Validity and Risk of Adopting PGA ≤ 2 As A Remission Criteria of Boolean in Clinical Practice in Patient With Rheumatoid Arthritis

Ichiro Yoshii (ichiroyoshii@gmail.com)
Yoshii Hospital

Tatsumi Chijiwa
Kochi Memorial Hospital

Naoya Sawada
Dohgo Onsen Hospital

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Abstract

Validity and risk of setting patient's global assessment (PGA) ≤ 2 as a Boolean remission criteria substituting PGA ≤ 1 in treating rheumatoid arthritis (RA) was investigated

Patients were recruited from an area cohort, of whom attained Boolean remission (Boolean-1) or near remission with PGA ≤ 2 and the rest components were ≤ 1 (Boolean-2). Simplified disease activity index (SDAI) score was compared according to the criteria variations.

A total of 517 patients were studied. Mean SDAI score of patients with Boolean-1 was significantly lower than that of patients with Boolean-2 at acquisition. The trend was evident in the patients who attained Boolean-1 remission. Mean SDAI score at acquisition, 6 months after, and 1 year after of patients who attained Boolean-2 first and then Boolean-1, was significantly inferior to that of patients who attained the remissions at the same time. The mean SDAI score at month 6 in the Boolean-2 was not SDAI remission at all.

We concluded that setting PGA ≤ 2 as a remission criteria may not have statistical difference in disease activity from PGA ≤ 1, however, there was an determinant risk to misread that includes patient who losses clinical remission after acquisition.

Introduction

Treat-to-target (T2T) strategies are now the global mainstay of treatment for rheumatoid arthritis (RA) [1, 2]. One of the main points is to aim for early clinical remission and to set the basic disease activity index and to monitor patients [3]. ACR/EULAR Boolean remission is the most stringent measure of disease activity [4], and it is known that patients who achieve Boolean remission can maintain stable disease activity control and activities of daily living for a long period after achieving remission [5].

The reason for the difficulty in achieving a Boolean remission is the patient's comprehensive evaluation (PGA) [6]. It is difficult to achieve a PGA score of ≤ 1, and it has been argued that even mildly lax criteria can be regarded as a clinical remission, which may lead to assurance of maintenance of activities of daily living (ADL) [7, 8]. Recent reports have argued that even with PGA ≤ 2, a patient's ADL after 1 year of acquired remission changes only slightly compared with PGA ≤ 1, and PGA ≤ 2 may serve as a remission criterion [9].

Of the four components of the Boolean remission criteria: tender joint count (TJC), swollen joint count (SJC), serum C-reactive protein level (CRP), and PGA, only PGA is a patient-related outcome, and the assessment is patient subjective. SJC, TJC, and CRP reflect inflammatory status, and their trends are often associated [10]. However, it cannot be denied that PGA alone deviates from the three other indicators that are often encountered in clinical practice and confuses the assessment of the efficacy of RA therapy [11, 12]. On the other hand, PGA correlates well with patient pain, and PGA minimization works well for pain relief [13]. The pain is an important decision index for the RA patient, and it cannot be

judged that the RA treatment is good for the patient, if it is not improved. When pain is also taken into account as a clinical decision index, Boolean remission is considered to be a rational index configuration.

What are the clinical differences between PGA ≤ 1 and PGA ≤ 2? This study sought to evaluate differences in clinical practice between PGA ≤ 1 based Boolean remissions and PGA ≤ 2 based Boolean remissions in a retrospective cohort study.

Results

A total of 517 patients consisted of 507 in Group-1 and 517 in Group-2, including 414 in Group-same1PGA, 93 in Group-step1PGA, and 10 in Group-2PGA. 73.2% in Group-1 and 72.7% in Group-2 were female, compared with 72.2% in Group-same1PGA, 77.4% in Group-step1PGA, and 50.0% in Group-2PGA. Mean age at baseline was 65.6 and 65.7 years for Group-1 and Group-2, respectively, whereas it was 65.7, 65.1 and 70.0 years for Group-same1PGA, Group-step1PGA, and Group-2PGA, respectively. The demographic and clinical characteristics at baseline and initial visit were as shown in Table 1.

Table 1
Demographic and clinical characteristics of groups

		Group-1 (n = 507)	Group-same1PGA (n = 414)	Group-step1PGA (n = 93)	Group-2PGA (n = 10)	Group-2 (n = 517)
	female (%)	73.2	72.2	77.4	50.0	72.7
at first consult	age (years)	64.3 (13.9)	64.6 (14.1)	63.5 (13.1)	70.0 (19.2)	64.5 (14.1)
	disease duration (years)	6.2 (8.1)	6.7 (8.6)	4.3 (5.1)	6.2 (9.0)	6.2 (8.1)
	ACPA positive rate (%)	80.1	81.2	75.7	55.0	79.6
	RF positive rate (%)	77.3	77.4	76.7	65.0	77.0
	SDAI	22.0 (21.8)	21.6 (21.8)	23.6 (21.7)	19.3 (18.2)	22.0 (21.8)
	HAQ-DI	0.463 (0.578)	0.457 (0.580)	0.489 (0.568)	0.700 (0.731)	0.468 (0.582)
	PS-VAS	34.1 (29.1)	33.0 (29.8)	39.1 (25.0)	40.4 (19.3)	34.2 (28.9)
	SHS	46.9 (62.2)	48.5 (65.6)	39.6 (43.3)	57.3 (91.1)	47.1 (62.9)
	time span from first consultation to Boolean-1 (months)	14.9 (14.6)	13.9 (14.2)	19.1 (16.1)		14.7 (14.4)
	time span from first consultation to Boolean-2 (months)	13.0 (13.1)	13.9 (14.2)	9.2 (7.2)	7.8 (6.4)	12.9 (12.9)
	time span from Boolean-2 to Boolean-1 (months)	1.9 (1.4)	0.0	9.9 (8.8)		1.9 (1.4)
	average MTX dosage by Boolean-1 (mg/week)	8.0 (2.6)	7.9 (2.6)	8.2 (2.8)		8.0 (2.6)
	average MTX dosage by Boolean-2 (mg/week)	7.9 (2.6)	7.9 (2.6)	8.1 (2.7)	7.4 (2.5)	7.9 (2.6)
	GCS administration rate by Boolean-1 (%)	35.7	35.0	38.7		35.0
	GCS administration rate by Boolean-2 (%)	35.1	35.0	35.5	30.0	35.0
	SDAI at Boolean-1	1.07 (1.04)	1.07 (1.07)	1.06 (0.90)		1.07 (1.07)

	Group-1 (n = 507)	Group-same1PGA (n = 414)	Group-step1PGA (n = 93)	Group-2PGA (n = 10)	Group-2 (n = 517)
SDAI at Boolean-2	1.43 (1.35)	1.07 (1.07)	3.06 (1.28)	2.97 (1.17)	1.46 (1.37)
HAQ-DI at Boolean-1	0.416 (0.569)	0.410 (0.564)	0.440 (0.588)		0.416 (0.574)
HAQ-DI at Boolean-2	0.415 (0.564)	0.410 (0.564)	0.435 (0.564)	0.700 (0.731)	0.421 (0.569)
PS-VAS at Boolean-1	15.3 (20.5)	14.9 (20.3)	17.5 (21.1)		15.3 (20.5)
PS-VAS at Boolean-2	15.5 (19.4)	14.9 (20.3)	18.6 (14.0)	27.4 (16.4)	15.8 (19.4)

The values are presented as mean (SD) unless indicated otherwise.

Group-1: a patient group who attained Boolean remission with all of tenderness joint count (TJC), swollen joint count (SJC), patient's global assessment (PGA), and serum C-reactive protein level (CRP) ≤ 1 (Boolean-1) during follow up ; Group-2, a patient group who attained Boolean near remission with TJC, SJC, CRP ≤ 1, and PGA ≤ 2 (Boolean-2) during follow up ; Group-same1PGA, a patient group who attained Boolean-1 and Boolean-2 at the same time ; Group-step1PGA, a patient group who attained Boolean-2 first and then achieved Boolean-1 ; Group-2PGA, a patient group who attained Boolean-2 but not attained Boolean-1.
Abbreviations: ACPA, anti-citrullinated polypeptide antibodies ; RF, rheumatoid factor ; SDAI, simplified disease activity index ; HAQ-DI, Health Assessment Questionnaire Disability Index ; PS-VAS, pain score with visual analog scale ; SHS, Sharp/van der Heijde score ; MTX, methotrexate ; GCS, glucocorticoid steroid.

Mean SDAI scores in Group-1 for Boolean-1 and in Group-2 for Boolean-2 were 1.07 and 1.46, 3.78 and 3.94, and 3.89 and 4.16 at baseline, 6 months after, and 1 year after, respectively. Mean SDAI score at baseline in Group-1 was significantly smaller than in Group-2. Mean HAQ scores in Group-1 for Boolean-1 and in Group-2 for Boolean-2 were 0.400 and 0.403, 0.388 and 0.396, and 0.390 and 0.400 at baseline, 6 months after, and 1 year after, respectively. Mean PS-VAS in Group-1 for Boolean-1 and in Group-2 for Boolean-2 were 15.3 and 15.7, 20.6 and 21.1, and 21.6 and 22.2, at baseline, 6 months after, and 1 year after, respectively. There were no significant differences between the two groups in either HAQ score or PS-VAS (Fig. 1).

On the other hand, mean SDAI scores in Group-same1PGA and Group-step1PGA were 1.07 and 1.06, 3.62 and 4.51, and 4.02 and 3.31 at baseline, 6 months after, and 1 year after Boolean-1, respectively. Mean SDAI score at 6 months after in Group-same1PGA was significantly smaller than in Group-step1PGA. Mean SDAI scores in Group-same1PGA, Group-step1PGA, and Group-2PGA were 1.07, 3.06, and 2.97, 3.62, 4.73, and 10.08, and 4.02, 4.39, and 7.75 at baseline, 6 months after, and 1 year after the Boolean-2, respectively. Mean SDAI score in Group-same1PGA was significantly lower than in Group-step1PGA and Group-2PGA at any time point, but the mean SDAI score in Group-step1PGA at 6 months after was

significantly lower than in Group-2PGA (Fig. 2-A). Although the mean SDAI score at baseline was significantly lower in the Group-2PGA than at 6 and 12 months ($p < 0.0001$), the SDAI scores of the other groups at 6 and 12 months did not show a significant increase from baseline, there was a common trend in all groups that the mean SDAI score increased from baseline to the following period.

Mean HAQ scores in Group-same1PGA and Group-step1PGA were 0.410 and 0.440, 0.393 and 0.417, and 0.396 and 0.413, at baseline, 6 months after, and 1 year after Boolean-1, respectively. There was no significant difference between the two groups. Mean HAQ scores in Group-same1PGA, Group-step1PGA, and Group-2PGA were 0.410, 0.435, and 0.700, 0.393, 0.423, and 0.725, and 0.396, 0.425, and 0.725 at baseline, 6 months after, and 1 year after the Boolean-2, respectively. Mean HAQ scores of Group-2PGA were relatively greater compared to that of Group-same1PGA and the Group-step1PGA, however, no the difference was not significant (Fig. 2-B).

Mean PS-VASs in Group-same1PGA and Group-step1PGA were 14.9 and 17.5, 20.3 and 21.8, and 21.4 and 22.3 at baseline, 6 months after, and 1 year after the Boolean-1, respectively. There was no significant difference between the two groups. Mean PS-VASs in Group-same1PGA, Grpup-step1PGA, and Group-2PGA were 14.9, 18.6, and 27.4, 20.3, 22.1, and 42.9 at baseline, 6 months after, and 1 year after the Boolean-2, respectively. Mean PS-VAS of Group-same1PGA were significantly lower than that of Group-step1PGA at baseline of the Boolean-2, whereas mean PS-VAS of Group-step1PGA was significantly lower than that of Group-2PGA at 6 months after the Boolean-2. PS-VASs of Group-same1PGA were significantly lower than that of Group-2PGA (Fig. 2-C).

Discussion

Our institute is the only RA center in the region (population approximately 100,000), covering 80% of RA patients. More than 90% of patients in the region have completed treatment, and approximately 70% of patients with RA are receiving treatment. Although the population is small, it is almost complete as a medical area, and it seems to be appropriate as a material for the regional cohort study.

The results of the present study suggest that both PGA ≤ 2 and PGA ≤ 1 can ensure a stable clinical course and maintenance of ADL after achieving Boolean remission. The way one results showed no statistically significant differences in PGA ≤ 1 and PGA ≤ 2, except for SDAI at Boolean remission acquisition. However, this is because most patients achieved both Boolean-1 and Boolean-2 at the same time. After achieving PGA ≤ 2, the SDAI score in the Group-step1PGA was significantly inferior to that of the Group-same1PGA. There was no significant difference, however in the Group-2PGA, the HAQ score tended to be high all the time. PS-VAS also tend to making high scores.

These results suggest that RA patients may be divided into two groups: one group in which clinical symptoms resolve abruptly by therapeutic intervention and the other group in which clinical symptoms gradually improve. Incorporating a PGA ≤ 2 into the remission criteria appears to be at greater risk of misjudging clinical remission in a group with gradual improvement. Patients in the current study also tend to have higher disease activity after achieving Boolean remission, but it is also feared that

incorporating a PGA ≤ 2 into the remission criteria increases the risk of further increased disease activity after achieving remission. Adopting PGA ≤ 2 in the Boolean remission criteria has a determinant risk.

In every groups, SDAI score tend to have increased after the first Boolean remission, probably because SDAI responds to mild pain and elevated CRP during maintenance therapy. In the Group-same1PGA, there was no significant difference between acquisition and subsequent SDAI. The same applies to the Group-step1PGA. However, there was a significant increase in the Group-2PGA. This also indicates the risk of adopting PGA ≦ 2.

There is a limitation in the research. One is a single-center study that has the risk of collecting maldistributed patients, but the institute is one center for rheumatic diseases in the region. Second, the number of patients with group 2 PGA was small to make a statistically significant difference. One more risk in the Group-2PGA is curious background; relatively higher age, lower ACPA and RF positive rate, higher HAQ score, and higher SHS. These made a conjecture that the Group-2PGA included other comorbidities such as osteoarthritis or crustal associated arthritis, and that majority of the Group-2PGA was elderly onset RA. However, the use of PGA ≤ 2 rather than PGA ≤ 1 in the Boolean remission criteria shares an important message in this study that it shares the risk of including patients inappropriate for determining remission with a stable clinical course after acquisition.

Materials And Methods

Patients who met the ACR/EULAR classification criteria for RA [14] and were followed continuously without serious infections nor acute incidental events such as stroke, cardiovascular event, and others, were recruited. Our treatment protocol for RA is based on a T2T strategy that aims for clinical remission with simplified disease activity index (SDAI) within 6 months [15]. Patients were interviewed, and were measured components of SDAI, Health Assessment Questionnaire Disability Index (HAQ), and pain score using visual analogue scale (PS-VAS) at least every 3 months.

Boolean remission criteria was set in two levels; Boolean-1, all of four components (TJC, SJC, CRP, and PGA) achieved ≤ 1; Boolean-2, TJC, SJC, and CRP achieved ≤ 1, but PGA ≤ 2. Recruited patients were furtherly selected in the analysis of whom disease activity matched Boolean-1 or Boolean-2 once or more in treating, and they were followed up at least one year after acquisition.

Patients were classified into groups using two ways of classification according to the first acquisition of Boolean remission criteria. The way one; Group-1, a patient group who attained Boolean-1 ; Group-2, a patient group who attained Boolean-2. The way two; Group-same1PGA, a patient group who attained Boolean-1 and Boolean-2 at the same time ; Group-step1PGA, a patient group who attained Boolean-2 first and then attained Boolean-1 later ; Group-2PGA, a patient group who attained Boolean-2 but not achieved Boolean-1. We set the date when achieved each of Boolean remissions as baseline. Mean SDAI score, HAQ score, and PS-VAS for each group in each of the two ways were calculated, and compared their mean values using Mann-Whitney U-test. Mean values of each parameter at 6 months and 1 year

after the baseline were also compared using Mann-Whitney U-test as well. Mean SDAI score at baseline and subsequent period for each group was compared statistically using paired T-test.

Software used in the statistical procedures

All the statistical procedures were performed using StatPlus:mac® (AnalystSoft, Inc., Walnut, CA, USA), and significance level was set within 5%.

List Of Abbreviations

T2T, treat-to-target ; RA, rheumatoid arthritis ; ACR, American College of Rheumatology ; EULAR, European League against Rheumatism ; PGA, patient's global assessment ; ADL, activities of daily living ; SDAI, simplified disease activity index ; TJC, tenderness joint count ; SJC, swollen joint count ; CRP, C-reactive protein ; Boolean-1, Boolean remission with PGA ≤ 1, TJC ≤ 1, SJC ≤ 1, and CRP ≤ 1 ; Boolean-2, Boolean remission with PGA ≤ 2, TJC ≤ 1, SJC ≤ 1, and CRP ≤ 1 ; Group-1, a patient group who attained Boolean-1 remission ; Group-2, a patient group who attained Boolean-2 ; Group-same1PGA, a patient group in the Group-1 who attained Boolean-1 and Boolean-2 remissions at the same time ; Group-step1PGA, a patient group in the Group-1 who attained Boolean-2 remission first and then attained Boolean-1 remission ; Group-2PGA, a patient group who attained Boolean-2 remission but not attained Boolean-1 remission ; PS-VAS, pain score using visual analog scale ; HAQ, Health Assessment Questionnaire Disability Index.

Declarations

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Author contributions

IY wrote manuscript

TC gave numerous data

NS also gave data used in the study.

All authors have read the manuscript and agreed with the content.

Conflict of interest statement: None of author and his families have share income, property with any person, or any grants or other financial supports of the study.

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Ethics and consent

The study protocols and patient consent requirements were approved by Yoshii Hospital Ethics Committee (approval number: Y-2020-RA-2). The subjects and their families were informed that the personal information obtained in this study was anonymous and would only be used for analysis. Informed consent was obtained from all participants enrolled in the study and all subjects and their families provided signed consent.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Methods confirmation statement:

All of methods in this study were carried out in accordance with relevant guidelines and regulations.

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Figures

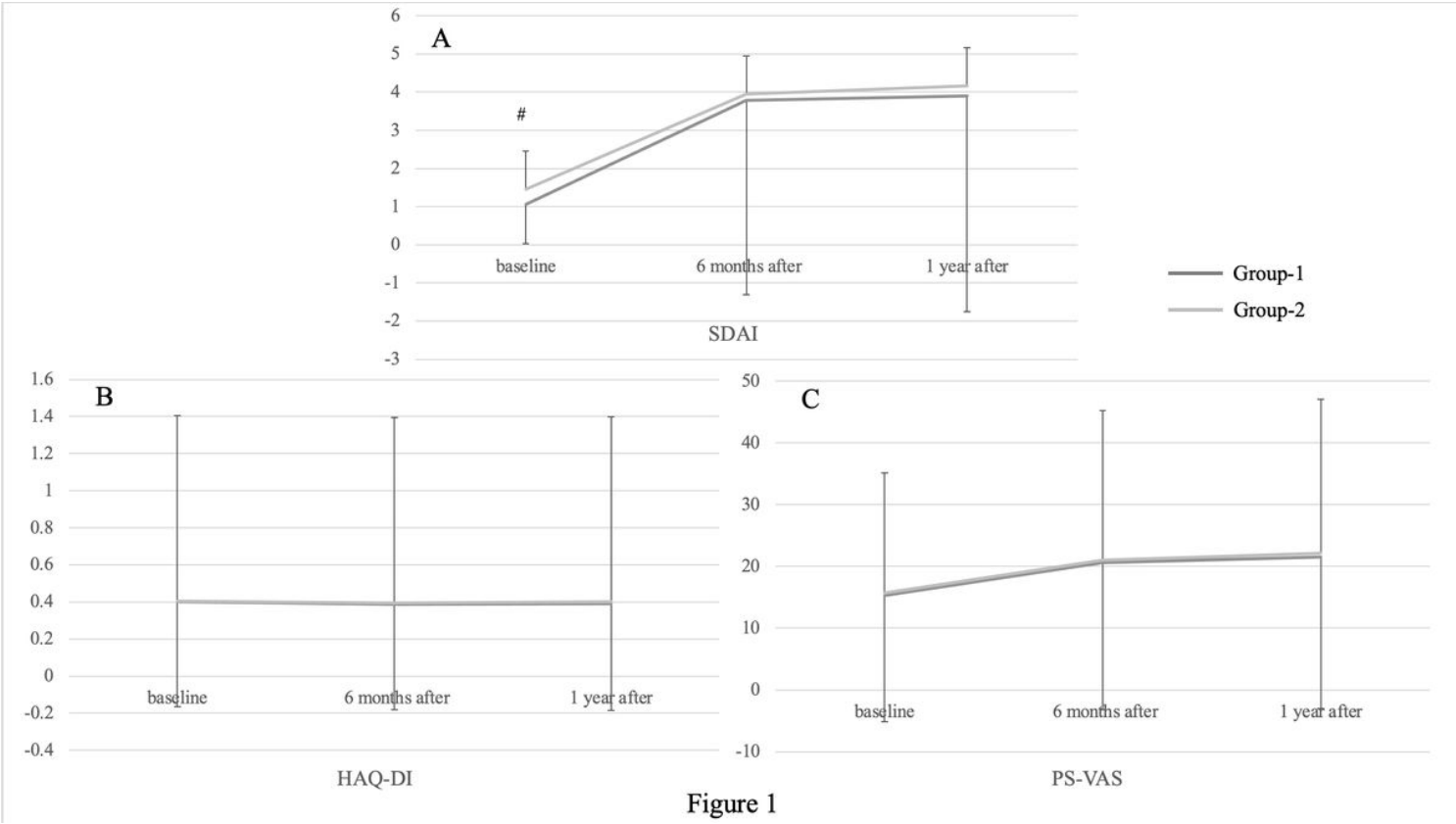

Figure 1

Mean SDAI score, HAQ score, and PS-VAS of the Group-1 and the Group-2 in the way one classification at baseline, 6 months after, and 1 year after each Boolean remission A: Mean SDAI of the Group-1 at baseline was significantly lower than that of the Group-2 (#; p < 0.0001) B: Mean HAQ score demonstrated no significant difference between the two groups C: Mean PS-VAS demonstrated no significant difference between the two groups

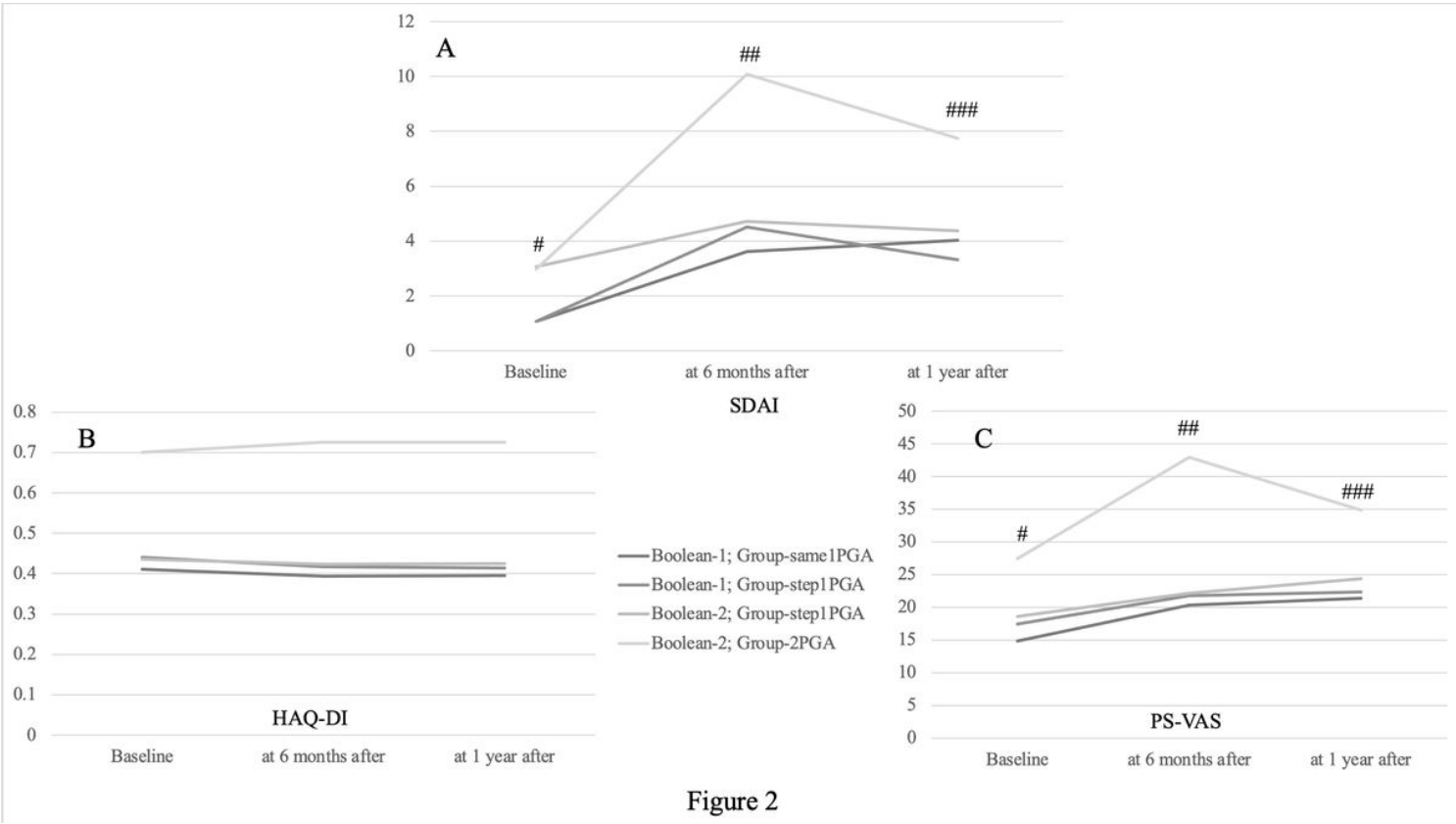

Figure 2

Mean SDAI score, HAQ score, and PS-VAS of the Group-same1PGA, Group-step1PGA, and Group-2PGA in the way two classification at baseline, 6 months after, and 1 year after each Boolean remission A: Mean SDAI score of the Group-samePGA1 of Boolean-1 was significantly lower than that of the Group-step1PGA and the Group2PGA of Boolean-2 at baseline (#; p < 0.0001), 6 months after (##; p < 0.001), and 1 year after (###; p <0.05), whereas mean SDAI score of the Group-step1PGA was significantly lower than that of the Group-2PGA (##; p < 0.05). Mean SDAI score in the Group-2PGA was significantly lower than that at 6 months and 12 months (p < 0.0001). B: Mean HAQ score demonstrated no significant difference between any pairs of the groups C: Mean PS-VAS of the Group-same1PGA was significantly lower than that of the Group-step1PGA at baseline (#; p <0.0001) of Boolean-2, and was lower than that of the Group-2PGA at baseline (#; p < 0.01), 6 months after (##; p < 0.01), and 1 year after (###; p < 0.05), whereas mean PS-VAS of the Group-step1PGA was significantly lower than that of the Group-2PGA at 6months after (##; p < 0.05). demonstrated no significant difference between the two groups