

HAE-AS, a specific disease activity scale for hereditary angioedema with C1-inhibitor deficiency

Short title: Activity scale for hereditary angioedema

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Abstract

Background: Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) shows variability in disease activity among patients and within individual patients.

Objective: This study aims at developing a disease activity scale for C1-INH-HAE (HAE-AS) with sound measurement properties.

Methods: Eleven countries participated in a prospective multicentre cohort study. A clinical questionnaire was self-completed by 290 adult patients with C1-INH-HAE. Patients also completed two quality of life (QoL) scales, the SF-36v2 and the HAE-QoL. Rasch analysis and classical psychometric methods were used in a pre-selection of clinical items: number of attacks by location and number of treated attacks, emergency room visits, psychological/psychiatric treatment, missed school/work days in the last 6 months; general health; and impairment in everyday work/activities due to pain.

Results: The sample presented a mean age of 41.5 (SD=14.7; range: 18-84) years, with 69% of females. The final Rasch model with 12 items showed that the HAE-AS had a satisfactory reliability (person separation index = 0.748), local item independence, unidimensionality and no item bias by age or gender. The HAE-AS provided scores in a linear measure, with mean 10.66 (SD=3.92; range: 0-30). Further analysis with classical psychometric methods indicated that the HAE-AS linear measure presented moderate-to-high convergent validity with QoL scales (SF-36v2: physical component, $r=-0.33$, mental component 0.555; HAE-QoL: -0.61) and good discriminative validity by age, gender and disease severity ($p<0.05$).

Conclusions: The HAE-AS is a short, valid, reliable and psychometrically sound measure of disease activity for C1-INH-HAE, which may be useful for research studies.

Key words: C1-INH-HAE, Clinical activity, Hereditary angioedema, Psychometric properties, Rasch analysis.

Resumen

Antecedentes: El angioedema hereditario por déficit de inhibidor de C1 (C1-INH-HAE) muestra variabilidad en la actividad de la enfermedad entre los pacientes y en cada paciente individualmente.

Objetivo: Este estudio tiene como objetivo desarrollar una escala de actividad de la enfermedad para C1-INH-HAE (HAE-AS) con propiedades sólidas de medición.

Métodos: Participaron once países en un estudio multicéntrico prospectivo de cohorte. 290 pacientes adultos con C1-INH-HAE completaron un cuestionario clínico. Los pacientes también completaron dos escalas de calidad de vida (QoL), el SF-36v2 y el HAE-QoL. El análisis Rasch y los métodos psicométricos clásicos se utilizaron en una preselección de ítems clínicos: número de ataques por ubicación y número de ataques tratados, visitas a emergencias, tratamiento psicológico / psiquiátrico, días de escuela / trabajo perdidos en los últimos 6 meses; salud general; y deterioro en el trabajo / actividades cotidianas debido al dolor.

Resultados: La muestra presentó una edad media de 41,5 (DE = 14,7; rango: 18-84) años, con 69% de mujeres. El modelo final Rasch con 12 ítems mostró que el HAE-AS tenía una confiabilidad satisfactoria (índice de separación de personas = 0,748), independencia local del ítem, unidimensionalidad y ningún sesgo de ítems por edad o género. El HAE-AS proporcionó puntuaciones en una medida lineal, con una media de 10,66 (DE = 3,92; rango: 0-30). Un análisis posterior con métodos psicométricos clásicos indicó que la medida lineal HAE-AS presentaba validez convergente de moderada a alta con las escalas de calidad de vida (SF-36v2: componente físico, $r = -0,33$, componente mental $-0,555$; HAE-QoL: $-0,61$) y buena validez discriminativa por edad, sexo y gravedad de la enfermedad ($p < 0,05$).

Conclusiones: El HAE-AS es una medida breve, válida, confiable y psicométricamente sólida de la actividad de la enfermedad para C1-INH-HAE, que puede ser útil para estudios de investigación.

Palabras clave: C1-INH-HAE, Actividad clínica, Angioedema hereditario, Propiedades psicométricas, Análisis Rasch.

Introduction

Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is a genetic disease in which C1-inhibitor (C1-INH) function or levels are reduced [1,2]. It is considered a rare disease, difficult to diagnose and has an estimated prevalence of approximately 1 in 50,000 inhabitants [2] and a minimal prevalence which varies from 1.09 to 1.75 per 100,000 inhabitants [3-4].

C1-INH-HAE is characterized by unpredictable and recurrent episodes of non-erythematous, nonpruritic submucosal or subcutaneous oedema in different areas of the body (extremities, face, upper airways, genitals, and gastrointestinal tract), which last between two and five days if left untreated [1,5,6]. Angioedema attacks can produce significant morbidity and may require patients to be admitted to hospital [7]. Upper airway oedema can lead to airway compromise and fatal asphyxiation [8]. The impact of C1-INH-HAE on patient health-related quality of life (HRQoL) has been documented [9,10,11].

C1-INH-HAE disease severity has been recently defined as the “overall disease experience of the patient and includes the previous problems that the disease has imposed on the patient since its onset, the current burden of disease, and the long-term risks and prognosis, including the patient’s fears of potential problems to arise” [12]. It is important to emphasize that C1-INH-HAE disease severity can vary during a patient’s lifetime, but not always in a progressive way [1,6]. Several instruments have been proposed for measuring C1-INH-HAE disease severity [12], yet not one has been validated. Comprehensive psychometric studies have not been developed to describe their measurement properties. In addition, C1-INH-HAE disease activity is considered to be “the sum of current problems (over a specified period of time) that a patient has experienced with his or her disease” [12]. C1-INH-HAE disease activity often fluctuates throughout a patient’s life, mainly due to different levels of exposure to eliciting triggers and in response to treatment [13,14]. Both C1-INH-HAE disease activity and severity may differ among family members, patients with the same mutation in *C1NH* gene and, as previously mentioned, may change in individual patients during their lifetime [1,12]. There is currently no specific, validated instrument to measure C1-INH-HAE disease activity. However, the

Angioedema Activity Score (AAS), which was developed as a symptom specific Patient Reported Outcome (PRO), has been used in a variety of angioedema cases, including C1-INH-HAE [15].

C1-INH-HAE disease activity has been proposed as an important parameter on which to decide long-term prophylaxis indication [16]. A specific disease activity outcome, validated for its application in C1-INH-HAE, could be useful for designing studies on this pathology. This study aims to develop a disease activity scale for C1-INH-HAE, the Hereditary Angioedema Activity Score (HAE-AS), with sound psychometric properties evaluated through psychometric analysis following the Rasch model and the Classical Test Theory.

Methods

Patients and Measures

A prospective multicentre cohort study of 290 adult patients was performed in 11 countries: Spain (n=44), Hungary (n=38), Austria (n=18), Germany (n=42), Argentina (n=16), Brazil (n=34), Canada (n=21), Denmark (n=27), Israel (n=9), Poland (n=22) and Romania (n=19).

A convenience sample was selected with heterogeneity regarding gender, age, age at onset of clinical symptoms, level of studies, geographical origin and severity of the disease. Patients were selected by their HAE physicians to complete the questionnaires. All the participating patients signed an informed consent form. The inclusion criteria were patients aged 18 years or older with a confirmed laboratory diagnosis of C1-INH-HAE (type I or type II). The exclusion criteria were cognitive impairment that prevented understanding the questions and lack of fluency in the target language. Ethical approval for the study was provided by the Research Ethics Committee of Hospital Universitario La Paz (approval number PI-281) and local ethics committees as required. An *ad hoc* demographic and clinical self-administered questionnaire about the characteristics of disease (CQ-HAE) was completed by patients during hospital visits or at home. CQ-HAE was culturally adapted a priori to a chosen common language (American

English) using the standard method for linguistic validation. The resultant CQ-HAE in American English was subsequently adapted following the same forward-backward methodology for each of the target languages spoken in participant countries [17].

Patients also completed two health-related quality of life (HRQoL) scales: a generic one, the Short Form 36-item Health Survey (SF36v2), and a C1-INH-HAE specific one, the Hereditary Angioedema Quality of Life (HAE-QoL). Validated versions of the SF-36v2 and the HAE-QoL in every participating country language version were used.

The SF-36v2 is a generic patient-reported measure of health status [18]. It yields a health-profile measure that has been extensively used in clinical and population studies. The SF-36v2 is summarized into two components, physical and mental summary. Raw data from SF-36v2 were used, with no missing data imputation. The HAE-QoL is a specific measure of QoL in patients with C1-INH-HAE [17,19]. It contains 25 items on seven dimensions (total score range: 25 - 135). On both HRQoL scales, higher values indicate higher QoL.

A descriptive, qualitative *ad hoc* score on disease severity in the last six months was used [17]. The four categories were: 1) asymptomatic (no angioedema episodes, no long term prophylactic treatment); 2) mild (no life-threatening angioedema episodes, no long term prophylactic treatment and ≤ 3 episodes in the last 6 months); 3) moderate (no life-threatening angioedema episodes and ≤ 6 episodes in the last 6 months with long term prophylactic treatment [excluding maintenance treatment with plasma derived human C1-inhibitor concentrate, pdhC1INH] or 4-12 episodes in the last 6 months without long term prophylactic treatment); and 4) severe (at least one life-threatening angioedema episode and/or long term prophylactic treatment with pdhC1INH and/or > 6 episodes in the last 6 months despite long term prophylactic treatment and/or >12 episodes in the last 6 months without long term prophylactic treatment).

The HAE-AS was initially designed using a set of 14 clinical items from the CQ-HAE clinical questionnaire: number of attacks by location; treated attacks; emergency room visits; psychological/psychiatric treatment; missed school/work days in the last 6 months; general health; and impairment in everyday work/activities due to pain. These clinical items were

chosen based on a literature review, patient interviews, and discussion with physicians who have extensive experience in the management of C1-INH-HAE. The time frame was 6 months for all but two items (“11-general health” and “12-impairment on everyday work and activities due to pain”), which were limited to the last month. The 6-month time interval is similarly used in other studies on HRQoL in hereditary angioedema [17] and as a follow-up interval in longitudinal studies [1,14].

Data analysis

Data management was centralized at Hospital Universitario La Paz (Madrid, Spain). Data entry was performed twice using a program designed to detect inconsistencies in order to guarantee accuracy. Three researchers evaluated discrepancies.

Rasch model was analysed using the RUMM2030 software [20]. The following properties were iteratively examined in this analysis: fit to the Rasch model; categories response ordering (ordered thresholds); reliability; local independence of items; unidimensionality; and differential item functioning (DIF) by gender, age (split by median, 40 years), family C1-INH-HAE history and type. Rasch analysis for polytomous items requires a sample size of 250 or higher to get accurate estimates [21]. Detailed explanation of Rasch data analysis may be found in Supplemental material.

After obtaining the interval linear measure through Rasch analysis, further analyses were performed using SPSS software: acceptability (scores distribution), known-groups validity and convergent validity of the linear scale with related measures. The known-groups validity was evaluated with independent t-tests by gender and age at onset of clinical symptoms, with significantly higher scores expected for women and patients with early onset of clinical symptoms [22]. Convergent validity was assessed with Pearson correlations, hypothesising moderate ($r=0.30-0.59$) to high correlations (>0.59) with the two components of SF-36 and HAE-QoL [23]. In addition, an analysis of variance (ANOVA) of the linear measure by severity C1-INH-HAE score was performed. The standard error of measurement (SEM), calculated as

SD $\sqrt{(1-r)}$, where SD=standard deviation and r=reliability, was taken as a precision indicator [24]. Values equal to or less than half of the SD were considered as satisfactory.

Lastly, a receiver operating characteristic (ROC) curve was developed to establish a cut-off for classifying severe disease of the HAE-AS linear measure. The severity HAE score was used as a gold standard (asymptomatic/mild/moderate vs. severe). The optimal cut-off was assessed using the Youden index (highest sum of sensitivity and specificity) [25].

Results

The sample presented a mean age of 41.5 (standard deviation SD=14.7; range: 18-84) years, and 69.0% were females. The majority of patients had a family C1-INH-HAE history (69.7%) and a diagnosis of C1-INH-HAE type I (80.0%). The SF-36 physical and mental components showed a mean (SD) of 49.7 (8.8) and 46.2 (10.4), respectively. The mean HAE-QoL was 95.5 (SD=25.5). 38.6% of the patients presented a severe disease in accordance with severity scores. Information about the initial HAE-AS items is shown in supplemental Table S1.

Results of Rasch analysis are presented in Supplemental material, Tables S2 and S3 and Figure S1. In sum, the final analysis with 12 items provided a good fit to the Rasch model, with good reliability (PSI =0.748, absence of local dependency, unidimensionality, and no relevant DIF. The final HAE-AS questionnaire is provided in Table 1.

Table 2 displays the transformation of the ordinal ratings into an interval linear measure of the HAE-AS scale. The linear measure in a 0-30 scale showed a mean (SD) of 10.66 (3.92) and a normal distribution, with a skewness and kurtosis coefficient of -0.469 and -0.230, respectively. The SEM was 1.984.

The linear measure of the HAE-AS presented higher scores in women (mean difference=-1.597; p-value=0.001) and in patients with early onset of clinical symptoms (mean difference=1.182; p-value=0.009). The linear measure showed a negative, moderate correlation with physical and mental components of SF-36 ($r = -0.330$ and $r = -0.555$, respectively, $p < 0.001$) and a high

correlation with HAE-QoL ($r = -0.641$). A higher score of linear measure was associated to a greater severity C1-INH-HAE score (linear trend $F=182.938$, $p < 0.001$, Figure 1).

The ROC curve presented a large area under the curve (0.859; CI 95% = 0.813-0.906). According to the Youden index, a value greater than 12 on the linear scale was considered as the best cut-off for severe C1-INH-HAE: sensitivity=73.2%, specificity= 88.3%; predictive positive and negative values=81.2% and 82.7%, respectively.

Discussion

HAE-AS provides a linear measure that assesses the disease activity of C1-INH-HAE, which was specifically developed for C1-INH-HAE. It was found to have satisfactory reliability and construct validity. Therefore, this scale might be useful for analysing the determinants of C1-INH-HAE severity in future studies.

The scale's reliability is satisfactory [26]. Furthermore, items were locally independent and formed a unique dimension indicating that the HAE-AS is measuring only one construct, and supports items being taken together and assigned a single score. Adequate fit was achieved by removing two of the 14 items included in the initial questionnaire. The item "treatment maintenance in the last 6 months" appeared to be measuring a different construct, whereas "attack frequency in the last 6 months" was identified as a redundant item (fit residual=-4.778), possibly due to the fact that this item is the sum of the items regarding attacks by location.

Seven of the 12 items refer to number of angioedema attacks in the last 6 months. The number of attacks has been previously used as an indicator of disease severity/activity in clinical trials [27-30], case series [22,30] and in some non-validated disease severity or disease activity clinical scores [1,17,31]. Moreover, number of angioedema attacks has been found to be a driven factor of HRQoL in C1-INH-HAE [11].

Rasch analysis also provides an item hierarchy (Figure S1), showing that facial attacks, upper airway attacks and attacks in "other locations" represent the highest activity, whereas peripheral

attacks and a good general health represent the lowest clinical activity. Laryngeal or upper airway attacks had been previously described by patients as the most severe type of attacks [32] and had been considered as indicative of more severe disease in some disease severity scales [33]. Two items expressing the impact of the disease on the patient's lives (item 10: days not attending school/work due to C1-INH-HAE in the last 6 months; and item 12: impairment on everyday work and activities due to pain in the last month) are located in the middle of the activity score. In other words, these items are endorsed even by patients with only mild to moderate disease severity. The disruption caused by the disease in everyday life has been described before [13,32,34,35]. In summary, the item hierarchy reflects the scale's content validity.

The HAE-AS measure was free from bias associated with several group characteristics: gender, age, family history and C1-INH-HAE type. However, small sample sizes prevented DIF analysis by country, and further studies are called for. The HAE-AS linear measure presented a normal distribution, thereby allowing for the use of parametric statistical analysis. The scale also presented a good discriminative ability by gender and age at onset of symptoms, which are not due to item bias. As expected, women and patients with early onset of symptoms, which had been linked to higher disease activity, presented higher HAE-AS scores [5,31,36,37].

Insofar as convergent validity is concerned, there was a significant and moderate-to-high relationship between the HAE-AS scale and HRQoL measures. As hypothesized, the higher the C1-INH-HAE activity score is on the HAE-AS scale, the greater is the impact the condition has on a patient's life and the lower is HRQoL. We observed a higher association of the HAE-AS with mental SF-36v2 component than with physical component. Congruently, a previous study showed that, following treatment, there were greater changes in the SF-36 mental component than in the physical one [9]. This might be due to the fact that, as demonstrated in both longitudinal and cross-sectional studies of C1-INH-HAE patients, the SF-36v2 mental component is more sensitive to changes than the physical component.

The HAE-AS showed a stronger association with the HAE-QoL than with the SF-36v2, which is probably because both HAE-AS and HAE-QoL were specifically designed for C1-INH-HAE, and thus both capture important disease features that are not covered by a generic QoL measure such as the SF-36v2. Indeed, the SF-36v2 failed to capture gender or age differences in a study on C1-INH-HAE and QoL [10]. Therefore, the use of HAE-AS and HAE-QoL is recommended for studying C1-INH-HAE.

A ROC curve was used to determine a cut-off for assessing responses that indicated a high degree of severity of C1-INH-HAE disease. This cut-off showed acceptable sensitivity, specificity and predictive values, and could be extremely useful for research or clinical practice.

HAE-AS is the first validated scale developed specifically for measuring C1-INH-HAE activity. The Angioedema Activity Score (AAS) [15] a validated scale already in existence for measuring angioedema activity, could potentially be used to measure prospectively disease activity in any kind of angioedema. Although the period it refers to may be prolonged as needed, it was actually designed and validated to measure disease activity only for one month. A 6-month evaluation period, as that of HAE-AS, could be more suitable for C1-INH-HAE, in which the general frequency of follow-up visits is once every 6-12 months and the frequency of angioedema attacks varies greatly from month to month [1,6,7,13,14]. Another drawback is that patients are required to complete AAS on a daily basis, which creates a heavy burden for patients resulting in poor patient adherence. Finally, there is a lack of knowledge about the psychometric properties of the AAS according to the Rasch model and classic test theory in a large, international sample [15].

Nevertheless, this study presents several limitations. First, as C1-INH-HAE is a rare genetic disease, it was not possible to get a random sample. However, the multicentre nature of the study and a relatively large sample size broadened the applicability of our findings. Second, further studies are needed to assess other psychometric features such as test-retest reliability, sensitivity to change or concurrent validity with the AAS score. However, its good reliability, good precision and proven ability to discriminate between groups, including severity, indicate

that the scale's sensitivity to change might also be appropriate for making comparisons over time or for types of treatment. Third, patients might not accurately remember the disease activity in the last six months. Further studies should compare patient's reports with clinical records. It would also be interesting to study the HAE-AS in patients with non-hereditary angioedema. Thus, HAE-AS presents several strengths and some weaknesses and leaves room for improvement like almost all outcome measures reported by patients, and the HAE-AS is no exception.

In conclusion, we present the first validated scale developed specifically for measuring C1-INH-HAE activity. It is a short psychometrically sound questionnaire that provides a linear measure of disease activity, with satisfactory reliability and good content and construct validity, as well as discriminative validity. We recommend the use of HAE-AS in future studies on C1-INH-HAE.

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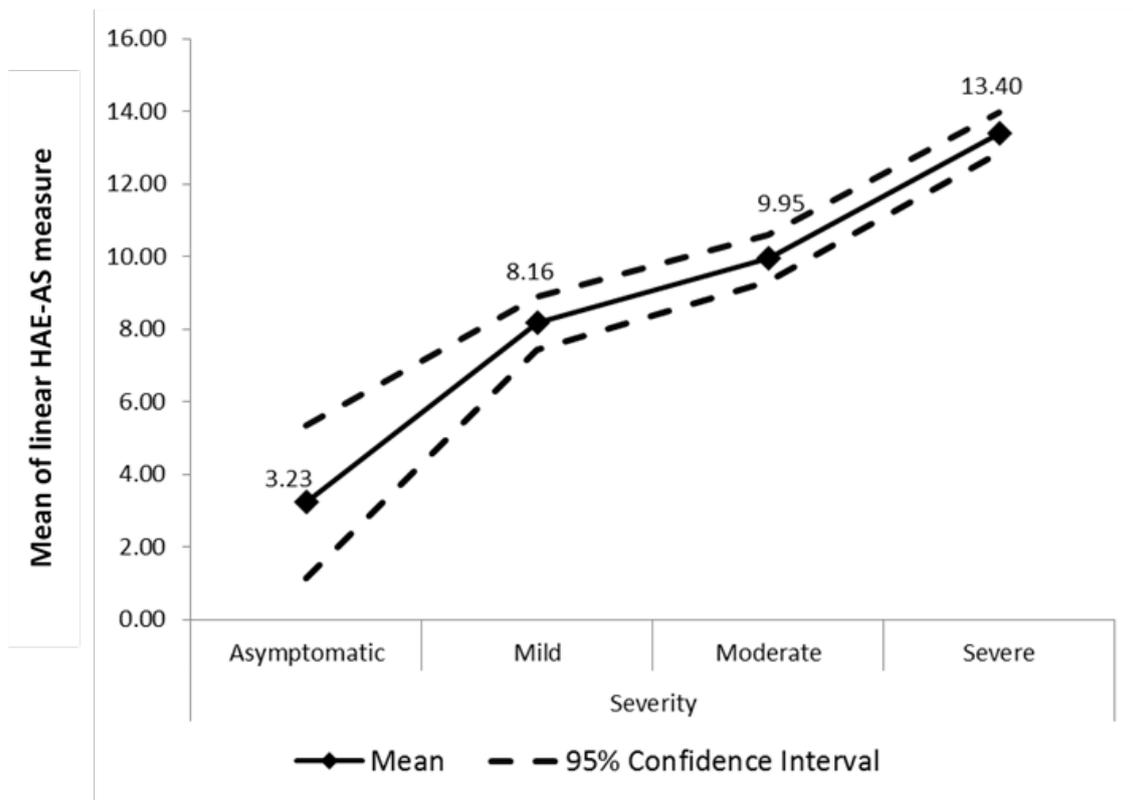
Table 1. Disease Activity Scale for Hereditary Angioedema (Hereditary Angioedema Activity Score: HAE-AS)

1. Peripheral attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 5 attacks
 - 2.- 6 to 20 attacks
 - 3.- >20 attacks
2. Abdominal attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 5 attacks
 - 2.- 6 to 20 attacks
 - 3.- >20 attacks
3. Facial attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 20 attacks
 - 2.- >20 attacks
4. Genital attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 5 attacks
 - 2.- 6 to 20 attacks
 - 3.- >20 attacks
5. Upper airway attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 20 attacks
 - 2.- >20 attacks
6. Other location attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 20 attacks
 - 2.- >20 attacks
7. Number of treated attacks in the last 6 months
 - 0.- No attacks
 - 1.- 1 to 20 attacks
 - 2.- >20 attacks
8. Emergency visits in the last 6 months
 - 0.- No
 - 1.- 1 to 10 visits
 - 2.- >10 visits
9. Psychological and/or psychiatric treatment due to C1-INH-HAE in the last 6 months
 - 0.- No
 - 1.- Yes
10. Days not attending school/work due to C1-INH-HAE in the last 6 months
 - 0.- 0 day
 - 1.- 1 to 5 days
 - 2.- 6 to 15 days
 - 3.- >15 days
11. General health in the last month
 - 0.- Excellent
 - 1.- Good
 - 2.- Regular
 - 3.- Poor
12. Impairment on everyday work and activities due to pain in the last month
 - 0.- Not at all
 - 1.- A little bit
 - 2.- Quite a bit
 - 3.- Extremely

Table 2. Conversion table of ordinal scores into an interval linear measure (cut-off for severe activity: 12-13).

Raw score	Linear measure		Raw score	Linear measure	
	Logit scale	0-30 scale		Logit scale	0-30 scale
0	-5.504	0.000	15	-0.081	16.148
1	-4.214	3.841	16	0.097	16.678
2	-3.388	6.301	17	0.277	17.214
3	-2.86	7.873	18	0.462	17.765
4	-2.466	9.046	19	0.653	18.333
5	-2.145	10.002	20	0.854	18.932
6	-1.869	10.824	21	1.067	19.566
7	-1.623	11.556	22	1.298	20.254
8	-1.399	12.223	23	1.551	21.007
9	-1.189	12.849	24	1.834	21.850
10	-0.991	13.438	25	2.158	22.815
11	-0.801	14.004	26	2.539	23.949
12	-0.616	14.555	27	3.013	25.361
13	-0.436	15.091	28	3.667	27.308
14	-0.258	15.621	29-30	4.571	30.000

Note: This table is not valid for cases with missing data. To use this table, sum the item scores according to the Table 1. For instance, a sum score of 9 corresponds to -1.189 logits or to a score of 12.8 in a 0-30 scale (mild disease). Dotted line: cut-off score (12-13).

Figure legends:Figure 1. HAE-AS by severity (significant linear trend, $p < 0.001$).Figure 1. HAE-AS by severity (significant linear trend, $p < 0.001$).