A Cluster Analysis of Bronchial Asthma Patients with Depressive Symptoms

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ABSTRACT

Objective: Whether or not depression affects the control or severity of asthma is unclear. We performed a cluster analysis of asthma patients with depressive symptoms to clarify their characteristics.

Methods and subjects: Multiple medical institutions in Niigata Prefecture, Japan, were surveyed in 2014. We recorded the age, disease duration, body mass index (BMI), medications, and surveyed asthma control status and severity, as well as depressive symptoms and adherence to treatment using questionnaires. A hierarchical cluster analysis was performed on the group of patients assessed as having depression.

Results: Of 2,273 patients, 128 were assessed as being positive for depressive symptoms (DS[+]). Thirty-three were excluded because of missing data, and the remaining 95 DS[+] patients were classified into 3 clusters (A, B, and C). The patients in cluster A (n = 19) were elderly, had severe, poorly controlled asthma, and demonstrated possible adherence barriers; those in cluster B (n = 26) were elderly with a low BMI and had no significant adherence barriers but had severe, poorly controlled asthma; and those in cluster C (n = 50) were younger, with a high BMI, no significant adherence barriers, well-controlled asthma, and few were severely affected. The scores for depressive symptoms were not significantly different between clusters.

Conclusion: About half of the patients in the DS[+] group had severe, poorly controlled asthma, and these clusters were able to be distinguished by their ASK-12 score, which reflects adherence barriers. The control status and severity of asthma may also be related to the age, disease duration, and BMI in the DS[+] group.

Key words: Adherence, ASK-12, Bronchial Asthma, Cluster Analysis, Depression, J-PHQ-9

INTRODUCTION

Many studies have examined the relationship between bronchial asthma and depression. Depression reduces the health-related quality of life (HR-QOL) and can worsen asthma management (1). It correlates with asthma severity, particularly in subjective evaluations by patients (1-5), and also affects the asthma control status and treatment adherence (6-10). The results of a large survey adjusted for age and sex showed that asthma patients had a 1.6-times greater risk of depression than non-asthma patients (11-13). However, other studies have not found a connection between the severity of depression and the severity of asthma (14, 15) or have observed that asthma does not increase the risk of depression (15,16). Thus, this relationship is still under debate.

In 2008, we used the Japanese version of the Patient Health Questionnaire-9 (J-PHQ-9) on more than 2,000 asthma patients as a scale for measuring depression in order to verify the relationship between depression and the severity and control of asthma (17). The results showed that patients with high J-PHQ-9 scores tended to score lower on the Japanese version of the Asthma Control Test (ACT-J). Furthermore, when the distributions of J-PHQ-9 total scores were compared by asthma severity level, the most severe group (step 4) included a large proportion of patients with J-PHQ-9 scores of 10 or higher. This suggests that depression may be a factor in severe, poorly controlled, refractory asthma.

However, when only patients with J-PHQ-9 total scores of 10 or higher were examined, the severity and control of asthma was not significantly correlated with the J-PHQ-9 total score. One interpretation of this is that depression only affects the severity and control of asthma in some patients with depressive symptoms. If it were possible to understand and extract the characteristics of patients with refractory asthma caused by depression, treatment of these patients' depression could be linked to therapeutic interventions for asthma, which could improve their QOL. A hierarchical cluster analysis is a means of eliminating an *a priori* bias and extracting populations with similar characteristics. Although cluster analyses have been performed on asthma patients (18,19), they have not been performed on asthma patients with depressive symptoms.

In 2014, we again surveyed asthma patients in Niigata Prefecture using a questionnaire that included the ACT-J and J-PHQ-9. As a scale for treatment adherence, the Adherence Starts with Knowledge-12 (ASK-12) was also administered. The present study, based on the results of this survey, had the following objectives: First, we compared the characteristics of a group of asthmatic patients with depression to such a group without depression in order to verify the reproducibility of the J-PHQ-9 data and other elements of the previous study; we then performed a cluster analysis on patients with depressive symptoms in order to extract groups of patients whose depression was affecting their

72 asthmatic condition and to examine the characteristics of these groups.

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METHODS

Study population

The subjects of the survey were adult (≥ 16 years of age) asthma patients, treated at medical institutions in Niigata Prefecture belonging to the Niigata Society for Asthma Treatment and Research in September and October 2014, and their attending physicians. The diagnosis of asthma by a physician was performed according to the Japanese Society of Allergology's "Asthma Prevention and Management Guidelines 2012" (JGL2012), based on the patients' medical history, physical examination findings, or test results (e.g. lung function test and bronchodilator reversibility test). The medical institutions were 28 large hospitals (≥ 200 beds), 14 mid-sized or small hospitals (≤ 200 beds), and 62 clinics with no beds. Of the questionnaire items described below, only patients who completed the J-PHQ-9 were included.

This study was designed according to the Declaration of Helsinki and was conducted with the approval of the ethics committees of each institution and of the Niigata University School of Medicine (#1886). Before responding to the questionnaire, all of the patients received an explanation of the study from their attending physician and gave their written consent.

Contents of the questionnaire

The questionnaire was composed entirely in Japanese. It included sections to be filled out by the patient and sections to be filled out by the attending physician. It covered the age, sex, body mass index (BMI), disease duration, smoking status, severity classification, comorbidities, medications (inhaled corticosteroid [ICS] alone/combined, use of other medications), history of exacerbation, recent asthma control status (asthma symptoms prior to the last two weeks before the questionnaire administration [frequency of attacks, morning symptoms, and night symptoms]), year-round asthma control status (temporary increase in oral steroid dose [OCS burst], frequency of attacks), the asthma control test ACT-J, the depression scale J-PHQ-9, and the Adherence Starts with Knowledge-12 (ASK-12) questionnaire. Severity classifications were based on JGL2012.

Items on the severity, history of exacerbation, OCS bursts, medications, and complications were assessed and filled out by the attending physician. All other items were filled out by the patient.

The ACT is a five-question test of asthma control status developed by Nathan et al. (20). It is a simple, self-administered test that can be performed at primary care centers; it correlates well with objective markers of control, such as lung function tests and with the Global Initiative for Asthma (GINA) control classification, and its reliability and validity

have been confirmed (21-24). Each question is scored on a scale from 1 to 5 points, and the total score (max. 25 points) represents the asthma control status. The cut-off for poor control was ≤ 19 points (20).

The PHQ-9 is a self-administered tool developed by Kroenke et al. for screening and evaluating the severity of depression (25). This feature has been used not only for patients in the mental health field but also in depression-related research on patients with cardiovascular disease (26), diabetes (27), chronic kidney disease (28), and other disorders. It consists of nine questions extracted from the major depressive disorder module of the "Primary Care Evaluation of Mental Disorders" (PRIME-MD) questionnaire. Muramatsu et al. translated it into Japanese after going through a linguistic validation process (29). Its reliability and validity have been confirmed for primary care and for patients with physical diseases (30,31). Patients rate the frequency of 9 items over the previous 2 weeks, from "not at all" (0 points) to "nearly every day" (3 points), for a maximum score of 27 points. The total score can be used to evaluate the level of the symptoms or to screen for depression using a diagnostic algorithm based on the DSM-IV (32). In the present study, we adopted the latter application, and patients "suspected of having major depressive disorder" or "suspected of having another depressive disorder" were defined as depressive symptom-positive (DS[+]), and all other patients were defined as depressive

128 symptom-negative (DS[-]).

129 The ASK-12 is an adherence scale developed by Matza et al. (33,34). It is
130 composed of 12 questions taken from the adherence scale ASK-20 on factors found to be
131 frequently related to reduced drug adherence (35). Each question is scored from 1 to 5
132 points to create a total score. There are additional subscale scores for
133 inconvenience/forgetfulness, treatment beliefs, and behavior. In the present study, the 12
134 questions used in the ASK-12 were taken from the Japanese version of the ASK-20 (36).

135

136 *Cluster analyses*

137 A hierarchical cluster analysis was performed on the DS[+] group using Ward's method.
138 There is no established rationale for determining the variables that should be chosen in a
139 cluster analysis. While there are several reports using a factor analysis to determine which
140 variables should be used for a cluster analysis (37,38), in some reports, the variables were
141 determined in other ways (39,40). We performed a cluster analysis in the same manner as
142 reported previously (19). In brief, we chose candidate variables that were significantly
143 different between DS(+) and DS (-): BMI, smoking status, JGL severity, OCS burst episode,
144 frequency of asthma attacks in the previous year, comorbidities (heart diseases), the drug
145 used (long-acting muscarinic antagonists [LAMA], oral sustained-released theophyllines

146 [OSRT], oral corticosteroids [OCS]), and ACT-J and ASK-12 scores. Each recent asthma
147 control indicator (the ACT score and asthma symptoms [frequency of attacks, morning
148 symptoms, and night symptoms]) prior to the last two weeks before questionnaire
149 administration strongly influenced each other; the ACT score was chosen as a
150 representative from among the indicators and used for a cluster analysis. Each variable was
151 standardized by subtracting the mean and dividing by the standard deviation. Thirty-three
152 patients with missing continuous variables (e.g. BMI, ACT score, ASK 12 score.) were
153 excluded from the analysis (Figure 1).
154
155 *Statistical analyses*
156 For continuous variables, significant differences between two groups were tested using
157 Wilcoxon's rank-sum test, significant differences among three groups were tested using the
158 Kruskal–Wallis test, and multiple comparisons were performed using Bonferroni's
159 correction. Intergroup comparisons of distributions and percentages (treatment content,
160 severity classification, etc.) were tested using a chi-squared test. The statistical software
161 JMP® 10.0 for Macintosh (SAS Institute Inc., Cary, NC, USA) was used for the statistical
162 analyses. $P < 0.05$ was considered statistically significant.
163

RESULTS

A comparison of subject characteristics between the depressive and non-depressive groups

Table 1 summarizes the results of the survey. Complete responses to the PHQ-9 were obtained from 2,273 patients. Of these, 128 patients (5.6%) were placed in the DS[+] group using the J-PHQ-9 diagnostic algorithm. The median PHQ-9 score in the DS[+] group was 13 points, which was greater than the cut-off value for major depressive disorder in primary care screenings (10 points) (25).

Significant differences between the DS[+] and DS[-] groups were observed for BMI, smoking status, JGL severity, OCS burst episode, frequency of asthma attacks in the previous year, comorbidities (heart diseases), the drug used (LAMA, OSRT, OCS), and ACT-J and ASK-12 scores. The DS[+] group had a higher BMI, a larger proportion of smokers, more severe cases, more patients with poor control status, a higher ratio of non-ICS drug use, and lower ACT-J and higher ASK-12 scores than the DS[-] group.

Cluster analyses and comparisons

As described above, items that were significantly different between the DS[+] and DS[-] groups were used as variables in a cluster analysis using Ward's method. After excluding patients with missing values, 95 patients were categorized into 3 clusters (Figure 2).

Table 2 shows the characteristics of the clusters. Significant differences among the three clusters were observed for age, BMI, disease duration, JGL severity, OCS burst episode, acute exacerbation episodes, frequency of asthma attacks in the previous year, comorbidities (osteoporosis, cerebrovascular disease), proportion using ICS alone, long-acting beta-agonist [LABA]-use rate, and ACT-J and ASK-12 scores. The clusters' J-PHQ-9 scores were not significantly different.

Cluster A contained 20% of the patients with both depression and asthma. Their median age was 67 years, and the median disease duration of asthma was 9.5 years. In terms of severity levels, 68.4% were rated as moderate or higher, and there were no mild-intermittent cases. In terms of the control status, the median ACT score was poor, at 14 points. ICS was the only therapy in 15.8% of patients, with 73.7% combining other drugs. Among these three clusters, the ASK-12 score was significantly higher in Cluster A. The ASK-12 score in cluster A was also significantly higher than in the DS[-] group. In addition to the total score, the inconvenience/forgetfulness and behavior scores were higher in this than in other clusters.

Cluster B comprised 27.3% of the total patients. Their median age was 69 years, and the median disease duration was 6 years. The median BMI was 21.5, which is somewhat low for Japanese individuals. In terms of the severity level, 69.3% were rated

moderate or higher. In terms of asthma control, the median ACT score was poor, at 16 points. The median ASK-12 score was 21.5, which is significantly lower than that in cluster A.

Cluster C comprised 49.5% or about half of the total patients. Their median age was 52 years, and the median disease duration was 13.5 years, which was significantly longer than in the other clusters. The mean BMI was 25.5, the highest among the clusters; the patients were slightly obese compared to Japanese individuals in general. In terms of severity, 50% were mild-intermittent and mild-persistent cases; only 10% were severely persistent cases, and there were no most-severe−persistent cases. The median ACT score was 24, which was significantly higher than in the other clusters, indicating good control. There were no cases of osteoporosis or cerebrovascular incidents, which were found in clusters A and B. The ASK-12 score in this cluster was 27.5, which is significantly lower than that in cluster A.

DISCUSSION

A comparison of subject characteristics between DS[+] and DS[-] groups

Using the J-PHQ-9 diagnostic algorithm, 5.6% of the patients were placed in the DS[+] group, which is consistent with the results of our previous survey.[17] Despite some overlapping patients and institutions, the populations were not identical; as such, changes over time could not be captured. However, as both surveys covered similar populations in the same region, the results are considered to be reproducible.

As in the previous survey, the ACT-J score of the DS[+] group was significantly lower than that of the DS[-] group. The frequency of asthma symptoms and exacerbations was significantly higher in the DS[+] than in the DS[-] group. In addition, the ASK-12 total score was higher in the DS[+] group, suggesting a higher risk for poor treatment adherence. While the existence of causative relationships is unclear, because of the limitation associated with the cross-sectional study design, it may be possible that depression causes a decline in treatment adherence and leads to insufficient asthma treatment, or that poor adherence causes severe, poorly controlled asthma, which triggers depressive symptoms (41, 42).

Cluster analyses and comparisons

Both clusters A and B contained many patients with severe, poorly controlled asthma, and depression may have been affecting the asthma pathology in these populations. However, these clusters differed in their ASK-12 scores, i.e. in their adherence barriers.

The patients in cluster A demonstrated a higher risk for poor treatment adherence than those in cluster B. They may have forgotten to take or have stopped taking their medication willfully; as such, interventions aimed at increasing adherence may help to improve their asthma control. In some patients, depression may have caused adherence to decline, and therefore, treating their depression may improve their asthma control.

Although the ASK-12 scores were lowest in cluster B and these patients were receiving adequate drug therapy involving multiple medications, without significant adherence barriers, asthma control was poor in this population. It may be possible to link the treatment of depression to the treatment of asthma in these patients. Furthermore, this cluster may include truly refractory asthma, and this poor asthma control may have caused their depression to worsen. To improve both the asthma control and depression status, it is recommended that patients in cluster B have consultations with mental health specialists.

Cluster C, which contained about half the patients in the DS[+] group, was a population of young patients and patients with mild symptoms and good asthma control. The patients showed depressive symptoms, but these symptoms might have had little

influence on the asthma activity. However, we should consider that many studies have examined the relationship between bronchial asthma and depression (1-16) and that both the bronchial asthma activity and depression scales were subjective. Regardless of the asthma control or asthma severity, it is also recommended that these individuals consult mental health specialists if they need intervention for depression. As the ASK-12 score of cluster C patients was lower than that in cluster A, these patients might demonstrate lower adherence barriers than those in cluster A.

The J-PHQ-9 total scores of clusters A and B, which included many severe cases of poorly controlled asthma, were not significantly different from that of cluster C. One interpretation of this result might be that the severity of depression was unrelated to the severity and control of asthma in the DS[+] group.

The age and BMI differed between cluster C and clusters A and B. The ages and disease durations indicate onset at older ages in clusters A and B and at younger ages (≤ age 40 years) in cluster C. A number of reports have evaluated the timing of the asthma onset and patient characteristics (age, control status, cause of atopy, etc.) (43, 44), but these findings were not completely consistent with the results of the present study. There is scope for further longitudinal studies and research in this area in future.

Furthermore, a recent study found that asthma control was poor in a group of obese

patients and that depression was a mediator of obesity and a worsened control (45). In the present study, the BMI was the highest in cluster C; however, the control was not poor in this cluster. As with depression, it is possible that the BMI only affects the asthma control in some patients.

Among the variables used to determine the cluster characteristics, the items for assessing the asthma control and severity contained some subjective evaluations by the patient. These merit caution, as the actual condition of the asthma may differ based on the answers given in the questionnaire. In a previous study, we reported that a patient group with J-PHQ-9 scores of ≥ 5 exhibited a lower ACT cut-off value than did the remaining group (46). Thus, despite having low ACT scores, some of these patients actually had a better asthma status than was indicated by their responses. Patients with such factors may respond excessively to the ACT questions and describe more attacks than actually occur. Patients whose objective symptoms are not severe may have to miss school or work due to strong subjective symptoms, and patients who complain repeatedly about their symptoms may be given increased or excessive treatment by their attending physician. In these cases, therapeutic intervention for depression might restore patients' subjective evaluation and lead them to complete their asthma therapy.

286 *Strengths and limitations*

287 The most important findings of this study were that about half of the patients with both
288 depression and asthma had severe, poorly controlled asthma, and that these patients were
289 able to be divided according to their ASK-12 score, which reflects treatment barriers. Our
290 results suggest the possibility that depression may affect the severity and control of asthma
291 only in some patients and describe the characteristics of such patients. Furthermore, while
292 the severity of depression did not significantly correlate with the asthma severity or control
293 in the DS[+] group, the results suggest that the BMI, age, and disease duration might be
294 related to the asthma severity and control.

295 Patients with physical diseases, including asthma, are known to overestimate the
296 depressive symptoms that overlap with their physical symptoms (1,47). In the present study,
297 the J-PHQ-9 diagnostic algorithm was used to include patients who felt “depressive
298 feelings” and/or “loss of interest or happiness” in the DS[+] group, which excluded patients
299 with only physical symptoms (32). Compared to studies that only used the PHQ-9 total
300 score, the depression identified in our study was closer to that defined using the DSM-IV
301 criteria.

302 This study was conducted in Japan; as such, patients were able to fully understand
303 and respond to the questionnaire written in Japanese. Linguistic barriers that could have

304 hindered therapeutic guidance or interventions were unlikely. Furthermore, the health
305 insurance system in Japan enables patients to receive treatment, regardless of income.
306 Therefore, we believe this study had a sufficient sample size to reflect the physiological
307 and psychological characteristics of the patients and their level of adherence without being
308 affected by socio-economic factors.

309 However, several limitations associated with the present study warrant mention.
310 First, due to the cross-sectional design, the relationship between depressive symptoms and
311 other markers could only be assessed at the time of the survey. For example, we were
312 unable to determine whether poor asthma control caused depression to worsen, or whether
313 depression led to worse asthma control. Longitudinal studies and surveys are needed to
314 address the causative relationships between depression and other markers. Second, we used
315 the J-PHQ-9 diagnostic algorithm, which is based on the DSM-IV; diagnoses of depression
316 were not made by specialists. Third, we did not survey the patients' past depressive
317 episodes or their history of treatment for depression; thus, the DS[+] group did not include
318 patients whose depression was in remission. Fourth, this study used a questionnaire based
319 on patient self-reporting. Thus, the evaluations of the asthma control and severity,
320 depressive episodes, and adherence might have been influenced by subjective factors.

321 In conclusion, about half of the patients (clusters A and B) in the DS[+] group had

322 severe, poorly controlled asthma, and these clusters were able to be distinguished by the
323 ASK-12 score, which reflects adherence barriers. Improving the control status and severity
324 of asthma in these patients may require consideration of interventions intended to improve
325 adherence to asthma therapy or consultations with mental health specialists. As depression
326 might affect patients' subjective evaluation of asthmatic symptoms, we should be careful of
327 administering increased or excessive treatment for asthma. In addition, although the age,
328 disease duration, and BMI showed possible relationships with asthma control and severity
329 in the DS[+] group, these associations require further study.
330

331 **Conflicts of Interest**

332 The authors state that they have no conflicts of interest.
333

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Table 1. Characteristics of the DS[–] and DS[+] groups

	DS[-] group	DS[+] group
Number of cases	2145	128
Age (median [IQR])	61 [46-71]	63 [44.8-76]
Male gender (%)	41.7	34.4
BMI	22.8 [20.6-25.5]	23.8 [21.4-26.9]*
Disease duration (years, median[IQR])	11 [4-22]	11 [4-19]
Smoking status (Ns/Ex/Cur/UK %)	51.9/36.9/9.4/1.8	43.0/36.7/12.5/7.8**
JGL Severity (MI/MP/MODP/SP/MSP/UK %)	25.9/25.5/34.7/6.0/1.2/6.7	17.2/18.0/43.8/7.8/2.3/10.9*
OCS burst episode during the previous year before completing the questionnaire (Y/N/UK %)	16.0/78.9/5.0	25.8/66.4/7.8**
Exacerbation episode during the previous year before completing the questionnaire (Y/N/UK %)	37.0/58.5/4.5	43.0/50.0/7.0*
Frequency of asthma attacks during the previous year before completing the questionnaire (P/S/AN/UK %)	6.9/27.7/57.0/8.5	14.8/33.6/41.4/10.3**
Heart disease (%)	4.7	10.2*
ICS alone or combined (On/Co/No/UK %)	30.4/61.7/7.1/0.8	28.9/57.8/10.9/2.3
LAMA use rate (%)	4.6	9.4*
OSRT use rate (%)	24.8	33.6*
OCS use rate (%)	3.6	4.7*
J-PHQ-9		
Number of patients	2145	128
Total (median [IQR])	1 [0-3]	13 [10-17]**
ACT-J		
Number of patients	1710	107
Total (median [IQR])	23 [20-24]	21 [16-24]**
ASK-12		
Number of patients	2125	128
Total (median [IQR])	24 [19-30]	28 [23-32]**
Inconvenience/forgetfulness	6 [3-8]	6 [4-9]*
Treatment belief	8 [7-10]	9 [8-11]**
Behavior	10 [6-12]	11 [7-14]**

* $p < 0.05$, ** $p < 0.01$ according to Wilcoxon rank sum test or Chi-square test

DS[-], depressive symptoms negative; DS[+], depressive symptoms positive

UK, unknown; Ns, non-smoker; Ex, ex-smoker; Cur, current-smoker;

MI, mild-intermittent; MP, mild-persistent; MODP, moderate-persistent; SP, severe-persistent; MSP, most-severe-persistent;

ICS, Inhaled corticosteroid; On, only; Co, combined; No, None;

LAMA:Long-acting muscarinic receptor antagonist; OCS:Oral corticosteroid; OSRT:Oral sustained-release theophilines

Table 2. Patient characteristics in DS[+] group clustered

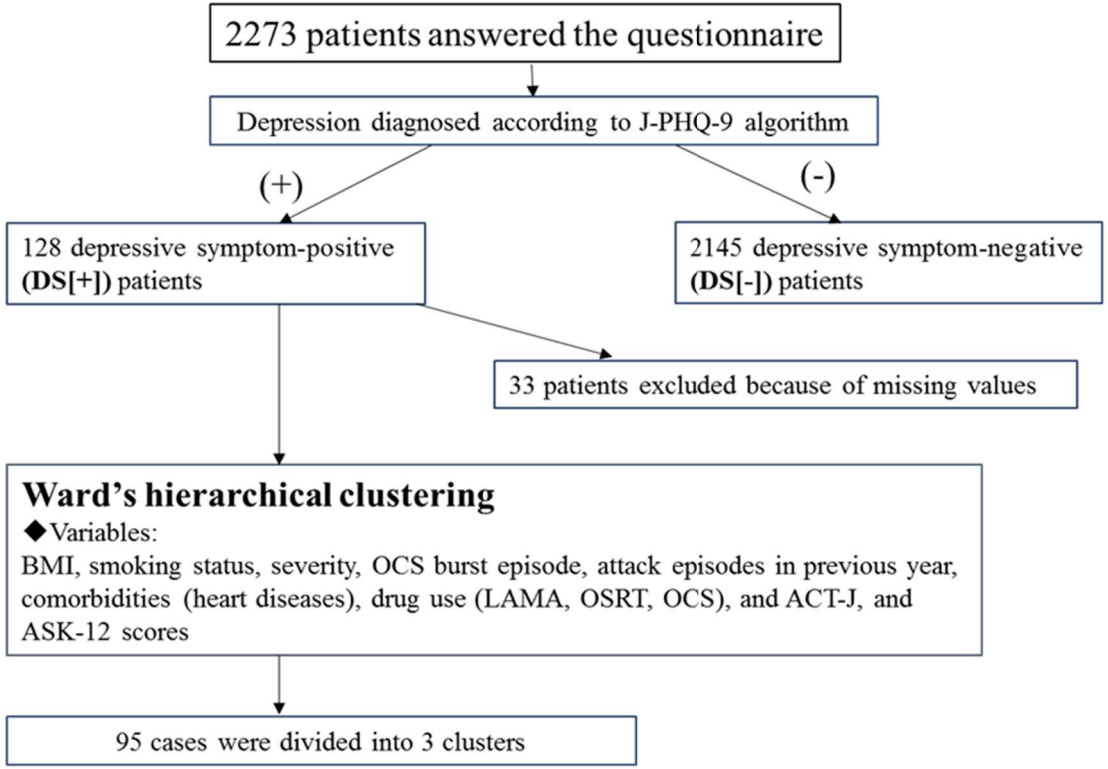
	Cluster A	Cluster B	Cluster C
Number of cases	19	26	50
Age (median[IQR]) †	67 [41.8-78.3]	69 [51-80]	52 [40-72.5]
Male gender (%)	36.8	38.5	34.0
BMI††	24.0 [20.6-26.7]	21.5 [19.7-23.4]	25.5 [22.7-29.1]‡‡‡
Disease duration (years, median [IQR])†	9.5 [4-16]	6 [3.3-12.3]	13.5 [7-22.5]‡‡‡
Smoking status (N/Ex/C/UK %)	31.6/47.4/15.8/5.3	42.3/34.6/19.2/3.9	42.0/40.0/12.0/6.0
JGL Severity (MI/MP/MODP/SP/MSP/UK %)††	0/21.1/47.4/10.5/10.5	11.5/19.2/57.7/7.7/3.9	30.0/20.0/40.0/10.0/0
OCS burst episode during the previous year before completing the questionnaire (Y/N/UK %)††	47.4/42.1/10.5	23.1/73.1/3.9	8.0/84.0/8.0**
Exacerbation episode during the previous year before completing the questionnaire (Y/N/UK %)††	68.4/26.3/5.3	42.3/53.9/3.9	22.0/68.0/10.0**
Frequency of asthma attacks during the previous year before completing the questionnaire (Per/Sea/AN/UK %)†††	47.4/36.8/10.5/5.3	23.1/38.5/26.9/11.5	2.0/26.0/64.0/8.0***‡‡
Cerebrovascular disease (%)†	10.5	11.5	0
Osteoporosis (%)†	10.5	11.5	0
ICS only or combined (On/Co/No/UK %)†	15.8/73.7/5.3/5.3	26.9/69.2/3.9/0	42.0/40.0/18.0/0
LABA use rate (%)†	73.7	69.2	44.0
J-PHQ-9			
Total (median [IQR])	14 [10-17]	13 [10-17.3]	13.5 [9.8-18]
ACT-J			
Total (median [IQR])†††	14 [11-21]	16 [15-19]	24 [22-25]***‡‡‡
ASK-12			
Total (median [IQR])†††	37 [32-40]	21.5 [18-26]***	27.5 [24-31]***‡‡‡
Inconvenience/forgetfulness†††	11 [6-12]	4 [3-6]***	6 [4-9]***‡‡‡
Treatment belief†	10 [9-14]	8.5 [8-10.3]**	9 [8-11]
Behavior†††	15 [13-18]	8 [6-10.3]***	11 [7-13]***‡‡‡

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$, according to Kruskal-Wallis test or Chi-squared test

** $p < 0.01$, *** $p < 0.001$ vs. Cluster A, with the Bonferroni correction

‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ vs. Cluster B, with the Bonferroni correction

LABA, Long-acting beta-agonist



J-PHQ-9, Japanese version of the Patient Health Questionnaire-9;
ACT-J, Japanese version of the Asthma Control Test; ASK-12, Adherence Starts with Knowledge-12
LAMA, long-acting muscarinic-antagonists; OSRT, oral sustained-release theophilines; OCS, oral corticosteroid

Figure 1. Variables used in patient selection and cluster analysis.
Items that were significantly different between the DS[+] and DS[-] groups were used as variables in the cluster analysis.

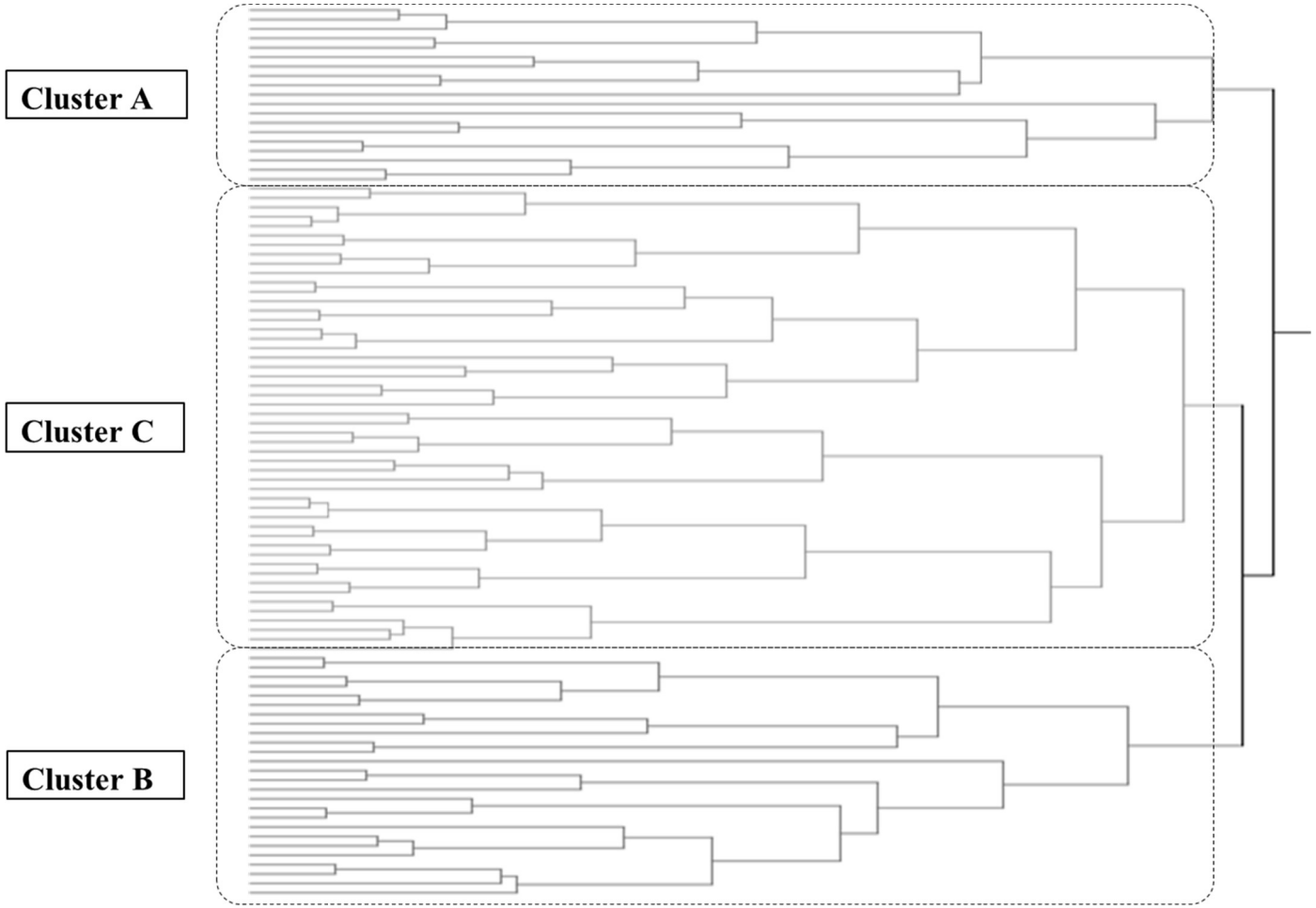


Figure 2. Cluster Dendrogram.
After excluding patients with missing values, 95 patients were categorized into 3 clusters.