

Original Article

# The Influence of Different Phrasing of the "Patient Global Assessment of Global Health" on the Patient's Rating and Disease Activity Score in Ankylosing Spondylitis

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# **Abstract**

**Objective:** The standardized phrasing for the patient's global assessment of general health (PtGA-GH) is not defined yet, and the phrasing of question could vary the patient's response. This study aimed to evaluate whether different phrasings of the PtGA-GH affect the patient's rating, and whether PtGA-GH and patient's global assessment of disease activity (PtGA-DA) could be used interchangeability to calculate the Ankylosing Spondylitis Disease Activity Score (ASDAS) in ankylosing spondylitis (AS).

Methods: In this retrospective cross-sectional study, the patient's perception of their own general health was evaluated with PtGA-GH question (PtGA-GHQ) and the third question of RAPID3 (RAPID3-Q3). A difference ≥1 between PtGA-GHQ and RAPID3-Q3 was considered discordance. Lin's concordance coefficient (LCC) and Bland–Altman plots were used to determine the equivalence. The kappa (κ) statistics were used to evaluate the level of agreement in disease activity classification.

**Results:** Three-hundred twenty-one AS patients were included. Discordance was detected in 192 (59.8%) patients. Demographic and clinical characteristics were similar between concordant and discordant groups. In the sensitivity analysis, the number of discordant patients reduced to 91 (28.3%), but the patient's characteristics remained similar between groups. The LCC of 0.792 and Bland–Altman's limits of agreement of -4.169 to 3.172 indicated that PtGA-GHQ and RAPID3-Q3 are not interchangeable. The LCC was 0.750 for ASDAS-C-reactive protein (ASDAS-CRP) and RAPID3-Q3-based ASDAS-CRP, but the  $\kappa$  value was 0.190. The LCC was 0.982 for Ankylosing Spondylitis Disease Activity Score-erythrocyte sedimentation rate (ASDAS-ESR) and RAPID3-Q3-based ASDAS-ESR, and  $\kappa$  was 0.825 with 87.5% absolute agreement.

**Conclusion:** Different question patterns may not be used interchangeability as individual variables for AS activity assessment. The RAPID3-Q3 may be used to calculate ASDAS-ESR.

Keywords: Ankylosing spondylitis, ASDAS, disease activity, patient's global assessment, RAPID3

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## Introduction

Ankylosing spondylitis (AS), also called radiographic axial spondyloarthritis, is a chronic systemic inflammatory disease affecting the sacroiliac joint and spine. Some patients also suffer from peripheral involvement and/or extra-musculoskeletal manifestations.<sup>1</sup> Also, the disease activity is closely associated with chronic pain, functional impairment, mood disturbance, fatigue, reduction in work productivity, and loss of quality of life.<sup>2</sup> Since there is no biomarker to assess disease activity, prognosis, and response to therapy in AS, a comprehensive clinical evaluation of these patients is very important in the management of the disease.<sup>3</sup>

Patient-reported outcomes (PROs) provide valuable information on patient's own assessments of global health, pain, stiffness, physical function, and life quality in AS. The PROs can be used as a facilitating tool for shared decision making in clinical settings and as an efficiency assessment tool in clinical trials.<sup>3,4</sup> Due to the heterogeneous nature of inflammatory diseases, there is no single instrument that can well define the disease process for every patient. This has led to the development of composite scores that more accurately reflect the overall disease status compared to individual measures. The Assessment in SpondyloArthritis International Society (ASAS) recommends several core sets for use in clinical research and daily practice, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) for disease activity and the Bath Ankylosing Spondylitis Functional Index (BASFI) for physical function. While BASDAI and BASFI include only PROs, ASDAS incorporates laboratory data in addition to the PROs.<sup>5</sup> Also, a recently developed and validated alternative-ASDAS score was

found truthful, discriminative, and feasible for research purposes, when patient global assessment (PtGA) of perceived disease activity in the past week is unavailable.<sup>6</sup>

Patient global assessment is one of the widely used PROs in the field of rheumatology. In fact, PtGA could be used to evaluate 2 very different condition: either patient's assessment of general/global health (PtGA-GH), or patient's global assessment of disease activity (PtGA-DA). The Routine Assessment of Patient Index Data 3 (RAPID3) is a composite index of three patient's self-reported measures including physical function, pain, and patient global estimate of status computed from the multidimensional health assessment questionnaire.<sup>7,8</sup> Although RAPID3 was developed initially to assess disease status and changes over time in patients with rheumatoid arthritis (RA), it is provided consistent and quantitative information in other rheumatic diseases such as osteoarthritis, systemic lupus erythematosus, spondyloarthropathy, and gout.9 In patients with AS, RAPID3 score is correlated with the ASDAS and BASDAI values.<sup>10</sup> Furthermore, in patients with axial spondyloarthritis, the RAPID3 provides similar information to BASDAI in longitudinal follow-up.11

To date, the standardized phrasing for PtGA-GH is not defined, and the wording used for PROs and also used scoring method could vary the responses of patients.<sup>12</sup> This study aimed to evaluate whether a) different phrasings of PtGA-GH affect patients' scores, b) patient

## **Main Points**

- In this study, 3 out of 5 patients with ankylosing spondylitis (AS) gave different scores to 2 different questions evaluating the same patient-reported outcomes, independent of demographic and clinical characteristics.
- Wording used for patient's global assessment of general/global health (PtGA-GH) may influence the response, and different question patterns may not be used interchangeably as individual variables for AS activity assessment.
- Although PtGA-GH and patient's global assessment of disease activity (PtGA-DA) may not be used interchangeably for the calculation of Ankylosing Spondylitis Disease Activity Score-C-reactive protein, PtGA-GH may be used in the calculation of Ankylosing Spondylitis Disease Activity Score-erythrocyte sedimentation rate, when PtGA-DA is unavailable.

characteristics and disease-related factors cause differences between responses, c) different PtGA-GH scores affect disease activity states according to RAPID3, and d) PtGA-GH and PtGA-DA could be used interchangeability to calculate the ASDAS.

#### Methods

## Study Participants and Data Collection

This retrospective and cross-sectional study was conducted on patients who were admitted to rheumatology outpatient clinics of the tertiary hospital, between January 1, 2022, and March 31, 2022. In the department, standard clinical and laboratory assessments are made at each visit to evaluate the disease activity status of patients with AS. After taking a detailed medical history and comprehensive physical examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemogram, kidney function tests, and liver function tests are routinely evaluated. Normal values were up to 5 mg/L for CRP and up to 20 mm/h for ESR. Disease activity of AS patients is assessed with BASDAI, ASDAS-CRP, ASDAS-ESR, and RAPID3. Functional status is assessed with BASEL

In the present study, clinical characteristics and laboratory results of the most recent visit were retrospectively retrieved from medical records. A total of 339 consecutive AS patients who met the modified New York criteria were evaluated for inclusion.<sup>13</sup> Patients with severe heart, lung, liver, and kidney disease, missing data, and those younger than 18 years of age were excluded from the study. Consequently, 321 patients with AS were included in this study.

### **Patients Assessments**

The BASDAI, ASDAS-ESR, ASDAS-CRP, and RAPID3 were used to assess disease activity status. Bath Ankylosing Spondylitis Disease Activity Index is an entirely PROs measurement and consists of 6 questions including fatigue, spinal pain, pain or swelling of peripheral joints, pain of enthesitis, overall level of morning stiffness, and duration of morning stiffness.14 The ASDAS-ESR and ASDAS-CRP were calculated using the defined formula, which contains back pain (BASDAI question 2), duration of morning stiffness (BASDAI question 6), peripheral joint pain and/or swelling (BASDAI guestion 3), PtGA-DA and ESR or CRP, respectively.<sup>15</sup> Physical function was evaluated with the BASFI. It is self-report index consisting of 8 item pertaining to activities of daily living and 2 items evaluating the patient's ability to cope with daily life.16 All questions of BASDAI, ASDAS, and BASFI were graded on the 11-point NRS ranges

from 0 to 10. The RAPID-3 consists of 3 section including physical function, a PGA for pain and a PGA for global health. Physical function section contains 10 questions, and each question is scored from 0 (without any difficulty) to 3 (unable to do). A template is used to convert total score of this section to a 0-10 composite score. The pain and PtGA of global health are scored on 21 numbered circle to facilitate scoring.<sup>8</sup> Alternative-ASDAS was calculated as (0.12 × second question of BASDAI)+(0.06 × sixth question of BASDAI)+(0.11 × 0.99 × BASDAI total score)+(0.07 × third question of BASDAI)+0.58 × Ln (CRP+1).<sup>6</sup> Fatigue was evaluated with the first question of BASDAI.

## Patient's Global Assessment of General Health Was Evaluated with the Following 2 Questions

- 1. PtGA-GH question (PtGA-GHQ): "In general, how would you say your health is" on the 21-numbered circle from 0 to 10.
- 2. In RAPID3 questionnaire, PtGA-GH is assessed by the third question "Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing? on the 21-numbered circle from 0 to 10."

A difference ≥1 between PtGA-GHQ and the third question of RAPID3 (RAPID3-Q3) was considered as discordance. This yielded 2 groups as follows: concordant group and discordant group. Age, gender distribution, age at disease onset, disease duration, history of peripheral involvement, history of extra-musculoskeletal manifestations, acute phase reactants levels, medications, disease activity scores, and functionality score were compared between these 2 groups. Also, a sensitivity analysis with a difference ≥2 was performed to assess the robustness of the cut-off level.

### Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package version 26 (IBM SPSS Corp.; Armonk, NY, USA). Normally distributed continuous values were expressed as mean ± standard deviation (SD), non-normally distributed parameters as median values with interquartile range (IQR) (25th and 75th percentiles) and categorical variables as number and percentage. The  $\chi^2$  test was used for comparing the qualitative variables between the groups. Normally distributed data were compared with Student's t-test, and non-normally distributed data were compared with Mann-Whitney U test. P < .05 was accepted as statistically significant.

Lin's concordance coefficient (LCC) with 95% CIs was calculated to quantify the level of concordance between PtGA-GHQ and RAPID3-O3. The LCC values are interpreted as: 0.81-1.00 almost perfect, 0.61-0.80 substantial, 0.41-0.60 moderate, 0.21-0.40 fair, and <0.20 poor. To visually demonstrate the consistency, the Bland-Altman plots were constructed with plotting the mean of PtGA-GHQ and RAPID3-Q3 vs. the difference between PtGA-GHQ and RAPID3-Q3. To assess the impact of different phrasing of same PRO on composite indices, RAPID3 was calculated with both RAPID3-Q3 and PtGA-GHQ. The LCC was used to to quantify the level of concordance between RAPID3-Q3 based RAPID3 score and PtGA-GHQ based RAPID3 score. The  $\kappa$  statistic was used to evaluate the degree of agreement between these 2 scores in categorizing AS patients according to their disease status. The κ values were interpreted as: 0-0.20 very poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.0 perfect agreement.<sup>17</sup>

Finally, to test whether PtGA-DA and PtGA-GH could be used interchangeability in assessing disease activity, ASDAS-ESR and ASDAS-CRP were recalculated using RAPID3-Q3 instead of PtGA-DA. The LCC was used to evaluate the level of concordance between PtGA-GH and PtGA-DA based ASDASs. Also, the  $\kappa$  statistic was conducted to evaluate the degree of agreement in classification of patients according to the activity status (inactive disease, moderate, high, and very high) between RAPID3-Q3-based ASDASs and PtGA-DA based ASDASs.

#### **Ethical Considerations**

The Committee on the Human Research Ethics of the Human Research Ethics of Health Sciences University, Gulhane School of Medicine approved this study protocol (date: April 06, 2022, number: 2022/31). This study was conducted in accordance with principles of the Declaration of Helsinki.

## Results

A total of 321 AS patients with a mean age  $34.94 \pm 9.72$  years, consisting of 259 (80.69%) males were included in this study. The disease duration was  $11.11 \pm 6.09$  years. Human leukocyte antigen-B27 (HLA-B27) test result was available for 213 patients and found to be positive in 142 (66.67%) of them. Throughout the disease course, 91(28.3%) patients had peripheral arthritis, 83 (25.9%) patients had enthesitis, and 82 (25.5%) patients had uveitis. Sixty-seven (20.9%) patients

had a family history of spondyloarthritis. The median BASDAI score was 4.65 (IQR: 2.48-6.38), median BASFI score 3.00 (IQR: 0.93-5.40), median ASDAS-CRP score 3.00 (IQR: 2.10-3.80), median ASDAS-ESR score 2.50

(IQR: 1.55-3.20), and median RAPID3 score 13.00 (IOR: 7.50-17.82).

Discordance between PtGA-GHQ score and RAPID3-Q3 score was detected in 192

**Table 1.** Demographic and Clinical Characteristics of the Patients

	Concordant Group n: 129	Discordant Group n: 192	Р
Age (years), median (IQR)	36.00 (26.50-41.50)	34.00 (27.00-41.00)	.749
Males, n (%)	99 (76.7)	160 (83.3)	.143
Age at symptom onset (years), median (IQR)	23.00 (19.00-30.00)	29.00 (18.00 – 29.00)	.361
Age at diagnosis (years), median (IQR)	28.00 (21.00-35.50)	27.00 (21.25-33.00)	.348
Disease duration (years), median (IQR)	10.00 (6.00-14.50)	10.00 (6.00-14.00)	.679
Duration from symptom to diagnosis (years), median (IQR)	4.00 (2.00-7.00)	3.00 (2.00-6.00)	.325
Comorbidity, n (%)	13 (10.1)	16 (8.3)	.593
Extra-axial involvement			
Uveitis, n (%)	35 (27.1	47 (24.5)	.593
Peripheral arthritis, n (%)	34 (26.4)	57 (29.7)	.516
Enthesitis, n (%)	34 (26.4)	49 (25.5)	.867
Psoriasis, n (%)	1 (0.8)	2 (1.0)	1.00
Family history, n (%)	26 (20.2)	41 (21.4)	.795
*HLA-B27 positivity, n (%)	48 (62.3)	94 (69.1)	.313
ESR (mm/h), median, (IQR)	9.00 (3.10-20.20)	8.00 (3.10-20.65)	.741
ESR > 20 mm/h, n (%)	32 (24.8)	49 (25.5)	.885
CRP (mg/L), median, (IQR)	9.00 (3.65-22.00)	10.00 (3.35-20.75)	.901
CRP > 5 mg/L, n (%)	87 (67.4)	128 (66.7)	.885
Fatigue, median (IQR)	5.00 (1.50-7.50)	6.00 (3.50-7.00)	.175
Total BASDAI score, median (IQR)	4.10 (1.80-6.48)	4.90 (3.10-6.29)	.051
Total BASFI score, median (IQR)	2.90 (0.55-5.73)	3.00 (1.23-5.10)	.805
Total RAPID3 score, median (IQR)	12.67 (4.50-17.59)	13.50 (8.50-17.83)	.117
ASDAS-CRP, median (IQR)	2.90 (1.90-3.80)	3.10 (2.20-3.80)	.251
ASDAS-ESR, median (IQR)	2.40 (1.40-3.15)	2.50 (1.70-3.30)	.291
Alternative-ASDAS, median (IQR)	2.11 (1.25-2.84)	2.34 (1.56-2.96)	.051
Physician global assessment, median (IQR)	3.50 (1.50-5.00)	3.50 (2.00-5.50)	.331
Drug treatments, n (%)			
NSAID	87 (67.4)	119 (62.0)	.317
DMARD's	59 (45.7)	89 (46.4)	.913
Anti-TNF alpha	55 (42.6)	76 (39.6)	.585

ASDAS, Ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; RAPID3, routine assessment of patient index data 3; SD, standard deviation; TNF, tumor necrosis factor.

<sup>\*</sup>Result of HLA-B27 test was available for 213 patients.

(59.8%) patients. Among discordant group, 123 patients had scored to PtGA-GHQ higher than RAPID3-Q3 and 69 patients had scored to RAPID3-Q3 higher than PtGA-GHQ. Demographic characteristics, disease activity scores, functionality scores, frequency of extra-axial involvement, and levels of acute phase reactants were similar between groups (Table 1). In the sensitivity analysis with a difference ≥2, as expected, number of discordant patients reduced to 91 (28.3%). Demographic and clinical characteristics remained similar between groups.

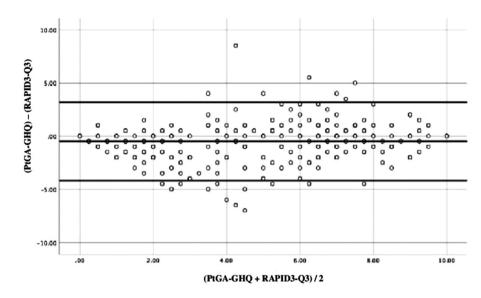
When the level of concordance between PtGA-GHO and RAPID3-O3 was evaluated, LCC was 0.792 (95% CI 0.749 to 0.829). The Bland-Altman plot was shown in Figure 1. Bland-Altman's limits of agreement for PtGA-GHQ and RAPID3-Q3 were from -4.169 to 3.172, with a mean difference of -0.498. The Bland-Altman's 95th percentile limits of agreement between 2 scores was too broad for reasonable clinical interchangeability. The RAPID3 was calculated with both RAPID3-O3 and PtGA-GHO. for assessing the effect of different phrasing of same PRO on composite indices. The LCC was 0.90 (95% CI: 0.950-0.967). The level of agreement in good ( $\kappa$  value: 0.737, P < .001) with 83.5% absolute agreement (Table 2).

When evaluating the interchangeability of PtGA-DA and RAPID3-Q3 in calculating ASDAS, LCC was 0.750 (95% CI 0.715-0.782) for ASDASCRP and RAPID3-Q3-based ASDAS-CRP, but the  $\kappa$  statistic for agreement in disease status was 0.190 (P < .001) with 41.1% absolute agreement. Also, LCC was 0.982 (95% CI 0.977-0.985) for ASDAS-ESR and RAPID3-Q3 based ASDASESR, and the  $\kappa$  statistic for level of agreement in disease status was 0.825 (P < .001) with 87.5% absolute agreement.

## Discussion

To the best of knowledge, this is the first study that evaluated the effect of different phrasing of PtGA-GH on the answers of patients with AS and the interchangeability of PtGA-GH and PtGA-DA in the calculating of composite indices used to assess AS activity. Independent of demographic or clinical characteristics, 192 (59.8%) gave different scores to 2 different questions that evaluated the same PRO.

Treatment for axial spondyloarthritis should be individualized and involve the patient in the treatment process. In addition to clinical signs, laboratory tests, and imaging modalities relevant to the clinical presentation, PROs should also be included for monitoring disease



**Figure 1.** Bland–Altman plot for agreement between PtGA-GHQ and RAPID3-Q3. PtGA-GH, patient's assessment of general/global health; RAPID3-Q3, third question routine assessment of patient index data-3.

status.<sup>18</sup> From the patient's perspective, the majority of patients feel that the PROs help doctors to understand their current health status, improve their dialogue with healthcare professionals, and develop a sense of control over their own care.<sup>19</sup>

The PROs have gained increasing attention for their value in providing patients' perspectives on their own disease activity status or their global health. Patient global assessment is one of the widely used PROs in the rheumatology field and can be used for patients to score their experiences of either disease activity or global health. However, differences in the wording of the question (e.g., "arthritis" or "health"), wording of the anchors (e.g., "worst possible," "most active," or "very active"), type of rating scale (e.g., VAS or NRS; horizontal or vertical), and reference period (e.g., "today" or "last week") cause different scoring of patients. 12

In this study, PtGA-GH was evaluated with 2 questions using the same rating scale but different expressions. One hundred ninety-two (59.8%) of 321 patients gave different scores to 2 different questions that evaluated the same PRO. Demographic characteristics, disease activity scores, functionality score, fatigue level, frequency of extra-axial involvement, levels of acute phase reactants, and presence of comorbidity were similar between groups. After the sensitivity analysis with a difference ≥2, the number of discordant patients reduced as expected, but demographic and clinical characteristics were still similar between groups. Although LCC indicated substantial

degree of agreement between PtGA-GHQ score and RAPID3-Q3, the wide range of the Bland–Altman's 95% limits of agreement between 2 scores indicated a clear lack of evidence for clinical interchangeability. This suggests that different phrasing of PtGA-GH may capture different information on a per-patient basis. On the other hand, in disease activity state classification, there was nearly perfect concordance between RAPID3 and PtGA-GHO based RAPID3 and 83.5% absolute agreement  $(\kappa \text{ value: } 0.737, P < .001). Although these 2$ questions evaluating PtGA-GH with different phrasing may not be used interchangeability as individual variables for AS, they may be used interchangeability for calculating composite indices for AS activity assessment.

In the current literature, there are few studies evaluating the interchangeability of different versions of PtGA in RA patients. In RA, the commonly used composite disease activity indices for the definition of remission are as follows: the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) Boolean-based remission, Disease Activity Score 28 (DAS28)-based remission, the Clinical Disease Activity Index (CDAI)-based remission, and the Simplified Disease Activity Index (SDAI)-based remission. All of these indices include PtGA but use different phrasing. Ferreira et al<sup>20</sup> performed a study to evaluate the interchangeability of these 4 different PtGA formulas and PtGA formulated by researchers. They reported that, although all PtGA versions correlated well with each other, the agreement between formulations was low according to the Bland-Altman plots. Also,

Table 2. Disease Activity Status for RAPID3 Indices Calculated Using Third Question of RAPID3 and PtGA-GHQ

		RAPID3					
		Remission, n (%)	Low, n (%)	Moderate, n (%)	High, n (%)	Absolute Agreement	κ
RAPID3 based on PtGA-GH	Remission, n (%)	35 (10.90)	7 (2.2)	1 (0.3)	0 (0)	83.5%	0.737
	Low, n (%)	1 (0.3)	22 (6.9)	20 (6.2)	1 (0.3)		
	Moderate, n (%)	0 (0)	2 (0.6)	47 (14.6)	12 (3.7)		
	High, n (%)	0 (0)	0 (0)	9 (2.8)	164 (51.1)		

PtGA-GH, patient's assessment of general/global health; RAPID3, Routine Assessment of Patient Index Data-3.

when different formulations of PtGA were used in each index, differences in remission rates were reported up to 4.7% for ACR/EULAR Boolean, up to 4.7% for SDAI, up to 6.3% for CDAI, and up to 5.2% for DAS28-CRP.20 Similarly, in a study evaluating the effect of different PtGAs on DAS28 in patients with RA, 5 different versions of PtGA were evaluated based on feeling, disease activity, well-being, best/worst, and Arthritis Impact Measurement Scales (AIMS). This study, which used Bland-Altman plots, reported broad 95% limits of agreement between AIMS and each of the other PtGA versions. Also, when DAS28 scores were calculated for each patient using these different PtGA scores, the largest difference in DAS28 scores was found 0.63 points.<sup>21</sup> Thus, a standardized definition of PtGA is crucial for accurately assessing the change in disease status during the disease course in clinical practice and comparing the results of clinical trials with each other.

In the recently published ASAS-EULAR recommendations for the treatment of axial spondyloarthritis, ASDAS, preferentially CRP based ASDAS, is recommended to use for the assessment of disease activity.<sup>18</sup> The ASDAS is a wellbalanced index covering the same underlying construct without too much redundancy, in contrast to BASDAI.<sup>22</sup> The ASDAS takes into account the patient's perception on back pain, peripheral joint pain and/or swelling, global disease activity, and duration of morning stiffness, and as well as preferably CRP or alternatively ESR as an objective measure of inflammation. The PtGA of disease activity is assessed by the question "How active was your spondylitis on average during the last week?" on a VAS (from 0 to 10 cm) or a NRS (from 0 to 10). However, Boel et al<sup>23</sup> reported that test-retest reliability of PtGA-DA was poor in radiographic axial spondyloarthritis who had a maximum time interval of 28 days between both visits. Recently, Ortolan et al<sup>6</sup> developed an alternative ASDAS score for use in axial spondyloarthritis studies when PtGA is not available. They reported that alternative-ASDAS using BASDAI total score instead of PtGA was truthful, discriminative, and feasible instrument and also showed good agreement with original-ASDAS in major improvement/clinically important improvement criteria.6 The study evaluated whether PtGA-DA and PtGA-GH could be used interchangeability in assessing disease activity with ASDAS. As mentioned above, since PtGA-GHQ and RAPID3-Q3 were not found interchangeability in this study and RAPID3 is a standardized and widely used index, PtGA-GH-based ASDASs were calculated only with RAPID3-Q3. Although substantial concordance was detected for ASDAS-CRP and RAPID3-Q3based ASDAS-CRP, level of agreement in disease status was found to be very poor. On the other hand, almost perfect concordance was detected for ASDAS-ESR and RAPID3-Q3-based ASDAS-ESR and also level of agreement in disease status was excellent. Similarly, another study, which investigated the interchangeability of PtGA-DA and PtGA-GH in calculating the composite index in RA patients, reported that they may be used interchangeability for calculation DAS28, CDAI and RAPID3.24

The retrospective design of this study is major limitations. However, the number of excluded patients due to the missing data was very small. The lack of information about the patient's education level, which may play an important role in the understanding of questions, is also a limitation of this study.

As a conclusion, although they are evaluating the same PRO, phrasing of the question may affect the response. In this study, 3 out of 5 patients with AS gave different scores to the 2 questions evaluating PtGA-GH with the same rating scale but with different phrasing. The wide range of the Bland–Altman's 95% limits of agreement between 2 scores indicated that different question patterns may not be used interchangeability as individual variables for AS activity assessment. Thus, standardization of PtGA formulation is crucial for both to evaluate the changes in the patient's disease activity with the same index at each visit in clinical practice and to compare the results of different

clinical researches. On the other hand, PtGA-GH may be used interchangeability for the calculation of ASDAS-ESR, when PtGA-DA is not available. Further well-designed, prospective, controlled studies with larger sample size are needed to validate usefulness of ASDAS based on PtGA-GH in AS patients.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: The Committee on the Human Research Ethics of the Human Research Ethics of Health Sciences University, Gulhane School of Medicine approved this study protocol (date: April 06, 2022, number: 2022/31). This study was conducted in accordance with principles of the Declaration of Helsinki.

**Informed Consent:** Written/Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.T., M.N.K.; Design – D.T., M.N.K.; Supervision – D.T., S.Y.; Resources – D.T., M.N.K., M.S.Ö.; Materials – D.T., M.N.K., M.S.Ö.; Data Collection and/or Processing – D.T., M.N.K., M.S.Ö.; Analysis and/or Interpretation – D.T.; Critical Review – S.Y., M.Ç.

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