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VALIDATION STUDIES

# Defining functioning categories in axial Spondyloarthritis: the role of the ASAS Health Index

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**Abstract** The Assessment of SpondyloArthritis international Society Health Index (ASAS HI) is an inclusive questionnaire, able to describe the total impairments and restrictions due to axial spondyloarthritis (axSpA). Considering the relationship between ASAS HI and the Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, the aim of this study is to establish the ASAS HI cut-off values for functioning categories employing the ASDAS-CRP disease activity states in axSpA patients. ASAS HI and ASDAS-CPR were obtained from 140 consecutive axSpA patients, divided in the four ASDAS-CRP disease activity categories. High and very high disease activity were considered together. The ASAS HI cut-offs were obtained from the arithmetic mean, rounded off to the closest whole number, of the 75th percentile mean value of a lower rank and the 25th percentile mean value of the adjacent higher rank. This approach was applied in the transition from inactive disease and moderate disease activity, and in the transition from moderate disease activity and high/very high disease activity. Twenty-three patients were classified as having inactive disease, 36 were classified as having moderate disease activity, and 81 were in a high/very high disease activity state. Using the approach of the 75th–25th percentile mean values of adjacent disease activity states, the ASAS HI cut-offs resulted: ≤4 to dinstinguish a normal functioning, >4 and ≤8 to distinguish a moderate impairment of functioning, and >8 to distinguish a severe impairment of functioning. ASAS HI seems a reliable tool to define functioning categories in patients with axSpA.

**Keywords** ASAS HI · Cut-offs · Axial spondyloarthritis · Functioning categories · Disease activity · Health-related quality of life

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## Introduction

Axial spondyloarthritis (axSpA) is a group of chronic articular inflammatory conditions characterized by prevalent inflammatory spinal involvement [1].

Life of patients with axSpA is overturned in many aspects, such as pain, stiffness, limitations in working and social activities, and moveover concerns could raise about future, physical appearence and drugs side effects [2, 3].

Recently, next to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [4], the Assessment of SpondyloArthritis international Society (ASAS) introduced the Ankylosing Spondylitis Disease Activity Score (ASDAS) [5] as disease activity index. The ASDAS combines both patient-reported outcome (PRO) measures and

the acute-phase reactants levels. For this instrument the cut-off values distinguishing inactive disease, moderate disease activity, high disease activity, and very high disease activity have been defined [6].

The function and quality of life in axSpA are usually assessed with validated and disease specific questionnaires, such as the Bath Ankylosing Spondylitis Functional Index (BASFI) [7] and the Ankylosing Spondylitis Quality of Life Scale (ASQoL) [8], respectively.

An inclusive questionnaire, able to describe the total impairments and restrictions due to axSpA, was not available since the creation of ASAS Health Index (ASAS HI) [9]. Generated by a pool of 251 items obtained from questionnaires for axSpA, ASAS HI is composed of 17 selected points addressing to domains including pain, emotional status, sleep, sexual function, mobility, self-care and community life. These fields have been selected according to the International Classification of Functioning, disability and health (ICF) categories [10]. This classification supports the bio-psyco-social model, highlighting the influence of environmental and personal features on functioning and disability. Thus, ASAS HI can apprise of a wide section of common problems distressing patients with axSpA [9].

The feasibility, reliability, and construct validity of the ASAS HI have been evaluated, comparing its clinimetric properties to the current available measures of disease activity, functional limitation and health status assessment in patients with axSpA [11]. In particular, it has been demonstrated that high disease activity, measured by ASDAS-CRP, is the only independent variable associated with ASAS HI using a logistic regression model. Other variables, such as age, sex, disease duration, educational level, and comorbidities did not show to substantial contribution to the ASAH HI score.

A potential limitation for a wide application of ASAS HI is the lack of cut-off values that reduces the interpretability of this instrument in the everyday clinical practice.

Keeping in mind these considerations and the excellent clinimetric findings, in particular the strong correlation with ASDAS-CRP, the aim of this study is to establish the ASAS HI cut-off values for functioning categories employing the ASDAS-CRP disease activity states in a "real life" cohort of axSpA patients.

## Materials and methods

### Patient characteristics

The cohort was composed of 140 consecutive axSpA (93 ankylosing spondylitis [AS], 47 non radiographic axSpA [nr-axSpA]), enrolled from May 2015 to October 2015. One-hunded and one were male (72.1%) while 39 were female (27.9%). The diagnosis of axSpA based on the fulfillment of the ASAS classification criteria [12, 13]. Exclusion criteria were the following: other active inflammatory musculoskeletal diseases (e.g. rheumatoid arthritis, gout and calcium pyrophosphate dyhidrate crystal deposition), concomitant fibromyalgia, cancer or lymphoproliferative disease, uncontrolled diabetes, unstable ischemic heart disease or congestive heart failure, and history of active tuberculosis. Ninety-nine patients were on treatment with TNF-blockers (70.7%), including infliximab (39 patients), adalimumab (27 patients), etanercept (22 patients), golimumab (9 patients) and certolizumab pegol (2 patients). Non-steroidal anti-inflammatory drugs on-demand were allowed to all the patients. The subjects enrolled were attending the outpatient and inpatient clinics of a tertiary rheumatology center and they represent a "real life" sample of axSpA. Each patient underwent to clinical examination and was requested to fill in a questionnaire package including socio-demographic data (sex, age, disease duration and years of school attendance), ASAS HI, BASDAI, Patient Global Assessment of disease activity (PaGA). The acute fase reactants, in particular the C-Reactive Protein (CRP) (mg/l) serum levels, were recorded. With these informations ASDAS-CRP has been obtained.

### ASAS HI questionnaire

ASAS HI is made up of 17 items, with a dichotomous response option ("I agree" or "I do not agree"). Each affirmative ("I agree") reply is counted 1, while a negative ("I do not agree") response is scored 0. The final ASAS HI value is the arithmetic sum of the affirmative items (range 0–17). Higher values mirror a worse functioning and health status, with a relevant level of impairments, limitations and restrictions. In this study, ASAS HI Italian translation has been used [14].

### ASDAS

ASDAS is a composite score to measure disease activity in axSpA. It considers together self-reported answers and objective measures including: back pain, duration of morning stiffness, peripheral joint pain and/or swelling, PaGA, and a serologic marker of inflammation (ESR or CPR) [5]. ASDAS has been endorsed by the ASAS and by the Outcome Measures in Rheumatology (OMERACT). The cut-offs defining the disease activity ranks are the following: $<1.3$ inactive disease, $\geq 1.3$ and $<2.1$ moderate disease activity, $\geq 2.1$ and $<3.5$ high disease activity, $\geq 3.5$ for very high disease activity. An amelioration $\geq 1.1$ units is a "clinically important improvement", while an enhancement $\geq 2.0$ represents a "major improvement" [6].

### Statistical analysis

All data were recorded in a Microsoft Excel file, and analyses were performed using MedCalc® version 16.0 (MedCalc Software, Ostend, Belgium) for Windows XP.

Patients were categorized in the four ASDAS-CRP disease activity categories. Very high disease activity patients were assembled to high disease activity patients due to the small number of subjects in this status.

For each ASDAS-CRP disease activity rank, we calculated the ASAS HI arithmetic means with standard deviations (SDs), medians, and were also described the 25th and 75th percentiles. To define the ASAS HI cut-off values of functioning categories, we applied the following approach: the cut-off of "normal functioning" was marked taking the ASAS HI mean value of the 75th percentile of inactive disease and the ASAS HI mean value of the 25th percentile of moderate disease activity. Then, the arithmetic mean between these two values was calculated, and the mean was rounded off to the closest whole number. This final number represents the ASAS HI cut-off value of normal functioning. With the same method we defined the cut-off values of "moderate impairment in functioning" and of "severe impairment in functioning": the arithmentic mean rounded off to the closest whole number was obtained from the ASAS HI mean value of the 75th percentile of moderate disease activity and the ASAS HI mean value of the 25th percentile of high/very high disease activity.

## Results

### Cohort distribution

The mean age of our cohort was 46.2 ± 12.0 years (range 22–77). The mean duration of disease was 6.7 ± 4.8 years. Considering the extra-articular involvement, 15 patients (10.7%) had a concomitant inflammatory bowel disease (respectively 10 patients (7.1%) Crohn disease and 5 patients (3.6%) ulcerative colitis), while 11 patients (7.9%) had at least one episode of anterior uveitis. ASAS HI showed a non-normal distribution, the lowest value of ASAS HI was 0 while the highest value was 15.

Of the 140 patients examined, following the ASDAS-CRP definition, 23 were classified as having an inactive disease activity, 36 were classified as having a moderate disease activity, and 81 were in a high/very high disease activity state (respectively 70 patients were in a high disease activity state, and 11 patients were in a very high disease activity state).

The complete statistics and the percentiles distribution of ASAS HI for each disease activity state without the high/very high grouping are described in the Supplementary Material.

The summary statistics of ASAS HI values for each ASDAS-CRP disease activity category, with the high/very high grouping, is summarized in Table 1. The ASAS HI median value of inactive disease patients was 3.0, the ASAS HI median value of moderate disease activity was 7.0, and the ASAS HI median value of high/very high disease activity was 10.0.

**Table 1** Summary statistics of ASAS HI for each ASDAS-CRP disease activity state

| | ASDAS-CRP disease activity states | | |
|---|---|---|---|
| | Inactive disease | Moderate disease activity | High/very high disease activity |
| Sample size | 23 | 36 | 81 |
| Lowest value | 0.00 | 0.00 | 0.00 |
| Highest value | 9.00 | 11.00 | 15.00 |
| Arithmetic mean | 3.26 | 6.44 | 9.46 |
| 95% CI for the mean | 1.86–4.66 | 5.27–7.62 | 8.75–10.18 |
| Median | 3.00 | 7.00 | 10.00 |
| 95% CI for the median | 1.00–4.00 | 6.00–8.34 | 9.00–11.00 |
| Variance | 10.47 | 12.02 | 10.30 |
| Standard deviation | 3.24 | 3.47 | 3.21 |
| Relative standard deviation | 0.99 (99.25%) | 0.54 (53.81%) | 0.34 (33.92%) |
| Standard error of the mean | 0.67 | 0.58 | 0.36 |
| Coefficient of Skewness | 1.16 ($P=0.02$) | −0.37 ($P=0.33$) | −0.66 ($P=0.02$) |
| Coefficient of Kurtosis | 0.68 ($P=0.36$) | −1.01 ($P=0.05$) | 0.43 ($P=0.35$) |
| Kolmogorov–Smirnov test[a] for normal distribution | 0.24 reject normality ($P=0.0018$) | 0.15 reject normality ($P=0.0476$) | 0.13 reject normality ($P=0.0012$) |

[a]Lilliefors significance correction

In Table 2 is reported the percentiles distribution of ASAS HI scores distincted for the disease activity states.

Thus, to define the ASAS HI cut-off of normal functioning, the 75th percentile ASAS HI mean value of the lower category (4.0) and the 25th percentile ASAS HI mean value of the higher rank (3.5) have been considered. Then, the arithmetic mean of these two values (3.75) was rounded off to closest whole number (4), that represents the ASAS HI cut-off point between normal functioning and moderate impairment in functioning. With the same approach, the ASAS HI cut-off value obtained in the transition from moderate impairment in functioning and severe impairment in functioning was 8 (8.25 the arithmetic mean between 9—the 75th percentile ASAS HI mean value of moderate disease activity—and 7.5—the 25th percentile ASAS HI mean value of high/very high disease activity).

In summary, the ASAS HI cut-off values for functioning categories were: ≤4 normal functioning, >4 and ≤8 moderate impairment of functioning, and >8 severe impairment of functioning.

Figure 1 depicts the relationship of ASAH HI values and disease activity categories.

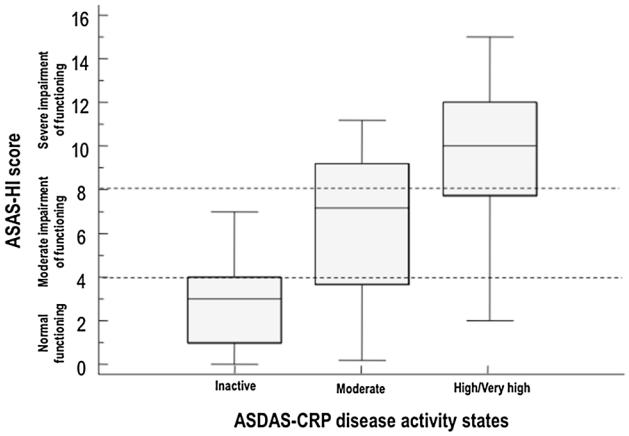


**Fig. 1** *Box*- and- *Whisker* plot of ASAS HI values (*y*-axis) for each ASDAS-CRP disease activity state (*x*-axis). The *boxes* represent the ASAS HI values from 25th to 75th percentiles for each disease activity state. The *middle lines* inside *boxes* are the medians. The *dotted lines* are the ASAS HI cut-off values obtained (respectively 4 and 8) for the functioning categories

## Discussion

In this paper, we described the ASAS HI cut-off values to define functioning referring to the ASDAS-CRP categories.

AxSpA represent a major burden for patients, not only in terms of pain but also for the impaired motility and physical function, for the decrease in work ability and in social partecipation [2, 3, 15].

A clear evaluation of the severity of the disease is hard to establish and should inevitably consider multiple aspects. Even in early disease, nr-axSpA can determine the same disadvantages of AS [16].

The core set of the features to be evaluated in AS has been pointed out by ASAS in 2010 on the basis of the ICF of World Health Organization (WHO) [17]. ICF categories are the universally recognized structure to detail the range

**Table 2** Percentiles distribution of ASAS HI scores for each disease activity state

| Percentiles | ASDAS-CRP disease activity states | | | | | |
|---|---|---|---|---|---|---|
| | Inactive disease | | Moderate disease activity | | High/very high disease activity | |
| | ASAS HI distribution | 95% Confidence interval | ASAS HI distribution | 95% Confidence interval | ASAS HI distribution | 95% Confidence interval |
| 1 | | | | | 0.30 | |
| 2.5 | 0.00 | | 0.40 | | 1.50 | |
| 5 | 0.00 | | 1.00 | | 3.50 | 0.20–5.00 |
| 10 | 0.00 | | 1.00 | 0.05–2.00 | 5.00 | 2.68–7.00 |
| 20 | 0.10 | 0.00–1.09 | 2.00 | 1.00–6.00 | 7.00 | 5.81–8.00 |
| 25 | 1.00 | 0.00–2.50 | 3.50 | 1.00–6.00 | 7.50 | 7.00–8.30 |
| 40 | 1.70 | 0.24–3.35 | 6.00 | 3.28–7.00 | 9.00 | 8.00–10.00 |
| 60 | 3.30 | 1.65–4.00 | 7.00 | 7.00–9.00 | 11.00 | 10.00–11.00 |
| 75 | 4.00 | 3.00–9.51 | 9.00 | 7.00–11.00 | 12.00 | 11.00–12.00 |
| 80 | 4.00 | 3.91–10.29 | 10.00 | 8.36–11.00 | 12.00 | 11.00–13.00 |
| 90 | 9.20 | | 11.00 | 10.00–11.00 | 13.50 | 12.00–14.32 |
| 95 | 10.35 | | 11.00 | | 14.00 | 13.32–15.00 |
| 97.5 | 10.93 | | 11.00 | | 15.00 | |
| 99 | | | | | 15.00 | |

of problems in activities, and could be employed for a functional assessment, as well as an outcome measure for treatment planning and monitoring. Born in this context, ASAS HI is the first PRO disease-specific built on the ASAS/WHO/ICF core set criteria for AS [9].

Its clinimetric properties have been already evaluated [11], showing that the better concurrent validity was with ASQoL, one disease-specific health-related quality of life (HRQoL) tool. It has been also demonstrated how ASDAS-CRP high disease activity is the only indipendent variable related to ASAS HI. The method to define cut-off points considering the arithmetic mean of the 75th percentile mean value of a lower rank, and the 25th percentile mean value of adjacent higher rank, has been already used in rheumatology. Recently, Schoels et al. employed this approach to determine the cut-off points for the Disease Activity Index for Psoriatic Arthritis [18]. After all, cut-offs are fundamental to increase the interpretability and the meaning of a score, not only in the research setting but also in clinical practice [19].

It must be highlighted that ASAS HI is neither a health-related quality of life instrument nor a disease activity index. However, despite this face validity concern, we decided to use the ASDAS-CRP ranks to determine the ASAS HI functioning categories thanks to their relationship, already investigated in a previous study [11].

This research presents some limitations. First of all, our cohort of patients was non-randomly selected and the majority of the patients were in a high disease activity, with few subjects in a very high disease activity. This possible selection bias could derive from the fact that our cohort is coming from a tertiary center, where the more severe cases refer to. Moreover, due to the low number of patients in a very high disease activity state, we gathered this category with the high disease activity.

However, we think that the unification of these two categories does not seems to condition the meaning of the cut-offs obtained, since these patients experience a great burden on function and health state. Second, our single evaluation did not permit to appreciate the responsiveness (sensitivity to change) of this score.

In conclusion, ASAH HI seems an easy, quick, and reliable tool to help rheumatologists in defining function and health in patients with axSpA. More extended researches will be needed to generalize our results.

**Compliance with ethical standards**

**Funding sources that supported the work** None.

**Conflict of interest** FS has attended advisory board meetings and has received speaking fees from Bristol-Myers Squibb, Abbvie, Roche, Pfizer and Janssen. MC has attended advisory board meetings and has received speaking fees for Bristol-Myers Squibb, Abbvie and Janssen. MDC has attended advisory board meetings for Abbvie. VL and ADM declare that they have no conflict of interest.

**Ethical approval** All the procedures in this work were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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