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ORIGINAL ARTICLE **Asthma and Rhinitis**

# Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis

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## Summary

*Background* Severe or life-threatening asthma exacerbation is one of the worst outcomes of asthma because of the risk of death. To date, few studies have explored the potential heterogeneity of this condition.

*Objectives* To examine the clinical characteristics and heterogeneity of patients with severe or life-threatening asthma exacerbation.

*Methods* This was a multicentre, prospective study of patients with severe or life-threatening asthma exacerbation and pulse oxygen saturation < 90% who were admitted to 17 institutions across Japan. Cluster analysis was performed using variables from patient- and physician-orientated structured questionnaires.

*Results* Analysis of data from 175 patients with severe or life-threatening asthma exacerbation revealed five distinct clusters. Cluster 1 ($n$ = 27) was younger-onset asthma with severe symptoms at baseline, including limitation of activities, a higher frequency of treatment with oral corticosteroids and short-acting beta-agonists, and a higher frequency of asthma hospitalizations in the past year. Cluster 2 ($n$ = 35) was predominantly composed of elderly females, with the highest frequency of comorbid, chronic hyperplastic rhinosinusitis/nasal polyposis, and a long disease duration. Cluster 3 ($n$ = 40) was allergic asthma without inhaled corticosteroid use at baseline. Patients in this cluster had a higher frequency of atopy, including allergic rhinitis and furred pet hypersensitivity, and a better prognosis during hospitalization compared with the other clusters. Cluster 4 ($n$ = 34) was characterized by elderly males with concomitant chronic obstructive pulmonary disease (COPD). Although cluster 5 ($n$ = 39) had very mild symptoms at baseline according to the patient questionnaires, 41% had previously been hospitalized for asthma.

*Conclusions & Clinical Relevance* This study demonstrated that significant heterogeneity exists among patients with severe or life-threatening asthma exacerbation. Differences were observed in the severity of asthma symptoms and use of inhaled corticosteroids at baseline, and the presence of comorbid COPD. These findings may contribute to a deeper understanding and better management of this patient population.

**Keywords** cluster analysis, exacerbation, heterogeneity, life-threatening asthma, near-fatal asthma

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## Introduction

Severe or life-threatening asthma exacerbation, including near-fatal asthma, is one of the most serious outcomes of asthma [1–3]. Despite its relevance to asthma management, severe or life-threatening asthma exacerbation has not been well studied compared with persistent asthma. The primary reason for the lack of published literature is that severe exacerbations have become relatively rare [4], making it difficult to perform large-scale studies in this patient population.

Some researchers have focused on the heterogeneity of disease presentation, that is clinical asthma phenotype [5–7]. In particular, cluster analyses have demonstrated that substantial variability exists in the demographic and immunological profiles of patients with severe persistent asthma [8–13]. However, heterogeneity in severe asthma exacerbation or near-fatal asthma has not been well studied [14]. Previous studies have implied the possibility of heterogeneity among asthmatic patients with severe or life-threatening exacerbation. Near-fatal asthma has been reported in patients with mild, moderate, and severe asthma [15–17], and age-related differences in the clinical presentation of severe asthma exacerbation have been documented [18, 19]. Detailed knowledge of the heterogeneity of severe or life-threatening asthma exacerbation is important because it will contribute to improving the management of this condition and healthcare planning to prevent asthma-related deaths.

The aim of this study was to elucidate the clinical characteristics and heterogeneity of patients with severe or life-threatening asthma exacerbation. $SpO_2$ was used to select patients because it is routinely measured in patients with respiratory symptoms at almost all hospitals in Japan. It is a simple, objective recruitment criterion, and hypoxia is likely to be a common cause of death in asthma exacerbation [20]. In addition, $SpO_2 < 90\%$ is generally considered to indicate the need for aggressive therapy [21]. Cluster analysis was performed to assess the heterogeneity of severe or life-threatening exacerbation and to identify patient subgroups.

## Methods

For more details, please refer to the Supplementary Methods in the Supporting Information.

### *Study setting*

This was a prospective, multicentre, observational study of patients with severe or life-threatening asthma exacerbation. It was conducted by the Innovative Asthma Association (IAA), which is a nationwide research group comprised of 351 pulmonologists and allergists from 244 institutions across Japan. All patients were recruited between October 2011 and December 2012. Eligible patients met the following criteria: (1) > 16 years old; (2) hospitalization for severe or life-threatening asthma exacerbation, with the major cause of respiratory distress being asthma exacerbation, not other respiratory diseases such as chronic obstructive pulmonary disease (COPD) or congestive heart failure; (3) the asthma exacerbation was not complicated by pneumonia, atelectasis, or pneumothorax as determined by chest X-ray; and (4) $SpO_2 < 90\%$ on room air before treatment at the time of either hospitalization or ambulance transportation [15]. Severe or life-threatening exacerbation was defined in accordance with the definition in the 2009 version of the Japanese Society of Allergology guidelines (the same definition can be found in the 2014 version of the Japanese guidelines [22]). The primary diagnostic criterion for the severe or life-threatening asthma exacerbation was inability to move because of dyspnoea. Abasia, difficulty in speaking, and objective findings (peak expiratory flow < 60%, $SpO_2 < 90\%$, partial pressure of oxygen in arterial blood ($PaO_2$) ≤ 60 mmHg, and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) ≥ 45 mmHg) were also taken into account.

The study was reviewed and approved by the ethical committee of Sapporo Medical University (No. 23–47), and the central institutional review board of Sagamihara National Hospital (No. 21 in 2011). The study protocol was registered on the University Hospital Medical Information Network in Japan (number 000006448).

### *Questionnaire*

Patient- and physician-reported structured questionnaires were completed during hospitalization. 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. The severity of asthma was determined by the physician according to symptomatic evaluation and the step of the daily medication regimen according to the GINA guidelines 2005 [21].

### *Parameters used for the cluster analysis*

The entire data set provided 173 variables. The number of variables, 91 patient-reported (Appendix S1) and 82 physician-reported (Appendix S2), was reduced before performing cluster analysis. Variables with a substantial amount of missing data were immediately excluded if they were not relevant to disease phenotype or not a risk factor for near-fatal asthma in the literature. Some

questions in the patient- and physician-reported questionnaires were similar, and the results for these answers were pooled (Appendix S3). Ultimately, 24 variables were used for clustering, and the details of these variables are shown in Table S1.

### *Statistical analysis*

To identify risk factors for severe or life-threatening exacerbations, patients with severe or life-threatening exacerbation (cases) were compared with the age- and sex-matched controls recruited from outpatients with asthma at Sagamihara National Hospital, and odds ratios and 95% confidence intervals were calculated. Risk factors were identified using a backward selection technique in multivariate conditional logistic regression analysis.

The K-medoids clustering algorithm [23], known as a partitioning around medoids algorithm, with Gower's distance metric, was adopted for clustering patients with similar baseline characteristics. Baseline differences between clusters were tested using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. The same cluster analysis was repeated after removing patients with comorbid COPD.

Stratified rates of patients requiring supplemental oxygen in each cluster were calculated using the Kaplan–Meier method, and log-rank test was used to compare between clusters. To make a simple decision tree for constructing clusters, tree-based recursive partitioning by conditional inference was performed. The splitting criterion was a $P$-value of $< 0.05$. All analyses were performed using R version 3.0.2 and SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). The functions 'pam' (package: cluster) and 'ctree' (package: party) in the R program were used.

## Results

### *Characteristics of patients with severe or life-threatening exacerbation compared with control outpatients with asthma*

Although the target sample size was 300 patients, only 223 patients at 17 institutions met the eligibility criteria (Fig. 1). Among these, 33 patients were not included because of the reasons listed in Fig. 1, while the remaining 190 patients were registered and monitored until discharge. After excluding 15 patients for whom data on the variables used in cluster analysis were not available, analyses were performed on 175 patients.

The characteristics of patients with severe or life-threatening exacerbation compared with those of control outpatients with asthma are displayed in Table 1. Patients with severe or life-threatening exacerbation were more likely to be obese, smoke, own furred pets, present with comorbid diabetes or inactive pulmonary tuberculosis, have a history of hospitalization and/or unscheduled visits for asthma, and have severe symptoms prior to hospitalization. Compared with the outpatient group, the severe or life-threatening exacerbation group had used ICSs less frequently, but short-acting beta-agonists (SABAs) more frequently in the 3 months prior to hospitalization. Conditional logistic regression analysis demonstrated that current smoking, history of hospitalization for asthma, comorbid inactive pulmonary tuberculosis, a lower frequency of ICS usage, and a higher frequency of SABA usage in the 3 months prior to hospitalization were significantly associated with an increased risk of severe or life-threatening exacerbation.

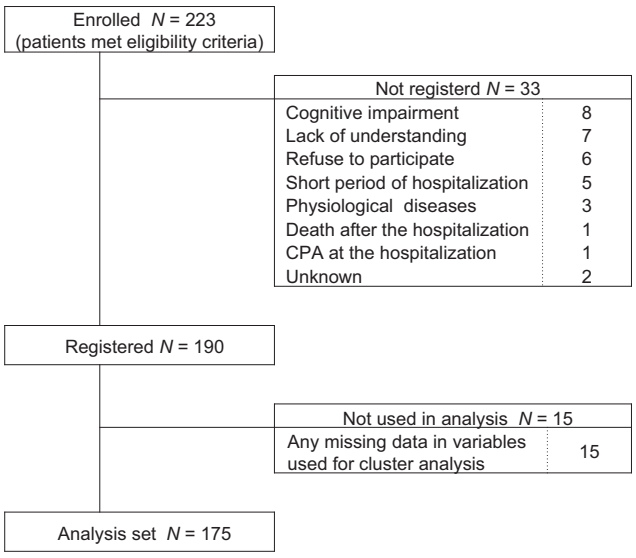


**Fig. 1.** Study flow. Among the 223 eligible patients from 17 institutions, 33 patients were not registered because the attending physicians considered it inappropriate to include them in the study, and 190 patients were registered and followed up until discharge. After excluding 15 patients who had missing data in the variables used for cluster analysis, analyses were performed on 175 patients.

### *Cluster analysis of patients with severe or life-threatening asthma exacerbation*

Patients with severe or life-threatening exacerbation were divided into five clusters comprising 27, 35, 40, 34, and 39 patients, respectively. Demographic characteristics, comorbid diseases, asthma severity, previous exacerbations, asthma triggers, disease control, and medication use are displayed in Tables 2, 3, and 4. A summary of these findings is also shown in Table 5. Near-fatal asthma requiring mechanical ventilation occurred in 11 patients (6.3%), and the frequency did not differ significantly between clusters (data not shown). Results of arterial blood gas, other laboratory tests, and positivity for serum-specific IgE antibodies in each cluster are presented in Tables S2 and S3 (see

**Table 1.** The characteristics of the patient population with severe or life-threatening asthma exacerbation in comparison with control outpatients with asthma

| | SLT asthma exacerbation ($n$ = 175) | Control outpatients ($n$ = 175) | Crude OR[‡] (95% CIs) | Adjusted OR[§] (95% CIs) |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Male, *n* (%) | 77 (44) | 77 (44) | NA | NA |
| Age (years), mean ± SD | 57 ± 18 | 57 ± 18 | NA | NA |
| BMI ≥ 30.0 kg/m$^2$, *n* (%) | 16 (10) | 6 (4) | 2.7 (1.0–6.8) | |
| Current smoker, *n* (%) | 69 (39) | 18 (10) | 7.4 (3.5–15.4) | 13.0 (3.0–56.5) |
| Pack-year, mean ± SD | 17 ± 21 | 12 ± 24 | 1.012 (1.000–1.024) | |
| Pet ownership, *n* (%)* | 53 (30) | 34 (19) | 2.0 (1.2–3.5) | |
| Comorbid diseases, *n* (%) | | | | |
| Allergic rhinitis | 84 (48) | 76 (43) | 1.2 (0.9–1.8) | |
| Atopic eczema | 18 (10) | 19 (11) | 0.9 (0.5–1.9) | |
| Chronic hyperplastic rhinosinusitis/nasal polyposis | 27 (15) | 42 (24) | 0.6 (0.3–1.0) | |
| Diabetes | 20 (11) | 8 (5) | 2.5 (1.1–5.7) | |
| Chronic obstructive pulmonary disease | 19 (11) | 21 (12) | 0.9 (0.5–1.9) | |
| Inactive pulmonary tuberculosis | 10 (6) | 2 (1) | 5.0 (1.1–22.8) | 14.4 (1.3–158.5) |
| Any psychological diseases | 9 (5) | 6 (4) | 1.5 (0.5–4.2) | |
| Baseline asthma | | | | |
| Asthma duration, mean ± SD | 19 ± 17 | 18 ± 16 | 1.002 (0.989–1.016) | |
| Severity, *n* (%) | | | | |
| Intermittent | 60 (34) | 22 (13) | 1.0 | |
| Mild persistent | 31 (18) | 28 (16) | 0.4 (0.2–0.9) | |
| Moderate persistent | 44 (25) | 63 (36) | 0.2 (0.1–0.5) | |
| Severe persistent | 40 (23) | 62 (35) | 0.2 (0.1–0.5) | |
| Aspirin-intolerant asthma, *n* (%) | 5 (3) | 20 (12) | 0.3 (0.1–0.7) | |
| Previous asthma exacerbation, *n* (%)* | | | | |
| Unscheduled visits in the past year (≥ once) | 74 (42) | 32 (18) | 4.2 (2.3–7.7) | |
| History of hospitalization for asthma | 89 (51) | 47 (27) | 3.5 (2.0–5.9) | 7.9 (2.6–24.5) |
| Hospitalizations for asthma in the past year (≥ once) | 31 (18) | 3 (2) | 10.3 (3.2–33.8) | |
| History of NFA requiring mechanical ventilation | 13 (7) | 5 (2) | 2.6 (0.9–7.3) | |
| Asthma symptom in the previous 3 months | | | | |
| Daytime symptoms, *n* (%) | | | | |
| Absent | 48 (27) | 109 (62) | 1 | |
| Less than once a week | 60 (34) | 39 (22) | 3.7 (2.0–6.7) | |
| Once or more a week, not every day | 41 (23) | 23 (13) | 4.1 (2.1–8.2) | |
| Every day | 26 (15) | 4 (2) | 16.7 (4.7–59.8) | |
| Limitation of activities, *n* (%) | | | | |
| Absent | 47 (27) | 110 (63) | 1 | |
| Mild and brief | 78 (45) | 44 (25) | 4.7 (2.6–8.7) | |
| Disturbs daily life or sleep ≥ once a month | 15 (4) | 9 (5) | 3.2 (1.3–8.0) | |
| Disturbs daily life or sleep ≥ once a week | 28 (16) | 8 (5) | 10.1 (3.8–26.5) | |
| Restricts daily life | 7 (4) | 4 (2) | 4.9 (1.2–19.5) | |
| Nocturnal symptoms/awakening, *n* (%) | | | | |
| Absent | 99 (57) | 134 (77) | 1 | |
| Less than twice a month | 31 (18) | 22 (13) | 1.9 (1.0–3.5) | |
| Twice or more a month | 13 (7) | 9 (5) | 1.9 (0.8–4.5) | |
| Once or more a week | 13 (7) | 4 (2) | 4.3 (1.3–13.7) | |
| Frequently | 19 (11) | 6 (3) | 4.4 (1.6–12.2) | |
| Drug usage in the previous 3 months | | | | |
| ICS, *n* (%) | | | | |
| Do not use | 64 (37) | 1 (1) | 78.2 (10.6–576.8) | 185.8 (20.3–1701.7) |
| Less than once per week | 5 (3) | 1 (1) | 7.3 (0.8–69.7) | 53.4 (2.1–1334.8) |
| Occasionally (1–3 days per week) | 18 (10) | 8 (5) | 4.8 (1.7–14.0) | 9.2 (1.1–77.2) |
| Almost every day (≥ 4 days per week) | 88 (50) | 165 (94) | 1 | 1 |

(continued)

**Table 1** (continued)

| | SLT asthma exacerbation ($n$ = 175) | Control outpatients ($n$ = 175) | Crude OR[‡] (95% CIs) | Adjusted OR[§] (95% CIs) |
|---|---|---|---|---|
| SABA, *n* (%) | | | | |
| Do not use | 96 (55) | 141 (81) | 1 | 1 |
| Less than once per week | 23 (13) | 20 (11) | 1.7 (0.8–3.3) | 2.2 (0.6–7.3) |
| Occasionally (1–3 days per week) | 25 (14) | 7 (4) | 6.7 (2.4–18.8) | 15.7 (2.0–124.9) |
| Almost every day (≥ 4 days per week) | 31 (18) | 7 (4) | 6.9 (2.7–17.6) | 16.9 (3.2–89.9) |
| OCS regular use[†], *n* (%) | 13 (7) | 3 (2) | 6.0 (1.3–26.8) | |
| LTRA regular use[†], *n* (%) | 49 (28) | 72 (49) | 0.5 (0.3–0.8) | |
| LABA regular use[†], *n* (%) | 78 (45) | 119 (68) | 0.3 (0.2–0.5) | |
| Theophylline regular use*, *n* (%) | 34 (19) | 37 (21) | 0.9 (0.5–1.5) | |

Patient numbers may not add up to the total because of missing data. SLT, severe or life-threatening; NA, not assessed; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; NFA, near-fatal asthma; ICS, inhaled corticosteroid; SABA, short-acting beta-agonist; OCS, oral corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting beta-agonist.

*For cases, data are provided from patient-reported questionnaire; whereas, for controls, data are complemented by chart review by the attending physician.

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

[‡]Univariate conditional logistic regression analysis.

[§]Multivariate conditional logistic regression analysis ($n$ = 350).

Supporting Information). Of note, the frequency of patients with elevated C-reactive protein (> 5 mg/dL or > 10 mg/dL) was high in cluster 4. Among cases with data on arterial blood gas, 49% had an elevated $PaCO_2$ level (≥ 45 mmHg).

*Cluster 1 (*n = *27): Younger-onset asthma with severe baseline asthma symptoms*. Cluster 1 was characterized by severe asthma symptoms at baseline. Among these patients, 85% reported disturbances to daily life or sleep due to asthma one or more times per week during the previous 3 months, and 52% were deemed to have severe persistent asthma by the attending physician. Patients in cluster 1 had the youngest age of asthma onset (mean ± SD, 24 ± 19 years) and a long disease duration (mean ± SD, 25 ± 18 years). This cluster was also characterized by a higher frequency of oral corticosteroid use in the previous month (22%), and SABA in the previous week (67% had used SABA treatment almost every day), as well as the highest frequency of hospitalization (33%) or unscheduled visits (65%) in the previous year compared with the other clusters. Despite the presence of severe baseline asthma symptoms, the frequency of current smokers was relatively high (37%), whereas the frequency of patients who regularly used ICS was low (63%). Three patients (11%) in this cluster had aspirin-intolerant asthma.

*Cluster 2 (*n = *35): Female-predominant elderly asthma*. Cluster 2 was predominantly comprised of elderly (mean age ± SD, 65 ± 13 years) females (89%). Although adherence to ICS treatment was relatively good compared with the other clusters, asthma symptoms in the previous 3 months had not been adequately controlled. Moderate and severe persistent asthma were diagnosed by the attending physician in 43% and 23% of the respective patients in this cluster. Cluster 2 had the highest frequency of comorbid, chronic hyperplastic rhinosinusitis/nasal polyposis (60%), and the longest disease duration (mean ± SD, 29 ± 17 years).

*Cluster 3 (*n = *40): Allergic asthma without baseline ICS treatment*. Cluster 3 was distinguished by a low frequency of regular ICS use (10%) and milder asthma symptoms in the previous 3 months. As assessed by the attending physician, 53% of patients had intermittent asthma. This cluster had the lowest frequencies of unscheduled visits in the past year (28%), previous hospitalization for asthma (23%), and hospitalization for asthma in the past year (8%). On the other hand, there was a high frequency of patients with atopy, and the highest frequencies of comorbid allergic rhinitis (78%), and hypersensitivity symptoms to furred pets (33%). Furred pets were owned by 42% of patients in this cluster, and 25% reported exposure to furred pets as the trigger of the current exacerbation leading to hospital admission. The frequencies of positivity for IgE antibodies to pollens and cat dander were also highest in this cluster, but this did not reach statistical significance (Table S3). Of note, cluster 3 had highest frequency of current smokers (60%).

*Cluster 4 (*n = *34): Male-predominant COPD-overlapped elderly asthma*. Cluster 4 was predominantly male (79%) and elderly (mean ± SD, 68 ± 12 years), with a

**Table 2.** Demographic characteristics, comorbid diseases, and baseline asthma by cluster

| Factor and category, $N = 175$ | Cluster 1 ($n = 27$) | Cluster 2 ($n = 35$) | Cluster 3 ($n = 40$) | Cluster 4 ($n = 34$) | Cluster 5 ($n = 39$) | *P*-value |
|---|---|---|---|---|---|---|
| Demographic characteristics | | | | | | |
| Male, *n* (%) | 13 (48) | 4 (11) | 14 (35) | 27 (79) | 19 (49) | < 0.001 |
| Age (years), mean ± SD | 49 ± 18 | 65 ± 13 | 48 ± 16 | 68 ± 12 | 57 ± 21 | < 0.001 |
| BMI ≥ 25.0 kg/m$^2$, *n* (%) | 5 (19) | 6 (17) | 10 (25) | 8 (24) | 14 (36) | 0.367 |
| BMI ≥ 30.0 kg/m$^2$, *n* (%) | 4 (15) | 0 (0) | 4 (10) | 3 (9) | 5 (13) | 0.263 |
| Lifetime smoker, *n* (%) | 15 (57) | 15 (43) | 30 (75) | 33 (97) | 21 (54) | < 0.001 |
| Current smoker, *n* (%) | 10 (37) | 5 (14) | 24 (60) | 14 (41) | 11 (28) | 0.001 |
| Pack-year, mean ± SD | 6 ± 10 | 9 ± 13 | 12 ± 13 | 41 ± 23 | 14 ± 20 | < 0.001 |
| Pet ownership, *n* (%) | 5 (19) | 12 (34) | 17 (42) | 8 (24) | 11 (28) | 0.224 |
| Hypersensitivity symptoms to furred pets, *n* (%) | 8 (30) | 6 (17) | 13 (33) | 4 (12) | 5 (13) | 0.087 |
| Comorbid diseases, *n* (%) | | | | | | |
| Allergic rhinitis | 13 (48) | 15 (43) | 31 (78) | 9 (27) | 18 (46) | < 0.001 |
| Atopic eczema | 4 (15) | 4 (11) | 5 (13) | 2 (6) | 4 (10) | 0.837 |
| Chronic hyperplastic rhinosinusitis/nasal polyposis | 7 (26) | 21 (60) | 5 (13) | 10 (29) | 9 (23) | < 0.001 |
| Diabetes | 1 (4) | 5 (14) | 3 (8) | 5 (15) | 7 (18) | 0.374 |
| Chronic obstructive pulmonary disease | 0 (0) | 0 (0) | 1 (3) | 20 (59) | 0 (0) | < 0.001 |
| Inactive pulmonary tuberculosis | 2 (7) | 2 (6) | 0 (0) | 3 (9) | 3 (8) | 0.484 |
| Any psychological diseases | 1 (4) | 2 (6) | 3 (8) | 2 (6) | 1 (3) | 0.884 |
| Baseline asthma | | | | | | |
| Asthma duration, mean ± SD | 25 ± 18 | 29 ± 17 | 10 ± 11 | 14 ± 19 | 17 ± 13 | < 0.001 |
| Asthma onset age, mean ± SD | 24 ± 19 | 36 ± 20 | 37 ± 22 | 54 ± 20 | 40 ± 25 | < 0.001 |
| Severity, *n* (%) | | | | | | < 0.001 |
| Intermittent | 0 (0) | 4 (11) | 21 (53) | 10 (29) | 25 (64) | |
| Mild persistent | 3 (11) | 8 (23) | 6 (15) | 10 (29) | 4 (10) | |
| Moderate persistent | 7 (26) | 15 (43) | 10 (25) | 4 (12) | 8 (21) | |
| Severe persistent | 14 (52) | 8 (23) | 3 (8) | 10 (29) | 2 (5) | |
| Aspirin-intolerant asthma, *n* (%) | 3 (11) | 0 (0) | 0 (0) | 0 (0) | 2 (5) | 0.032 |
| Previous asthma exacerbation, *n* (%) | | | | | | |
| Unscheduled visits in the past year (≥ once) | 17 (65) | 21 (60) | 11 (28) | 14 (44) | 11 (28) | 0.002 |
| History of hospitalization for asthma | 24 (89) | 25 (71) | 9 (23) | 15 (44) | 16 (41) | 0.331 |
| Hospitalizations for asthma in the past year (≥ once) | 9 (33) | 11 (31) | 3 (8) | 5 (15) | 3 (8) | 0.005 |
| History of NFA requiring mechanical ventilation | 4 (15) | 4 (11) | 2 (5) | 1 (3) | 2 (5) | 0.077 |
| Usual trigger of worsening of symptoms, *n* (%) | | | | | | |
| Exposure to irritant | 13 (48) | 22 (63) | 17 (43) | 18 (53) | 14 (36) | < 0.001 |
| Dampness/Storm | 11 (41) | 12 (34) | 10 (25) | 11 (32) | 7 (18) | 0.280 |
| Alcohol/Meal | 9 (33) | 11 (31) | 8 (20) | 7 (21) | 5 (13) | 0.227 |
| Cold air/Climate change | 26 (96) | 27 (77) | 23 (58) | 19 (56) | 19 (49) | < 0.001 |
| Strain/Stress | 22 (82) | 30 (83) | 18 (45) | 13 (38) | 21 (54) | < 0.001 |
| Exposure to furred pets | 5 (19) | 6 (17) | 8 (20) | 2 (6) | 3 (8) | 0.271 |
| Exposure to house dust | 9 (33) | 14 (40) | 16 (40) | 11 (32) | 11 (28) | 0.781 |

BMI, body mass index; NFA, near-fatal asthma.

high pack-year (mean ± SD, 41 ± 23), and high frequencies of current smokers (41%) and comorbid COPD (59%). The age at disease onset was older (mean ± SD, 54 ± 20 years), and the disease duration was relatively low (mean ± SD, 14 ± 19 years). In 15% of patients, the trigger of the current asthma exacerbation was bacterial infection, which was in accordance with the high frequency of patients with elevated C-reactive protein > 5 mg/dL (29%).

*Cluster 5 (*n *= 39): Asthma with almost no baseline symptoms*. Cluster 5 was defined by negligible asthma symptoms in the previous 3 months, with only 2 (6%) patients reporting any asthma symptoms. The majority of patients were deemed to have intermittent asthma (64%) by the attending physician, and the frequency of patients who used ICS almost every day was not high (46%), which is compatible with very mild baseline asthma symptoms. However, the frequency of patients with a history of hospitalization for asthma (41%) was not significantly lower than that in the other clusters. Although common triggers were strain/stress (74%) and viral infection (69%), for 28% of patients,

**Table 3.** Asthma symptom and medication usage before hospitalization by cluster

| Factor and category, $N = 175$ | Cluster 1 ($n = 27$) | Cluster 2 ($n = 35$) | Cluster 3 ($n = 40$) | Cluster 4 ($n = 34$) | Cluster 5 ($n = 39$) | $P$-value |
|---|---|---|---|---|---|---|
| Asthma symptom in the previous 3 months | | | | | | |
| Daytime symptoms, *n* (%) | | | | | | < 0.001 |
| Absent | 0 (0) | 3 (9) | 5 (13) | 2 (6) | 38 (97) | |
| Less than once a week | 0 (0) | 18 (51) | 25 (63) | 17 (50) | 0 (0) | |
| Once or more a week, not every day | 11 (41) | 12 (34) | 9 (23) | 8 (24) | 1 (3) | |
| Every day | 16 (59) | 2 (6) | 1 (3) | 7 (21) | 0 (0) | |
| Limitation of activities, *n* (%) | | | | | | < 0.001 |
| Absent | 0 (0) | 3 (9) | 5 (13) | 2 (6) | 37 (95) | |
| Mild and brief | 2 (7) | 23 (66) | 29 (73) | 24 (71) | 0 (0) | |
| Disturbs daily life or sleep ≥ once a month | 2 (7) | 4 (11) | 5 (13) | 3 (9) | 1 (3) | |
| Disturbs daily life or sleep ≥ once a week | 19 (70) | 4 (11) | 1 (3) | 3 (9) | 1 (3) | |
| Restricts daily life | 4 (15) | 1 (3) | 0 (0) | 2 (6) | 0 (0) | |
| Nocturnal symptoms/awakening, *n* (%) | | | | | | < 0.001 |
| Absent | 1 (4) | 13 (37) | 29 (73) | 18 (53) | 38 (97) | |
| Less than twice a month | 1 (4) | 15 (43) | 7 (18) | 8 (24) | 0 (0) | |
| Twice or more a month | 6 (22) | 3 (9) | 0 (0) | 3 (9) | 1 (3) | |
| Once or more a week | 7 (26) | 3 (9) | 2 (5) | 1 (3) | 0 (0) | |
| Frequently | 12 (44) | 1 (3) | 2 (5) | 4 (12) | 0 (0) | |
| Drug usage in the previous month | | | | | | |
| ICS, *n* (%) | | | | | | < 0.001 |
| Do not use | 1 (4) | 4 (11) | 29 (73) | 9 (26) | 17 (44) | |
| Less than once per week | 3 (11) | 2 (6) | 1 (3) | 5 (15) | 2 (5) | |
| Occasionally (1–3 days per week) | 6 (22) | 4 (11) | 6 (15) | 0 (0) | 2 (5) | |
| Almost every day (≥ 4 days per week) | 17 (63) | 25 (71) | 4 (10) | 20 (59) | 18 (46) | |
| SABA, *n* (%) | | | | | | < 0.001 |
| Do not use | 2 (7) | 6 (17) | 26 (65) | 24 (71) | 25 (64) | |
| Less than once per week | 3 (11) | 16 (46) | 2 (5) | 3 (9) | 4 (10) | |
| Occasionally (1–3 days per week) | 11 (41) | 8 (23) | 9 (23) | 3 (9) | 5 (13) | |
| Almost every day (≥ 4 days per week) | 11 (41) | 5 (14) | 3 (8) | 4 (12) | 5 (13) | |
| OCS regular use*, *n* (%) | 6 (22) | 4 (11) | 0 (0) | 3 (9) | 2 (5) | 0.025 |
| LTRA regular use*, *n* (%) | 9 (33) | 15 (43) | 4 (10) | 14 (41) | 8 (21) | 0.006 |
| LABA regular use*, *n* (%) | 14 (52) | 19 (54) | 6 (15) | 17 (50) | 13 (33) | 0.002 |
| Theophylline regular use*, *n* (%) | 9 (33) | 10 (29) | 2 (5) | 7 (21) | 4 (11) | 0.012 |
| SABA usage in the previous week, *n* (%) | | | | | | < 0.001 |
| Do not use | 2 (7) | 6 (17) | 26 (65) | 24 (71) | 25 (64) | |
| Less than once per week | 2 (7) | 6 (17) | 1 (3) | 1 (3) | 0 (0) | |
| Occasionally (1–3 days per week) | 5 (19) | 14 (40) | 6 (15) | 3 (9) | 6 (15) | |
| Almost every day (≥ 4 days per week) | 18 (67) | 9 (26) | 7 (18) | 6 (18) | 8 (21) | |

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

*Patients who reported use of the drug almost every day ( ≥ 4 days per week).

bacterial infection was the trigger of the current exacerbation.

### *Cluster analysis after removing patients with COPD/COPD at risk*

The analysis described above included asthmatic patients with comorbid COPD. To clarify the possible effect of comorbid COPD on the presentation of asthma exacerbations and the constitution of clusters, the same cluster analysis was repeated after removing patients with COPD (self-reported and doctor-diagnosed) as well as elderly patients with high pack-years who were considered to be at high risk of comorbid COPD ('COPD at risk'). The distribution of patients with COPD/COPD at risk between clusters is shown in Table S4. The frequencies of patients with COPD/COPD at risk were not significantly different between clusters 1, 2, 3, and 5, whereas all the patients in cluster 4 were COPD/COPD at risk. The re-analysis after removing these patients yielded four clusters (data not shown), which correlated well with clusters 1, 2, 3,

**Table 4.** $SpO_2$ on admission and trigger of the current exacerbation by cluster

| Factor and category, $N = 175$ | Cluster 1 ($n = 27$) | Cluster 2 ($n = 35$) | Cluster 3 ($n = 40$) | Cluster 4 ($n = 34$) | Cluster 5 ($n = 39$) | $P$-value |
|---|---|---|---|---|---|---|
| $SpO_2$ on admission, *n* (%) | | | | | | 0.337 |
| 1st quartile (< 84%) | 11 (41) | 9 (26) | 8 (20) | 12 (35) | 7 (18) | |
| 2nd quartile (84% to < 88%) | 8 (30) | 4 (11) | 10 (25) | 6 (18) | 13 (33) | |
| 3rd quartile (88% to < 89%) | 5 (19) | 11 (31) | 11 (28) | 8 (24) | 10 (26) | |
| 4th quartile (89% to < 90%) | 3 (11) | 11 (31) | 11 (28) | 8 (24) | 9 (23) | |
| Trigger of the current exacerbation, *n* (%) | | | | | | |
| Strain/stress | 22 (82) | 33 (94) | 31 (78) | 22 (65) | 29 (74) | 0.050 |
| Viral infection/common cold | 9 (33) | 31 (89) | 28 (70) | 22 (65) | 27 (69) | < 0.001 |
| Bacterial infection | 1 (4) | 6 (17) | 1 (3) | 5 (15) | 11 (28) | < 0.001 |
| Exposure to furred pets | 1 (4) | 5 (14) | 10 (25) | 3 (9) | 0 (0) | 0.005 |
| Overuse of SABA | 4 (15) | 1 (3) | 1 (3) | 0 (0) | 0 (0) | 0.010 |
| Stop using anti-asthma medication | 5 (19) | 6 (17) | 4 (10) | 3 (9) | 2 (5) | 0.366 |
| Exposure to irritant | 5 (19) | 6 (17) | 12 (30) | 4 (12) | 8 (21) | 0.384 |
| Exposure to NSAIDs | 4 (15) | 3 (9) | 4 (10) | 2 (6) | 2 (5) | 0.672 |
| Exposure to house dust | 6 (22) | 7 (20) | 13 (33) | 9 (27) | 8 (21) | 0.691 |
| Cold air/climate change | 5 (19) | 4 (11) | 4 (10) | 4 (12) | 2 (5) | 0.553 |

$SpO_2$, pulse oxygen saturation; NSAIDs, non-steroidal anti-inflammatory drugs.

**Table 5.** Summary of the characteristics of clusters of patients with severe or life-threatening asthma exacerbation

| | | Cluster 1 Younger-onset asthma with severe baseline symptoms | Cluster 2 Female-predominant elderly asthma | Cluster 3 Allergic asthma without baseline ICS treatment | Cluster 4 Male-predominant COPD-overlapped elderly asthma | Cluster 5 Asthma with almost no baseline symptoms |
|---|---|---|---|---|---|---|
| Demographics | Gender | M = F | M ≪ F | M < F | M ≫ F | M = F |
| | Age, mean, years. | 49 | 65 | 48 | 68 | 57 |
| | Current smoker | ++ | + | +++ | ++ | ++ |
| | Pack-year | + | ++ | ++ | ++++ | ++ |
| Comorbidity | Allergic rhinitis | ++ | ++ | ++++ | ++ | ++ |
| | Sinusitis/nasal polyposis | ++ | +++ | + | ++ | + |
| | COPD | – | – | – | +++ | – |
| Baseline asthma | Duration of asthma | +++ | +++ | ++ | +++ | +++ |
| | Asthma onset age, mean, years | 24 | 36 | 37 | 54 | 40 |
| | Previous hospitalization for asthma | ++++ | +++ | + | ++ | ++ |
| | Symptoms of asthma* | ++++ | + | – | + | – |
| | ICS regular use | ++ | ++ | – | ++ | + |
| | SABA treatment (almost every day) | +++ | ++ | + | + | + |
| | OCS regular use | + | + | – | – | – |
| Trigger of the current exacerbation | Strain/stress | ++++ | ++++ | ++++ | +++ | +++ |
| | Viral Infection | ++ | ++++ | +++ | +++ | +++ |
| | Bacterial infection | – | + | – | + | ++ |
| | Exposure to furred pets | – | + | ++ | – | – |

–, < 10%, + 10–< 25%; ++, 25–< 50%; +++, 50–< 75%, ++++, 75–100%. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; SABA, short-acting beta-agonist; OCS, oral corticosteroid.

*Frequency of patients with asthmatic symptoms that disturbs daily life or sleep ≥ once a week.

and 5 of the former analysis (concordance rate, 76.3%; Table S4 in the Supporting Information). This result indicates that comorbid COPD was unique to cluster 4, and does not have an effect on the constitution of the other four clusters.

### *Difference in prognosis during hospital admission between the clusters*

Dosages of maximum oxygen inhaled during hospitalization, the duration of supplemental oxygen, and the

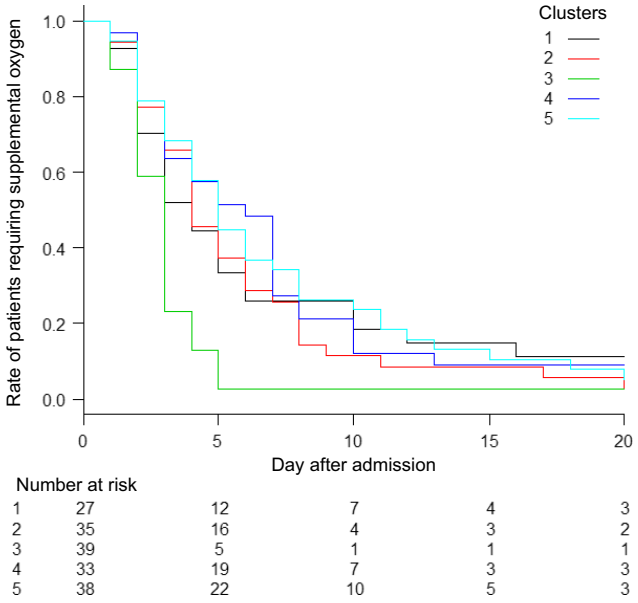


Fig. 2. Kaplan–Meier curve for rates of patients requiring supplemental oxygen by cluster.

duration of hospitalization were compared between the clusters. Kaplan–Meier analysis demonstrated that the duration of supplemental oxygen was shorter in cluster 3 compared with the other clusters ($P < 0.001$ by log-rank test for cluster 3 vs. others; Fig. 2).

### *Tree-based recursive partitioning*

The results of tree-based recursive partitioning, which were a good fit to the clusters, are presented in Fig. 3. This analysis demonstrated that limitation of activities because of asthma, comorbid COPD, and ICS use in the month prior to hospitalization were important distinguishing factors.

## Discussion

The present study demonstrated the heterogeneity in clinical phenotypes among patients with severe or life-threatening asthma exacerbation. Using cluster analysis, five clusters were identified that differed in terms of baseline asthma symptoms, comorbid COPD, and ICS use in the 3 months prior to hospitalization. Patients with severe or life-threatening asthma exacerbation are an important subgroup because improvements in interventional education and compliance, and optimal use of ICSs may reduce the incidence of recurrent, near-fatal events [24]. The findings of this study may advance the understanding and management of severe or life-threatening asthma exacerbation. Indeed, given the significant heterogeneity in the clinical and demographic presentation of severe or life-threatening asthma exacerbation, phenotype-specific interventions may be necessary.

Many studies have explored risk factors for near-fatal asthma by comparing the clinical characteristics of patients with and without a history of this condition. A history of near-fatal asthma requiring mechanical ventilation [25, 26], hospitalization or unscheduled emergency department visits for asthma exacerbation in the past year [25], underuse of ICSs [15, 27], overuse of SABA [28, 29], more frequent baseline asthma symptoms [30], and comorbid psychological diseases [31, 32] have been shown to be associated with an increased risk of near-fatal or fatal asthma. In the present study, current smoking, a history of hospitalization for asthma, a lower frequency of ICS use, and a higher frequency of SABA use in the 3 months prior to hospitalization were identified as risk factors for severe or life-threatening exacerbation. These findings are in accordance with previous studies and indicate that the present study population had a similar clinical background to that of patients with near-fatal asthma in studies conducted in the United States or Europe.

Cluster 1 comprised patients with younger-onset asthma and the most severe baseline asthma symptoms among the five clusters. Although low adherence to controlled ICS use and overuse of SABA was a baseline characteristic of the majority of patients with severe or life-threatening exacerbations, it was particularly common in patients in cluster 1. The strategy for prevention of severe or life-threatening exacerbations in such patients should involve smoking cessation [33, 34] as well as patient education using a detailed action plan, including information on the correct use of anti-asthma medication [35, 36]. Considering the tendency of patients to overuse SABA for relief therapy, the combination of formoterol with an ICS in a single inhaler may be preferable to SABA alone [37].

An important feature of cluster 2 was a high frequency of comorbid chronic hyperplastic rhinosinusitis/nasal polyposis (60%). This finding is consistent with previous studies demonstrating a link between rhinosinusitis and severe asthma [38], especially among females [39], and patients with asthma exacerbation [40]. In addition, it is possible that patients in this cluster require greater attention because old age has been associated with a higher rate of post-hospitalization mortality [2].

Cluster 3 was allergic asthma without baseline ICS treatment. Although baseline asthma symptoms were relatively mild and 77% of patients had not previously been hospitalized for asthma exacerbation, a severe or life-threatening exacerbation occurred. Thus, it was presumed that asthma exacerbations developed rapidly, and predicting severe or life-threatening events in this patient population, based on current asthma control

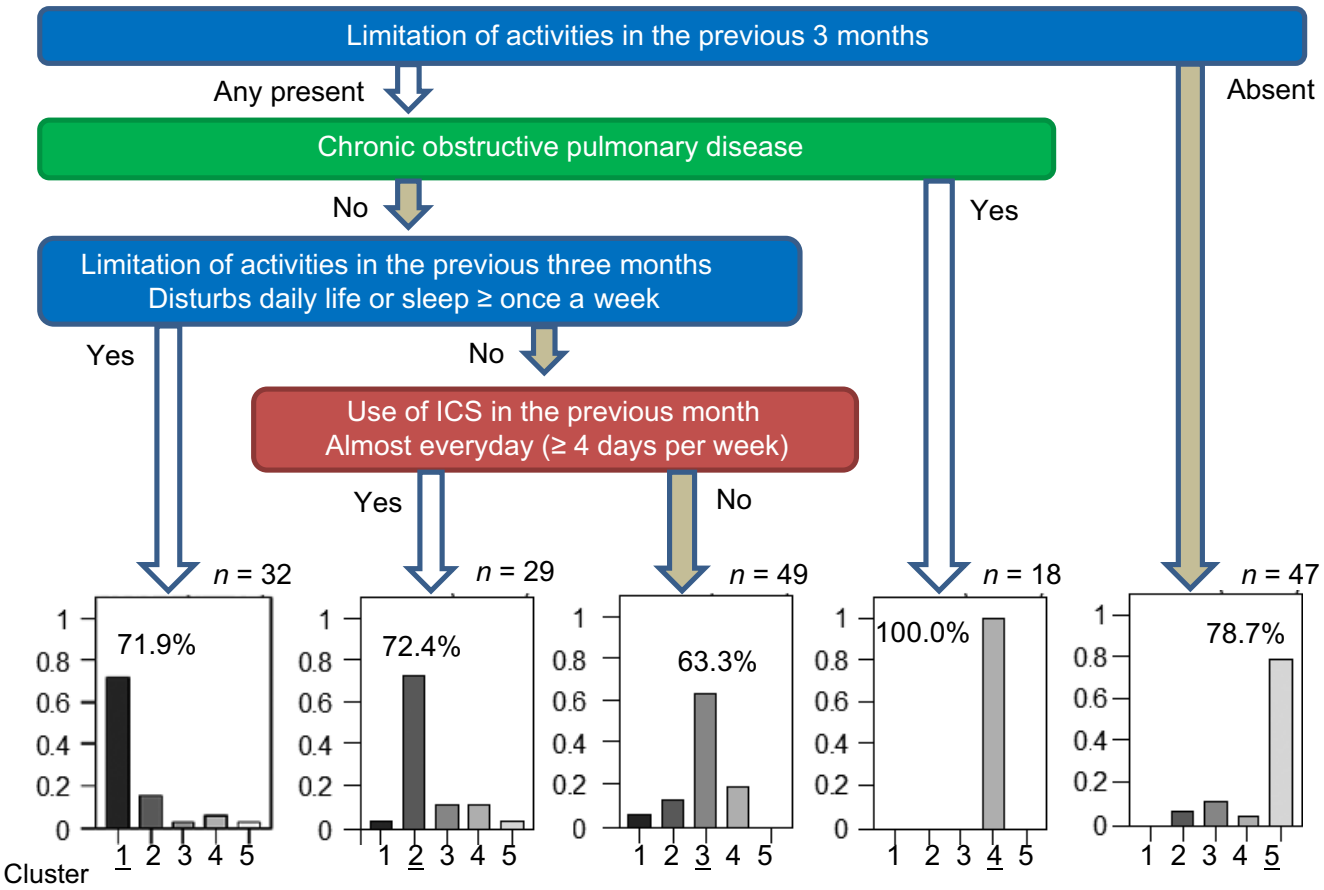


Fig. 3. Regression tree analysis and performance on cluster prediction. Using four variables, patients were assigned to one of the five clusters: cluster 1 (younger-onset asthma with severe baseline asthma symptoms), cluster 2 (female-predominant elderly asthma), cluster 3 (allergic asthma without baseline ICS treatment), cluster 4 (male-predominant elderly, COPD–asthma-overlapped elderly asthma), and cluster 5 (asthma with almost no baseline symptoms). The percentage of cases in each cluster that were correctly assigned is indicated numerically within the bar chart.

and previous hospitalizations, may be challenging. The disease course during hospitalization was significantly better than that of other clusters, as evidenced by rates of patients requiring supplemental oxygen.

Of note, some of the patients in this cluster had IgE antibodies to furred pets and reported exposure to furred pets as the trigger of the current exacerbation. Thus, IgE-mediated allergic reactions to furred pets may be the cause of the rapid development of severe or life-threatening exacerbations in some patients in cluster 3. Therefore, allergen avoidance, including furred pet avoidance, may be an effective strategy to prevent future episodes of severe asthma exacerbation for patients in this cluster [41].

Clusters 4 comprised male-predominant elderly asthma with a high frequency of comorbid COPD. Many studies have identified asthma–COPD overlap as a distinct asthma phenotype [42–44], and a high frequency of asthma exacerbation/hospitalization among patients with asthma–COPD overlap has been documented [45, 46]. Thus, the results of the present study are compatible with previous studies. The predominance of males in cluster 4 is thought to be related to a higher rate of smoking among males than females in the Japanese population [47].

Cluster 5 was a fairly unique cluster. The majority of patients did not have any asthma symptoms in the previous 3 months according to patient-oriented questionnaires. This suggests that it would be difficult to predict the risk of severe or life-threatening exacerbations because patients had very mild asthma symptoms, and unscheduled visits were rarer than in other clusters. In a previous study, a discrepancy was identified between subjective symptoms and objective measurement of asthma severity, such as lung function and fractional exhaled nitric oxide, in young adults [48]. Thus, objective measurements may be useful for the prediction of severe or life-threatening exacerbation in this patient cluster [49, 50].

Comorbid psychological disorders or vocal cord dysfunction can mimic asthma exacerbation in real-life clinical settings [51]. Patients with emergency

department visits triggered by these disorders were excluded from the present study because an objective criterion, $SpO_2$, was used for patient recruitment [52]; however, it should be noted that a minority of patients with vocal cord dysfunction have a decline in $SpO_2$ [51]. Despite the heterogeneity of patients with severe or life-threatening exacerbation, the trigger of asthma exacerbation was less variable, with respiratory viral infection (69%) and strain/stress (78%) being the two major triggers for the current exacerbation (Table 4), which was also similar to the findings of previous studies [24, 30, 53]. Obesity-related asthma is an important phenotype to consider in patients with persistent asthma [5, 54–56]. However, in the present study, obesity was not a significant clustering factor for patients with severe or life-threatening exacerbation (Table 2).

More recently, Serrano-Pariente et al. demonstrated the heterogeneity of near-fatal asthma by analysing data from the multicentre, life-threatening asthma study performed in Spain between 1997 and 1999 [14]. Cluster analysis ($n = 84$) led to the identification of three clusters of patients with near-fatal asthma. This result has both similarities and differences to the findings of our study. Serrano-Pariente et al. identified a single younger atopic cluster, whereas this cluster was subdivided into two clusters (cluster 1 and 3) in our study. The identification of clusters 4 and 5 was unique to our study. The differences between the results of these two studies are likely to be related to increased adherence to clinical practice guidelines for asthma in more recent years, because the study analysed by Serrano-Pariente et al. was performed in the late 1990s.

The key limitation of this study concerns the reliability of the questionnaire-based data used in the cluster analysis. Low perception of dyspnoea in patients with near-fatal asthma has previously been shown [57, 58], indicating that questionnaire-based evaluation of asthma symptoms may not be reliable in all patients with severe or life-threatening exacerbation. In addition, objective data, including lung function, blood eosinophil count, and laboratory parameters, were not available for cluster analysis or to define severe or life-threatening asthma exacerbation. In particular, data on lung function were not available because these parameters were not recorded in the emergency setting at most of the hospitals that participated in this study, and it is possible that patients with isolated COPD without asthma were not completely excluded, especially in cluster 4. Another limitation may be the applicability of the present findings to other populations because all the patients studied were Japanese, and there was no validation against an external cohort. Furthermore, study registration was not possible for some patients with mental/psychological diseases (Fig. 1). This may have altered the clustering of these patients because mental/psychological diseases are known to be an important risk factor of severe or life-threatening exacerbation [59, 60]. In addition, controls were not registered at the same hospitals from which the cases were studied. A further limitation may relate to the lack of information on the long-term prognosis of the study population. Thus, the association between the identified cluster and the risk of recurrence of severe or life-threatening exacerbation was not determined in this study. Despite these limitations, the present findings confirm the heterogeneity of patients with severe or life-threatening asthma exacerbation.

In conclusion, this study revealed heterogeneity among patients with severe or life-threatening asthma exacerbation. These findings may contribute to the understanding of the pathogenesis of severe or life-threatening exacerbations and improve the management of patients as well as future healthcare planning for the prevention of recurrent exacerbations. Future studies are necessary to evaluate the possibility of phenotype-specific interventions for the prevention of recurrent severe or life-threatening events.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

KS, EN, YF, MT, and HT designed the study and contributed to the interpretation of data. EN and HK performed the statistical data analysis. The manuscript was drafted by KS, EN, and YF, and it was critically revised by SH, MT, and HT. All the other authors were involved in patient recruitment.

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## Supporting Information

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

**Appendix S1**. Original variables for patient-reported questionnaires (Variable Identifier PT01 to PT91).

**Appendix S2**. Original variables for the physician-reported questionnaire (Variable Identifier PY01 to PY82).

**Appendix S3**. Composite variables used in this study.

**Table S1**. List of variables used in the cluster analysis.

**Table S2**. Arterial blood gas and laboratory data by cluster.

**Table S3**. Total IgE and positivity for serum-specific IgE Abs by cluster.

**Table S4**. Frequencies of patients with COPD/COPD at risk by cluster, and the concordance between cluster analyses using the entire study population (n=175) and after removing patients with COPD/COPD at risk (n=97).

**Figure S1**. Regional distribution of institutions involved in this study.

**Figure S2**. Average silhouette widths for assessing best number of clusters (A), and Silhouette width for each patient in clusters (B).