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ORIGINAL ARTICLE

Analysis of Depression in Asthmatic Patients Using the Japanese Version of Patient Health Questionnaire-9

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ABSTRACT

Background: Previous studies show that depression plays an important role in asthma. However, the association between asthma control and severity, and depression is inconclusive.

Methods: To investigate the association between asthma control and severity, and depression, we assessed differences in asthma control and asthma severity between groups with various grades of depressive state as defined by the PHQ-9 score using data from the Japanese version of Patient Health Questionnaire-9 (J-PHQ-9) and a questionnaire survey including the Asthma Control Test (ACT).

Results: The ACT scores in the symptom-screen positive (SP) and major/other depressive disorder (MDD/ODD) group were significantly lower than those in the symptom-screen negative (SN) and non-MDD/ODD groups, respectively. The rate of step1 and of step 3 and 4 in the SP group were significantly lower and higher than those in the SN group, respectively. When the SP group was divided into three, that is minimal, mild, and more than mild (MTM) depressive state subgroups, the ACT scores in the mild and MTM depressive state subgroups were significantly lower than those in the minimal depressive state subgroup. When the MTM subgroup was divided into moderate, moderate-severe and severe depressive state groups, however, there was no significant variation in ACT score and asthma severity among these three depressive state groups.

Conclusions: This study is the first, large-scale investigation of the use of the J-PHQ-9 in asthma patients. Using the J-PHQ-9 and the questionnaire, there was a clear association between asthma control and severity, and depression. As the depression became more severe, the existence of other depression-associated factors unrelated to asthma control and severity might be assumed, although further investigation will be required.

KEY WORDS

ACT, asthma, control, J-PHQ-9

ABBREVIATIONS

ACT, Asthma Control Test; ICS, inhaled corticosteroid; IQR, interquartile range; J-PHQ-9, the Japanese version of the PHQ-9; JSA, the Japanese Society of Allergology; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; MDD, major depressive disorder; OCS, oral corticosteroid; ODD, other depressive disorder; OSRT, oral sustained-released theophylline; PEFM, peak flow meter; PHQ-9, the Patient Health Questionnaire-9; MTM subgroup, moderate, moderate-severe and severe groups.

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INTRODUCTION

The association between asthma and psychological factors has been recognized for centuries.[1] After varying degrees of confusion about the relationship between these two conditions, it is currently thought that the condition of asthma is not due to but is affected by psychological factors.[2] Among the various factors, depression plays a key role in the management of asthma, because health-related quality of life, one of the most important goals of asthma management, is reduced by the onset of depression.[3,4] In secondary care populations up to 50% of patients with asthma have been reported to have clinically significant depressive symptoms and over a third of asthmatic outpatients have been found to have a major depressive episode.[5-10] Large-scale studies found an age- and sex-adjusted odds ratio of 1.6 for depression in people with asthma compared to people without asthma.[11-13]

While it seems logical that having more severe asthma and asthma that is difficult to treat would be associated with an increased risk of depression, studies have reported somewhat mixed results. In investigations that used objective measures of asthma severity (i.e. clinician diagnoses, airway reactivity testing), some studies report that more severe asthma was associated with increased depressive symptoms.[14] Likewise, two studies that used patients' subjective ratings of their own asthma severity found significant relationships between perceived asthma severity and depressive symptoms.[15,16] However, this association was not found in other studies,[17,18] indicating that the evidence so far does not strongly support a direct relationship between objective asthma severity and depression. Thus, there is some controversy about the relationship between the severity/control of asthma and depression.

The Niigata Asthma Treatment Study Group has been carrying out a regular questionnaire on problems related to asthma management since 1998. The subjects surveyed are adult patients with bronchial asthma who visited medical institutions in Niigata Prefecture; the attending physicians of these patients are included in the survey. On the basis of these surveys, we have reported the clinical characteristics of adult bronchial asthma patients,[19] bronchial asthma in the elderly,[20] near-fatal asthma,[21] perimenstrual asthma,[22] the effect of obesity,[23] factors that exacerbate asthma,[24] the selection of ICS,[25] the relationship between smoking and gender in asthmatics,[26] and changes in asthma management.[27,28]

The Patient Health Questionnaire-9 (PHQ-9) consisted of nine questions related to depression alone, and the sensitivity and specificity were reported to be high compared with other questionnaires for depression.[29] The PHQ-9 differs from other questionnaires in that it contains no questions associated with anxiety, resulting in a lower likelihood of overestimation of the depression. Therefore, the PHQ-9 was developed for the evaluation of the depressive state in actual clinical care. Recently, the PHQ-9 was found to be a useful tool for both the evaluation of antidepressive medicines[30,31] and depressive state in various common disease and pathologic conditions.[32-37] In 2007, the validity of the Japanese version of the PHQ-9 (J-PHQ-9) was confirmed by Muramatsu *et al*..[38] In addition, the Asthma Control Test (ACT) has been disseminated as an excellent tool for the assessment of asthma control.[39,40] Although the ACT was based on subjective measures of asthma control,[41,42] it was reported that the ACT score was strongly associated with objective indicators of asthma control such as lung function.[40] In 2008, the ACT was added to our every two years questionnaire survey. We then attempted to evaluate the association between depression and control and severity of asthma in Japanese asthmatic patients, using our survey data and the J-PHQ-9 data.

METHODS

Participation in this study was open to all medical institutions in Niigata Prefecture if they intended to join the Niigata Asthma Treatment Study Group. This study was performed with the approval of the Ethics Committee at the School of Medicine of Niigata University in Niigata Prefecture, Japan, or at the relevant participating institution, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). The study involved 28 large hospitals (200 beds or more), 14 small hospitals (less than 200 beds), and 62 clinics (no beds). A total of 5260 questionnaires were prepared, and 3146 responses were received (response rate: 59.8%). The contents of the questionnaire were written in Japanese. The questionnaire study was performed over two months from September to October 2008. Subjects were adult patients (aged 16 years and more) with bronchial asthma who regularly visited the participating institutions for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Individual patients were thus expected to understand technical terms such as "attack" in the questionnaire. In addition to this questionnaire, the ACT and the J-PHQ-9 were separately carried out at the same time.

Apart from the ACT and the J-PHQ-9, in order to evaluate their asthma control, patients were asked about their peak flow meter (PEFM) use, smoking status, and the incidence of asthma attacks during the two weeks prior to answering the questionnaire. The questionnaire included questions on asthma-related symptoms in the two weeks prior to answering the questionnaire, including those regarding cough and sputum in the morning and at night, and

Table 1 Background and characteristics of study participants

cases	2289
age (years)	55.1 +/- 17.6
gender (male/female/unknown, %)	43.4/55.4/1.2
disease duration (years)	14.2 +/- 13.6
rate of PEFM Use (%)	26.3
smoking status	
non-smoker (%)	51.6
ex-smoker (%)	29.5
current smoker (%)	16.4
unknown (%)	2.5
disease type (atopic/non-atopic, unknown %)	68.2/26.1/5.7
ACT score (median [IQR])	23 [20-25]
attack rate during the last 2 weeks PQ (%)	22.4
morning symptom rate during the last 2 weeks PQ (%)	42.2
nocturnal symptom rate during the last 2 weeks PQ (%)	29.7
sleep disturbance rate during the last 2 weeks PQ (%)	13.1
disease severity (step 1, 2, 3, 4 and unknown [%])	24.6, 29.3, 26.0, 4.9, 15.2
persistent symptoms during the past year PQ (%)	9.0
work absenteeism rate during the past year PQ (%)	9.9
ICS use rate (%)	86.2
OCS use rate (%)	4.8
LABA use rate (%)	38.0
LTRA use rate (%)	42.4
OSRT use rate (%)	42.9
J-PHQ-9 score (median [IQR])	1 [0-4]

PEFM, peak-flow meter; ACT, Asthma Control Test; IQR, interquartile range; PQ, prior to the questionnaire; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; OSRT, oral sustain-released theophylline; J-PHQ-9, the Japanese version of patient health questionnaire-9.

sleep disturbances. To evaluate the patients' condition in the year prior to answering the questionnaire, they were also asked to provide information about their asthma by selecting one of the following three answers: "few attacks," "seasonal attacks," and "frequent attacks." Furthermore, they were asked about asthma-related absences from work or school. To evaluate problems with asthma management and treatment related to normal activity levels, the questionnaire also asked patients about their satisfaction with daily life. The subjects answered by choosing one of five answers: "very satisfied," "fairly satisfied," "mediocre," "slightly dissatisfied," and "dissatisfied."

In addition to monitoring the completion of the questionnaire by the patients, physicians were asked to supply details on current treatment, medication used for primary control, the type of asthma (atopic or non-atopic) in accordance with the elevation in serum total IgE or detection of a specific IgE for allergens, and the severity of asthma in accordance with Asthma Prevention and Management Guideline 2006 (in Japanese) published by Japanese Society of Allergology (JSA). The definition of the severity of asthma was essentially the same as that used by the Global Initiative for Asthma.

We measured depressive symptoms using the nine-item questionnaire of J-PHQ-9. The PHQ-9 is the 9-item depression module from the full PHQ (Patient Health Questionnaire).[43] The PHQ-9 has been developed from the original PRIME-MD PQ (Patient Questionnaire).[43,44] In the PRIME-MD PQ, the response categories were dichotomous ('yes' or 'no').[43] As the first evaluation, we assessed the J-PHQ-9 scores according to the original PRIME-ME Patient Health Questionnaire (PQ) and divided the scores into the following two groups: 'J-PHQ-9 score = 0 point group' is the symptom-screen negative group (SN group). 'J-PHQ-9 score ≥ 1 point' is the symptom-screen positive group (SP group). In the second evaluation, we used the J-PHQ-9. In contrast to other depression questionnaires, the PHQ-9 is a dual-purpose instrument that has both the diagnostic measure and the measure of depression severity. The PHQ-9 can evaluate the nine *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for major depressive disorder (MDD). The diagnosis of MDD can be made by a categorical algorithm using these nine items. MDD should be considered in patients who endorse ≥ 5 of 9 symptoms as present "more than half the days" (the 9th item counts if en-

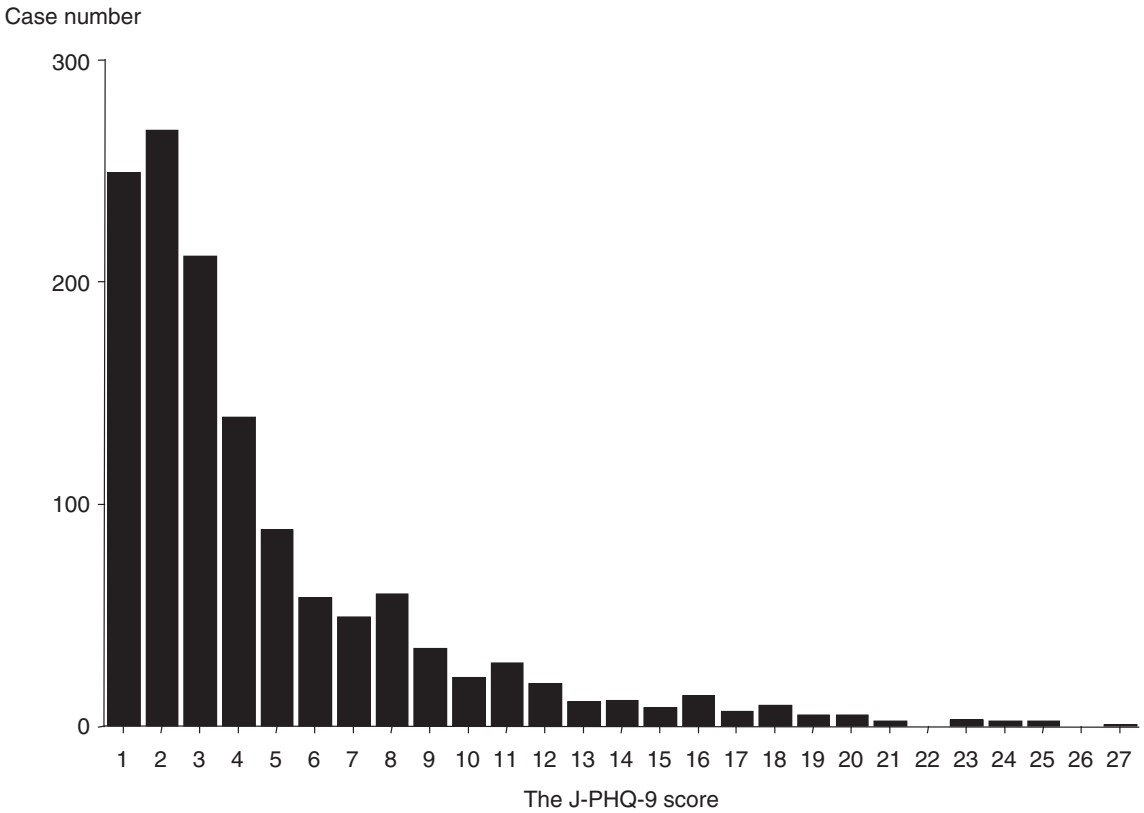

Fig. 1 Number of cases for each Japanese version of patient health questionnaire (J-PHQ-9) score. There were no cases with J-PHQ-9 scores of 22 and 26. The number of cases with a J-PHQ-9 score of 0 was 981 (excluded from this Figure).

dorsed "several days") in past 2 weeks, 1 of the first two symptoms (depressed mood or loss of interest) is endorsed. Other depressive disorder (ODD) is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days in past 2 weeks. As a severity measure, the PHQ-9 can be assessed by calculating a summary score. Though, we assessed the categorical algorithm diagnosis of major depressive disorder (MDD), other depressive disorder (ODD) using J-PHQ-9 at the first stage. We divided patients into the following groups: 'the MDD cases or ODD cases' are the MDD/ODD group, 'non-MDD cases and non- ODD cases' are the non-MDD/ODD group. Next, we also measured the severity of depressive states according to the total score of J-PHQ-9 at the second stage, the score is ranging from 0 to 27, and the points of 0-4, 5-9, 10-14, 15-19, 20-27 respectively represent minimal, mild, moderate, moderate-severe, and severe state of depressive symptoms. The clinical description of each depressive state is as follows[45,46]:

1) Minimal depressive state; An individual with minimal depressive state is distressed from one depressive symptom to four symptoms very occasionally and has slight difficulty in continuing with ordinary work and social activities. The recommended treatment for minimal depressive state is reassurance or supportive counseling. 2) Mild depressive state; An individual with mild depressive state is usually distressed from one depressive symptom to four symptoms and has some difficulty in continuing ordinary work and social activities, but will probably not cease to function completely. The recommended treatment for mild depressive state is reassurance or supportive counseling by general physician or medical staff. If the symptoms get worse, the patient is recommended to consult a mental professional physician (psychosomatic medicine) or psychiatrist. 3) Moderate depressive state; An individual with moderate depressive state is usually distressed from two depressive symptoms to four symptoms and usually has considerable difficulty in continuing social, work or domestic activities. The recommended treatment for moderate depressive state is watchful waiting and supportive counseling by a mental professional physician (psychosomatic medicine) or psychiatrist. If there is no improvement after one or more months, the physician may consider use of an antidepressant and brief psychological counseling (CBT: cognitive behavior therapy). 4) Moderately severe and severe depressive state; An individual with moderately severe and severe depressive symptoms has considerable dis-

Table 2 Numbers and rates for each group

	J-PHQ-9 Score (median [IQR])	case number (%)
SN group	0 [0-0]	981 (42.9)
SP group	3 [2-6]	1308 (57.1)
minimal DS subgroup	2 [1-3]	868 (37.9)
mild DS subgroup	6 [5-8]	289 (12.6)
more than mild DS subgroup	13 [11-16]	151 (6.6)
moderate DS group	11 [11-11.3]	92 (4.0)
moderate-severe DS group	16.5 [16-18]	44 (1.9)
severe DS group	23 [20-24]	15 (0.7)

J-PHQ-9, the Japanese version of patient health questionnaire-9; IQR, interquartile range; SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.

Table 3 Comparison of age, gender and disease duration in each group

	age (mean +/- SD, years)	gender (male/female [%])	disease duration (mean +/- SD, years)
SN group	58.8 +/- 16.4	482/486 (49.1/49.5)	14.1 +/- 13.5
SP group	52.3 +/- 16.4***	512/781 (39.1/59.7)***	14.3 +/- 13.7
minimal DS subgroup	52.8 +/- 17.6	351/506 (40.4/58.3)	14.3 +/- 13.7
mild DS subgroup	51.8 +/- 18.6	111/174 (38.4/60.2)	14.0 +/- 13.1
more than mild DS subgroup	50.6 +/- 19.7	50/101 (33.1/66.9)	15.2 +/- 15.0
moderate DS group	50.5 +/- 20.7	30/62 (32.6/67.4)	14.8 +/- 13.8
moderate-severe DS group	50.8 +/- 18.2	15/29 (34.1/65.9)	18.4 +/- 17.4
severe DS group	50.6 +/- 20.2	5/10 (33.3/66.7)	7.3 +/- 11.2¢

SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.
***$P < 0.001$ v.s. SN DS group, ¢$P < 0.05$ v.s. moderate-severe DS group.

Table 4 Comparison of disease type, peak flow meter use and smoking status in each group

	disease type (atopic/non-atopic [%])	PEFM use rate (%)	smoking status (non-smoker/ex-smoker/current smoker [%])
SN group	64.3/29.2	27.4	50.4/30.7/15.9
SP group	71.0/23.9**	26.2	52.5/28.7/16.8
minimal DS subgroup	72.4/22.1	26.7	53.5/28.9/15.8
mild DS subgroup	67.1/27.5	24.9	48.4/30.1/19.0
more than mild DS subgroup	70.9/27.2	25.8	55.0/24.5/18.5
moderate DS group	71.8/25.0	27.2	63.0/21.7/15.2
moderate-severe DS group	65.9/34.1	20.5	45.5/27.3/20.5
severe DS group	80.0/20.0	33.3	33.3/33.3/33.3

PEFM, peak flow meter; SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.
**$P < 0.01$ v.s. SN group.

tress and has a marked feature such as agitation, loss of self-esteem or feelings of uselessness or guilt and risk of suicide. The sufferer usually has severe difficulty in continuing with social, work, or domestic activities. The recommended treatment for moderately severe and severe depressive states is antidepressants alone or in combination with psychological counseling (CBT) by psychiatrist. Comparisons were performed between the SN and SP groups and between the MDD/ODD and non-MDD/ODD groups, among the minimal, mild and more than mild (MTM) depressive state subgroups that included moderate, moderate-severe and severe depressive state group, and among the moderate, moderate-severe and severe depressive state groups.

Representative results for continuous variables

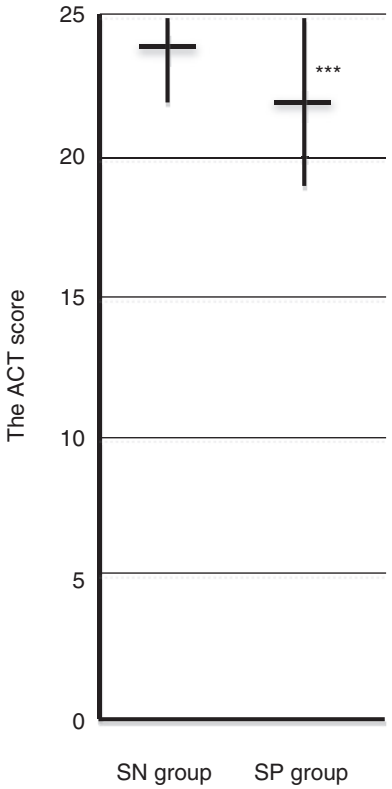

Fig. 2 The ACT score in the symptoms-screen negative (SN) and symptoms-screen positive (SP) groups. The transverse short line expressed the median of the ACT score and the vertical line indicates the interquartile range of the ACT score. The ACT score in the SP group was significantly lower (***$p < 0.001$) than that in SN group.

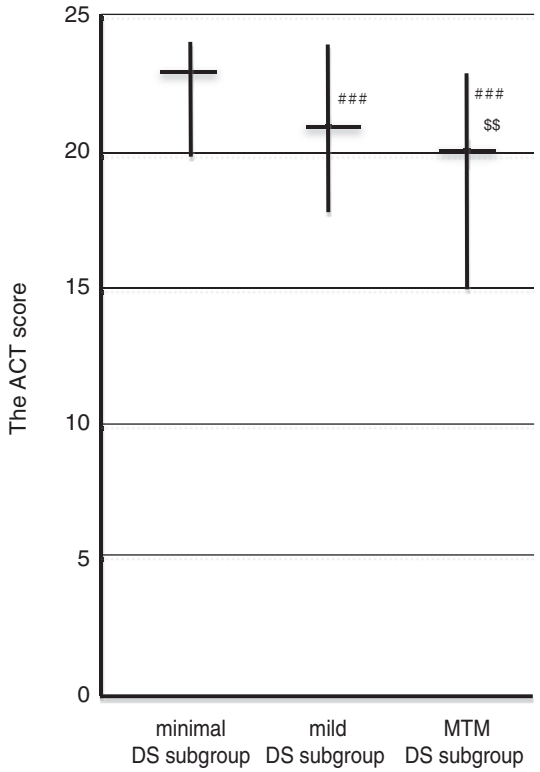

Fig. 3 The ACT score in the minimal 'depressive case' subgroup, mild subgroup and MTM DS subgroup. The transverse short line expresses the median of the ACT score and the vertical line indicates the interquartile range of the ACT score. There was a significant variation of the ACT score among the minimal, mild MTM DS subgroups. The ACT score in the mild and more than mild subgroups was significantly lower (###$p < 0.001$) than that in the minimal DS subgroup. The ACT score in the MTM DS subgroup was significantly lower ($$$p < 0.01$) than that in the mild DS subgroup. MTM, more than mild; DS, depressive state.

were expressed as arithmetic means and standard deviations. Intergroup differences in terms of continuous variables were evaluated using the Kruskal-Wallis test and Wilcoxon's rank sum test with the Bonferroni correction. A Chi-square test with the Bonferroni correction was also used to assess the significance of differences in proportions among groups. All statistical analyses were performed with the statistical software StatView 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a *P*-value < 0.05 was considered to be significant.

RESULTS

PATIENT CHARACTERISTICS

Patient characteristics are summarized in Table 1. Of the asthmatic patients who answered the questionnaire, 2289 subjects who completed the J-PHQ-9 and ACT were analyzed in this study. The age (mean ± SD), gender (male/female [%]), disease duration (mean ± SD), disease type (atopic/non-atopic [%]) and the rate of peak-flow meter use were 55.1 ± 17.6 years, 43.4%/55.4%, 14.2 ± 13.6 years, 68.2%/26.1% and 26.3%, respectively. Rates of non-smokers, ex-smokers and current smokers were 51.6%, 29.5% and 16.4%, respectively. The ACT and J-PHQ-9 scores (median [interquartile range (IQR)]) were 23 [20-25] and 1 [0-4], respectively. The attack rate during the two weeks prior to answering the questionnaire was 22.4%, and rates of morning symptoms, nocturnal symptoms and sleep disturbance were 42.2%, 29.7% and 13.1%, respectively. The rates of persistent symptoms and absenteeism from work during the year prior to answering the questionnaire were 9.0% and 9.9%, respectively. While the rate of use of inhaled corticosteroids (ICS) was over 80%, rates for use of long-acting beta agonists (LABAs), leukotriene receptor antagonists (LTRAs) and oral sustained-released theophylline (OSRT) were around 40%. On the other hand, oral corticosteroids (OCS) were used in under 5%.

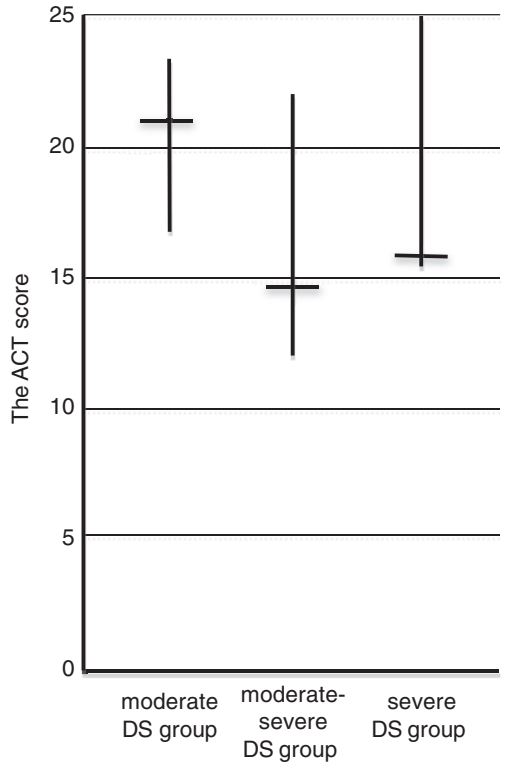

Fig. 4 The ACT score in the moderate 'depressive case' group, moderate-severe group and severe DS groups. The transverse short line expresses the median of the ACT score and the vertical line indicates the interquartile range of the ACT score. There was no significant variation of the ACT score among the moderate, moderate-severe and severe DS groups. DS, depressive state.

NUMBERS AND RATES FOR EACH GROUP

A visual representation of the distribution of J-PHQ-9 scores in these patients with asthma is shown in Figure 1, which shows the numbers for each J-PHQ-9 score except the score of zero; the numbers and the rates for each group, including the SN and SP group, are summarized in Table 2. There were 981 (42.9%) and 1314 (57.1%) cases in the SN and SP groups, respectively. The respective numbers (rates) in minimal, mild, moderate, moderate-severe and severe depressive state groups were 868 (37.9%), 289 (12.6%), 92 (4.0%), 44 (1.9%) and 15 (0.7%), respectively. The numbers (rate) for the MTM subgroup were 152 (6.6%). There were 74 MDD (3.2%) and 57 ODD cases (2.5%) in the MDD/ODD group, although these were not described in Table 2.

COMPARISON OF PATIENT DEMOGRAPHICS IN EACH GROUP

Tables 3 and 4 summarize our results. Patients in the SP group were significantly younger and more were female than in the SN group, but there was no significant difference in the duration of illness between the groups. There were no significant differences in age, gender and disease duration among the minimal, mild and MTM depressive state subgroups. Within the moderate, moderate-severe and severe depressive state groups, those in the severe depressive state group were significantly younger than those in the moderate-severe depressive state group, without any other significant differences. On examination of disease type, rate of use of PEFM and smoking status, the only difference between groups was related to disease type (Table 4). There was a significantly higher rate of atopic type in the SP group than in the SN group. There were no significant differences in age, gender, disease duration, disease type, rate of use of PEFM and smoking status between the MDD/ODD and non-MDD/ODD groups.

COMPARISON OF THE ACT SCORE

Figure 2 shows ACT scores in the SN and SP groups. The ACT score in the SP group was significantly lower than that in the SN group. Figure 3 shows ACT scores in the minimal, mild and MTM depressive state subgroups. There was a significant variation in the ACT score among the minimal, mild and MTM depressive state subgroups. The ACT score in the mild and MTM depressive state subgroups was significantly lower than that in the minimal depressive state subgroup. The ACT score in the MTM depressive state subgroup was also significantly lower than that in the mild depressive state subgroup. There was no significant variation in the ACT score among the moderate, moderate-severe and severe depressive state groups (Fig. 4). The ACT score in the MDD/ODD group (21 [15-24]) was significantly lower than that in the non-MDD/ODD group (23 [20-25]).

COMPARISON OF ATTACK RATES, MORNING SYMPTOM RATES, NOCTURNAL SYMPTOM RATES AND SLEEP DISTURBANCE RATES DURING THE TWO WEEKS PRIOR TO ANSWERING THE QUESTIONNAIRE

These data are summarized in Table 5. The attack rate, morning symptom rate, nocturnal symptom rate and sleep disturbance rate during the two weeks prior to answering the questionnaire were significantly higher in the SP group than in the SN group. Among the minimal, mild and MTM depressive state subgroups, although there was no significant variation in attack rates, there was significant variation in the morning symptom rates, nocturnal symptom rates and sleep disturbance rates. The sleep disturbance rate in the mild depressive state subgroup and the rates of morning symptoms, nocturnal symptoms and sleep disturbance in the MTM depressive state subgroup were significantly higher than those in the minimal depressive state subgroup. There were no significant variations in the attack rate, morning symptom rate, nocturnal symptom rate and sleep

Table 5 Comparison of attack rates, morning symptom rates, nocturnal symptom rates and sleep disturbance rates during the 2 weeks prior to the questionnaire, in each group

	AR during 2W (%)	MSR during 2W (%)	NSR during 2W (%)	SDR during 2W (%)
SN group	14.6	29.6	16.4	3.7
SP group	28.3***	51.8***	39.7***	20.2***
minimal DS subgroup	26.6	48.4	36.4	16.2
mild DS subgroup	31.1	54.7	43.6	24.6##
more than mild DS subgroup	31.8	65.6##	51.0##	34.4###
moderate DS group	27.2	62.0	46.7	27.2
moderate-severe DS group	40.9	75.0	61.4	40.9
severe DS group	33.3	60.0	46.7	60.0

AR, attack rate; 2W, the 2 weeks prior to the questionnaire; MSR, morning symptom rate; NSR, nocturnal symptom rate; SDR, sleep disturbance rate; SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.

***$P < 0.001$ v.s. SN group, ###$P < 0.001$, ##$P < 0.01$ v.s. minimal DS subgroup.

Table 6 Comparison of rates of persistent symptoms and work absenteeism during the year prior to the questionnaire, and satisfaction with daily life, in each group

	PS during 1Y (%)	WAR during 1Y (%)	satisfaction with daily life (VS + S/M + SU + U [%])
SN group	5.2	3.9	89.7/9.4
SP group	11.9***	12.6***	70.0/29.8***
minimal DS subgroup	9.1	9.6	81.8/18.1
mild DS subgroup	16.3##	17.3##	52.2/47.8###
more than mild DS subgroup	19.9###	21.2###	36.4/62.9###, $$
moderate DS group	14.1	14.1	41.3/57.6
moderate-severe DS group	34.1¥	31.8¥	27.3/72.7
severe DS group	13.3	33.3	33.3/66.7

PS, persistent symptoms; 1Y, the year prior to the questionnaire; WAR, work absenteeism rate; VS + S, very satisfied and satisfied; M + SU + U, mediocre, slightly dissatisfied and not satisfied; SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.

***$P < 0.001$ v.s. SN group, ###$P < 0.001$, ##$P < 0.01$ v.s. minimal DS subgroup, $$$P < 0.01$ v.s. mild DS subgroup, ¥$P < 0.05$ v.s. moderate DS group.

disturbance rate during the two weeks prior to answering the questionnaire among the moderate, moderate-severe and severe depressive state groups. Morning symptom rate (57.3% vs. 41.3%), nocturnal symptom rate (42.7% vs. 28.9%) and sleep disturbance rate (32.1% vs. 12.0%) during the two weeks prior to answering the questionnaire in the MDD/ODD group were also higher than those in the non-MDD/ODD group, although there was no significant difference of attack rate (MDD/ODD vs. non-MDD/ODD group).

COMPARISON OF RATES OF PERSISTENT SYMPTOMS AND ABSENTEEISM FROM WORK DURING THE YEAR PRIOR TO ANSWERING THE QUESTIONNAIRE, AND SATISFACTION WITH DAILY LIFE

These findings are summarized in Table 6. The rates of persistent symptoms and absenteeism during the year prior to answering the questionnaire were significantly higher in the SP group than in the SN group. Among the minimal, mild and MTM depressive state subgroups, there was significant variation in the rates of persistent symptoms and absenteeism, and these metrics were significantly greater in the mild and MTM depressive state subgroups than in the minimal depressive state subgroup. There was significant variation in the rates of persistent symptoms and absenteeism among the moderate, moderate-severe and depressive state severe groups, and these parameters were greater in the moderate-severe depressive state group than in the moderate depressive state group. The rates of persistent symptoms (16.8% vs. 8.6%) and absenteeism (19.1% vs. 8.2%) during the year prior to answering the questionnaire were significantly higher in MDD/ODD group than in the non-MDD/ODD group. As regards satisfaction with daily life, responses were classified into

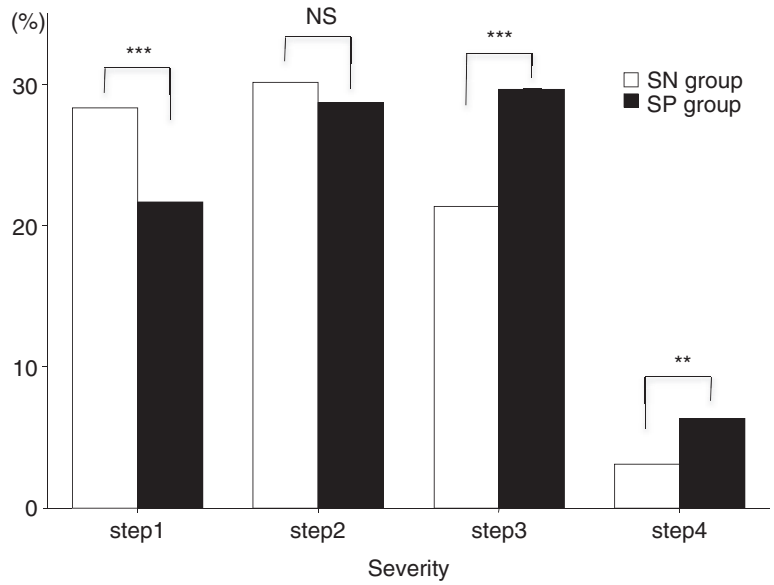

Fig. 5 The open and closed square bars represent the rate of each step in disease severity, as defined by the Japanese Society of Allergology (JSA), in the symptoms-screen negative (SN) and symptoms-screen positive (SP) groups, respectively. The rate of step 1 in the SP group was significantly lower than that in the SN group. The rates for steps 3 and 4 in the SP group were significantly higher than those in the SN group. There was no significant difference in the rate of step 2 between the SN and SP groups. $^{**}p < 0.01$, $^{***}p < 0.001$ v.s. SN group. NS, not significant.

two, those who answered "very satisfied and satisfied" and those who responded with "mediocre, slightly unsatisfied or unsatisfied", and then analyzed. The rate of the later was significantly greater in the SP group than in the SN group. There was significant variation in the rate of a "very satisfied and satisfied" response among the minimal, mild and MTM depressive state subgroups, and the response rate for this choice was significantly lower in the mild and STM depressive state subgroups than that in the minimal depressive state subgroup. The rate of "very satisfied and satisfied" in the MTM depressive state subgroup was also significantly lower than that in the mild depressive state subgroup. There was no significant variation in the rate of "very satisfied and satisfied" among the moderate, moderate-severe and severe depressive state groups. The rate of the "mediocre, slightly unsatisfied or unsatisfied" (63.4% vs.18.5%) was significantly greater in the MDD/ODD group than in the non-MDD/ODD group.

COMPARISON OF DISEASE SEVERITY

Comparisons of disease severity are summarized in Figure 5-7. Step 1 severity was significantly less frequent in the SP group than in the SN group, and step 3 and 4 rates were more common in the SP group (Fig. 5). Although there were no significant variations among the minimal, mild and MTM depressive state subgroups, there was significant variation in disease severity among these groups, and the step 4 rate in the MTM depressive state subgroup was significantly higher than that in the minimal depressive state subgroup (Fig. 6). There was no significant variation in disease severity among the moderate, moderate-severe and severe depressive state groups (Fig. 7). The J-PHQ-9 scores (median [IQR]) in each group of Step 1, 2, 3 and 4 was 1 [0-3], 1 [0-3], 2 [0-4] and 2.5 [0-7.25], respectively. The J-PHQ-9 scores in the groups of Step 3 and 4 were significantly higher than those in the groups of Step 1 and 2.

COMPARISON OF MEDICATIONS

A summary of medication is shown in Table 7. Rates of use of OCS, ICS, LTRA and LABA were significantly higher in the SP group than in the SN group, although there was no significant difference in rates of use of OSRT between the SP and SN groups. There were no significant variations in rates of use of OCS, ICS, LABA, LTRA and OSRT among the minimal, mild and MTM depressive state subgroups and among the moderate, moderate-severe and severe DS groups. Rate of use of OCS in the MDD/ODD group (10.7% vs. 4.4%) was significantly higher than that in the non-MDD/ODD group.

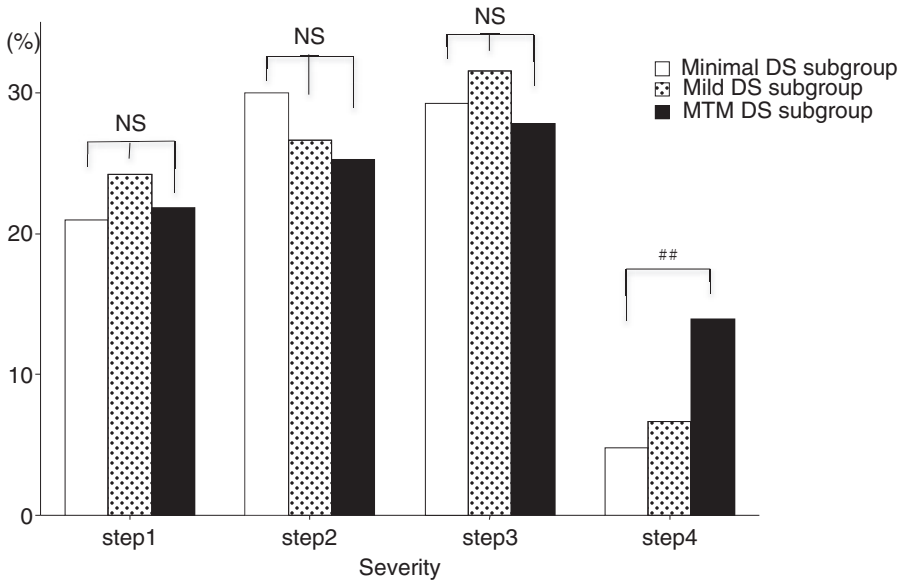

Fig. 6 The open, dotted and solid bars represent the rate of each step in disease severity, as defined by the Japanese Society of Allergology (JSA), in the minimal, mild and MTM DS subgroups, respectively. There were no significant variations in the rates of steps 1, 2 and 3 among the minimal, mild and MTMDS subgroups. There was a significant variation in the rate of step 4 among the minimal, mild and MTM DS subgroups, and the rate of step 4 in the DS MTM subgroup was significantly higher than that in the minimal DS subgroup. $^{\#\#}p < 0.01$ v.s. minimal DS subgroup. NS, not significant; DS, depressive state; MTM, more than mild.

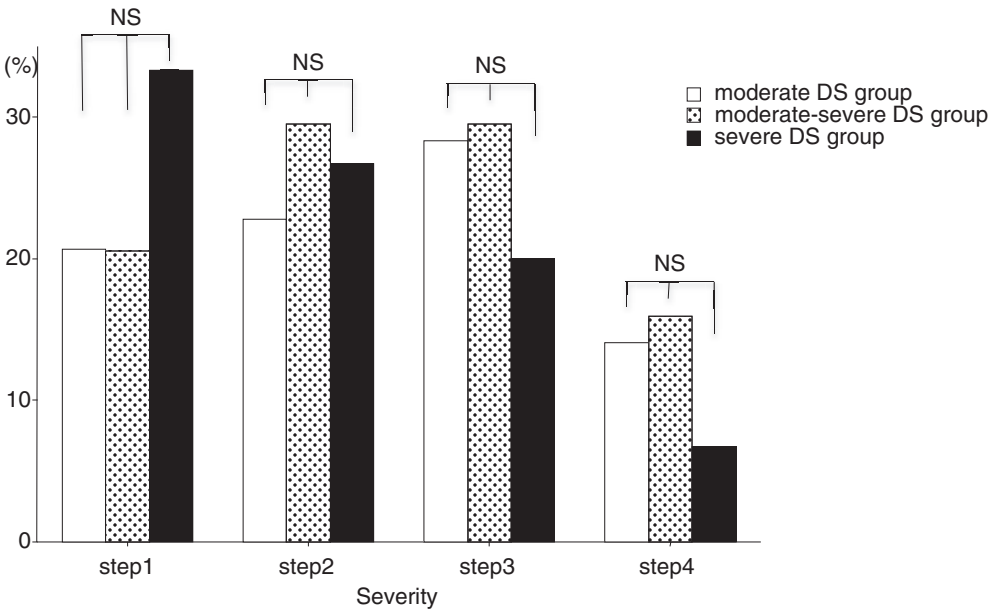

Fig. 7 The open, dotted and filled bars represent the rate of each step in disease severity, as defined by the Japanese Society of Allergology (JSA), in the moderate, moderate-severe and severe DS groups, respectively. There were no significant variations in the rates of steps 1, 2 , 3 and 4 among the moderate, moderate-severe and severe DS groups. NS, not significant; DS, depressive state.

Table 7 Comparison of medication in each group

	OCS use rate (%)	ICS use rate (%)	LABA use rate (%)	LTRA use rate (%)	OSRT use rate (%)
SN group	3.3	83.4	31.3	38.5	42.5
SP group	5.9**	88.2***	43.0***	45.3**	43.3
minimal DS subgroup	5.1	88.9	42.1	44.0	41.0
mild DS subgroup	6.2	87.5	45.0	47.8	48.1
more than mild DS subgroup	9.9	85.4	44.4	47.7	47.0
moderate DS group	9.8	82.6	44.6	48.9	44.6
moderate-severe DS group	13.6	93.2	47.7	43.2	52.3
severe DS group	0.0	80.0	33.3	50.0	46.7

OCS, oral corticosteroid; ICS, inhaled corticosteroid; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; OSRT, oral sustained-released theophylline; SN group, symptom-screen negative group; SP group, symptom-screen positive group; DS, depressive state.

***$P < 0.001$, **$P < 0.01$ v.s. SN group.

DISCUSSION

The aim of this study was to investigate the association between asthma control and severity, and depression, using a questionnaire survey containing the ACT and the PHQ-9. A remarkable finding was that just 42.9% of patients with asthma had no evidence of a depressive state, although other studies show an odds ratio of 1.6 for depression in those with asthma, compared to those without asthma.[11-13] Although the PHQ-9 was reported to be an excellent tool for the evaluation of depression in various common diseases and conditions[32-37] in actual clinical care, there have been few studies of depression in asthmatic patients using the PHQ-9. This study appears to be the first report of analyses of depression in patients with asthma using the PHQ-9. We cannot therefore compare our findings with those from other studies of depression in asthma using the PHQ-9.

In studies of depression that used the PHQ-9 in patients with heart failure, rates of PHQ-9 scores over 11 and scores between 9 and 11 were 24% and 15%, respectively.[47] In our study, the former rate was 4.5% and the latter was 4.8% (data not shown). In patients with acute myocardial infarction, a PHQ-9 score of more than 9 was present in 29%,[33] while the rate was just 8.1% in this study. With head and neck cancer, the mean value of the J-PHQ-9 score in patients with stage 4 disease was approximately twice that in patients at step 4 in our study.[48] Compared with these pathologic conditions of heart disease and cancer, depression might play a lesser role in asthma. However, with step 4 severity, the J-PHQ-9 score was over 9 in 18.8% (data not shown), indicating that more attention should be paid to depression in patients with severe asthma.

The most reliable indicator of asthma control in this study was the ACT score. It was very clear that asthma in those with depression was less well controlled than in those without depression (Fig. 2 and the comparison of the ACT score between the MDD/ODD and non-MDD/ODD group), and asthma control was worse with increasing levels of depressive state (Fig. 3). Other indicators of asthma control, including asthma attacks and symptoms during the two weeks prior to answering the questionnaire (Table 5), and asthma-related conditions during the year prior to answering the questionnaire (Table 6), supported the findings revealed by the ACT score. Note that not only subjective indicators of asthma control such as patients' asthma symptoms but also the ACT score, accepted as being strongly associated with objective indicators of asthma control,[40] showed a negative association between asthma control and severity of depression. Among the moderate, moderate-severe and severe depressive state groups, however, there was no consistent association between asthma control and severity of depression. Although there may have been too few cases in the analysis to detect a difference among these subgroups, it was difficult to explain why absolute values of several indicators of control, such as the ACT score in the moderate-severe depressive state group, did not follow the trend. These findings suggest that the relationship between asthma control and severity of depressive state might be influenced by two characteristics, and that independent factors that affect asthma control might play an important role in advanced depression associated with asthma. Further study will be required to clarify these issues.

There were also associations between asthma severity and the severity of depressive state, just as there were between asthma control and severity of depressive state (Fig. 5-7). Because asthma severity was influenced not only by asthma control but also the medication required to achieve asthma control, there were fewer differences between asthma severity and severity of depressive state than there were

between asthma control and severity of depressive state, among the minimal, mild and MTM depressive state subgroups. This finding suggests that the differences in medication (Table 7) might be related to the association between disease severity and severity of depressive state. The reason why there were no significant variations in the rates of steps 1, 2, 3 and 4 among the moderate, moderate-severe and severe depressive state groups (Fig. 7) might be same as that why the ACT score in the moderate-severe depressive state group did not follow the trend as mentioned above. As satisfaction with daily life was thought to reflect basic asthma control, it is credible that the proportion of those who felt "very satisfied or satisfied" decreased as the degree of depression became more severe. Satisfaction with daily life might influence and be influenced by asthma severity.

In this study, there were three differences in patients' characteristics in the SP and SN groups, that is their age, gender and disease type. When patients were divided into two groups by gender or disease type, there was no significant difference in ACT score, indicating that gender and disease type might influence the depressive state, independent of asthma control. When divided into two groups by age (<64: 'young' group, ≥64: 'elderly' group), there was a small but significant difference in ACT score, and the mean ACT score in the younger group was 0.6 below that in the elderly group (data not shown), while the difference in the ACT mean score between the SP and SN groups was 2.1, suggesting that the age has only a minor effect on the asthma control through its effects on the severity of depressive state.

In summary, we tried to determine the association between asthma control and severity, and depressive state using a questionnaire that included the ACT and PHQ-9 questionnaires. This study is the first large-scale investigation of the use of the PHQ-9 in patients with asthma. There was a clear association between asthma control, mainly evaluated with the use of the ACT score, and asthma severity (based on JSA criteria) on the one hand, and the presence of a depressive state, evaluated using the J-PHQ-9, on the other. With progression from moderate to severe depression based on the J-PHQ-9 score, the existence of other depression-associated factors unrelated to asthma control and severity might be assumed. Further investigation of this hypothesis will be required.

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