Treatable Traits in Elderly Asthmatics from the Australasian Severe Asthma Network: A Prospective Cohort Study

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BACKGROUND: Data on treatable traits (TTs) in different populations are limited.
OBJECTIVE: To assess TTs in elderly patients with asthma and compare them to younger patients, to evaluate the association of TTs with future exacerbations, and to develop an exacerbation prediction model.
METHODS: We consecutively recruited 521 participants at West China Hospital, Sichuan University based on the Australasian Severe Asthma Network, classified as elderly (n [62) and nonelderly (n [459). Participants underwent a multidimensional assessment to characterize the TTs and were then followed up for 12 months. TTs and their relationship with future exacerbations were described. Based on the TTs and asthma control levels, an exacerbation prediction model was developed, and the overall performance was externally validated in an independent cohort.
RESULTS: A total of 38 TTs were assessed. Elderly patients with asthma had more chronic metabolic diseases, fixed airflow limitation, emphysema, and neutrophilic inflammation, whereas nonelderly patients with asthma exhibited more allergic characteristics and psychiatric diseases. Nine traits were associated with increased future exacerbations, of which exacerbation prone, upper respiratory infectioneinduced asthma attack, cardiovascular disease, diabetes, and depression were the strongest. A model including exacerbation prone, psychiatric disease, cardiovascular disease, upper respiratory infectioneinduced asthma attack, noneosinophilic inflammation, cachexia, food allergy, and asthma control was developed to predict exacerbation risk and showed good performance.
CONCLUSIONS: TTs can be systematically assessed in elderly patients with asthma, some of which are associated with future exacerbations, proving their clinical utility of evaluating them. A model based on TTs can be used to predict exacerbation risk in people with asthma.

Key words: Asthma; Elderly; Treatable traits; Exacerbation;
Prediction model; The Australasian Severe Asthma Network

INTRODUCTION

Asthma in the elderly is extraordinarily complex and is an increasingly serious health issue, with a prevalence ranging from 4% to 13%.1 For the worldwide trend of increased average life expectancy, the number of people older than 64 years is expected to reach

approximately 1.5 billion by 2050.2 Thus, the number of elderly patients with asthma will also increase.3 Unfortunately, the rates of hospitalization and mortality of elderly patients with asthma are higher than those of younger patients with asthma,4 which may be explained by underdiagnosis and undertreatment in elderly people.5 The management of asthma in the elderly is complicated by comorbidities and polypharmacotherapy. Given these complexities, comprehensive multidimensional assessment approaches have been advocated.6

To optimize disease control in the context of advanced modern medicine,7 "treatable traits (TTs)" have been proposed as a new paradigm for the 21st-century management of chronic airway diseases.8-11 TTs involve the application of personalized medicine based on a multidimensional assessment, then the identification of pulmonary, extrapulmonary, and behavioral/risk factors that are identifiable, clinically relevant, and modifiable.11 The implementation of a TTs approach can form the basis of a precision medicine strategy in which specific investigations and treatments are tailored.10 This label-free approach could be useful for patients with airway diseases, particularly those with complex conditions such as severe asthma, and provide individualized care and improve outcomes.11

In this study, we first characterized TTs in elderly patients with asthma and compared them with younger patients from the Australasian Severe Asthma Network (ASAN). Second, we assessed the relationship between TTs and future exacerbations. Third, an exacerbation prediction model based on the asthma control level and critical risk factors among TTs was developed, and the overall performance was externally validated in an independent cohort.

METHODS Study design and participants

The ASAN (https://www.severeasthma.org.au) is a multicenter clinical research network (Australia, Singapore, China, and New Zealand) in a real-world setting. This prospective observational cohort study was conducted from March 2014 to December 2019 at West China Hospital, Sichuan University, China's ASAN center. Participants 18 years or older with stable asthma (no respiratory tract infection and no exacerbation in the previous 4 weeks) were consecutively recruited and followed up for 12 months. The recruitment period of our study was from March 2014 to December 2018, and the follow-up period was from March 2014 to December 2019 (Figure 1). Asthma in the elderly was defined as asthma in people older than 64 years.1 Ethics approval was received from the Clinical Trial and Biomedicine Ethics Committee of West China Hospital of Sichuan University (no. 2014-244). Written and oral informed consent was obtained from all the participants. The detailed inclusion and exclusion criteria of the participants are described in this article's Online Repository at www.jaci-inpractice.org.

Sociodemographic information and clinical data collection

FIGURE 1. Flowchart of the cohort included in this study.

At baseline, all participants underwent a multidimensional assessment to identify TTs present within the pulmonary, extrapulmonary, and behavioral/psychosocial domains. Sociodemographic information and data including height, weight, asthma history, medications and adherence, asthma triggers, comorbidities, smoking history, asthma-related exacerbation (in the past 12 months), Asthma Control Test (ACT)12 score, and the Asthma Quality of Life Questionnaire13 score were collected. Data on other medical investigations performed within the last 6 months, including highresolution computed tomography of the chest, chest X-ray, sinus computed tomography, esophagoscopy,

polysomnography, rhinoscopy, and 24-hour esophageal pH, were included. During the follow-up period, patients underwent face-to-face visits (or telephone if unable to attend) to collect detailed information about exacerbation. Early-onset asthma was defined as younger than 12 years at the onset of asthma.14 More details are provided in this article's Online Repository at www.jaci-inpractice.org.

Depression and anxiety assessment

Depression or anxiety was assessed using the 14-item Hospital Anxiety and Depression Scale and defined as a score of 8 or more on the respective Hospital Anxiety and Depression Scale-Depression or Hospital Anxiety and Depression Scale-Anxiety domains.15

Lung function and bronchodilator test

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines.16 FEV1 and forced vital capacity (FVC) were measured before and 15 minutes after 400 mg of salbutamol was delivered by a metered-dose inhaler and spacer.

Sputum induction and processing

Sputum was induced and processed on the basis of a standardized operating procedure as previously described.17,18

Fractional exhaled nitric oxide, fat-free mass, and peripheral blood

Fractional exhaled nitric oxide (FeNO) levels were measured according to the American Thoracic Society19 guidelines. Fat-free mass was measured through body composition measurements using a bioimpedance analyzer. Fasting blood samples were collected for complete blood cell counts, total IgE, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting plasma glucose. Biomarkers, including the blood eosinophil count and serum IgE and FeNO levels, were used to define T2 inflammation if 2 or more of the following were present: eosinophil count greater than or equal to 0.14 109 cells/L, IgE level greater than or equal to 100 IU/mL, or FeNO greater than or equal to 30 parts per billion (ppb).20,21 Eosinophilic inflammation was defined as a sputum eosinophil count greater than or equal to 3% and/or FeNO greater than or equal to 30 ppb and/or blood eosinophil count greater than or equal to 0.3 109/L.22

Skin prick tests

Skin prick tests were performed on 11 common allergens, including dog hair, cat hair, cockroach, pollen (ragweed, birch, maize, and London plane), mold (Alternaria tenuis and Aspergillus fumigatus), and house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae). Allergen sensitization was confirmed if the participant exhibited a positive skin response to 1 or more of the tested allergens of skin prick tests.22

TTs identification

The TTs assessed in this study were based on published recommendations relevant to this concept.8-11,22-26 A total of 38 TTs were assessed, and the traits identified within the pulmonary (n ¼ 12), extrapulmonary (n ¼ 18), and behavioral/psychosocial domains (n ¼ 8) are presented in Table I.

Outcomes

The outcomes of the study were moderate to severe asthma exacerbations during the 12 months after enrollment. Severe asthma exacerbation30,31 was defined as worsening of asthma symptoms that led to 1 of the following: temporary use of systemic corticosteroids or an increase in use from a stable maintenance dose for at least 3 days, an asthma-specific hospitalization, an emergency room visit, or an intensive care unit visit requiring systemic corticosteroids. Moderate asthma exacerbation30,31 was defined as any increase in rescue bronchodilator use for at least 2 days or any temporary increase in inhaled corticosteroids,

an emergency department visit, or an unscheduled visit while not requiring systemic corticosteroids due to worsening asthma symptoms.

Statistical analysis

Normally distributed data are expressed as the mean SD and nonnormally distributed data as the median (quartiles 1, 3). Categorical variables are summarized as numbers and percentages. A student t test, c2 test, Fisher exact test, or Wilcoxon rank-sum test was used to assess the differences in TTs from the cross-sectional

TABLE I. A full description of the definitions of TTs, including the assessment method and guide for identification

Exposure/TTs	Assessment method	Guide for identification
Pulmonary traits		
Spirometry		
Postbronchodilator FEV1/FVC < 0.7		
Fixed airflow limitation		
Bronchodilator reversibility	Spirometry	Postbronchodilator increases in FEV1 >12% and >200 mL
Small airway dysfunction	Spirometry	MMEF < LLN
Eosinophilic inflammation	Induced sputum; FeNO; fasting blood	Sputum eosinophils 3% and/or FeNO9 30 ppb and/or blood eosinophils 0.3 10 /L
T2 inflammation	Blood eosinophil count; FeNO; IgE	Meet 2 or more of the following: eosinophil count 0.14109 cells/L, IgE 100 IU/mL, or FeNO 30 ppb
Neutrophilic inflammation	Induced sputum	Sputum neutrophil count 61% and eosinophil count < 3%
Bronchial hyperresponsiveness	Bronchial provocation challenge test	Decrease in FEV1 20% with methacholine provocative concentration <8 mg/mL
Emphysema	Chest CT	Doctor and/or radiologist diagnosis
Bronchiectasis	Chest CT	Doctor and/or radiologist diagnosis
Exacerbation prone	Questionnaire	3 courses of systemic corticosteroids in the last 12 mo
Cough*	AQLQ	AQLQ: Question 12 score 4
URI	Questionnaire	Self-report of upper respiratory tract infection as a trigger of asthma attack
Extrapulmonary traits		
Rhinitis	Questionnaire	Doctor diagnosis
Rhinosinusitis	Questionnaire; sinus CT	Doctor diagnosis
Nasal polyps	Questionnaire; rhinoscopy	Doctor diagnosis
Vocal cord dysfunction	Questionnaire	Doctor diagnosis
Obstructive sleep apnea	Questionnaire; polysomnography	Doctor diagnosis
Gastroesophageal reflux disease	Questionnaire; 24-h esophageal pH	Doctor diagnosis
Cardiovascular disease	Questionnaire	Doctor diagnosis
Systemic inflammation	Leukocyte	Leukocyte count > 9 109/L
Osteoporosis	Questionnaire; bone mineral density	Doctor diagnosis
Eczema	Questionnaire	Doctor diagnosis

Allergen sensitization	Skin prick test	1 positive skin response to tested allergens
Underweight	BMI	BMI < 18.5 kg/m2
Obesity	BMI	BMI 30 kg/m2
Anemia	Hemoglobin	Hb < 120 g/L in males and <110 g/L in females
Cachexia27	FFMI ¼ FFM/Height2	FFMI of <15 kg/m2 for females and 16 kg/m2 for males
Impaired fasting glucose	FPG	IFG was defined as an FPG of 6.1-7.0 mmol/L
Diabetes	Plasma glucose	RPG 11.1 mmol/L or FPG 7.0 mmol/L or OGTT 2hPG 11.1 mmol/L
Dyslipidemia28	TG, TC, HDL-C, LDL-C	TC 5.2 mmol/L or LDL-C 3.4 mmol/L or TG 1.7 mmol/L or HDL-C 1.0 mmol/L
Behavioral/psychosocial traits		
HADS or doctor diagnosis		
Smoking	Report current smoking	

HADS: anxiety domain score 8 or doctor diagnosis		
Psychiatric disease		
Anxiety		
Depression	HADS or doctor diagnosis	HADS: depression domain score 8 or doctor diagnosis
Inhaler device polypharmacy	Questionnaire	Prescription of 3 or more different inhalers
Poor medication adherence29	Questionnaire	Participants who used <70% of their prescribed dose of inhaled corticosteroid
Low socioeconomic status*	Questionnaire	Education, vocation, and income
Aspirin sensitivity	Questionnaire	Self-report of aspirin as an asthma trigger
Food allergy	Questionnaire	Self-report of certain food as an asthma trigger

AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; CT, computed tomography; FFM, fat-free mass; FFMI, fat-free mass index; FPG, fasting plasma glucose; Hb, hemoglobin; HADS, Hospital Anxiety and Depression Scale; GERD, gastroesophageal reflux disease; HDM, house dust mite; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; LLN, lower limit of normal; LDL-C, low-density lipoprotein cholesterol; MMEF, maximum midexpiratory flow; OGTT, oral glucose tolerance test; PG, plasma glucose; PSG, polysomnography; RPG, random plasma glucose; SPT, skin prick test; TC, total cholesterol; TG, triglyceride.
Psychiatric disease includes anxiety and/or depression.
Inhaler device types: pressurized metered-dose inhaler, turbuhaler, autohaler, nebulizer, accuhaler, aerolizer, handihaler, intranasal spray.
*The detailed definitions of socioeconomic status and cough are listed in this article's Online Repository at www.jaci-inpractice.org.

assessment between the elderly asthma and nonelderly asthma groups, as appropriate. Correlations between the TTs were expressed using Spearman correlation coefficients. Negative binomial regression was used to assess the association between TTs and

exacerbations during follow-up. The association between each of trait and exacerbation was measured as the ratio of the rate of exacerbations in the trait-positive group to the rate in the trait-negative group and summarized as incidence rate ratio (IRR). These analyses were conducted using SPSS version 25.0 (IBM Corp, Armonk, NY). In all statistical analyses, a P value of less than .05 was considered statistically significant.

Clinical prediction model derivation

An exacerbation prediction model was developed on the basis of TTs and the asthma control level (ACT).32 In the data set of variables in our study, there were a total of 13 variables with missing data, with missing rates ranging from 1.3% to 47.3% (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Variables with missing data were imputed using multiple imputation,33 as described to reduce bias and increase statistical power. Before imputation we diagnosed the mechanism of missingness, and variables with missing data thought to be missing not at random were not considered in the multiple imputation process (see the detailed information about the diagnosis of the mechanism of missingness including Tables E2 and E3 in this article's Online Repository at www.jaci-inpractice.org). We used the least absolute shrinkage and selection operator (LASSO) method, which is appropriate for highdimensional and multicollinear data, to select the most useful predictors of future exacerbation. A multivariate logistic regression analysis was used to build a prediction model by incorporating all the features selected from the LASSO regression analysis. The final prediction model's relationships among predictors were visualized using a nomogram. Detailed information about the handling of missing values, nomogram, and LASSO are described in this article's Online Repository at www.jaci-inpractice.org.

Clinical prediction model performance and validation

The concordance index (C-index) and the area under the receiveroperating characteristics curve with the calculation of the area under curve (AUC) replies were used to quantify the discrimination performance of the clinical model. The Hosmer-Lemeshow goodnessof-fit test and calibration curves were used to assess the model calibration. A P value of more than .05 for the Hosmer-Lemeshow test suggests no evidence of poor goodness-of-fit, which is the desired outcome for a predictive model.34 The internal and external validity of the model were determined. Internal validation was performed using both 1000 bootstrap sampling and 10-fold cross-validation to produce bias-corrected estimates of the model's performance. External validation (temporal validation) was evaluated by studying participants who were recently recruited from a completely different cohort of participants with asthma. These participants were prospectively and consecutively recruited from January 2019 to December 2019 at West China Hospital, Sichuan University, on the basis of ASAN (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The follow-up period for the temporal validation cohort was from January 2019 to December 2020. In addition, a sensitivity analysis was conducted to test the influence of age on the model. The model performance and validation were performed using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Detailed information about the model performance and validation are described in this article's Online Repository at www.jaci-inpractice.org.

RESULTS Sociodemographic and clinical characteristics

Of the 521 eligible participants screened, 62 were classified into the elderly group (>64 years old) and 459 were classified into the nonelderly group (64 years old; Table II). The median ages of the elderly and nonelderly groups were 70.0 (first quartile [Q1], third

quartile [Q3]: 67.0, 72.3) years and 43.0 (Q1, Q3: 34.0, 52.0) years, respectively. The proportion of female participants in the elderly group was lower than that in the nonelderly group (46.8% vs 65.6%; P ¼ .004). Among the smokers, the pack-years was higher in the elderly group (median [Q1, Q3], 25.5 [14.7, 44.5]) than in the nonelderly group (median [Q1, Q3], 12.0 [3.0, 27.0]) (P ¼ .002). The elderly asthma group showed a lower proportion of early-onset asthma than the nonelderly asthma group (4.8% vs 17.6%; P¼ .010). Of the 62 elderly participants, 11 (17.7%) had severe asthma, 21 (33.9%) had moderate asthma, and 30 (48.4%) had mild asthma as defined by the Global Initiative for Asthma. Furthermore, the elderly group participants had worse airway obstruction (FEV1% predicted, 63.03 [21.29] vs 70.51 [21.25]; FEV1/FVC, 57.60 [12.27] vs 67.55 [13.21]; all P < .001). Compared with the nonelderly group, the elderly group included a greater proportion of patients with FEV1/FVC less than lower limit of normal (82.0%) (P¼ .035) and a lower DFEV1/FVC, % (median [Q1, Q3], 14.76 [45.22, 1.75] %) (P ¼ .010). Regarding exacerbation history, the elderly group included a higher proportion of patients who had experienced at least 1 severe exacerbation in the past year compared with the nonelderly group (46.8% vs 32.5%; P¼ .027). A greater proportion of patients in the elderly asthma group than in the nonelderly asthma group had been admitted to hospital (41.9% vs 22.7%; P¼ .001). The sociodemographic and clinical characteristics of the 521 participants are presented in Table E4 in this article's Online Repository at www.jaci-inpractice.org. The sociodemographic and clinical characteristics of the temporal validation cohort are presented in Table E5 in this article's Online Repository at www.jaci-inpractice.org.

TTs and prevalence

We assessed 38 TTs in total, including 12 pulmonary traits, 18 extrapulmonary traits, and 8 behavioral/psychosocial traits. The median (Q1, Q3) number of traits assessed in the elderly and nonelderly groups were 8 (Q1, Q3: 7, 10) and 8 (Q1, Q3: 6, 10; P¼ .51), respectively. The proportion of the possible traits present in the 3 domains between the 2 groups were similar (see Figure E2 in this article's Online Repository at www.jaciinpractice.org).

The prevalence of TTs in participants classified as elderly or nonelderly is presented in Table III. The prevalence of TTs of all participants is presented in Table E6 in this article's Online Repository at www.jaci-inpractice.org. In the pulmonary domain, the prevalence of fixed airflow limitation (73.3% vs 41.0%; P< .001), neutrophilic inflammation (40.0% vs 23.0%; P ¼ .028), and emphysema (8.1% vs 1.3%; P < .001) was significantly higher in the elderly group than in the nonelderly group. However, eosinophilic inflammation (48.4% vs 70.0%; P¼ .001) and T2 inflammation (32.3% vs 67.5%; P< .001) were less common in the elderly group than in the nonelderly

Characteristic	n1*	Elderly (n [62)	n2*	Nonelderly (n [459)	t/c2/Z	P value
Age (y), median (Q1, Q3)	62	70.0 (67.0, 72.3)	459	43.0 (34.0, 52.0)	12.792	<.001
Sex: female, n (%)	62	29 (46.8)	459	301 (65.6)	8.317	.004
BMI (kg/m2), mean SD	62	23.71 (3.49)	459	23.18 (3.70)	1.303	.193†
Smoking, Never/Former/Current, n	61	45/11/5	459	336/80/43	0.094	.954
Pack-years, median (Q1, Q3)	25	25.5 (14.7, 44.5)	111	12.0 (3.0, 27.0)	3.082	.002

Age of asthma onset (y), mean SD 62 53.8 (19.5) 459 30.7 (16.0) 8.277 <.001
Early-onset asthma, n (%) 62 3 (4.8) 459 81 (17.6) 6.626 .010
Asthma family history, n (%) 61 24 (38.7)z 459 150 (32.7) 0.222 .638
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3) 62 200 (0, 400) 459 200 (0, 400) 0.251 .801
Additional medications, n (%)
LABA 62 32 (51.6) 459 266 (58.0) 0.897 .344
LTRA 62 17 (27.4) 459 152 (33.1) 0.809 .369
LAMA 62 5 (8.1) 459 11 (2.4) 4.145 .042
OCS 62 5 (8.1) 459 14 (3.1) 2.612 .106
SABA 62 9 (14.5) 459 77 (16.8) 0.202 .653
Theophylline 62 14 (22.6) 459 80 (17.4) 0.980 .322
Asthma severity (mild/moderate/severe), nx 62 30/21/11 459 204/198/57 0.540 .734
Spirometry,
Prebronchodilator FEV1% 61 63.03 21.29 453 74.91 19.91 4.302 <.001
Prebronchodilator FEV1/FVC% 61 57.60 12.27 453 67.55 13.21 5.380 <.001
Prebronchodilator FEV1/FVC < LLN, n (%) 61 50 (82.0)z 453 312 (68.9)z 4.425 .035
DFEV1/FVC (%), median (Q1, Q3)k 61 14.76 (45.22, 1.75) 453 8.30 (25.82, 2.34) 2.562 .010
AQLQ scores, median (Q1, Q3) 62 6.03 (5.41, 6.50) 451 5.88 (5.22, 6.38) 1.181 .238
ACT scores, median (Q1, Q3) 62 20 (17, 23)

35 (56.5) 459

459 20 (16, 23)

233 (50.8) 1.129 .259

Asthma control levels assessed by ACT score, n (%){ 62

Controlled
Somewhat controlled 62 18 (29.0) 459 127 (27.7)

Poorly controlled 62 9 (14.5)
459
99 (21.6)

Exacerbation in the past year
Moderate exacerbation
n (%) 62 19 (30.6) 459 192 (41.8)
2.836 .092
Median (Q1, Q3) 62 0 (0, 1)

29 (46.8) 459

459 0 (0, 1)

149 (32.5) 1.369 4.920 .171

.027
Severe exacerbation 62
n (%)
Median (Q1, Q3) 62 0 (0, 1) 459 0 (0, 1)
2.359 .018
Unscheduled visit
n (%) 62 16 (25.8) 459 156 (34.0)
1.653 .199
Median (Q1, Q3) 62 1 (0, 3)

8 (12.9) 459

459 1 (0, 3)

65 (14.2) 0.957 0.061 .339

.805
Emergency room visit 62
n (%)
Median (Q1, Q3) 62 0 (0, 1) 459 0 (0, 1)
0.468 .640
Hospitalization
n (%) 62 26 (41.9) 459 104 (22.7)
10.840 .001
Median (Q1, Q3) 62 1 (0, 2)

2 (3.2) 459

459 1 (0, 1)

2 (0.4) 2.405
NA .016

.070#
Intensive care admission 62

n (%)
Median (Q1, Q3) 62 0 (0, 0) 459 0 (0, 0)
2.385 .017

TABLE II. Sociodemographic and clinical characteristics of the study participants with asthma, classified as elderly (age > 64 y) or nonelderly (age 64 y)
AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting b agonist; LAMA, long-acting muscarinic antagonist; LLN, lower limit of normal; LTRA, leukotriene receptor antagonist; NA, not available; OCS, oral corticosteroid; Pre, prebronchodilator; SABA, short-acting b agonist.
*n1 and n2 represent the total number of people actually assessed for each characteristic in the elderly group and the nonelderly group, respectively. †Data are transformed to normal distribution. zPercentages calculated on nonmissing data. xThe severity of asthma classified as mild, moderate, and severe was defined on the basis of Global Initiative for Asthma guidelines. kDFEV1/FVC, % ¼ (Pre-FEV1/FVC FEV1/FVCLLN)/Pre-FEV1/FVC100%.
{ACT levels were graded using the ACT total score: “poorly controlled” (score < 16), “somewhat controlled” (score 16-19), and “controlled” (score 20). #Fisher exact probabilities.
TABLE III. Prevalence of TTs in the study participants with asthma, classified as elderly (age > 64 y) or nonelderly (age 64 y)
Elderly (n [62) Nonelderly (n [459)

TTs Expressed/Assessed* % Expressed/Assessed* % t/c2/Z P value
Pulmonary traits
44/60
73.3
173/422
41.0
22.194 <.001
Fixed airflow limitation
Bronchodilator reversibility 28/61 45.9 193/421
45.8 0.000 .993
Small airway dysfunction 41/62 66.1 292/459 63.6 0.128 .721
Eosinophilic inflammation 30/62 48.4 321/459
70.0 11.537 .001
T2 inflammation 20/62 32.3 306/453 67.5 29.239 <.001
Neutrophilic inflammation 14/35 40.0 62/270 23.0
4.807 .028
Bronchial hyperresponsiveness 23/26 88.5 234/248 94.4 0.574 .449
Emphysema 5/62 8.1 6/459 1.3 9.020
.003
Bronchiectasis 0/62 0.0 25/460 5.4 2.455 .117
Exacerbation prone 6/62 9.7 23/459 5.0
1.462 .227
Cough 18/61 29.5 143/444 32.2 0.180 .671

URI	47/62	75.8	339/458	74.0	0.091	.762						
Extrapulmonary traits												
Rhinitis	19/62	30.6	258/458	56.3	14.474	<.001						
Rhinosinusitis	1/62	1.6	18/459	3.9	0.302	.583						
Nasal polyps	2/62	3.2	40/458	8.7	2.231	.135						
Vocal cord dysfunction	0/62	0.0	1/457	0.2	NA	>.999†						
Obstructive sleep apnea	0/62	0.0	5/458	1.1	NA	>.999†						
Gastroesophageal reflux disease	2/62	3.2	32/457	7.0	0.730	.393						
Cardiovascular disease	11/62	17.7	24/459	5.2	11.724	.001						
Systemic inflammation	8/62	12.9	43/451	9.5	0.691	.406						
Osteoporosis	8/62	12.9	19/458	4.1	6.817	.009						
Eczema	4/62	6.5	95/458	20.7	7.235	.007						
Allergen sensitization	21/57	36.8	240/400	60.0	10.923	.001						
Obesity	8/62	12.9	50/459	10.9	0.223	.637						
Underweight	2/62	3.2	35/459	7.6	1.005	.316						
Anemia	3/62	4.8	3/452	0.7	5.000	.025						
Cachexia	9/43	20.9	116/395	29.3	1.301	.254						
Impaired fasting glucose	6/39	15.4	6/298	2.0	14.272	<.001						
Diabetes	5/62	8.1	11/457	2.4	4.108	.043						
Dyslipidemia	29/40											
	8/61	72.5										
	12.9	124/299										
	41/458	41.5										
	9.0	13.717										
	0.999	<.001	.318									
Behavioral/psychosocial traits												
Smoking												
Psychiatric disease	1/62	1.6	68/459	14.8	8.286	.004						
Anxiety	0/62	0.0	40/459	8.7	4.687	.030						
Depression	1/62	1.6	48/459	10.0	4.706	.030						

Inhaler device polypharmacy 5/62 8.1 40/4598.7 0.029 .864
Poor medication adherence 14/50 28.0 125/390
32.1 0.337 .562
Low socioeconomic status 33/60 55.0 126/406 31.0 3.651 <.001
Aspirin sensitivity 2/62 3.2 7/458 1.5
0.196 .658
Food allergy 9/62 14.5 114/458 24.9 3.255 .071
NA, Not available.
*Expressed/Assessed represent the ratio of the number of people who expressed each TT by age group (elderly and nonelderly) to the number of people actually assessed in that

group.
†Fisher exact probability.
group. Compared with asthmatic patients in the nonelderly group, those with asthma in the elderly group had a higher prevalence of cardiovascular disease (17.7% vs 5.2%; P< .001), osteoporosis (12.9% vs 4.1%; P¼ .009), anemia (4.8% vs 0.7%; P¼ .025), impaired fasting glucose (15.4% vs 2.0%; P< .001), diabetes (8.1% vs 2.4%; P¼ .043), and dyslipidemia (72.5% vs 41.5%; P < .001) in the context of extrapulmonary traits. However, the prevalence of eczema (6.5% vs 20.7%; P¼ .007) and allergen sensitization (36.8% vs 60.0%; P¼ .001) was lower in the elderly group than in the nonelderly group. As for TTs in the behavioral/psychosocial domain, low socioeconomic status showed a higher prevalence in the elderly asthma group than in the nonelderly asthma group (55.0% vs 31.0%; P < .001). Elderly patients with asthma had a lower prevalence of depression (1.6% vs 10.0%; P ¼ .030) and anxiety (0.0% vs 8.7%; P ¼ .030) than nonelderly patients with asthma. The
TABLE IV. Predicting exacerbations over the follow-up period in participants with asthma (elderly and nonelderly, combined)
TTs IRR Unadjusted model

95% CI P value Adjusted model
IRR 95% CI P value
Total number of traits present 1.136 1.076 1.200
<.001 — — — —
Pulmonary traits
Fixed airflow limitation 1.024 0.784 1.337 .863
1.010 0.743 1.372 .949
Bronchodilator variability 0.796 0.607 1.043 .098 0.792 0.604 1.038 .091
Small airway dysfunction 0.979 0.746 1.285 .879
0.973 0.740 1.280 .844
Eosinophilic inflammation 0.688 0.526 0.901 .007 0.689 0.526 0.903 .007
T2 inflammation 0.736 0.563 0.962 .025
0.730 0.555 0.959 .024
Neutrophilic inflammation 1.385 0.952 2.015 .089 1.399 0.958 2.045 .083
Bronchial hyperresponsiveness 0.704 0.360 1.377
.306 0.813 0.412 1.602 .549
Emphysema 0.588 0.212 1.632 .308 0.553 0.197 1.551 .260
Bronchiectasis 1.397 0.784 2.489 .256 1.341
0.749 2.399 .324

Exacerbation prone	3.251	2.026	5.217	<.001	3.263	2.031	5.240	<.001		
Cough	1.146	0.866	1.517	.341	1.120	0.847	1.482	.426		
URI	2.066	1.482	2.880	<.001	2.073	1.484	2.897	<.001		
Total number of pulmonary traits present			1.143	1.049	1.247	.002	—	—	—	—
Extrapulmonary traits										
Rhinitis	0.955	0.735	1.241	.731	1.011	0.777	1.317	.933		
Rhinosinusitis	1.161	0.610	2.210	.649	1.158	0.604	2.223	.659		
Nasal polyps	1.411	0.925	2.154	.110	1.427	0.933	2.182	.101		
Vocal cord dysfunction	—	—	—	—	—	—	—	—		
Obstructive sleep apnea	0.592	0.141	2.492	.475	0.576	0.136	2.435	.454		
Gastroesophageal reflux disease	0.961	0.562	1.643	.884	0.929	0.543	1.590	.787		
Cardiovascular disease	2.347	1.484	3.712	<.001	2.623	1.599	4.302	<.001		
Systemic inflammation	0.816	0.516	1.291	.386	0.791	0.496	1.261	.323		
Osteoporosis	0.991	0.533	1.841	.977	0.931	0.493	1.756	.824		
Eczema	0.934	0.670	1.302	.687	0.908	0.648	1.272	.575		
Allergen sensitization	0.938	0.705	1.247	.658	0.878	0.658	1.172	.378		
Obesity	1.230	0.824	1.835	.312	1.223	0.817	1.831	.329		
Underweight	1.512	0.946	2.418	.084	1.537	0.946	2.499	.083		
Anemia	1.475	0.988	2.201	.057	1.510	0.999	2.283	.051		
Cachexia	1.934	1.388	2.696	<.001	1.839	1.295	2.611	.001		
Impaired fasting glucose	0.356	0.097	1.307	.120	0.347	0.093	1.297	.115		
Diabetes	2.434	1.288	4.600	.006	2.484	1.294	4.769	.006		
Dyslipidemia	1.024	0.730	1.437	.889	0.963	0.663	1.399	.843		
Total number of extrapulmonary traits present			1.092	0.995	1.200	.064	—	—	—	—
Behavioral/psychosocial traits										
Smoking	0.673	0.416	1.089	.107	0.649	0.390	1.081	.096		
Psychiatric disease	2.232	1.563	3.186	<.001	2.285	1.595	3.273	<.001		
Anxiety	1.641	1.022	2.636	.041	1.668	1.036	2.688	.035		
Depression	2.343	1.558	3.524	<.001	2.368	1.572	3.567	<.001		
Inhaler device polypharmacy	1.527	1.006	2.319	.047	1.588	1.034	2.439	.035		
Poor medication adherence	0.829	0.614	1.119	.221	0.817	0.604	1.105	.190		

Low socioeconomic status			1.298		0.974		1.729		.075
	1.305		0.968		1.760		.080		
Aspirin sensitivity	1.121	0.374	3.362	.838	1.116	0.370	3.361	.846	
Food allergy	1.544		1.147		2.079		.004		1.579
	1.165		2.140		.003				
Total number of behavioral/psychosocial traits present						1.149	1.032	1.280	.012
	—		—		—				

The “adjusted” model included adjustment only for age and sex.
associations between TTs are presented in Table E7 in this article’s Online Repository at www.jaci-inpractice.org.
TTs and moderate to severe exacerbations
TABLE V. Independent predictors of future exacerbation risk in participants with asthma (elderly and nonelderly, combined)

Variable	Prediction model			
	Odds ratio (95% CI)	b coefficients	P value*	
Exacerbation prone	5.497 (2.008-17.006)		1.7041	.002
Psychiatric disease†	2.613 (1.211-5.704)	0.9605	.014	
Cardiovascular disease	2.494 (0.976-6.440)		0.9139	.050
URI	2.880 (1.549-5.649)	1.0579	.001	
Noneosinophilic inflammation	1.482 (0.869-2.522)		0.3934	.140
Cachexia	1.882 (1.086-3.260)	0.6323	.024	
Food allergy	1.589 (0.879-3.263)		0.4630	.122
ACT poorly controlledz	2.039 (1.064-3.910)	0.7125	.032	

*The LASSO method was used to evaluate and screen the most important independent predictors of future asthma exacerbation. These independent predictors were then included in a final multivariate logistic regression. †Psychiatric disease includes anxiety and/or depression. zThe “ACT” variables are dummy variables, with the controlled level group serving as the reference category.
Of the 521 participants, 86.6% (n ¼ 451) completed the 1year follow-up. Among them, 33.5% (n ¼ 151) experienced at least 1 moderate to severe asthma exacerbation during the follow-up period, 15.1% (n ¼ 68) experienced at least 1 severe exacerbation, and 24.2% (n ¼ 109) experienced at least 1 moderate exacerbation. The relationships between TTs and exacerbations are presented in Table IV. For each additional trait present, there was a 13.6% increase in exacerbation risk (P< .001). The magnitude of risk was similar within the pulmonary (IRR, 1.143; P ¼ .002) and behavioral/psychosocial domains (IRR, 1.149; P ¼ .012). In the pulmonary traits, exacerbation prone (IRR, 3.263, P< .001) and upper respiratory infectioneinduced asthma attack (URI) (IRR, 2.073; P< .001) were associated with increased future exacerbations. Eosinophilic inflammation (IRR, 0.689; P ¼ .007) and T2 inflammation (IRR, 0.730; P ¼ .024) were associated with decreased risk of future exacerbations. Among the extrapulmonary traits, the presence of cardiovascular disease (IRR, 2.623; P < .001), cachexia (IRR, 1.839; P ¼ .001), and diabetes (IRR, 2.484; P¼ .006) could increase the risk of future exacerbations. In the behavioral/psychosocial domain, anxiety (IRR, 1.668; P¼ .035), depression (IRR, 2.368; P< .001), inhaler device polypharmacy

(IRR, 1.588; P¼ .035), and food allergy (IRR, 1.579; P¼ .003) were all predictive of future exacerbations.

Clinical prediction model

Eight variables with nonzero coefficients in the LASSO regression model remained and were then included in the final multivariate logistic regression model (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). These risk factors were exacerbation prone, depression, cardiovascular disease, URI, noneosinophilic inflammation, cachexia, food allergy, and ACT control. Among them, URI, ACT control, psychiatric disease, and cardiovascular disease were the main contributing factors (Table V). A model that incorporated the above 8 predictors was developed and visualized as a nomogram (Figure 2).

This model showed excellent discrimination in distinguishing between patients who did and did not experience exacerbation (C-index, 0.743, 95% CI, 0.629-0.857; AUC, 0.729, 95% CI, 0.615-0.843; Figure 3). The goodness-of-fit of the model was evaluated using the Hosmer-Lemeshow test and bias-corrected calibration curves. The Hosmer-Lemeshow test yielded a nonsignificant statistic (P ¼ .456), which suggested that the model fit was acceptable. Evaluating the bias-corrected calibration curves for the prediction model of our study indicated good agreement (see Figures E4 and E5 in this article's Online Repository at www.jaci-inpractice.org). On internal validation, both bootstrapping (bias-corrected C-index ¼ 0.727) and 10-fold cross-validation (bias-corrected C-index ¼ 0.719) suggested that the model discrimination was good. The temporal validation cohort included 154 participants, of which 131 (85.1%) completed 12 months of follow-up. The temporal validation of the AUC was 0.715 (95% CI, 0.602-0.828; see Figure E6 in this article's Online Repository at www.jaci-inpractice.org), indicating that the model discrimination was good and did not differ significantly from the AUC in our primary data set (P¼ .346). The model fit was acceptable (Hosmer-Lemeshow test, P¼ .478; calibration curve; see Figure E7 in this article's Online Repository at www.jaci-inpractice.org).

In addition, to assess the impact of age on the exacerbation prediction model, a sensitivity analysis was conducted. The final prediction model's relationship among the predictors with and without adjustment for age was investigated (Table V; see Table E8 in this article's Online Repository at www.jaciinpractice.org) and visualized using nomograms (Figure 2; see Figure E8 in this article's Online Repository at www.jaciinpractice.org). The results showed that age had a negligible impact on the clinical prediction model.

DISCUSSION

In a cohort study based on the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes project, 23 TTs were identified in white European adults with asthma. TTs were found to be more common in severe asthma than in nonsevere asthma.23 By analyzing the Australasian Severe Asthma WebBased Database, the Australian group we cooperated with reported the prevalence and exacerbation risk of 24 TTs and found that several traits were associated with future asthma exacerbation risk.22 In addition, they recently published a randomized controlled trial that applied a multidimensional assessment to define the number and type of traits present and demonstrated that a TT intervention could significantly improve the health status of people with severe asthma.26 Although the TT approach has been increasingly recommended by the scientific community to optimize the management of asthma,11 available data on the prevalence of TTs in different populations, particularly elderly patients with asthma, are limited.11

To our knowledge, our study is the first to describe TTs of asthma in the elderly. It is certainly the first to assess TTs in Chinese adults with asthma and compare the burden in elderly and nonelderly patients. We assessed the prevalence of 38 potential TTs, including 12 pulmonary traits, 18 extrapulmonary, and 8 behavioral/psychosocial traits. Although there was no statistically significant difference in the number of present TTs between the elderly and nonelderly groups, elderly patients with asthma had more chronic metabolic diseases, fixed airflow limitation, emphysema, and neutrophilic inflammation. In contrast,

FIGURE 2. Asthma future exacerbation nomogram. The asthma future exacerbation nomogram was developed on the basis of established multivariable regression models in the whole cohort population (elderly and nonelderly, combined). Using the nomogram, the probability of future asthma exacerbation in the following year can be estimated as follows. First, the judgment on predictor variables (eg, yes or no, somewhat controlled or poorly controlled) can be obtained from patients. Second, if a predictor is judged as "Yes," the value of the predictor can be designated by drawing an upward straight line from "Yes" up to the "Points" line. Third, add up the points of all the predictors assessed as "Yes" to get the total points. Finally, the probability of future asthma exacerbation in the following year can be obtained by drawing a straight line from the "Total Points line" down to the "Risk of exacerbation in the following year" line. Noneos,
Noneosinophilic inflammation.
nonelderly patients with asthma exhibited more allergic diseases or characteristics and psychiatric diseases. Nine traits were related to increased future exacerbations. The strongest of these were exacerbation prone, URI, cardiovascular disease, diabetes, and depression. In addition, we developed a model that showed good discrimination and calibration, allowing for personalized future exacerbation risk prediction.
TTs as therapeutic targets can provide more precise and inclusive individualized treatment, which could result in greater improvement of health status and fewer hospital admissions and exacerbations.26,35,36 In our study, 35 of 38 traits have been proposed as asthma TTs in previously published studies.8-11,22-26 Three of 38 traits including small airway dysfunction, food allergy, and impaired fasting glucose were first presented as TTs, which were described as asthma comorbidities, causes of asthma, or comorbid features in previous studies.37-39 It is necessary to stress that these new potentially TTs may be useful for the expansion of the candidate list of asthma TTs. In the pulmonary domain, we found that elderly adults with asthma had more fixed airflow limitation, neutrophilic inflammation, and emphysema than did nonelderly patients with asthma, which is in agreement with previous studies.4,40 In accordance with previous studies, this study demonstrated that eosinophilic inflammation and T2 inflammation were more common in nonelderly people with asthma.4,41 For metabolic diseases of extrapulmonary traits, cardiovascular disease, osteoporosis, impaired fasting glucose, diabetes, and dyslipidemia were more common in older participants, consistent with previous studies.42,43 In addition, we found that a larger proportion of elderly patients had anemia, which was in agreement with the conclusion that anemia is most frequent in older people.44 Conversely, nonelderly people with asthma were more likely to have rhinitis, eczema, and allergen sensitization, which is in agreement with previous studies.45,46 Our study found that the elderly were more likely to be in a lower socioeconomic status than the nonelderly in China. However, the generalization of this finding may be limited due to differences in the definitions of socioeconomic status

between countries.47 In contrast to a previous finding,48 anxiety and depression were found to be less common in elderly patients with asthma than in nonelderly in our study. Asthma exacerbation has always been an intractable problem because of its close association with morbidity, mortality, and health care costs. Its prevention is a vital metric for measuring the success of asthma treatments.49 We intended to determine whether TTs can be predictors of future exacerbations to inform key targets for future research. Therefore, we used negative binomial regression to evaluate the associations between TTs and future exacerbations. Just as the relationship between respiratory infection and asthma exacerbation has been recognized for centuries,50 our data also revealed that respiratory infection is strongly correlated with exacerbation. We also confirmed the findings of a previous study,22 that previous exacerbation was the strongest predictor of future exacerbations. In addition, cardiovascular disease, diabetes, anxiety, depression, inhaler device polypharmacy, and food allergy were found to be risk factors for future exacerbations, as has been previously reported in

FIGURE 3. Receiver-operating characteristic (ROC) curve of the prediction model. The x-axis specificity represents the true negative rate. The y-axis sensitivity represents the true positive rate. The AUC and the 95% CI are shown in the graph. asthma.22,25,38,50 Cachexia was significantly associated with future exacerbations of asthma in our study. Although it has not been clearly documented that components of metabolic diseases are significantly related to asthma exacerbations, cachexia is an independent risk factor for mortality in chronic obstructive pulmonary disease.51 These findings highlight important TTs that could be targeted in an effort to reduce exacerbation and inform future clinical trials. However, eosinophilic inflammation and T2 inflammation seemed to be protective factors in our study, which was inconsistent with a previous study.22 A possible explanation may be that patients with eosinophilic inflammation and/or T2 inflammation have a better response to inhaled corticosteroids.52 A previous study confirmed that personalized management of asthma based on eosinophilia results in
significant benefits.53

Using multivariable logistic regression, we developed a clinical prediction model with 8 factors to predict future exacerbation risk, and visualized it as a nomogram. Our model had good calibration and predictive performance, demonstrating that it can accurately predict future exacerbation. This nomogram can be conveniently used by clinicians.

We need to emphasize that this is a real-world pragmatic study. Randomized controlled trials designed to implement and test the TTs approach are complex but necessary. Prospective, longitudinal, interventional studies designed to explore whether modifying TTs makes a difference are still urgently needed. As such, our analyses are important for the progress of research in this area.

This study had several limitations. First, the sample size of elderly patients with asthma was relatively small. However, this was because our study was conducted in a real-world setting where the prevalence of asthma in the elderly was 11.9%, consistent with previous studies.1 In addition, the sample size of elderly patients with asthma experiencing exacerbation (n ¼ 19 [37.3%]) was not sufficient to establish a predictive model for future asthma exacerbation. To explore the effects of the identified TTs as predictors of future asthma exacerbation, we assessed predictors of future exacerbation in all patients in the cohort (the elderly and nonelderly) using a regression analysis and nomogram. However, to assess the impact of age on the exacerbation prediction model, a sensitivity analysis was conducted.

The results showed that age had a negligible impact on the clinical prediction model. Second, some TTs on our list are controversial. For example, fixed airflow obstruction, emphysema, bronchiectasis, and small airway disfunction may not be treatable. However, this is because there is no international consensus on the criteria for the establishment of TTs. The classification criteria for our TTs were determined by using published recommendations relevant to this concept. Third, although the identification of some TTs in our study was based on a doctor's diagnosis, all diagnoses were made by clinicians according to the specific combination of signs, symptoms, and laboratory testing recommended by guidelines. Fourth, as a hypothesis-generating (exploratory analysis) study, we used multiple testing on TTs to ensure that we did not miss out on something potentially interesting. We used a standard alpha level of 0.05, with a P value of less than .05, without adjusting a (type I errors), which may produce false-positive results. Thus, future studies are needed to validate the generalizability of our findings from the exploratory analyses. Finally, participants in our study were from a single center. Therefore, the generalizability of our results may be limited because no validation was conducted in another population from other countries or regions. However, to some extent, our findings from a real-world setting are generally characterized by relatively good external validity and generalizability.54

CONCLUSIONS

TTs can be systematically assessed in elderly patients with asthma. Some TTs were identified as associated with future exacerbations. Among the strongest of these were exacerbation prone, URI, cardiovascular disease, diabetes, and depression. In addition, we presented a nomogram based on specific TTs that can be conveniently used to allow personalized future exacerbation prediction in patients with asthma. Although many questions remain in relation to the TTs approach particularly concerning practical implementation, these data add new knowledge and a practical tool to aid implementation.

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