Clinical remission of mild-to-moderate asthma: Rates, contributing factors, and stability

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Background: Although clinical remission (CR) of severe asthma has been extensively investigated, CR of mild-to-moderate asthma remains unexplored.
Objective: This study aimed to determine CR rates, contributing factors, and stability in patients with mild-to-moderate asthma.
Methods: We retrospectively analyzed 263 patients with asthma. Three-component CR was defined as no exacerbation, no daily oral corticosteroid receipt, and an Asthma Control Test score equivalent to that of the well control; 4-component CR included these parameters plus forced expiratory volume in 1 second of ≥80% predicted. CR during the 1 year and stability of CR over 10 years were retrospectively analyzed in patients with mild-to-moderate and severe asthma.
Results: The CR rates were significantly higher (4-component, 73.2%; 3-component, 81.0%) in patients with mild-to-moderate asthma compared with the CR rate in patients with severe asthma (4-component, 33.9%; and 3-component, 30.6%). A lower smoking index contributed to 3- and 4-component CR. Lower body mass index contributed to 3-component remission, and later onset and shorter asthma duration contributed to 4-component remission. In patients experiencing 4-component remission 10 years before, 80.3% maintained disease in remission; 89.1% of patients experiencing 3-component remission maintained disease in remission. In patients with disease that did not maintain 4-component CR after 10 years, predicted forced expiratory volume decreased, but no differences in inhaled corticosteroid and long-acting β-agonists/long-acting muscarinic antagonists receipt were detected between 10 years ago and the present. The current muscarinic antagonist receipt remained low, at 16.7%.
Conclusion: CR, including normalized forced expiratory volume, is obtainable and sustainable in most Japanese patients with mild-to-moderate asthma. Assessing CR in these patients may help avoid undertreatment and reduce future risks. (J Allergy Clin Immunol Global 2025;4:100431.)

Key words: *Clinical remission, mild asthma, moderate asthma, stability, practical guidelines for asthma management, pulmonary function*

Clinical remission (CR) is defined as a state of low or no disease activity and clinical disease control with treatment. The concept of CR has been adopted for various chronic diseases, including inflammatory bowel disease[1] and collagen vascular disease,[2] as a therapeutic target. In rheumatoid arthritis, CR is defined as a favorable state with almost no disease activity, based on joint symptoms and blood tests, and CR is a treatment goal.[2]

In adults with asthma, the rate of off-treatment remission is as low as 10%,[3] and the concept of CR or on-treatment remission has been proposed as a realistic treatment goal. The definition of CR in asthma was first presented in the 2020 Consensus Report[4] and included the following criteria: no apparent asthma symptoms, optimized and stabilized pulmonary function, patient and health care provider agreement regarding presence of disease remission, and no systemic corticosteroid therapy for exacerbation treatment or long-term management. This led to discussions about the definition of CR in Italy,[5] Germany,[6] and the United States.[7] In Japan, a 3-component definition of CR for general practice settings, which excludes the forced expiratory volume in 1 second (FEV_1) component, was proposed in the Practical Guidelines for Asthma Management of 2023.[8,9]

CR has been assessed primarily in patients with severe asthma using biologic agents. Although remission criteria vary slightly, *post hoc* analyses of clinical trials reported CR rates using biologics of 14.5% to 37.6%,[10-22] with the CR rates ranging from about 20.6%[10] to 37.6%[13] for the 3-component definition and about 14.5%[10] to 38.9%[18] for 4-component definition. However, the concept of CR may also be important for patients with milder asthma. CR may be more obtainable in cases of nonsevere asthma without airway remodeling.[23] However, off-treatment remission is difficult to obtain, even in mild-to-moderate asthma.[3] To date, no studies have focused on the rates and contributing clinical factors for CR in patients with mild-to-moderate asthma. Studies concerning the relationship between current CR in patients with asthma and future risks are also lacking. Thus, the primary objective of the current study was to determine the CR rate in patients with mild-to-moderate asthma in real-world settings. The clinical factors contributing to CR were also analyzed. To determine the effects of CR on future CR, the stability of CR for 10 years was retrospectively investigated.

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Abbreviations used
ACT: Asthma Control Test
BMI: Body mass index
CR: Clinical remission
F_{ENO}: Fractional exhaled nitric oxide
FEV_1: Forced expiratory volume in 1 second
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
LAMA: Long-acting muscarinic antagonist
OCS: Oral corticosteroid

METHODS

Study population

Between April 2022 and March 2023, a total of 307 consecutive patients with asthma aged ≥20 years attending Teikyo University Hospital were recruited for the study. The diagnosis of asthma was made according to the 2021 Japanese guidelines for adult asthma by a respiratory physician or allergy specialist.[24] Asthma severity was classified according to these 2021 guidelines on the basis of ongoing treatment intensity and symptoms.[24] In GINA, severity is assessed in well-controlled cases,[23] whereas in the Japanese guidelines, severity is defined for all combinations of treatment intensity and control status.[24] The treatment intensity was defined by the dose of inhaled corticosteroid (ICS) based on the fluticasone propionate equivalent, as follows: low dose, <250 μg/d; medium dose, 251-500 μg/d; and high dose, 501-1,000 μg/d. Because as-needed-only low-dose ICS formoterol is currently not recommended in Japan,[24] all patients were treated with continuous ICS therapy. Mildly intermittent, mildly persistent, and moderately persistent asthma were placed in the mild-to-moderate asthma group, and severely persistent and most severely persistent asthma were placed in the severe asthma group.

Among the patients treated with a fixed dose of ICS (n = 100), the proportion of those who were actually prescribed drugs per year was 94.8%, and the proportion of patients prescribed 100% of the drug doses was 90.0%. No significant difference was observed in the proportion of actually prescribed drugs per year between the CR and non-CR groups of 4-component remission (CR, 92.2%; non-CR, 98.2%).

The Teikyo University Ethical Review Board for Medical and Health Research Involving Human Subjects approved this study (20-197, 20-197-2). All subjects provided written informed consent. This study was conducted according to the principles of the Declaration of Helsinki.

Definition of remission

CR was analyzed according to both the 3- and 4-component remission definitions. The 3-component remission definition was based on the definition in the Japan Asthma Society Guideline Committee's "Practical Guidelines for Asthma Management"[8] and consisted of the following items: (1) no daily oral corticosteroid (OCS) receipt, (2) no exacerbations, and (3) an Asthma Control Test (ACT) score of ≥23 points for 1 year. The 4-component remission definition, which was based on a 2020 consensus report,[4] includes the 3-component definition plus the FEV_1 criteria and a threshold ACT score of 20 points. For the FEV_1 criteria, normalization of FEV_1 (≥80% predicted) was adopted in this study because a high attainment rate in patients with mild-to-moderate asthma was estimated. The predicted value of FEV_1 was based on Japanese spirogram reference values defined by Japanese Respiratory Society.[25] Exacerbations were defined as worsening asthma provoking treatment with systemic glucocorticoids for at least 3 days.

Study design and end point

This was a single-center, retrospective cohort study. The primary end point was CR rate. The index date was between April 2022 and March 2023, and CR rates based on the 4-component and 3-component definitions were independently analyzed in patients with mild-to-moderate and severe asthma for a year from the index date. Secondary end points included the relationships between obtaining CR and clinical characteristics such as patient background, type 2 biomarkers, or treatments.

Among the 263 cases for which CR could be assessed at the index date, the CR status 10 years before the index date could be assessed in 178 cases. The CR status between the index date and 10 years before was retrospectively compared. CR at 10 years before the index date was assessed using information during 1 year over the 10 years before the index date (see Fig E1 in the Online Repository available at www.jaci-global.org).

Data collection

Asthma Control Test (QualityMetric, Lincoln, RI), type 2 biomarkers (blood eosinophils, fractional exhaled nitric oxide [F_{ENO}], and serum total IgE), and pulmonary function during the stable phase without exacerbation were evaluated. ACT scores and spirometry were evaluated at least twice at independent clinic visits, and the lowest total ACT score was recorded. ACT and spirometry were evaluated at intervals of at least 6 months. Blood eosinophil counts, serum total IgE levels, and specific IgE (ImmunoCAP) were obtained from the clinical laboratory. F_{ENO} was measured with a NIOX MINO device (Aerocrine, Morrisville, NC). The data from patients treated with OCS and/or biologics were analyzed under those treatments.

Statistical analyses

Nominal measures were compared by Pearson chi-square test, and data are presented as numbers and proportions. For continuous measures, variance was analyzed by the Bartlett test, and comparisons between groups were made by Student *t* tests for equal variance and Wilcoxon rank sum tests for unequal variance, and data are presented as means ± standard errors of the mean. Logistic regression analysis was used to estimate odds ratios with 95% confidence intervals. Statistical significance was defined as $P < .05$. All statistical analyses were performed by JMP v16 software (SAS Institute Japan, Tokyo, Japan).

RESULTS

A flow diagram of study participation is shown in Fig E2, which is available in the Online Repository available at www.jaci-global.org. Of the 307 patients recruited to the study, 44 patients were excluded because data were missing for determining the 4-component CR. Thus, 263 patients (142 with mild-to-moderate asthma and 121 with severe asthma) were included in the analysis. Of these 263 patients, 178 patients, including 102 patients with mild-to-moderate asthma and 76 patients with severe asthma,

TABLE I. Patient characteristics at index date

Characteristic	Total (N = 263)	Mild to moderate (n = 142)	Severe (n = 121)	*P* value
Male sex, no. (%)	97 (36.9)	52 (36.6)	45 (37.2)	.92
Age (years)	63.2 ± 0.9	64.9 ± 1.3	61.3 ± 1.4	.055
Age (years) at diagnosis	39.4 ± 1.2	42.2 ± 1.7	36.2 ± 1.8	.017†
Duration (years) of asthma	23.8 ± 0.9	22.7 ± 1.3	25.1 ± 1.4	.20
BMI (kg/m^2)	24.3 ± 0.3	23.9 ± 0.3	24.7 ± 0.4	.14
Smoking status, %				.44
Current	1.9	2.8	0.8	
Former	34.2	35.2	33.1	
Never	63.9	62.0	66.1	
Smoking index (pack years)	9.2 ± 1.2	8.9 ± 1.2	7.6 ± 1.3	.49
Blood eosinophils (/μL)	219 ± 17	211 ± 23	229 ± 25	.59
F_{ENO} (ppb)	36.7 ± 2.4	37.0 ± 3.3	36.4 ± 3.5	.91
Total IgE (IU/mL)	495 ± 77	502 ± 104	488 ± 113	.93
Specific IgE positive for perennial allergen	179 (68.3)	103 (72.5)	76 (63.3)	.11
FEV_1, % predicted	94.2 ± 1.4	98.1 ± 1.9	89.8 ± 2.1	<.01††
ACT score	22.4 ± 0.2	23.6 ± 0.3	20.9 ± 0.3	<.01††
Exacerbations in last year	0.49 ± 0.10	0.007 ± 0.14	1.06 ± 0.10	<.01††
Daily OCS	28 (10.6)	0	28 (24.4)	<.01††
Daily ICS	263 (100.0)	142 (100.0)	121 (100.0)	—
High-dose ICS	95 (36.1)	7 (4.9)*	88 (72.7)	<.01††
LABA	231 (87.8)	116 (81.7)	115 (95.0)	<.01††
LAMA	105 (40.0)	23 (16.2)	82 (67.8)	<.01††
LTRA	170 (64.6)	68 (47.9)	102 (84.3)	<.01††
Theophylline	73 (27.8)	16 (11.3)	57 (47.1)	<.01††
Biologics	72 (27.4)	0 (0.0)	72 (59.5)	<.01††

Data are presented as nos. (%) or means ± standard errors of the mean unless otherwise indicated.
LTRA, Leukotriene receptor antagonist.
*Controlled disease treated with high-dose ICS, but not highest dose, was classified as moderate asthma, following 2021 Japanese guidelines for adult asthma.[24]
†$P < .05$ and ††$P < .01$ between groups by Student *t* test, Wilcoxon rank sum test, or Pearson chi-square test.

had data available to evaluate the CR rate at 10 years before the index date.

Patient backgrounds are listed in Table I. The age at asthma diagnosis was significantly younger in patients with severe asthma. Baseline FEV_1, ACT score, and exacerbation rate were significantly better in patients with mild-to-moderate asthma.

The rates of obtaining CR are shown in Fig 1. In the overall analysis, the CR rate was 55.1% using the 4-component definition and 57.8% using the 3-component definition. The CR rate in patients with mild-to-moderate asthma was 73.2% using the 4-component definition and 81.0% using the 3-component definition. The CR rates in patients with mild-to-moderate asthma were significantly higher than the CR rates in patients with severe asthma (4-component, 33.9%; 3-component, 30.6%). No significant differences in CR rates were detected between the 4-component and 3-component definitions in patients with mild-to-moderate or severe asthma.

The attainment rates for each component of the CR definitions are shown in Fig 2. More than 80% of cases of mild-to-moderate asthma fulfilled the components of the CR definitions, except FEV_1 normalization (≥80% predicted). The rate of obtaining FEV_1 normalization was 78.9% and was lower than the other components (ACT score ≥20 points, 93.3%; ≥23 points, 81.7%; no exacerbations, 99.3%; no daily OCS receipt, 100%). Rates of obtaining CR for all individual components were significantly lower in patients with severe asthma compared with mild-to-moderate asthma.

The backgrounds of patients who experienced CR were compared with the backgrounds of patients who did not to identify factors related to CR. For the 4-component CR (Table II), the age at asthma diagnosis was significantly younger, the duration of asthma was significantly longer, and the smoking index was significantly higher in the non-CR group compared with the CR group in all patients with asthma. In the total analysis, FEV_1 and ACT scores were significantly lower in the non-CR group compared with the CR group. Although the receipt rates of therapies including high-dose ICS, long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists, and biologics were significantly higher in the non-CR group in the total analysis, no differences in receipt of those drugs were detected between the 2 groups in patients with mild-to-moderate asthma. No significant differences in type 2 biomarkers such as eosinophil counts, F_{ENO}, and serum total IgE levels were detected in the total analysis.

Comparisons using the 3-component remission definition are shown in Table III. Unlike the 4-component CR, no significant differences in the duration of asthma were detected between the CR and non-CR groups using the 3-component CR. However, body mass index (BMI) was significantly higher in the non-CR group compared with the CR group in the total and mild-to-moderate asthma analyses. Similar to the 4-component analysis, the smoking index was significantly higher and the ACT score significantly lower in the non-CR group in both the total and mild-to-moderate asthma analyses.

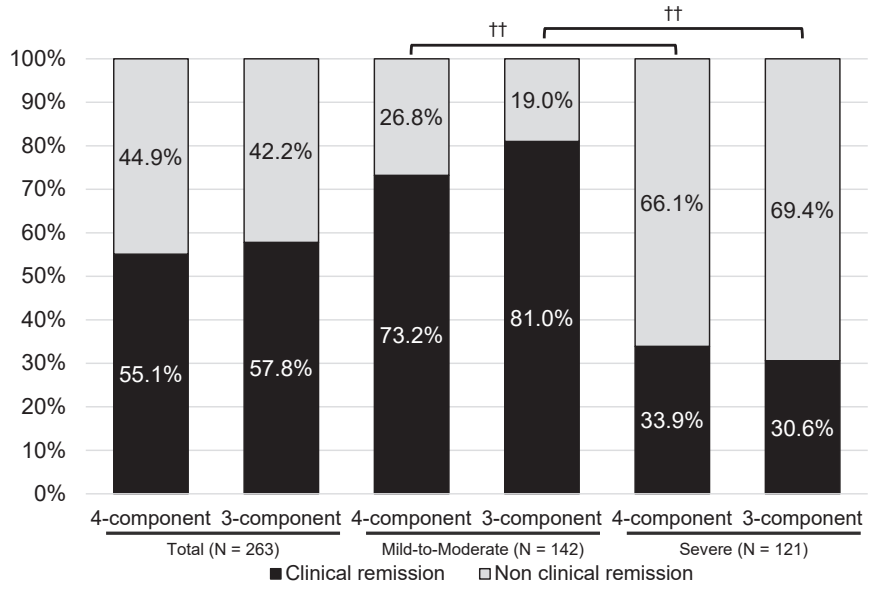

FIG 1. Rate of CR. Definition of 3-component remission included no corticosteroid receipt, no exacerbations, and ACT ≥ 23. Definition of 4-component remission included above parameters and $FEV_1 \geq 80\%$ predicted. †$P < .05$ and ††$P < .01$ between groups by Pearson chi-square test.

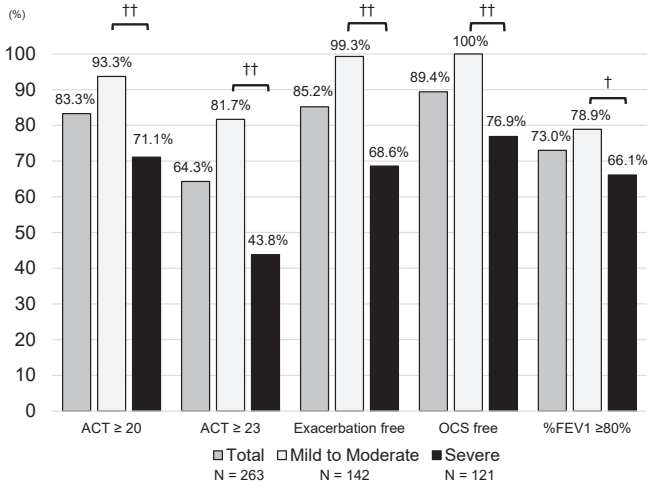

FIG 2. Rates of individual CR components. †$P < .05$ and ††$P < .01$ between groups by Pearson chi-square test.

Univariate analysis for both the 4- and 3-component CR revealed that smoking index and BMI contributed to CR (Fig 3). Age at asthma diagnosis and duration of asthma significantly contributed to the 4-component CR. The same trends were observed in patients with mild-to-moderate and severe asthma (see Fig E3 in the Online Repository available at www.jaci-global.org).

To determine the stability of CR, the CR rate at the current index date and the CR rate 10 years ago were retrospectively examined (n = 178). In patients with mild-to-moderate asthma, the 4-component CR rate did not change over 10 years (65.6-69.9%, Fig 4, *A*) and 3-component CR rate significantly increased (68.6-81.7%, Fig 4, *B*). In patients with severe asthma, the CR rate increased significantly (more than doubling) over 10 years based on both the 4-component (Fig 4, *C*) and 3-component CR definitions (Fig 4, *D*). In patients with mild-to-moderate asthma, 80.3% (49/61) of patients who experienced 4-component CR 10 years ago currently maintained 4-component CR (Fig 4, *A*). For the 3-component CR, 89.1% of patients with mild-to-moderate asthma (57/64) maintained CR (Fig 4, *B*).

To investigate the factors related to the unsustainability of CR, baseline characteristics 10 years ago and the present were compared after stratifying patients with mild-to-moderate asthma according to the transition of 4-component CR (n = 93, Table IV). In the CR → non-CR group, FEV_1 tended to decrease (96.1-84.9%, $P = .08$), but no differences in ICS dose or rate of long-acting β-agonist (LABA) and LAMA receipt were detected between 10 years ago and the present. The current rate of LAMA receipt remained low, at 16.7%. In the non-CR → CR group, ICS doses tended to increase (413-581 μg/d, $P = .054$), and the LABA (68.8-87.5%, $P < .05$) and LAMA (0-25.0%, $P < .05$) receipt rates significantly increased after 10 years. In both of the stratified groups, no differences in type 2 biomarkers such as eosinophil count and F_{ENO} were detected between 10 years ago and the present.

DISCUSSION

In a Japanese database study, 92.2% of patients had mild-to-moderate asthma.[26] Thus, a majority of patients with asthma have mild-to-moderate disease. However, the rate of CR in patients with mild-to-moderate disease is unclear, and reports have been limited primarily to patients with severe asthma treated with biologic agents.[10-22] Our study revealed a considerably higher CR rate (4-component, 73.2%; 3-component, 81.0%) in patients with mild-to-moderate asthma. Of note, the 4-component CR, which includes the normalization of FEV_1, could be obtained in a high proportion of patients with mild-to-moderate asthma, thus highlighting the need for severity-dependent FEV_1 goals for obtaining CR.

TABLE II. Differences in clinical backgrounds based on 4-component CR status

Characteristic	Total (N = 263)			Mild to moderate (n = 142)			Severe (n = 121)		
	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*
No. (%) of subjects	145 (55.1)	118 (44.9)		104 (73.2)	38 (26.8)		41 (33.9)	80 (66.1)	
Male sex	43 (29.7)	54 (45.8)	<.01††	31 (29.8)	21 (55.3)	<.01††	12 (29.3)	33 (41.2)	.20
Age (years)	63.9 ± 1.2	62.4 ± 1.4	.43	64.7 ± 1.5	65.2± 2.5	.88	61.7 ± 2.2	61.1 ± 1.6	.81
Age (years) at diagnosis	42.1 ± 1.7	36.1 ± 1.8	<.01††	43.2 ± 1.9	39.3 ± 3.4	.30	39.4 ± 3.4	34.6 ± 2.2	.23
Duration (years) of asthma	21.8 ± 1.2	26.3 ± 1.4	<.01††	21.5 ± 1.3	25.8 ± 2.1	.09	22.3 ± 2.7	26.5 ± 1.9	.20
BMI (kg/m^2)	23.9 ± 0.3	24.7 ± 0.4	.14	23.7 ± 0.4	24.5 ± 0.8	.30	24.5 ± 0.63	24.8 ± 0.5	.73
Smoking (%)			.70			.11			.29
Current	1.4	2.5		1.0	7.9		2.4	0	
Former	33.1	35.6		33.6	36.8		29.3	35.0	
Never	65.5	61.7		64.4	55.3		68.3	65.0	
Smoking index (pack years)	6.7 ± 1.6	12.0 ± 1.8	.04†	7.8 ± 1.5	11.7 ± 2.8	.19	4.8 ± 1.5	12.1 ± 3.1	.10
ACT score	23.9 ± 0.3	18.6 ± 0.3	<.01††	24.1 ± 0.2	22.2 ± 0.4	.01†	23.2 ± 0.6	19.7 ± 0.4	<.01††
Exacerbations in year	0	1.09 ± 0.22	<.01††	0	0.03 ± 0.03	.09	0	1.6 ± 0.3	<.01††
FEV_1, % predicted	105 ± 1.7	81.2 ± 1.9	<.01††	98.7 ± 1.7	90.2 ± 6.1	.18	103 ± 3.9	83.1 ±2.8	<.01††
High-dose ICS	30 (20.7)	65 (55.1)	<.01††	6 (5.8)	1 (2.6)	.42	24 (58.5)	64 (80.0)	.01†
LABA	123 (84.8)	108 (91.5)	.094	84 (80.8)	32 (84.2)	.63	39 (95.1)	76 (95.0)	.98
LAMA	43 (29.7)	62 (52.5)	<.01††	20 (19.2)	3 (7.9)	.08	23 (56.1)	59 (73.8)	.05
LTRA	82 (56.6)	88 (74.6)	<.01††	49 (47.1)	19 (50.0)	.76	33 (32.4)	69 (86.3)	.42
Theophylline	30 (20.7)	43 (36.4)	<.01††	14 (13.5)	2 (5.3)	.14	16 (39.0)	41 (51.3)	.20
Biologics	20 (13.8)	52 (44.0)	<.01††	0	0	—	20 (48.8)	52 (65.0)	.09
Daily OCS	0	28 (23.7)	<.01††	0	0	—	0	28 (35.0)	<.01††
Blood eosinophils (/μL)	207 ± 23	233 ± 25	.44	202 ± 19	233 ± 31	.39	220 ± 46	233 ± 41	.84
F_{ENO} (ppb)	37.8 ± 3.3	35.5 ± 3.5	.64	38.0 ± 3.8	34.3 ± 5.1	.59	37.2 ± 6.4	36.1 ± 4.8	.89
Total IgE (IU/mL)	391 ± 102	626 ± 114	.13	371 ± 123	860 ± 204	.04†	443 ± 127	512 ± 154	.76
Perennial allergen specific IgE (+)	99 (68.3)	80 (68.4)	.98	74 (71.2)	29 (76.3)	.54	25 (70.0)	51 (64.6)	.70

Data are presented as nos. (%) or means ± standard errors of the mean unless otherwise indicated.

LTRA, Leukotriene receptor antagonist.

†$P < .05$ and ††$P < .01$ between groups by Student *t* test, Wilcoxon rank sum test, or Pearson chi-square test.

TABLE III. Differences in clinical background based on 3-component CR status

Characteristic	Total (N = 263)			Mild to moderate (n = 142)			Severe (n = 121)		
	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*
No. of subjects	152 (57.8)	111 (42.2)		115 (81.0)	27 (19.0)		37 (30.6)	84 (69.4)	
Male sex	61 (40.1)	36 (32.4)	.20	46 (40.0)	6 (22.2)	.08	15 (40.5)	30 (35.7)	.61
Age (years)	64.5 ± 1.2	61.4 ± 1.4	.09	65.4 ± 1.4	62.7 ± 2.9	.41	62.0 ± 2.4	61.0 ± 1.6	.72
Age (years) at diagnosis	41.1 ± 1.6	37.1 ± 1.9	.11	42.0 ± 1.8	42.8 ± 3.8	.86	38.3 ± 3.4	35.3 ± 2.2	.45
Duration (years) of asthma	23.4 ± 1.2	24.3 ± 1.4	.64	23.3 ± 1.3	19.9 ± 2.6	.23	23.6 ± 2.8	25.7 ± 1.8	.54
BMI (kg/m^2)	23.7 ± 0.3	25.0 ± 0.4†	.01	23.6 ± 0.4	25.4 ± 0.8	.04†	24.2 ± 0.7	24.9 ± 0.4	.41
Smoking (%)			.72			.046†			.28
Current	1.3	2.7		0.9	11.1		2.7	0	
Former	34.2	34.2		35.6	33.3		29.7	34.5	
Never	64.5	63.1		63.5	55.6		67.6	65.5	
Smoking index (pack years)	7.1 ± 1.6	12.1 ± 1.9	.04†	7.7 ± 1.4	14.0 ± 3.0	.06	5.5 ± 3.9	11.5 ± 2.6	.20
ACT score	24.4 ± 0.2	19.4 ± 0.2	<.01††	24.5 ± 0.2	19.9 ± 0.3	<.01††	24.3 ± 0.6	19.4 ± 0.4	<.01††
Exacerbations in last year	0	1.2 ± 0.2	<.01††	0	0.04 ± 0.04	.04†	0	1.5 ± 0.2	<.01††
FEV_1, % predicted	96.5 ± 1.9	91.2 ± 2.2	.07	95.9 ± 3.7	98.6 ± 1.8	.52	90.0 ± 4.4	89.7 ±2.9	.96
High-dose ICS	23 (15.1)	72 (64.9)	<.01††	7 (6.1)	0	.08	16 (43.2)	72 (85.7)	<.01††
LABA	129 (84.9)	102 (91.9)	.08	94 (81.7)	22 (81.5)	.98	35 (94.6)	80 (95.2)	.88
LAMA	37 (24.3)	68 (61.3)	<.01††	18 (15.7)	5 (18.5)	.72	19 (51.3)	63 (75.0)	.01†
LTRA	82 (54.0)	88 (79.3)	<.01††	54 (47.0)	14 (51.9)	.65	28 (75.7)	74 (88.1)	.09
Theophylline	27 (17.8)	46 (41.4)	<.01††	12 (10.4)	4 (14.8)	.53	15 (40.5)	42 (50.0)	.34
Biologics	24 (15.8)	48 (43.2)	<.01††	0	0	—	24 (64.9)	48 (57.1)	.42
Daily OCS	0	28 (25.2)	<.01††	0	0	—	0	28 (33.3)	<.01††
Blood eosinophils (/μL)	233 ± 22	200 ± 26	.34	219 ± 18	176 ± 37	.30	277 ± 57	208 ± 38	.31
F_{ENO} (ppb)	39.3 ± 3.2	33.1 ± 3.7	.20	38.7 ± 3.4	29.5 ± 7.0	.23	41.2 ± 6.8	34.2 ± 4.6	.40
Total IgE (IU/mL)	510 ± 100	475 ± 119	.82	520 ± 119	424 ± 246	.73	481 ± 197	492 ± 133	.96
Perennial allergen specific IgE (+)	105 (69.1)	74 (67.3)	.76	83 (72.2)	20 (74.1)	.84	22 (59.5)	54 (65.1)	.56

Data are presented as nos. (%) or means ± standard errors of the mean unless otherwise indicated.

LTRA, Leukotriene receptor antagonist.

†$P < .05$ and ††$P < .01$ between groups by Student *t* test, Wilcoxon rank sum test, or Pearson chi-square test.

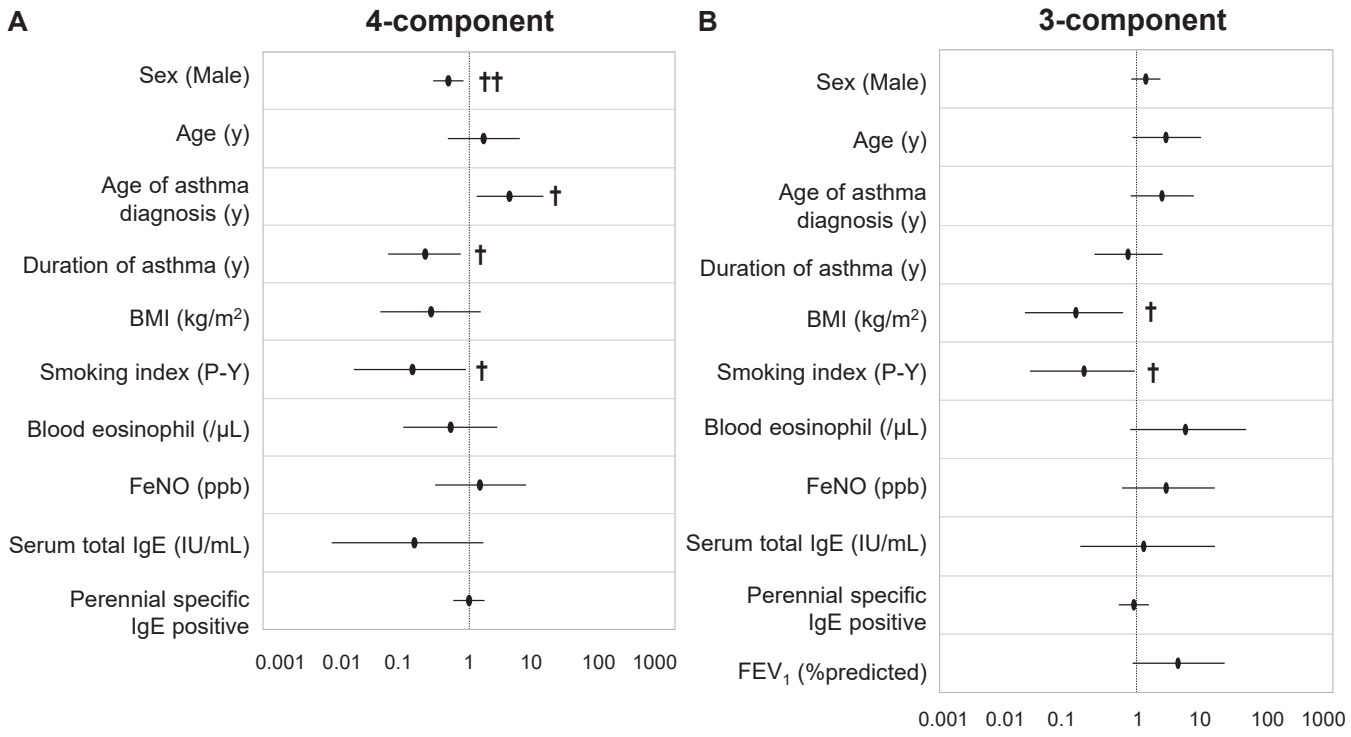

FIG 3. Factors contributing to CR. Odds ratio (OR) and 95% confidence interval (CI) are presented for different comparisons. **(A)** Four-component remission. **(B)** Three-component remission. †$P < .05$ and ††$P < .01$, significant contribution based on univariate analyses.

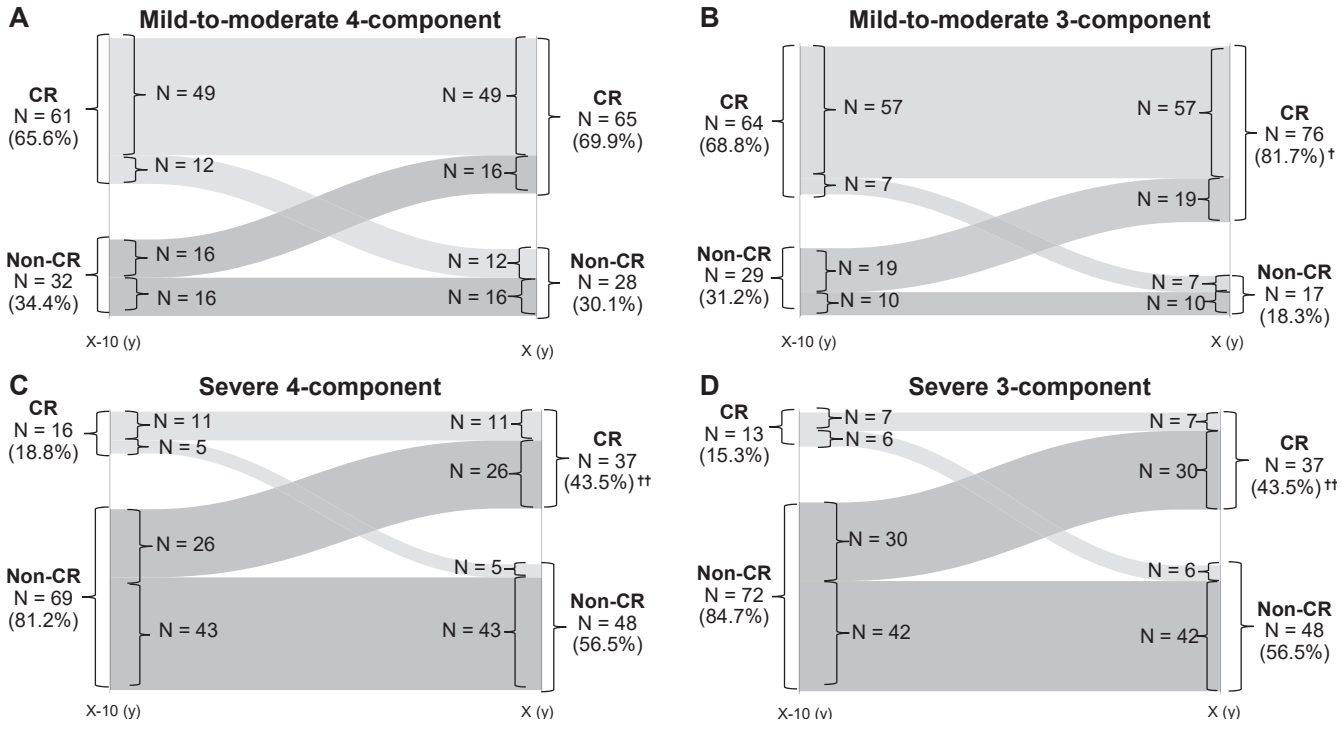

FIG 4. Comparison of CR rates between 10 years ago and current index date. (**A** and **B**) Mild-to-moderate asthma (n = 93) with *(A)* 3-component remission and *(B)* 4-component remission. (**C** and **D**) Severe asthma (n = 85) with *(C)* 3-component remission and *(D)* 4-component remission. †$P < .05$ and ††$P < .01$ between 10 years ago and current index date by Pearson chi-square tests.

TABLE IV. Transition of 4-component CR in patients with mild-to-moderate asthma

	CR → CR (n = 49)			CR → non-CR (n = 12)			Non-CR → CR (n = 16)			Non-CR → non-CR (n = 16)		
Characteristic	10 years ago	Current	*P*	10 years ago	Current	*P*	10 years ago	Current	*P*	10 years ago	Current	*P*
ICS dose (μg/d)	392 ± 237	438 ± 256	.36	375 ± 218	546 ± 348	.16	413 ± 231	581 ± 246	.05	413 ± 126	594 ± 304	.04†
LABA (%)	83.7	75.5	<.01††	66.7	83.3	.58	68.8	87.5	.02†	100	100	-
LAMA (%)	0	18.4	<.01††	0	16.7	.14	0	25	.03†	0	25	.03†
Daily OCS (%)	0	0	—	0	0	—	0	0	—	0	0	—
Biologics (%)	0	4.1	.15	0	16.7	.14	0	12.5	.14	0	0	—
ACT score	24.4 ± 0.9	24.6 ± 0.9	.32	23.0 ± 1.8	22.1 ± 3.4	.72	21.1 ± 3.5	23.6 ± 1.5	.04†	23.5 ± 2.1	22.9 ± 3.9	.97
Exacerbation in last year	0	0	—	0	0.25 ± 0.6	.17	1.0 ± 1.0	0	<.01††	0.3 ± 0.8	0.4 ± 1.0	.70
FEV_1, % predicted	107.0 ± 14.5	107.0 ± 15.8	.90	96.1 ± 11.9	84.9 ± 17.5	.08	100 ± 19.5	110 ± 14.5	.14	74.3 ± 11.1	67.2 ± 15.2	.14
Blood eosinophils (/μL)	374 ± 393	271 ± 234	.15	219 ± 106	272 ± 218	.66	171 ± 160	118 ± 109	.30	295 ± 215	257 ± 431	.21
F_{ENO} (ppb)	32.5 ± 30.1	43.6 ± 44.0	.14	23.2 ± 15.2	36.5 ± 36.2	.69	19.8 ± 12.7	31.1 ± 30.4	.64	28.6 ± 21.2	40.2 ± 39.5	.60

CR → CR indicates patients with CR 10 years ago and current CR; *CR → non-CR*, patients with CR 10 years ago and no current CR; *non-CR → CR*, patients without CR 10 years ago and current CR; and *non-CR → non-CR*, patients without CR 10 years ago and no current CR. Data are presented as nos. (%) or means ± standard errors of the mean unless otherwise indicated.
†$P < .05$ and ††$P < .01$ between groups by Student *t* test, Wilcoxon rank sum test, or Pearson chi-square test.

Another important finding from the current study was the long-term stability of CR in mild-to-moderate asthma over 10 years; 80.3% and 89.1% of patients who experienced 4- or 3-component CR, respectively, experienced maintenance of CR after 10 years (Fig 4, *A* and *B*). To date, the stability of CR in patients with mild-to-moderate asthma has been largely unexplored, and only the status of CR over 3 to 5 years in patients with severe asthma treated with biologics has been reported.[21,22] The relationships between the individual components of CR and future risks have been extensively investigated; current exacerbations are associated with rapid declines in pulmonary function[27,28] and future exacerbations.[29-31] Poor symptom control[30,32,33] and low FEV_1[34-36] are associated with future exacerbations or mortality. However, information about the relationship between CR as a composite index of individual components and long-term outcomes is lacking. Our results suggest that current CR may be related to remote CR, meriting further prospective investigation, as noted by the Global Initiative for Asthma.[23]

In this study, higher BMI and higher smoking index were associated with non-CR (Fig 3), in line with a previous report showing that obesity, smoking, and long-term morbidity were associated with non-CR in patients with severe asthma.[14] These factors are modifiable behavioral factors[37] and may serve as important treatable traits for experiencing CR. Interestingly, age at onset and disease duration significantly contributed only to 4-component CR (Fig 3), suggesting that the normalization of FEV_1 was related to remodeling derived from long-lasting disease. Normalization of FEV_1 was significantly more obtainable in patients with mild-to-moderate asthma compared with patients with severe asthma (78.9% vs 66.1%, $P < .05$, Fig 2). Thus, early intervention seems to be especially important in obtaining CR in patients with mild-to-moderate asthma.

The inclusion of type 2 biomarkers as a component of CR has been debated, with agreement rates ranging from 32.6% to 88%.[4,5,38] However, no consensus has been reached. In this study, no significant differences in type 2 biomarkers, including blood eosinophils and F_{ENO}, were detected between the CR and non-CR groups (Tables II and III), and no significant contribution to CR was observed (Fig 3). The importance of biomarkers in CR may vary depending on the situation of assessment; in patients with severe asthma treated with biologics, type 2 biomarkers predict CR.[12-14,39,40] Oishi et al[17] introduced the concept of deep remission, which includes the suppression of type 2 biomarkers; 31.5% of patients with severe asthma treated with biologics experienced deep remission. However, biologics are currently not generally indicated to treat mild-to-moderate asthma. Furthermore, while an association between type 2 biomarkers and exacerbations has been suggested for asthma overall,[41] the significance of these biomarkers in type 2–low asthma remains unclear. In this study, the asthma of 38% of patients was type 2–low (F_{ENO} < 25 ppb and blood eosinophils < 300/μL) during treatment. Therefore, the significance of type 2 biomarkers as a CR component is limited, at least in patients with mild-to-moderate asthma.

From the clinical point of view, the current results identify several considerations when assessing CR in patients with mild-to-moderate asthma. First, aiming for CR may help detect undertreatment in patients with mild-to-moderate asthma. In these patients, treatment intensity, indicated by high-dose ICS or LAMA receipt, was not significantly higher in the non-CR group compared with the CR group (Tables II and III). This

undertreatment may be related to long-term outcomes. When looking at the 10-year trajectory (Table IV), although FEV_1 tended to decrease in the CR → non-CR group, only 16.7% of the patients in this group had disease that was currently being treated with LAMA. In contrast, the non-CR → CR group received high-intensity treatment, and FEV_1 numerically increased. A recent study showed that patients receiving therapy with ICS, LABA, and LAMA were more likely to obtain CR than patients receiving ICS and LABA.[42] These findings suggest that even in the tertiary-care hospital setting, like ours, a lack of appropriate treatment intensity may exist, and targeting CR in daily practice may help detect undertreatment.

Second, obtaining CR may predict future CR based on the long-term stability of CR shown in this study. In the current study, more than 80% of patients with mild-to-moderate asthma who experienced CR 10 years earlier maintained both 3- and 4-component CR (Fig 4). This result suggests that practice aimed at CR may result in excellent control that fulfills multiple components over the long term and underscores the validity of CR as a treatment goal.

Conversely, the possibility that maintaining CR could lead to overtreatment should be considered. Patients with comorbid chronic obstructive pulmonary disease or impaired lung growth during childhood should be identified because these may prevent normalization of pulmonary function. Although it has not yet been established whether CR can be used as an indicator of successful treatment step-downs, this remains an important research question for the future.

Limitations

The limitations of the study are mainly related to its retrospective design and the real-life nature of the cohort. Although the definition of CR was not uniformly fixed, we adopted two definitions, including the widely recognized consensus report definition.[4] In this study, treatment step-downs and step-ups were not performed following a standardized protocol; thus, the physician's independent judgment may have influenced obtaining CR. However, treatment decisions in this study are believed to largely reflect the guideline-based management by asthma specialists. We compared CR at the current index date with CR of 10 years ago to assess its stability. However, because of the retrospective nature of the study, evaluating CR for all periods within the study period was difficult. Although our CR rate was based on full assessments by specialists and may serve as benchmark data, the rate of CR may depend on facility type. This study analyzed the Japanese population; therefore, the results are limited to Asians.

Conclusions

We found substantially high CR rates, including normalization of FEV_1 and long-term stability of CR in patients with mild-to-moderate asthma. Targeting CR may detect undertreatment and lead to a reduction of future risks. The reported off-treatment remission rate in adults with asthma is low.[3] However, the CR rate was high in patients with mild-to-moderate asthma, and experiencing CR might be a milestone for off-treatment remission. Recently, the definition of CR in moderate asthma has been under discussion,[38] and future investigations in patients with mild-to-moderate asthma who experience CR are needed.

DISCLOSURE STATEMENT

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