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Original Article

Characterization of low adherence population in asthma patients from Japan using Adherence Starts with Knowledge-12

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ACT, Asthma control test; ASK-12, Adherence Starts with Knowledge-12; COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; IQR, Interquartile range; OCS, Oral corticosteroid; PHQ-9, Patient Health Questionnaire-9

ABSTRACT

Background: Adherence Starts with Knowledge-12 (ASK-12) is a useful indicator of drug adherence. In this study, we analyzed patient background including social and psychological factors in a low-adherence group of patients with asthma defined using ASK-12.
Methods: From a questionnaire survey for patients with asthma from the Niigata Prefecture, Japan, conducted in the fall of 2016, we enrolled patients who answered all ASK-12 items and underwent a measured respiratory function test within 1 year. The low-adherence group (ASK-12 $\geq$ 28) was compared with the control group (ASK-12 < 28), and we conducted a cluster analysis of the low-adherence group.
Results: There were 170 patients in the low-adherence group and 402 patients in the control group. There was a significant difference between age, gender, working status, smoking history, the percentage of forced expiratory volume in one second (%FEV_1), asthma control test (ACT), and Patient Health Questionnaire-9 (PHQ-9) score between the two groups. Logistic analysis revealed that working status (working), % FEV_1 (<90%), and PHQ-9 score (>5) were independent factors for the low-adherence group. The cluster analysis identified three clusters in the low-adherence group. Among these, one cluster was characterized by elderly males with chronic obstructive pulmonary disease and another by middle-aged nonsmoking females with a depression tendency, had problems with asthma control.
Conclusions: Several factors were considered to be attributed to low drug-adherence. There were several phenotypes in the low-adherence population correlated with incomplete asthma control. Intervention with drug adherence should be a future goal for asthma treatment.

Introduction

Although drug adherence is an essential and indispensable factor in the treatment of chronic diseases, it is often difficult to maintain in bronchial asthma, which is commonly associated with the use of inhaled drugs.[1] The association between drug adherence and asthma control has been reported previously,[2–4] it is thought that it contributes to the inhibition of exacerbation and the amelioration of airway inflammation.[3,5]

Adherence Starts with Knowledge-12 (ASK-12) is a questionnaire consisting of 12 items related to drug adherence, it is considered to be a concise version of the ASK-20 consisting of 20 items.[6,7] ASK-12 contains three subscales “inconvenience/forgetfulness”, “health beliefs”, and “behavior”. Furthermore, barriers to each question are established, and the number of barriers is also an index of adherence. Although reports demonstrating the usefulness of ASK-12 for patients with asthma are limited, Takemura *et al.* reported it to be valid and a guide of poor adherence for patients with asthma in Japan.[8] Regarding the practical use of ASK-12 in a clinical setting, the intervention of adherence in patients with ASK-12 high score is thought to be useful. However, to the best of our

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knowledge, no previous studies have investigated patient background, such as clinical features or asthma control, in patients with high ASK-12 scores.

In this study, a high ASK-12 score group was defined as a low drug-adherence group and was characterized regarding its clinical factors, including biological, social, and psychological factors, in comparison with a control group in a real clinical setting. Moreover, through a cluster analysis, we aimed to clarify the clinical phenotypes that require intervention by identifying the features of the low-adherence group.

Methods

Subjects

The survey for this study was performed between September and October in 2016 in accordance with the ethical principles for medical research involving human subjects and the Declaration of Helsinki, with the approval of the ethics committee of Niigata University (approval number 2524). All patients were diagnosed with asthma from a physician according to the guidelines of the Japanese Society of Allergology. The institutions involved included 23 large hospitals (≥200 beds), 15 small hospitals (<200 beds), and 50 clinics (no beds). Patient eligibility was based on complete responses to ASK-12 and available data on respiratory function taken within the previous year. A total of 572 patients were enrolled in this study.

Protocol

After providing informed consent, patients completed a questionnaire on age, gender, smoking status, working status, living status, disease duration, and ASK-12. Working status was classed as either full-time (working), part-time (working), student or housewife or retired, or unemployed. Living status was selected from solitude, with spouse, family composition of two generations, or three generations. The Japanese versions of the Asthma Control Test (ACT) and Patient Health Questionnaire−9 (PHQ-9) were used. The PHQ-9, consisting of nine items related to depression alone, was developed for evaluating depressive states in actual clinical care. Its sensitivity and specificity have been shown to be high compared with other questionnaires for depression.[9] The validity of the Japanese version of PHQ-9 was confirmed by Muramatsu *et al.*[10,11] Several studies have reported PHQ-9 scores to be highly reliable and stable.[9,11,12]

Physicians, mainly pulmonary physicians, also completed content on therapy, disease type, disease severity, comorbidity, recent data of immunoglobulin E, pulmonary function test, and the existence of exacerbation. For the definition of exacerbation, systemic steroid use (increase) for 3 days or more due to asthma exacerbation, hospitalization due to worsening of asthma, emergency room visit for asthma exacerbation, or unscheduled consultation were accepted.

Statistical analysis

The results were expressed as medians (25th−75th interquartile range [IQR]) because the data for continuous variables were mainly non-normally distributed. To compare differences among the groups, one-way analysis of variance and Bonferroni's multiple comparison tests were used. The in-group comparisons were performed using Wilcoxon's signed-rank test. Comparisons for all pairs were performed using the Kruskal−Wallis test. Multivariate analysis was used to identify the variables that influenced asthma control. Variables that were statistically significant in the dichotomous analysis were applied in the multivariable logistic regression analysis. We performed a hierarchical cluster analysis on the exacerbation group using Ward's method, as reported previously.[13] In brief, we chose important variables for cluster establishment, including disease duration, gender, age, disease type, smoking status, ACT score, medication content, and $\%FEV_1$. All of these factors were modified to the nominal scale and input. Most statistical analyses were performed using JMP software version 11 (SAS Institute, Inc., Tokyo, Japan). For all statistical analyses, $p < 0.05$ was considered significant.

Results

A total of 572 patients were enrolled in this study. Table 1 presents the patients' backgrounds. One of the features of this study was the investigation of working status and living status. Of the patients, 52.5% were employed including part-time workers, 36.7% were students or housewives or retired, and 10.8% were unemployed. Furthermore, with regards to living status, 11.2%, 30.2%, 46.7%, and 12.4% were categorized as solitude, living with a spouse, family composition of two generations (mainly parents and children), and family composition of three generations, respectively. Asthma exacerbation in the previous year occurred in 39.3% of patients, and chronic obstructive pulmonary disorder (COPD) was recorded in 11.9% of patients as a comorbidity. Median PHQ-9 score was 1 (IQR: 0−4) (Table 1).

ASK-12 score distribution is shown in Figure 1. Median ASK-12 total score was 24 (IQR: 19−28). Furthermore, a cut-off value that represented a barrier to adherence was established, for each item of ASK-12.[6] The median number of total barriers for this study's participants was 2 (Table 2). Moreover, the median score and barrier positive rate of each item are shown in Supplementary Table 1. We assigned patients with a score above 28 into the low-adherence group and compared these with patients with an ASK-12 total score of 28 or less (control group).

In comparison with the control group, the low-adherence group was significantly lower in age, and higher in males and active workers. This group also had a higher smoking history in reflection

Table 1
Patients' clinical characteristics.

Number of cases	572
Age (year)	59 (45−71)
Male (%)	46
BMI (kg/m^2)	23.0 (20.7−25.4)
Working status (full-time/part-time/student or housewife or retired/unemployed	40.4/12.1/36.7/10.8
Livings status (solitude/with spouse/two generations, three generations) (%)	11.2/30.2/46.2/12.4
Duration of disease (years)	10 (3−20)
Non-smoker (%)	52
Atopic (%)	65.9
Severity (Mild/Mod/Severe) (%)	31/56/13
ACT Score	23 (21−24)
$\%FEV_1$ (%)	93.8 (81.2−106.5)
FEV_1/FVC (%)	76.3 (68.2−83.0)
IgE (IU/L)	165 (50.2−496.5)
ICS (μg/day) (equivalent for fluticasone)	400 (200−400)
Exacerbation in previous year (%)	39.3
COPD comorbidity (%)	11.9
PHQ-9 score	1 (0−4)
ASK-12 score	23 (12−44)
ASK-12 barrier	2 (0−10)

ACT, asthma control test; BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IgE, immunoglobulin E; ICS, inhaled corticosteroid; PHQ-9, Physical Health Questionnaire-9. Data are expressed as the median (interquartile range).

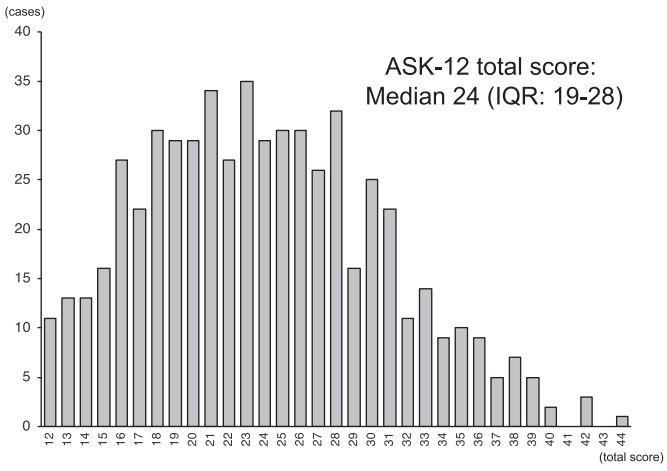

Fig. 1. Distribution of ASK-12 scores. Median ASK-12 total score is 24 (interquartile range: 19–28). We defined a score above 28 as a high ASK-12 value.

of its male dominance. The values of %FEV_1 were significantly lower than in the control group despite similar COPD prevalence. Furthermore, the ACT score of the low-adherence group was lower, while the PHQ-9 score was significantly higher than the control. ASK-12 contained three subscales; "inconvenience/forgetfulness", "health beliefs", and "behavior". In all three subscales, the low-adherence group scored higher than the control group. The total number of barriers in each item (Table 2) was also higher for the low-adherence group. Moreover, the score of each item and the barrier positive rate were also notably higher in the low-adherence group (Supplementary Table 2).

A logistic analysis was performed using items that significantly differed between the two groups. As a result, working status (working), % FEV_1 (<90%), and depressive symptoms (PHQ-9 > 5) were shown to be independently related to low adherence (ASK-12 > 28) (Table 3). In other words, not only the severity of asthma, but also social and psychological factors, were strongly involved in the low-adherence group.

In order to analyze the characteristics of the low-adherence group in detail, a cluster analysis was executed. Three clusters were identified (cluster A, B, and C). Cluster A contained older-aged patients, mainly males with a smoking history and high prevalence of COPD. It also included many patients of non-atopic and severe disease type, and approximately half of the patients experienced exacerbations within the previous year. Cluster B contained mainly relatively young females with a shorter disease duration, and an atopic disease type and milder disease severity. Their pulmonary function (% FEV_1) was mainly sustained, although their asthma control was not good, and exacerbation within previous year had been experienced in many patients. The PHQ-9 score in this cluster was the highest. Cluster C contained half males and half females with a milder severity of asthma, sustained pulmonary function, and a low rate of exacerbation within the previous year. This cluster probably included several cases of mild asthma (Table 4). There were no significant differences in the ASK-12 total score, subscale score, and total barriers among the clusters (Table 4). Furthermore, although, there were some differences among the clusters in the score and barrier positive rate for each item, their clinical significance could not be determined (Supplementary Table 3). To summarize the results of the cluster analysis, clusters A and B had poor asthma control and frequent exacerbation. Cluster A was characterized by severe asthma type, while cluster B could be identified by a social factor (working) and psychological factor (PHQ-9). In contrast, cluster C appeared to be a group that experienced less problems with asthma control.

Table 2
Comparison of clinical characteristics between the high score ASK-12 group (ASK ≥ 28) and control group (ASK < 28).

	ASK <28	ASK ≥28	p-value
Number of cases	402	170	
Age (years)	61 (47–72)	56 (42–67)	0.007
Male (%)	42.5	54.1	0.011
BMI (kg/m^2)	22.9 (20.6–25.2)	23.3 (20.9–26.2)	0.148
Working status (Working) (%)	48.3	62.4	0.002
Living status (Solitude) (%)	10.7	12.4	0.566
Disease duration (year)	9 (3–22)	10 (4–16)	0.773
Smoking (%)	43.8	58.2	0.002
Atopic type (%)	63.9	70.6	0.125
Severity-mild (%)	31.1	31.2	0.985
%FEV_1 (%)	95.3 (83.0–109.0)	89.2 (78.1–102.4)	0.003
Exacerbation in previous year (%)	39.3	39.4	0.981
ACT	24 (21–24)	23 (20–24)	0.005
ICS (μg/day) (equivalent for fluticasone)	400 (200–400)	400 (200–400)	0.547
OCS use (%)	5.5	2.4	0.102
COPD comorbidity (%)	11.9	11.8	0.953
PHQ-9	1 (0–3)	2 (0–5)	<0.001
ASK-12			
Total	21 (17–24)	31 (29–34)	<0.001
Inconvenience/Forgetfulness	4 (3–6)	9 (7–10)	<0.001
Health beliefs	8 (6–9)	10 (8–11)	<0.001
Behavior	8 (5–10)	13 (11–16)	<0.001
Barrier	2 (0–10)	5 (1–10)	<0.001

ACT, asthma control test; BMI, body mass index; ICS, inhaled corticosteroid; OCS, oral corticosteroid; PHQ-9, Physical Health Questionnaire-9. Data are expressed as the median (interquartile range).

Discussion

In this study, we analyzed the features of a low drug-adherence group of patients with asthma, defined with ASK-12, for the purpose of extracting factors related to low adherence in a real clinical setting. Factors analyzed included not only those related to disease type, but also social and psychological factors. Furthermore, we conducted a multilateral analysis and a cluster analysis of the low-adherence group to identify clinical characteristics.

The main findings of the present study were that the low-adherence group of patients could be divided into three clusters with distinct clinical features and patient backgrounds. There was a possibility that depression status using PHQ-9 was influencing the low-adherence group. Depression is a mental health condition that frequently occurs in patients with asthma.[14] It also has been reported that depression symptoms negatively affect drug adherence.[15] We have previously reported a relationship between asthma control and depression using PHQ-9 as a screening tool for depression status,[16,17] and performed a cluster analysis of patients with asthma in a depressed state.[13] Seino *et al.*[13] classified asthma cases with depression into three clusters based on asthma control status and ASK-12 score. The present study also shows that there is

Table 3
Multiple regression analysis of variables that influenced low-adherence.

	Odds ratio (95% confidence interval)	p-value
Age (<median)	1.16 (0.73–1.85)	0.534
Gender (male)	1.28 (0.82–1.98)	0.273
Working status (working)	5.71 (2.24–18.40)	0.039
Smoking	1.30 (0.85–2.01)	0.230
%FEV_1 (<90%)	1.69 (1.15–2.50)	0.008
ACT (<median)	1.23 (0.83–1.83)	0.306
PHQ-9 (>5)	2.09 (1.13–3.33)	0.002

ACT, asthma control test; FEV_1, forced expiratory volume in one second; PHQ-9, Physical Health Questionnaire-9.

Table 4
Demographic features of the low-adherence group identified by cluster analysis.

	Cluster A	Cluster B	Cluster C	p-value
Number of cases	43	47	80	
Age (years)	67 (60–74)	44 (36–55)	56 (43–67)	<0.001
Male (%)	83.7	34	50	<0.001
Working status (working) (%)	41.8	74.5	66.3	0.004
Living status (Solitude) (%)	16.3	12.8	10.0	0.598
Disease duration (years)	14 (6–22)	4 (2–8)	12 (5–19)	<0.001
Smoking (%)	93	40.4	50	<0.001
Atopic type (%)	44.2	91.5	72.5	<0.001
Severity-severe (%)	23.3	10.6	5	0.009
%FEV_1	77.2 (64.8–88.1)	89.9 (81.2–100.3)	97.0 (82.7–106.5)	<0.001
Exacerbation in previous year (%)	53.5	59.6	20	<0.001
ACT	21 (18–23)	20 (18–22)	24 (23–24)	<0.001
ICS (ug/day) (equivalent for fluticasone)	400 (400–800)	400 (200–400)	400 (400–400)	0.007
COPD comorbidity (%)	34.9	2.1	5	<0.001
PHQ-9	2 (1–7)	4 (2–7)	2 (0–4)	0.001
ASK-12				
Total	32 (30–36)	31 (29–36)	31 (29–33)	0.180
Inconvenience/Forgetfulness	8 (7–10)	9 (8–10)	8 ([6–9)	0.066
Health beliefs	10 (9–12)	9 (8–10)	10 (9–11)	0.038
Behavior	13 (11–15)	13 (11–17)	13 (11–15)	0.480
Barrier	5 (2–9)	4 (2–10)	5 (1–9)	0.150

ACT, asthma control test; ASK-12, Adherence Starts with Knowledge-12; COPD, chronic obstructive pulmonary disorder; ICS, inhaled corticosteroid; PHQ-9, Physical Health Questionnaire-9. Data are expressed as the median (interquartile range).

a cluster association between depression state and drug adherence. In the future, it should be clarified whether the changes in PHQ-9 due to asthma treatment are accompanied with changes in adherence. For establishing the asthma treatment strategy, it is important to determine whether depression is associated with asthma symptoms or if it exists independently.

Although drug adherence is closely related to asthma control, patients in cluster C in this study had good asthma control and respiratory function, and less exacerbation, despite low adherence. In a real clinical setting, there are cases in which low adherence is not particularly critical for asthma control, especially in mild disease types,[2] but this cluster seems to correspond to these cases. However, since this study was a cross-sectional study, it is unknown whether this cluster will continue to maintain good asthma control in the future.

The present questionnaire contained social factor items on working status and living status. The results showed that active working was a factor related to a decrease in adherence. In the case of chronic diseases, working has been shown to lead to a decrease in medication adherence in chronic diseases.[18,19] Even in asthma and COPD, in which inhaled drugs are essential for their treatment, active working status has been reported to be an important factor in decreasing drug adherence.[20] Based on these reports and our data, the choice of inhaled drugs according to a patient's lifestyle is thought to be important for improving drug adherence.

The cluster analysis in this study revealed several characteristics and background factors that influenced the low-adherence group. We believe that it is necessary to evaluate the differences in the clinical background of each patient and modify the therapeutic approach for each patient based on these findings. For example, cluster A comprised older patients and non-active workers. The factors affecting the decrease of adherence in this cluster are unclear, but probably include cognitive decline, lifestyle, personality, etc. In any case, repeated explanations may be necessary for the patients in this cluster. Moreover, evaluation of cognitive function and explanation to family members may be effective. For cluster B, the psychological factors should be considered in the patient approach. Moreover, drugs that require lesser frequency of inhalation should be prescribed to working individuals. On the other hand, in the case of cluster C, it may be possible to reduce the number drugs prescribed in order to secure adherence, by reconfirming the severity of the condition. Therefore, a patient-dependent approach is essential.

As a limitation of this study, drug adherence was only assessed using the ASK-12, and matching to actual adherence was not confirmed. In general, patients in a depressive state have many complaints and tend to score high in questionnaire surveys.[21–23] In this respect, the present study design might have overestimated cases of depression. Moreover, the patients in this study were managed by pulmonary physicians and may therefore differ from those managed by general physicians.

In summary, we used ASK-12 for the detailed analysis of a low adherence (ASK-12 $\geq$ 28) group. In this group, disease severity (% FEV_1 < 90%), a social factor (active working), and a psychological factor (PHQ-9 > 5) were independent factors of a reduction in adherence. Furthermore, patients in the poor adherence group were analyzed and divided into three clusters. Two clusters consisted of elderly males with severe disease type and COPD as a comorbidity, while the third contained middle-aged non-smoking females, with a depressed tendency, and problems with asthma control. Efforts should focus on improving drug adherence in these patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.07.006.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

YuK and TKo designed the study and wrote the manuscript. YuK,TKo, TH, HU, KY, YoK and MH contributed to data collection. YuK,TKo, TH, SW and TKi performed the statistical analysis and interpretation of the results. All authors have read and approved the final manuscript.

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