	
Neutrophilic	18 (12.3%)	9 (10.0%)	
Paucigranulocytic	102 (69.9%)	41 (45.6%)	
Mixed	1 (0.7%)	2 (2.2%)	
Full blood count[b] (N)	210	135	
White cell count, $\times 10^9$/L	6.51 (5.30, 8.03)	7.30 (6.0, 8.80)	*0.001*
Eosinophils, $\times 10^9$/L	0.20 (0.10, 0.34)	0.25 (0.10, 0.50)	0.052
Monocytes, $\times 10^9$/L	0.39 (0.30, 0.50)	0.47 (0.33, 0.60)	*0.0005*
Basophils, $\times 10^9$/L	0.03 (0.01, 0.04)	0.02 (0, 0.07)	0.507
Lymphocytes, $\times 10^9$/L	1.85 (1.49, 2.26)	2.19 (1.70, 2.70)	*<0.0001*
Neutrophils, $\times 10^9$/L	3.79 (3.05, 5.02)	4.11 (3.20, 5.30)	0.101
Platelets, $\times 10^9$/L	194.50 (155.0, 236.0)	222.0 (177.0, 262.0)	*0.0003*
Red cell count, $\times 10^9$/L	4.68 (4.40, 5.06)	4.83 (4.47, 5.20)	0.056
Serum biomarkers (N)	135	43	
Serum IgE[b], IU/mL	102.71 (36.26, 213.44)	187.0 (43.52, 441.15)	0.057

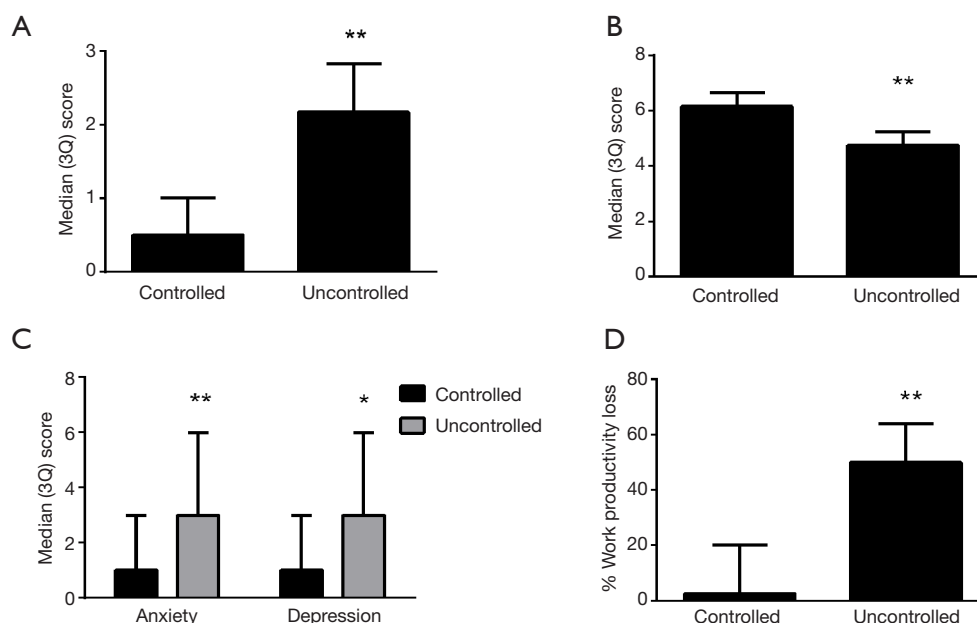Data given as [b]median (Q1, Q2), [c]No. (%), Italic face indicates significant.

Figure 2 Asthma control score (A), quality of life (B), psychological symptoms (C) and work productivity (D) in controlled and uncontrolled asthma. *P<0.001; **P<0.0001.

past year that required OCS treatment (41.8% *vs.* 31.6%, P=0.044), more exacerbations requiring parenteral CS (24.0% *vs.* 15.8%, P=0.05) and unscheduled doctor visits (34.3% *vs.* 21.8%, P=0.008). The patients with uncontrolled asthma had worse AQLQ [4.75 (4.06, 5.25) *vs.* 6.16 (5.59, 6.56), P<0.0001, *Figure 2*] than patients with controlled asthma. A greater proportion of patients with uncontrolled asthma had psychological symptoms (15.2% *vs.* 4.1%, P<0.0001 for HADS-A score ≥8; 17.8% *vs.* 6.3%, P<0.0001 for HADS-D score ≥8) and their symptoms were worse [3 (0, 6) *vs.* 1 (0, 3), P<0.0001 for HADS-A and P=0.0002 for HADS-D, *Figure 2*].

While ICS plus LABA use in uncontrolled asthma was similar to controlled asthma, a greater proportion of the patients with controlled asthma received additional treatment, i.e., triple controller therapy, with a LTRA (24.8% *vs.* 9.6%, P<0.0001) or theophylline (19.0% *vs.* 4.0%, P<0.0001). Using triple controller therapy (ICS/ LABA and one of LTRA, LAMA or theophylline) was associated with a significantly reduced risk of uncontrolled asthma [OR =0.32, 95% CI =(0.14, 0.75), P<0.0001] adjusted for age, gender, smoking and site.

Health-related work productivity impairment

The percentage of patients at work was similar in

uncontrolled and controlled asthma (48.4% *vs.* 50.4%, P=0.796) (*Table 4*). Of those working, 86% (18) of patients with uncontrolled asthma reported productivity loss due to health problems in comparison to 50% (23) of those with controlled asthma (P=0.007). More patients with uncontrolled asthma reported presenteeism (85.2% *vs.* 47.5%, P=0.001), and they had higher presenteeism scores [30 (10, 50), *vs.* 0 (0, 20), P<0.0001] compared to patients with controlled asthma. High scores for % absenteeism occurred in more patients with uncontrolled asthma (*Table 4*). Patients with uncontrolled asthma had greater overall health-problem related work productivity impairment [50.0 (20.0, 64.0) *vs.* 2.5 (0, 20), P<0.0001] and greater impairment of regular daily activities [30.0 (20.0, 60.0) *vs.* 10.0 (0.0, 30.0), P<0.0001] than those with controlled asthma.

Severe asthma and triple-controller therapy

Based on the pre-specific alternative definition of severe asthma, 14.8% of subjects (n=56) were defined as severe asthma with treatment of Step 4/5, but only 13 (3.4%) met the ERS/ATS definition of severe refractory asthma in our study. There were similar lung function and GINA asthma control assessment, but the patients in the severe asthma group had better asthma control by ACQ [0.58 (0, 1.17) *vs.*

Table 4 Work productivity outcomes in uncontrolled asthma and severe asthma

WPAI:GH questionnaire	Patients grouped by ACQ score			Patients grouped by GINA step 4/5 or not		
	Controlled asthma	Uncontrolled asthma	P value	Non-severe asthma	Severe asthma	P value
Participants currently working[c]	70/139 (50.4%)	30/62 (48.4%)	0.796	80/164 (48.8%)	20/40 (50.0%)	0.890
Any productivity loss[c]	23/46 (50.0%)	18/21 (85.7%)	*0.007*	30/50 (60.0%)	11/17 (64.7%)	0.731
Absenteeism[c]	4/46 (8.7%)	6/21 (28.6%)	0.060	7/50 (14.0%)	3/17 (17.7%)	0.706
Presenteeism[c]	29/61 (47.5%)	23/27 (85.2%)	0.001	41/68 (77.3%)	11/20 (55.0%)	0.672
% absenteeism[b]	0 (0, 0)	0 (0, 33.33)	0.019	0 (0, 0)	0 (0,0)	0.780
% presenteeism[b]	0 (0, 20)	30 (10, 50)	<0.0001	10 (0, 30)	10 (0, 40)	0.642
% work productivity loss	2.54 (0, 20)	50 (20, 64)	<0.0001	10 (0, 40)	20 (0, 40)	0.602
% activity impairment[b]	10 (0, 30)	30 (20, 60)	<0.0001	20 (0, 50)	10 (0, 30)	0.237
Hours missed due to health problems[b]; range	0 (0, 0); 0–24	0 (0,8); 0–48	0.006	0 (0, 0); 0–48	0 (0, 0); 0–24	0.468

WPAI, work productivity and activity impairment. Data given as [b]median (Q1, Q2), [c]No. (%), Chi^2 test or Fisher's exact test. Italic face indicates significant.

1.17 (0.5, 2.0), P<0.0001] and better quality of life scores (P=0.001) compared with the non-severe asthma group (*Figure 3*, *Table 5*). There was no difference in HADS scores [2.5 (1.0, 5.0) *vs.* 1.0 (0, 4.0), P=0.056, for HADS-A and 2.0 (0, 6.0) *vs.* 1.0 (0, 4.0), P=0.251, for HADS-D]. Health-related work productivity loss was equivalent in both severe and non-severe groups (*Figure 3*). In terms of comorbidities, the percentage of patients with nasal polyps and COPD in those with more severe asthma was increased in comparison to non-severe asthma (12.5% *vs.* 3.4%, P=0.006; 12.5% *vs.* 4.4%, P=0.015, respectively). Other comorbidities were similar between the two groups (data not shown). The levels of eosinophils in sputum and peripheral blood in the severe asthma group was significantly lower compared to the non-severe asthma group [0% (0, 0.75) *vs.* 0.6% (0, 4.5), P=0.026; 0.17×10^9/L (0.07, 0.31) *vs.* 0.2×10^9/L (0.1, 0.4), P=0.036, respectively] (*Table 6*, *Figure 1*). Most of the patients with severe asthma had a paucigranulocytic phenotype (73.7%) with only 15.8% exhibiting an eosinophilic phenotype.

As the first-line controller therapy, ICS plus LABA was used in all patients with severe asthma. To achieve better asthma control, the greater proportion of patients with severe asthma took the second-line controller therapies such as leukotriene modifier (87.5% *vs.* 6.5%, P<0.0001) and theophylline (62.5% *vs.* 4.3%, P<0.0001), but not LAMA or anti-IgE compared with non-severe asthma.

This suggests an approach where a third controller is added when there is insufficient control from two agents, which is consistent with a more severe form of asthma. The use of triple controller therapy indicated a high risk of ATS/ERS-defined severe asthma [OR =9.34; 95% CI: (2.53, 34.54), P=0.001] when data were adjusted for age, gender, smoking and site. The use of triple controller therapy in severe asthma was associated with better asthma control and quality of life and lower airway inflammation.

Discussion

In this study, patients with asthma from three centres underwent systematic evaluation of their condition. Although there was a relatively low proportion of severe asthma based on ERS/ATS criteria, two of five patients with asthma in China were uncontrolled, with an increased illness burden, impaired work productivity and airway eosinophilic inflammation. The use of triple controller therapy was associated with improved control and reduced eosinophilia, suggesting it may be a promising treatment approach in persistent asthma.

In our study, 39.4% of patients had uncontrolled asthma. This agrees with the Asthma Insight and Management survey which showed 42.0% of patients with uncontrolled asthma in China (2), however is different to the first national survey from China which found that 26.3% of
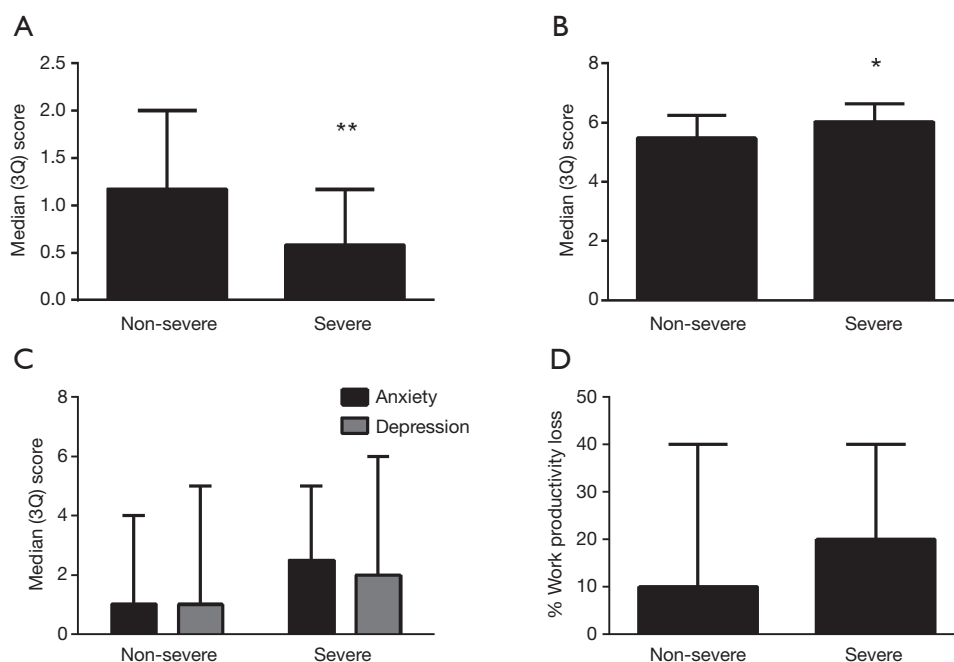
Figure 3 Asthma control score (A), quality of life (B), psychological symptoms (C) and work productivity (D) in non-severe and severe asthma. *, P<0.001; **, P<0.0001.

patients were uncontrolled (14,15). Some issues that can explain this inconsistency include study design, tools assessing asthma control, population and regional variation. The proportion of patients with uncontrolled asthma was substantially greater in China, which led to greater healthcare utilization such as exacerbations, severe exacerbations, more intensive therapy and unscheduled doctor visits.

We also found that psychological disturbance was important in the Chinese population. We identified 15.4% (n=57) of patients with psychological symptoms, which is similar to other studies (16,17). There was a higher prevalence of psychological symptoms in patients with uncontrolled or severe asthma, which is also similar to other studies (18). The mechanisms that underlie the relationship between psychological symptoms and asthma remain unclear (19). We recently found that anxiety symptoms are associated with greater perceived dyspnea intensity in asthma during bronchoconstriction (16); and that depression and high stress were associated with reduced bronchodilator response (20,21), and altered pattern of inflammation (22), which could be involved in therapy resistance. The relationship between psychological disturbance and asthma control needs further study.

Productivity loss is the opportunity cost due to foregone labor. It is described as absenteeism (the withdrawal of labor) or presenteeism (inefficiency of labor due to impairment). Few studies have reported on the relationship between asthma and productivity loss in the Chinese population. Su *et al.* identified that 28.6% of employed patients reported work loss during the previous year (15). In our study, we found that 14.9% of patients reported absenteeism and 59.1% reported presenteeism. We also found that productivity loss due to both absenteeism and presenteeism was associated with worse asthma control. By comparison, a prospective cross-sectional study from Canada found that 16.3% of employed adults reported absenteeism and 45.7% reported presenteeism from asthma, but they did not find that productivity loss due to absenteeism was associated with asthma control (23). This difference may be explained by different population characteristics and social circumstances. Interestingly, more severe asthma requiring treatment with triple controller therapy had no apparent effect on work productivity impairment. This is possibly because better asthma control was achieved using triple-controller therapy.

The definition of severe refractory asthma from the ERS/ATS Task Force Report (3) requires high dose ICS plus a second controller and/or systemic corticosteroids.

Table 5 Characteristics of patients with severe and non-severe asthma

Variables	Non-severe asthma	Severe asthma	P value
N	323	56	
Age[a]	47.20 (13.89)	48.15 (14.39)	0.639
Male/Female	142/181	21/35	0.367
Smoking[c]: never	183/296 (61.8)	34/48 (70.8)	0.099
Pack years (ex/current smokers)[b]	19.5 (7.5, 31.5)	21.9 (7.1, 37.75)	0.731
Atopy[c]	57/95 (60.0)	21/32 (65.6)	0.572
Pre-β_2 agonist spirometry[a] (N)	321	54	
FEV$_1$ % predicted	70.73(23.24)	75.92 (23.35)	0.131
FVC % predicted	87.76 (20.71)	91.85 (16.75)	0.170
FEV$_1$/FVC	66.23 (14.36)	67.87 (14.58)	0.463
Post-β_2 agonist spirometry[a] (N)	293	47	
FEV$_1$ % predicted	78.38 (23.61)	79.96 (22.79)	0.669
FVC % predicted	93.84 (20.31)	94.40 (15.17)	0.859
FEV$_1$/FVC	68.78 (14.10)	69.55 (15.24)	0.730
Asthma control			
Uncontrolled Asthma (ACQ score ≥1.5)[c]	138/317 (43.5)	9/56 (16.1)	*<0.0001*
ACQ6 score[b]	1.17 (0.5, 2.0)	0.58 (0, 1.17)	*<0.0001*
Exacerbation history			
≥1 severe exacerbation in past year requiring OCS	111/321 (34.6)	22/56 (39.3)	0.496
Hospital admission	87/323 (26.9)	26/56 (46.4)	0.101
ICU admission	3/323 (0.9)	0/56	1.000
ER visit	37/320 (11.6)	10/55 (18.2)	0.171
Unscheduled doctor visit	85/321 (26.5)	18/56 (32.1)	0.380
Respiratory medications			
OCS use[c]	4/323 (1.2)	2/56 (3.6)	0.217
ICS/LABA use[c]	103/322 (32.0)	56/56 (100.0)	*<0.0001*
ICS dose (BDPmcg/day)[b]	400 (200, 800)	650 (400, 1,000)	*0.0002*
Long acting anticholinergic[c]	7/323 (2.2)	1/56 (1.8)	1.0
Leukotriene modifier[c]	21/322 (6.5)	49/56 (87.5)	*<0.0001*
Theophylline[c]	14/323 (4.3)	35/56 (62.5)	*<0.0001*

ACQ, Asthma Control Questionnaire; BDP, beclomethasone dipropionate; ER, emergency room; ICS, Inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting beta2-agonist; OCS, oral corticosteroid. Data given as [a]mean (SD), [b]median (Q1, Q2), [c]No. (%). Italic face indicates significant.

Table 6 Blood and sputum biomarkers in severe and non-severe patients

Variables	Non-severe asthma	Severe asthma	P value
Sputum cell count			
Sputum[b] (N)	198	38	
Eosinophils (%)	0.6 (0, 4.5)	0 (0, 0.75)	*0.026*
Neutrophils (%)	4.4 (0.3, 35.75)	13.25 (2.75, 36.75)	0.069
Macrophage (%)	80.38 (46.50, 93.50)	70.63 (51.25, 92.0)	0.600
Lymphocyte (%)	1.0 (0.25, 2.50)	0.5 (0.25, 1.30)	0.320
Sputum absolute cell count[b] (N)	N=148	N=36	
Eosinophils, ×10⁴/mL	0.24 (0, 4.59)	0 (0, 0.27)	*0.020*
Neutrophils, ×10⁴/mL	3.53 (0.47, 13.89)	7.68 (1.26, 16.40)	0.197
Macrophage, ×10⁴/mL	43.78 (18.96, 273.33)	24.19 (16.98, 39.26)	*0.017*
Lymphocyte, ×10⁴/mL	0.8 (0.16, 5.39)	0.32 (0.11, 0.67)	*0.022*
Sputum inflammatory phenotype[c]			0.307
Eosinophilic	57 (28.8%)	6 (15.8%)	
Neutrophilic	23 (11.6%)	4 (10.5%)	
Paucigranulocytic	115 (58.1%)	28 (73.7%)	
Mixed	3 (1.5%)	0	
Full blood count[b] (N)	296	53	
White cell count, ×10⁹/L	7.0 (5.74, 8.50)	6.10 (5.10, 7.85)	*0.025*
Eosinophilis, ×10⁹/L	0.20 (0.10, 0.40)	0.17 (0.07, 0.31)	*0.036*
Monocytes, ×10⁹/L	0.40 (0.30, 0.52)	0.35 (0.27, 0.60)	0.184
Basophils, ×10⁹/L	0.03 (0, 0.05)	0.02 (0.01, 0.04)	0.756
Lymphocytes, ×10⁹/L	2.0 (1.64, 2.50)	1.69 (1.32, 2.0)	*0.0001*
Neutrophils, ×10⁹/L	3.90 (3.12, 5.14)	3.66 (3.12, 5.02)	0.597
Platelets, ×10⁹/L	210.5 (168.5, 252.5)	169.0 (131.0, 220.0)	*0.0009*
Red cell count, ×10⁹/L	4.76 (4.43, 5.18)	4.66 (4.37, 4.96)	0.076
Serum biomarkers (N)	139	42	
Serum IgE[b,] IU/mL	116.45 (41.36, 303.49)	95.48 (30.89, 306.37)	0.612

Data given as [b]median (Q1, Q2), [c]No. (%). Italic face indicates significant.

However, our study found that triple controller therapy, rather than high dose ICS, was more frequently taken in the Chinese population if optimal asthma control was not achieved, as reported in other studies from China (14,15). The second-line therapies that are added to moderate dose ICS and LABA include LTRA, theophylline or LAMA. Our results suggest that this approach can be effective, as it was associated with better asthma control and reduced levels of airway eosinophilia. This approach may allow patients to maintain moderate ICS dose (4) while at the same time achieve improved asthma control (5,24-26). A consequence of this approach, however, relates to the definition of severe asthma. This approach does not satisfy the ERS/ATS guideline definition of severe asthma and raises the question of whether patients on triple-controller therapy can be defined as severe asthma.

The use of triple controller therapy for asthma in China may be due to the perceived side effects of ICS (27,28).

Alternatively, LTRA may be used in those with comorbid rhinitis (25), and, theophylline as a bronchodilator, may be used for its anti-inflammatory effects (29). When theophylline was added to moderate ICS plus LABA it improved small airway function, airway inflammation and reduced asthma exacerbations in Chinese patients (5). These results suggest that triple controller therapy may be a useful option in more severe asthma, and that it is also a form of severe asthma.

We assessed the inflammatory phenotype of asthma using induced sputum, and found the distribution of phenotypes in this Chinese population with asthma to be similar to studies from western countries (30). Eosinophil % in both sputum and peripheral blood related with poor asthma control.

Conclusions

In conclusion, we found that, although there was a relatively low proportion of severe asthma based on ERS/ATS criteria, two of five patients with asthma in China were uncontrolled. Uncontrolled asthma had more psychological symptoms, work productivity and activity impairment as well as eosinophilic airway inflammation. Substantial gain in asthma control was apparent in patients treated with triple-controller therapy. This may represent a form of severe asthma, and our study has implications for the definition and systematic assessment of severe asthma.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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