ORIGINAL ARTICLE

Airway Diseases

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Identification of patterns of factors preceding severe or life-threatening asthma exacerbations in a nationwide study

H. Tanaka[1,2] (iD) | E. Nakatani[3,4] | Y. Fukutomi[5] (iD) | K. Sekiya[5] | H. Kaneda[4] | M. Iikura[6] | M. Yoshida[7] | K. Takahashi[8] | K. Tomii[9] | M. Nishikawa[10] | N. Kaneko[11] | Y. Sugino[12] | M. Shinkai[13] | T. Ueda[14] | Y. Tanikawa[15] | T. Shirai[16] | M. Hirabayashi[17] | T. Aoki[18] | T. Kato[19] | K. Iizuka[20] | M. Fujii[2] | M. Taniguchi[5]

[1]NPO Sapporo Cough Asthma, and Allergy Center, Sapporo, Japan

[2]Formerly at the Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine, Sapporo, Japan

[3]Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan

[4]Department of Biostatistics and Data Science, Osaka University Graduate School of Medicine, Suita, Japan

[5]Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Sagamihara, Japan

[6]Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan

[7]Division of Respiratory Medicine, National Hospital Organization Fukuoka Hospital, Fukuoka, Japan

[8]Department of Respiratory Diseases and Chest Surgery, Otsu Red Cross Hospital, Otsu, Japan

[9]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan

[10]Department of Respiratory Medicine, Fujisawa City Hospital, Fujisawa, Japan

[11]Department of Pulmonary Medicine, Kameda Medical Center, Kamogawa, Japan

[12]Department of Respiratory Medicine, Toyota Memorial Hospital, Toyota, Japan

[13]Respiratory Disease Center, Yokohama City University Medical Center, Yokohama, Japan

[14]The Department of Respiratory Medicine, Saiseikai Nakatsu Hospital, Osaka, Japan

[15]Department of Respiratory Medicine and Clinical Immunology, Toyota Kosei Hospital, Toyota, Japan

[16]Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan

[17]Department of Respiratory Diseases, Amagasaki General Medical Center, Amagasaki, Japan

[18]Department of Internal Medicine, Respiratory Division, Tokai University School of Medicine, Isehara, Japan

[19]Department of Respiratory Medicine and Allergology, Kariya Toyota General Hospital, Kariya, Japan

[20]Internal Medicine, Public Tomioka General Hospital, Tomioka, Japan

Correspondence
H. Tanaka, NPO Sapporo Cough Asthma, and Allergy Center, Chuo-ku, Sapporo, Japan.
Email: tanaka@idaimaes4-naika.com

Abstract

Background: Reducing near-fatal asthma exacerbations is a critical problem in asthma management.

Objectives: To determine patterns of factors preceding asthma exacerbations in a real-world setting.

Abbreviations: COPD, chronic obstructive pulmonary disease; IAA, Innovative Asthma Association; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, inhaled long-acting beta-agonist; PEF, peak expiratory flow; SABA, short-acting beta-agonist; SpO_2, oxygen saturation by pulse oximetry; VAS, visual analogue scale.

Methods: In a nationwide prospective study of 190 patients who had experienced near-fatal asthma exacerbation, cluster analysis was performed using asthma symptoms over the 2-week period before admission.

Results: Three distinct clusters of symptoms were defined employing the self-reporting of a visual analogue scale. Cluster A (42.1%): rapid worsening within 7.4 hours from moderate attack to admission, young to middle-aged patients with low Body mass index and tendency to depression who had stopped anti-asthma medications, smoked, and hypersensitive to environmental triggers and furred pets. Cluster B (40.0%): fairly rapid worsening within 48 hours, mostly middle-aged and older, relatively good inhaled corticosteroid (ICS) or ICS/long-acting beta-agonist (LABA) compliance, and low perception of dyspnea. Cluster C (17.9%): slow worsening over 10 days before admission, high perception of dyspnea, smokers, and chronic daily mild-moderate symptoms. There were no differences in overuse of short-acting beta-agonists, baseline asthma severity, or outcomes after admission for patients in these 3 clusters.

Conclusion: To reduce severe or life-threatening asthma exacerbation, personalized asthma management plans should be considered for each cluster. Improvement of ICS and ICS/LABA compliance and cessation of smoking are important in cluster A. To compensate for low perception of dyspnea, asthma monitoring of peak expiratory flow rate and/or exhaled nitric oxide would be useful for patients in cluster B. Avoidance of environmental triggers, increase usual therapy, or new anti-type 2 response-targeted therapies should be considered for cluster C.

KEYWORDS
cluster analysis, inhaled corticosteroid compliance, near-fatal asthma, visual analogue scale

1 | INTRODUCTION

Risk factors for incipient asthma exacerbation include sex, age, race, socioeconomic status, baseline lung function, smoking history, exposure to viruses, active sinusitis, and symptomatic gastroesophageal reflux disease.[1] Frequent asthma exacerbation is a risk factor associated with progression to severe disease and excessive decline in lung function.[2] Severe exacerbation is recognized as an indication for evaluating the required level of interventional asthma management to reduce the potential risk of death.[3-8] Using cluster analysis, many studies have described the heterogeneity of severe asthma symptoms during nonexacerbation periods.[1,9-12] However, to the best of our knowledge, no studies have reported on the heterogeneity of patient factors preceding worsening symptoms leading to severe or life-threatening exacerbation in a real-world setting.

Previous reports to date have relied on information extracted by physicians from limited medical histories and on information provided by relatives or friends of patients who died from severe asthma.[3-5] Other studies have shown that short-acting beta-agonist (SABA) usage was increased from around 5 days preceding emergency hospitalization.[13,14] However, these previous data were from strictly controlled clinical trials with good compliance to inhaled corticosteroid (ICS) or ICS/long-acting beta-agonist (LABA) use, while in

general clinical practice, variable asthma drug compliance and smoking habits prevail as confounding factors. To accurately predict and reduce exacerbation, it is necessary to determine the factors influencing the pattern of exacerbation in a real-world setting and adjust management strategies for each patient accordingly.

We recently performed a nationwide, prospective, multicenter study in which patients admitted for severe or life-threatening asthma were recruited at emergency hospitals throughout Japan.[15] The results demonstrated that significant heterogeneity exists among patients with severe or life-threatening asthma exacerbation. We further estimated trajectories of asthma symptoms using *k*-means for longitudinal data in this study.

Inaccurate assessment of asthma severity often delays the provision of an appropriately intensive treatment, consequently leading to hospital admission or even death. In recent real-world adult asthma studies, symptoms assessed by visual analogue scale (VAS) scoring have been proposed as potentially reliable tools for managing patients more effectively and for predicting uncontrolled asthma at home or the general practitioner's office.[16-18] To predict, prevent, and manage severe or life-threatening asthma exacerbation, we herein assessed serial VAS scores from the 14 days before emergency hospitalization and sought to identify predictors of asthma worsening using cluster analysis.

2 | METHODS

2.1 | Study setting

This study was a secondary analysis of a previously reported prospective, multicenter, observational study of patients with severe or life-threatening asthma exacerbation.[15] In the previous study[15], we did not analyze the serial asthma symptom using 10 cm VAS scores. This study was conducted by the Innovative Asthma Association (IAA), a nationwide group performing research across Japan. Patients were recruited from 17 hospitals between October 2011 and December 2012. Briefly, all eligible patients met the following criteria: (i) >16 years of age; (ii) requiring hospitalization due to severe or life-threatening asthma attacks with SpO_2 <90% on room air at the time of hospitalization or emergency transport before treatment, and (iii) no heart failure, pneumonia, pneumothorax, or other pulmonary diseases on X-ray. Severe or life-threatening exacerbation was defined according to the Japanese Society of Allergology guidelines,[19] that is, an inability to move because of dyspnea, difficulty in speaking, and the following objective findings: peak expiratory flow (PEF) <60%, SpO_2 <90%, partial pressure of oxygen in arterial blood (PaO_2) ≤60 mm Hg, and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) ≥45 mm Hg.

The study was reviewed and approved by the Ethics Committee of Sapporo Medical University (No. 23-47). The study protocol is registered with the University Hospital Medical Information Network in Japan (number 000006448).

2.2 | Questionnaire

A total of 173 variables were acquired consisting of 91 patient-reported questions and 82 physician-reported questions during admission period (see Supplementary Appendices 1 and 2 of the Supporting Information in reference 15). The patient-reported questionnaires were mainly used to obtain baseline information on risk factors, demographics, and asthma at baseline. The physician-reported questionnaires were mainly used to record clinical and laboratory findings and follow-up data on admission. The severity of asthma was determined by the physician according to symptomatic evaluation and the daily medication regimen according to the GINA guidelines 2005.[20]

2.3 | Serial VAS

Self-administered serial VAS of asthma symptoms comprising a 10-cm-long vertical segment was completed retrospectively, daily from 14 days before admission (day −14) to day −3, and then at −60, −48, −36, −24, −12, −6, and −3 hours, and finally at 0 hours (on admission). The patient was asked to indicate his/her actual perception of asthma symptoms by marking a point along the segment. In this study, a score of 0 corresponded to optimal symptom-free breathing, whereas 10 corresponded to the most severe asthmatic symptoms. Mild asthma exacerbation (0 < VAS ≤ 3.3) was defined as "wheeze or cough," "can lie down," and "daily life not disturbed"; moderate asthma exacerbation (3.3 < VAS ≤ 6.6) was defined as

"cannot lie down," "mildly disturbed daily life," and "mild dyspnea sensation"; finally, severe exacerbation (6.6 < VAS ≤ 10) was defined as "cannot move," "cannot speak," and "strong dyspnea." These "mild," "moderate," and "severe" categories were depicted by dotted lines on the VAS score sheet (Figures S1 and S2).

2.4 | Statistical analysis

Clusters (or trajectories) for the longitudinal VAS scores were estimated using k-means for longitudinal data.[21-23] This nonparametric procedure partitions cases into clusters. Each case is first assigned arbitrarily to 1 initial cluster. Next, each case is reassigned to the neighborhood cluster based on the center (average) of each cluster. The operation is repeated until that there is no change by mean adjustment in the clusters. This process to convergence is then repeated. The best cluster number is determined by clinical interpretability and a criterion that maximizes a ratio computed by dividing between variance by within variance (ie, maximizing the homogeneity within clusters and maximizing the differences between clusters). Missing VAS scores (<4% of total) were appropriately treated by linear interpolation. The interpolated VAS scores were divided by 10 and subjected to log-log transformation, and these values were then used in the cluster analysis.

Additionally, differences in characteristics at admission between clusters were tested using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. To construct a decision tree for identifying specific clusters, we performed a tree-based recursive partitioning by conditional inference. Analyses were performed using R version 3.3.2 (R Foundation, Vienna, Austria) with the functions "kml" (package: kml) and "ctree" (package: party).

3 | RESULTS

Patients meeting the eligibility criteria during the study period numbered 223 recruited from 17 hospitals throughout Japan.[15] Thirty-three patients were excluded because the attending physicians considered it inappropriate to include them in the study. Thus, cluster analysis was performed on 190 patients (Figure 1). Of these, 50% had a history of prior hospitalization for asthma exacerbation (Table 1), and all of them had been admitted to the hospital emergency room with SpO_2 <90%, allowing us to exclude psychosomatic exacerbation and other diseases such as vocal cord dysfunction. The 190 asthmatic patients were clustered into 3 separate groups according to serial VAS scores. These were characterized by rapidly (cluster A), fairly rapidly (cluster B), and slowly (cluster C) worsening asthma symptoms. Trajectories of changes in median VAS values of the 3 clusters in the total of 190 subjects from the day −14 up to hospital admission are shown in Figure 2. Asthma symptoms by VAS scoring gradually worsened from the day −8 to −6 before admission. The median VAS score reached 3.3 cm approximately 24 hours before subsequent admission in all 190 patients. A VAS score of 3.3 cm represents the border between mild and moderate

Enrolled n = 223
(patients met eligibility criteria)

Not registered n = 33	
Cognitive impairment	8
Lack of understanding	7
Refused to participate	6
Short period of hospitalization	5
Psychological diseases	3
Death after hospitalization	1
Cardiopulmonary arrest at hospitalization	1
Unknown	2

Registered n = 190
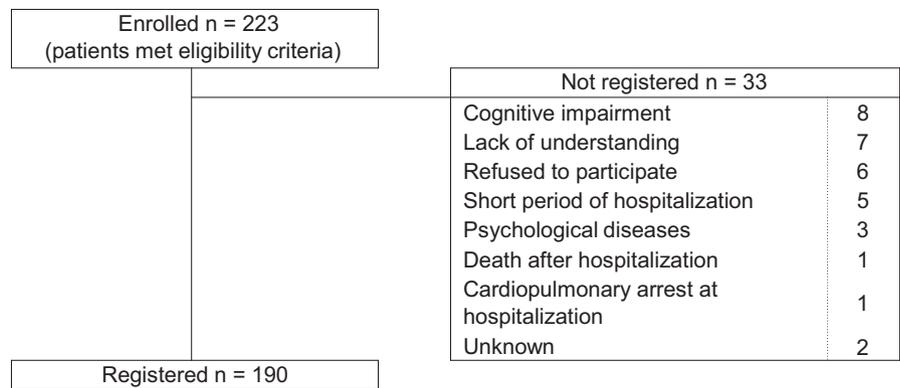
FIGURE 1 Patient characteristics

exacerbations. Histograms of the VAS score at day −6, −6 hours, −3 hours before admission, and 0 hours (at admission) for each cluster are depicted in Figure 3. Demographic characteristics, comorbidities, usual symptom triggers, current asthma condition, current triggers, and drug usage of patients in these 3 clusters are shown in Tables 1, 2, and S1.

The characteristics of cluster A were a rapidly worsening state (n = 80, 42.1%); median VAS score reached 3.3 or 6.6 cm by 7.4 or 2.7 hours before admission, respectively (Figure 2). The VAS score at admission was 10 cm in 100% of patients in this cluster (Figure 3). The trigger for current exacerbation given as "stopped using anti-asthma medication" was most frequent in cluster A relative to the other 2 clusters (P = .003, Table S1). Patients in cluster A were lean (25% with a body mass index <18.5), young or middle-aged (mean 51 year), had poor compliance with anti-asthma medication (only 36% of patients used their ICS 4 or more days a week), were current smokers (53%), and were allergic to furred pets, mites, and moths, sensitive to cold air or other climate variations (Tables 1, 2 and S1). It was founded a tendency (P = .071) for cluster A to have more psychological diseases; 6 of depression and 1 anxiety, as compared with cluster B and C (Table 1). A tree diagram separating cluster A from B and C is shown in Figure S3.

In contrast, patients in cluster B had rapid worsening (n = 76, 40.0%) with the median duration of 48 and 8.7 hours from the time of the VAS score reaching 3.3 and 6.6 cm, respectively, to the time of admission (Figure 2). They were middle-aged or older (63 year), with comorbidities including hyperlipidemia (25%) and high hemoglobin A_{1c} (P = .022), and had relatively good ICS or ICS/LABA compliance, but with a reduced sensation of dyspneic deterioration (Tables 1 and S2). Even at admission, 45% perceived mild-to-moderate dyspnea (Figure 3), with the lowest arterial blood oxygen concentration of all 3 clusters, at a mean PaO_2 of 72 Torr (Table S1).

Finally, cluster C (n = 34, 17.9%) consisted of patients with slowly worsening symptoms, with periods of approximately 10 days and 12 hours from the time of the VAS score reaching 3.3 and 6.6 cm, respectively, until admission (Figure 2). They were predominantly middle-aged (59 year) women (68%) of whom 32% were current smokers. The most characteristic features of this cluster were mild-to-moderate asthma symptoms manifesting daily, despite quite good compliance with ICS use. Severe asthmatic symptoms (VAS > 6.6)

were already present in 94% patients 6 hours before admission, in contrast to 25% in cluster A, and only 8% in cluster B (Figure 3).

These characteristics and the exacerbation status of patients in the 3 clusters are summarized in Table 3. Additionally, it can be stated that there were no differences among these patients regarding maximum oxygen inhalation dose, duration of supplemental oxygen, or duration of hospitalization (data not shown). There was no seasonal variation of the frequency of each cluster (data not shown).

4 | DISCUSSION

The work presented here is a secondary analysis of our previous study,[15] representing details of the events that occur shortly before and during severe or life-threatening asthma exacerbation. Our results document a gradual increase in the VAS score for asthmatic symptoms over 6-8 days before hospital admission, to hospital, leading to moderate severity (VAS > 3.3) at 24 hours before admission in all 190 patients surveyed (Figure 2). These results are consistent with a previous study by Tattersfield et al.[13] reported a gradual decline PEF over 5-7 days associated with severe exacerbation. These investigators also reported that changes in PEF, asthma symptoms, and use of rescue beta-agonists before exacerbation occurred in a parallel manner. Herein, using serial VAS scores of asthma symptoms, we have identified 3 groups of patients with diverse backgrounds but showing distinct characteristics leading up to severe or life-threatening exacerbation. As assessed in a real-world setting rather than a controlled trial, these patients fell into 3 groups with rapid, fairly rapid, or slow progression. We found that there were no differences among these 3 clusters in overuse of SABA before admission, baseline asthma severity, comorbid chronic obstructive pulmonary disease (COPD), or outcome after hospital admission. Interestingly, there were differences in ICS or ICS/LABA compliance, perception of dyspnea, and baseline hypersensitivity to environmental stimuli. These findings imply that optimal personalized management regimens, aimed at preventing severe or life-threatening asthma exacerbation in normal daily life, would differ even among patients within these clusters.

We found that patients assigned to cluster A showed rapid worsening just hours before moderate asthma attack and required emergency admission. Nonetheless, their subjective perception of asthma

TABLE 1 Demographic characteristics, comorbid diseases, and baseline asthma in each cluster

Variables and characteristics, N = 190	Cluster A (n = 80)	Cluster B (n = 76)	Cluster C (n = 34)	P-value
Demographic characteristics				
Female, n (%)	40 (50)	45 (59)	23 (68)	.190
Age (y), mean ± SD	51 ± 17	63 ± 18	59 ± 17	<.001
Up to 41 y	23 (29)	11 (14)	5 (15)	<.001
41 y to <65 y	38 (48)	21 (28)	15 (44)	
>65 y	19 (24)	44 (58)	14 (41)	
BMI <18.5 kg/m^2, n (%)	20 (25)	7 (9)	3 (8)	.015
BMI ≥30.0 kg/m^2, n (%)	8 (10)	5 (7)	5 (15)	.285
Lifetime smoker, n (%)	59 (74)	42 (55)	21 (62)	.052
Current smoker, n (%)	42 (53)	18 (24)	11 (32)	<.001
Pack-year, mean ± SD	18 (19)	15 (22)	18 (25)	.145
Pet ownership, n (%)	29 (36)	18 (24)	11 (32)	.227
Hypersensitivity symptoms to furred pets, n (%)	26 (33)	8 (11)	7 (21)	.004
Comorbid diseases, n (%)				
Allergic rhinitis	41 (51)	36 (47)	15 (44)	.763
Atopic eczema	9 (11)	9 (12)	2 (6)	.618
Chronic hyperplastic rhinosinusitis/nasal polyposis	21 (26)	22 (29)	10 (29)	.910
Diabetes	8 (10)	11 (15)	4 (12)	.692
Hyperlipidemia	4 (5)	19 (25)	4 (12)	.002
Hypertension	18 (23)	23 (30)	6 (18)	.304
Chronic obstructive pulmonary disease	8 (10)	11 (15)	5 (15)	.648
Inactive pulmonary tuberculosis	3 (4)	6 (8)	2 (6)	.541
Any psychological diseases	7 (9)	2 (3)	0 (0)	.071
Baseline asthma				
Asthma duration, mean ± SD	17 ± 14	21 ± 20	18 ± 18	.709
Severity, n (%)				
Intermittent	29 (36)	25 (33)	11 (32)	.803
Mild persistent	14 (18)	17 (22)	4 (12)	
Moderate persistent	22 (28)	18 (24)	9 (26)	
Severe persistent	15 (19)	16 (21)	10 (29)	
Aspirin-intolerant asthma, n (%)	3 (3.8)	0 (0.0)	2 (5.9)	.146
Previous asthma exacerbation, n (%)				
Unscheduled visits in the past year (≥once)	34 (43)	31 (41)	15 (44)	.944
History of hospitalization for asthma	40 (50)	38 (50)	17 (50)	1.000
Hospitalizations for asthma in the past year (≥once)	16 (20)	13 (17)	5 (15)	.775
History of NFA requiring mechanical ventilation	6 (8)	6 (8)	2 (6)	.939
Usual trigger of worsening of symptoms, n (%)				
Exposure to irritant	37 (46)	32 (42)	21 (62)	.156
Dampness/storm	25 (31)	20 (26)	11 (32)	.733
Alcohol/meal	18 (23)	18 (24)	7 (21)	.937
Cold air/climate change,	59 (74)	41 (54)	25 (74)	.019
Strain/stress	50 (63)	40 (53)	23 (68)	.256
Exposure to furred pets	17 (21)	6 (8)	5 (15)	.063
Exposure to house dust	31 (39)	21 (28)	13 (38)	.295

BMI, body mass index; NFA, near-fatal asthma.
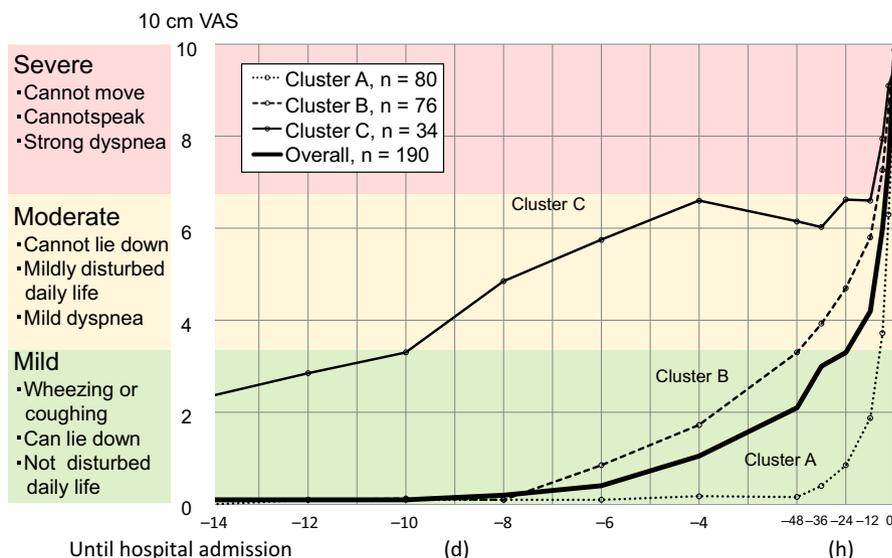
FIGURE 2 Trajectories of median 10 cm visual analogue scale values from the 14 d before hospital admission for severe or life-threatening asthma exacerbation
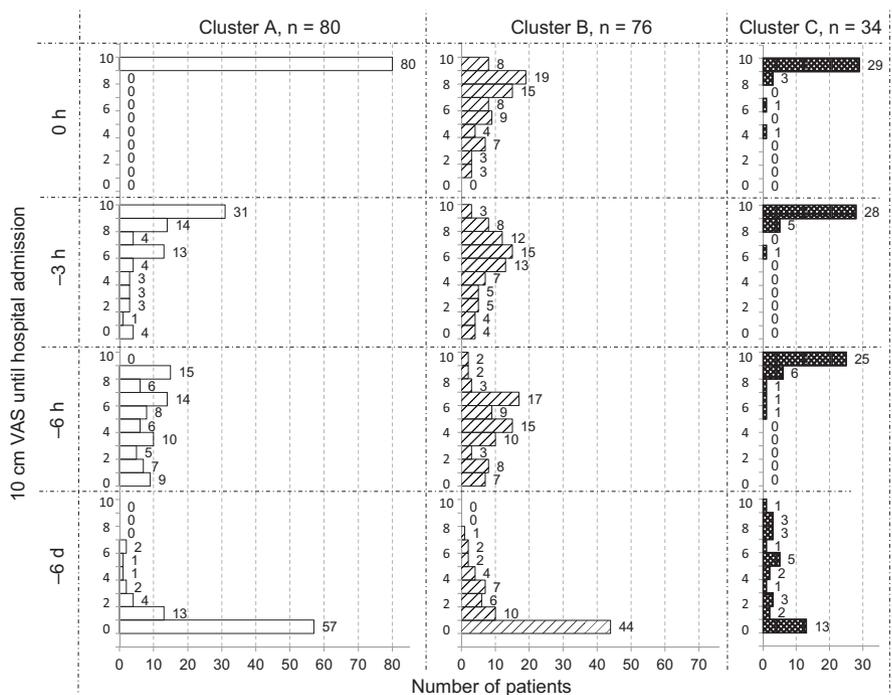
FIGURE 3 Serial changes in histogram of 10 cm visual analogue scale values at −6 d, −6 h, −3 h, and 0 h before hospital admission in each cluster

symptoms was essentially accurate, as reflected by their VAS score being 10 cm on admission for all patients in cluster A (Figure 3). They were lean young or middle-aged patients with poor anti-asthma medication compliance, were smokers, and were allergic to furred pets, mites, and moths, sensitive to cold air and other climate changes (Tables 1, 2 and S2). This cluster is thus characterized by rapidly worsening airway inflammation associated with smoking and cessation of ICS or ICS/LABA, with consequently enhanced responses to environmental triggers, potentially leading to rapid deterioration and asthma exacerbation. Not surprisingly, ICS or ICS/LABA noncompliance and smoking both increase asthma exacerbations.[11,12,24] Williams et al.[10] reported that ICS or ICS/LABA compliance rates exceeding 75% of the prescribed dose over 6 months appeared to represent a threshold above which moderate asthma exacerbations were significantly reduced. Nonetheless, this was not

associated with a decrease in the number of asthma-related emergency department visits and hospitalizations. Not only better ICS or ICS/LABA compliance but also education to encourage avoidance of environmental triggers would, therefore, be important for decreasing severe or life-threatening exacerbation in cluster A patients.

Cluster B patients, with a fairly rapid worsening before admission within 48 hours of a moderate asthma attack (VAS = 3.3) or within 8.7 hours of a severe attack (VAS = 6.6) were middle-aged or older, with hyperlipidemia, relatively good ICS or ICS/LABA compliance, and less perceived dyspnea. The most distinctive feature of patients in cluster B was their low perception of dyspnea during the exacerbation. VAS scores were lower than in clusters A or C even at hospital admission (Figure 3). A low degree of the sensation of dyspnea is recognized as a crucial problem in severe asthma frequently developing into a near-fatal attack. Our present results are therefore fully

TABLE 2 Asthma symptoms and medication usage before hospitalization in each cluster

Variable, N = 190	Cluster A (n = 80)	Cluster B (n = 76)	Cluster C (n = 34)	P-value
Asthma symptoms in the previous 3 mo				
Daytime symptoms, n (%)				
Absent	18 (23)	26 (35)	10 (29)	.093
Less than once a week	34 (43)	23 (31)	7 (21)	
Once or more a week, not every day	20 (25)	17 (23)	8 (24)	
Every day	8 (10)	9 (12)	9 (27)	
Limitation of activities, n (%)				
Absent	17 (22)	26 (35)	10 (29)	.151
Mild and brief	42 (53)	31 (41)	12 (35)	
Disturbs daily life or sleep ≥once a month	5 (6)	8 (11)	2 (6)	
Disturbs daily life or sleep ≥once a week	14 (18)	7 (9)	7 (21)	
Restricts daily life	1 (1)	3 (4)	3 (9)	
Nocturnal symptoms/awakening, n (%)				
Absent	39 (51)	47 (63)	20 (61)	.117
Less than twice a month	20 (26)	11 (15)	2 (6)	
Twice or more a month	5 (7)	6 (8)	2 (6)	
Once or more a week	7 (9)	4 (5)	2 (6)	
Frequently	5 (7)	7 (9)	7 (21)	
Drug use in the previous month				
ICS, n (%)				
Do not use	30 (38)	25 (33)	13 (38)	.047
Less than once per week	10 (13)	3 (4)	2 (6)	
Occasionally (1-3 d per week)	11 (14)	3 (4)	4 (12)	
Almost every day (≥4 d per week)	29 (36)	45 (59)	15 (44)	
SABA, n (%)				
Do not use	35 (44)	38 (50)	18 (53)	.197
Less than once per week	13 (16)	15 (20)	3 (9)	
Occasionally (1-3 d per week)	23 (29)	12 (16)	5 (15)	
Almost every day (≥4 d per week)	9 (11)	11 (15)	8 (24)	
OCS regular use[a], n (%)	4 (5)	9 (12)	3 (9)	.272
LTRA regular use[a], n (%)	20 (25)	20 (26)	13 (38)	.345
LABA regular use[a], n (%)	26 (33)	34 (45)	15 (44)	.255
Theophylline regular use[a], n (%)	9 (11)	19 (26)	4 (12)	.059
SABA usage in the previous week, n (%)				
Do not use	35 (44)	38 (50)	18 (53)	.399
Less than once per week	7 (9)	4 (5)	0 (0)	
Occasionally (1-3 d per week)	17 (21)	16 (21)	4 (12)	
Almost every day (≥4 d per week)	21 (26)	18 (24)	12 (35)	

ICS, inhaled corticosteroid; SABA, short-acting beta-agonist; OCS, oral corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting beta-agonist.

[a]Patients who reported use of the drug almost every day (≥4 d per week).

consistent with the literature.[25,26] For these patients, objective measurements, that is, daily monitoring of PEF[27] or fractional exhaled nitric oxide concentration, may be useful for early detection of exacerbation and recognizing the patient's actual objective asthmatic status.

Finally, cluster C consisted of patients gradually worsening from VAS = 3.3 and VAS = 6.6 over approximately 10 days and 12 hours, respectively. The most characteristic features of this cluster were mild-to-moderate asthmatic symptoms present daily despite relatively good compliance with ICS. Severe symptoms (VAS > 6.6) were already present in 94% of patients 6 hours before admission (Figure 3). Patients falling into this cluster are unique in that although they had strong perceptions of dyspnea, they failed to seek medical attention before respiratory failure, likely because they had become accustomed to experiencing mild-to-moderate symptoms every day. Patients in this cluster shared hypersensitivity to environmental triggers and furred pets with cluster A, as well as smoking. As shown in Table 1, baseline severity of asthma in cluster C patients was not different from the other 2 clusters. Only 29% of cluster C patients had severe persistent asthma poorly controlled by the current standard of care medication; for this subgroup, T-helper type 2 response-targeting therapies or other new drugs[28] might be considered. However, in most patients in this cluster, avoidance of environmental triggers, education on the necessity for even better ICS or ICS/LABA compliance, and changing to higher dose ICS or ICS/LABA may be effective.

Baseline disease severity of the patients in our study was mild intermittent in 34%, mild persistent in 18%, moderate persistent in 26%, and severe persistent in the remaining 22%, as shown in Table 1. Consistent with previous reports, these findings indicate that severe exacerbation or near-fatal asthma is not related to baseline asthma severity.[29,30] Surprisingly, 52% of the adult patients in this real-life setting had mild asthma, and their baseline disease severities did not differ among the 3 clusters (Table 1). In a Japanese study of asthma deaths in adults,[20] the most frequent degree of baseline asthma severity was "severe" in 39.2% of cases, followed by "moderate" in 33.0%. On the other hand, in a UK pediatric cohort study, half of asthma deaths were in patients with mild or moderate asthma.[31] It was also reported that near-fatal or severe asthma exacerbations show age-related differences in clinical presentation.[32,33] In our present study, relative to younger adults (<41 years), there was a trend toward increasing VAS symptom scores in middle-aged and elderly patients (≥41 years) between day −8 days and −24 hours before hospitalization. However, there were no differences over the period 12 hours before admission among our 3 groups (data not shown). The clustering was not affected by baseline disease severity or age.

We also found a tendency for patients in cluster A to have more psychological diseases; depression and anxiety, as comparing with cluster B and C (Table 1). As cluster A patients have poor ICS or ICS/LABA compliance, the psychological state might be associated with this poor compliance. Depression and anxiety are known to be important risk factors for severe or near-fatal asthma.[34-36] Psychosocial stress is well known to evoke asthma exacerbation, either as triggers or as covariates of worse outcomes,[34] and strain or stress is

TABLE 3 Summary of the characteristics of patients in each cluster

Variable, N = 190		Cluster A Rapid exacerbation	Cluster B Fairly rapid exacerbation	Cluster C Slow exacerbation
Demographics	Age, mean, years	51	63	59
	up to 41 y	++	+	+
	41 y to <65 y	+++	++	++
	≥65 y	+	+++	++
	BMI <18.5 kg/m^2	+++	−	−
	Current smoker	+++	+	++
	Hypersensitivity symptoms to furred pets	++	+	+
Comorbidity	Hyperlipidemia	−	++	+
Usual trigger of worsening of symptoms	Cold air/climate change, (%)	+++ (74)	+++ (54)	+++ (74)
Drug usage in the previous month	ICS regular use[a]	++	+++	++
Trigger of the current exacerbation	Stop using anti-asthma medication	+	−	−
Time to hospitalization	From VAS3.3, median, hour	7.4	48.0	240.0
	From VAS6.6, median, hour	2.7	8.7	12.0

ICS, inhaled corticosteroid; BMI, body mass index; VAS, visual analogue scale.

−, <10%, + 10-<25%; ++, 25-<50%; +++, 50-<75%, ++++, 75%-100%.

[a]Patients who reported use of the drug almost every day (≥4 d per week) of ICS use in the previous month in Table 2.

also believed to predispose to asthma. In our study, there is no difference in usual triggers of worsening asthma due to strain or stress among 3 clusters (Table 1). Psychosocial problems are very complex, and the relationship between perception of dyspnea sensations and actual asthma exacerbation is especially unclear, indicating the need for further research.

This study does have potential limitations. First, assessment of exacerbation was only carried out once per patient, such that whether a second or third exacerbation would have had the same predictors in each patient could not be determined. However, this study aimed to recognize factors leading to severe or life-threatening exacerbation. As half of our study population had already experienced the previous hospitalization for severe or life-threatening exacerbation, detailed medical histories of asthma exacerbations may partially compensate for this limitation. Therefore, long-term follow-up of this cohort is needed. Second, our study depends on the reliability of retrospective self-reporting asthma symptom VAS scoring used in the cluster analysis. Low perception of dyspnea in patients with near-fatal asthma has been reported in the literature,[25,26] suggesting questionnaire-based evaluations of symptoms may not necessarily be reliable. Certainly, in this study low perception of dyspnea was prominent in cluster B and high perception of dyspnea in cluster C. Objective measurements of lung function including PEF or fractional exhaled nitric oxide would be helpful for validating our results, but that is not practical in an actual clinical setting. It has also been reported that changes in asthma symptom scores, PEF, and use of rescue beta-agonists before exacerbation showed parallels.[13] Third, in this study we could not address the influence of ethnicity upon our cluster, because all participants are one race of Japanese.

In conclusion, we herein identified 3 distinct clusters of worsening patterns and factors associated with those patterns leading to severe or life-threatening asthma exacerbation in a real-life setting

rather than in a clinical trial. The most important factors contributing to being assigned to one of these 3 clusters were degree of ICS or ICS/LABA compliance, low or high perception of dyspnea, and baseline hypersensitivity to environmental stimuli, as well as smoking, and sensitivity to furred pets. Combinations of these factors were different for each cluster, such that daily-life asthma education and treatment action plans should also be explicitly tailored to the patients in each cluster. Another strength of our study is the finding that not only low perception but also high perception of dyspnea is a critical characteristic of incipient severe or life-threatening asthma exacerbation. Further studies are necessary to assess the usefulness of suggesting phenotypic interventions for the prevention of recurrent severe or life-threatening asthma exacerbation.

AUTHOR CONTRIBUTIONS

Hiroshi Tanaka, MD, Eiji Nakatani, PhD, Yuma Fukutomi, MD, Kiyoshi Sekiya, MD, and Masami Taniguchi, MD, designed this study and contributed to the interpretation of data. Eiji Nakatani, PhD, and Hideaki Kaneta, MD, performed the statistical data analysis. All other

authors have participated in completing case cards. The original manuscript was drafted by Hiroshi Tanaka, MD, and Eiji Nakatani, PhD, and all authors have participated in revision of the final submitted draft of this manuscript.

CONFLICT OF INTERESTS

All authors declare that they have no relevant conflict of interests.

ORCID

H. Tanaka https://orcid.org/0000-0002-1812-332X
Y. Fukutomi https://orcid.org/0000-0001-9913-4524

REFERENCES

1. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and co-morbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med*. 2017;195:302-313.
2. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbation predict excess lung function decline in asthma. *Eur Respir J*. 2007;30:452-456.
3. Fraser PM, Speizer FE, Waters SD, Doll R, Mann NM. The circumstances preceding death from asthma in young people in 1968 to 1969. *Br J Dis Chest*. 1971;65:71-84.
4. Sears MR, Rea HH. Patients at risk for dying of asthma: New Zealand experience. *J Allergy Clin Immunol*. 1987;80:477-481.
5. Beasley R, Pearce N, Crane J, Burgess C. Beta-agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? *J Allergy Clin Immunol*. 1999;104:518-530.
6. Royal College of Physicians. *Why Asthma Kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry Report*. London, UK: RCP; 2014.
7. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *Npj Prim Care Respir Med*. 2014;24:14009.
8. Ichinose M, Sugiura H, Nagase H, et al. Japanese guidelines for adult asthma 2017. *Allergol Int*. 2017;66:163-189.
9. Ministry of Health, Labour and Welfare. Japanese population Survey 2015. http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei15/dl/00_all.pdf. Accessed on 5 December 2016
10. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid noncompliance. *J Allergy Clin Immunol*. 2011;128:1185-1191.
11. Suissa S, Ernest P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalization for asthma. *Thorax*. 2002;57:880-884.
12. Williams LK, Pladevall M, Xi H, et al. Relationship between compliance to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol*. 2004;114:1288-1293.
13. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbation of Asthma: a descriptive study of 425 severe asthma exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med*. 1999;160:594-599.
14. Patel M, Pilcher J, Hancox RJ, et al. The use of β2-agonist therapy before hospital attendance for severe asthma exacerbation: a *post hoc* analysis. *Npj Prim Care Respir Med*. 2015;25:14099.
15. Sekiya K, Nakatani E, Fukutomi Y, et al. Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis. *Clin Exp Allergy*. 2016;46:1043-1055.
16. Ciprandi G, Schiavetti I, Ricciardolo FL. Symptom perception and asthma control. *Postgrad Med*. 2015;127:738-743.
17. Ciprandi G, Schiavetti I, Sorbello V, Ricciardolo FL. Perception of asthma symptoms as assessed on the visual analog scale in subjects with asthma: a real-life study. *Respir Care*. 2016;61:23-29.
18. Dhand R, Kalra S, Malik SK. Use of visual analogue scales for assessment of the severity of asthma. *Respiration*. 1988;54:255-262.
19. Nakazawa T, Dobashi K. Current asthma deaths among adults in Japan. *Allergol Int*. 2004;53:205-209.
20. GINA report, global strategy for asthma management and prevention. http://www.ginaasthma.org/.
21. Genolini C, Falissard B. KmL: a package to cluster longitudinal data. *Comput Methods Programs Biomed*. 2011;104:e112-e121.
22. Hartigan JA, Wong MA. Algorithm AS 136: a k-means clustering algorithm. *J R Stat Soc Ser C Appl Stat*. 1979;28:100-108.
23. Genolini C, Falissard B. KmL: k-means for longitudinal data. *Comput Statistics*. 2010;25:317-328.
24. Bender B, Zhang L. Negative affect, medication compliance, and asthma control in children. *J Allergy Clin Immunol*. 2008;122:490-495.
25. Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest*. 2002;121:329-333.
26. Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med*. 1994;330:1329-1334.
27. Mendoza GR. Peak flow monitoring. *J Asthma*. 1991;28:161-177.
28. Ray A, Raunhal M, Oriss TB, Ray P, Wenzel SE. Current concepts of severe asthma. *J Clin Invest*. 2016;126:2394-2403.
29. Kunitoh H, Yahikozawa H, Kakuta T, et al. Fatal and near fatal asthma. *Ann Allergy*. 1992;69:111-115.
30. Romagnoli M, Caramori G, Braccioni F, et al. Near-fatal asthma phenotype in the ENFMOSA cohort. *Clin Exp Allergy*. 2007;37:552-557.
31. Anagnostou K, Harrison B, Iles R, Nasser S. Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001–2006. *Prim Care Respir J*. 2012;21:71-77.
32. Tsai CL, Lee WY, Hanania NA, Camargo CA Jr. Age-related differences in clinical outcomes for acute asthma in the United State, 2006–2008. *J Allergy Clin Immunol*. 2012;129:1252-1258.
33. Sekiya K, Taniguchi M, Fukutomi Y, et al. Age-specific characteristics of inpatients with severe asthma exacerbation. *Allergol Int*. 2013;62:331-336.
34. Huovinen E, Kaprio J, Koskenvuo M. Asthma in relation to personality traits, life satisfaction, and stress: a prospective study among 11,000 adults. *Allergy*. 2001;56:971-977.
35. Serano J, Plaza V, Sureda B, et al. Alexithymia: a relevant psychological variable in near-fatal asthma. *Eur Respir J*. 2006;28:296-302.
36. Amelink M, Hashimoto S, Spinhoven P, et al. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. *Respir Med*. 2014;108:438-444.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.