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# Severity classes in adults with hypermobile Ehlers–Danlos syndrome/hypermobility spectrum disorders: a pilot study of 105 Italian patients

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## Abstract

**Objectives.** This study is aimed at identifying discrete severity classes among adults with hypermobile Ehlers–Danlos syndrome (hEDS)/hypermobility spectrum disorders (HSD).

**Methods.** Subjects were selected according to the old and new nomenclatures and all completed a set of questionnaires exploring pain, fatigue, dysautonomic symptoms, coordination and attention/concentration deficits and quality of life in general. Data were investigated by hierarchical clustering on principal components. Cluster comparisons were then performed by using the two-sample unpaired *t* test and the standardized mean difference was reported as a measure of effect size. Conditional classification tree analysis and multivariable logistic regression were carried out in order to identify the profiles that were at higher risk to belong to the more severe cluster. Weighted linear combination was used to identify a numerical score measuring this risk.

**Results.** A total of 105 patients were selected and distributed in two distinct severity groups. These groups were statistically separated on the basis of 47 of 59 items/characteristics. One group featured the worse values of most questionnaire items (complex/severe cluster) and the other was dominated by the better values (simplex/milder cluster). Only three items were able to stratify patients according to their risk to belong to the complex cluster. A severity score was then constructed on these three items.

**Conclusion.** Adults with hEDS/HSD can be separated in two severity classes, which do not mirror either the old or new criteria for hEDS. The identified severity score could allow a bi-dimensional approach to adults with hEDS/HSD for optimal management planning.

**Key words:** classification, Ehlers–Danlos syndrome, joint hypermobility, scoring, severity class.

**Rheumatology key messages**

- Adults with hypermobile Ehlers–Danlos syndrome/hypermobility spectrum disorders may be separated into two distinct severity classes.
- Severity class distinction (complex *vs* simplex) may reflect different management programmes in hypermobile Ehlers–Danlos syndrome/hypermobility spectrum disorders.
- A severity score for hypermobile Ehlers–Danlos syndrome/hypermobility spectrum disorders is proposed for future applications in clinical scenarios.

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CLINICAL SCIENCE

## Introduction

Ehlers-Danlos syndrome (EDS) is a group of clinically variable and genetically heterogeneous disorders mainly featuring joint hypermobility (JH), related musculoskeletal manifestations and a variety of extramusculoskeletal manifestations mirroring primary involvement of non-ossified tissues. The 2017 international classification identifies 13 EDS subtypes with causative variants in 19 different genes [1]. More recently, biallelic mutations in *AEBP1* have been identified as being responsible for an additional phenotype resembling classical EDS [2]. To date, the underlying genetic defect is demonstrable in all EDS variants except hypermobile EDS (hEDS), which lacks a confirmatory laboratory test. Hence the diagnosis of hEDS remains based on physical examination, personal history and formal exclusion of other, partially overlapping disorders [3].

hEDS is a clinical phenomenon with extensions in the routine activities of many clinical disciplines, including rheumatology and physical medicine. This happens because the medical consequences of hEDS are mainly related to JH and JH-related co-morbidities, such as fatigue, functional gastrointestinal disorders, cardiovascular dysautonomia and psychological distress [4]. Presumably the same pattern of clinical consequences characterizes the more heterogeneous hypermobility spectrum disorders (HSD). The latter refer to patients presenting symptomatic JH but not respecting the diagnostic criteria of hEDS. For this reason, a continuous spectrum of phenotypes is proposed ranging from asymptomatic, non-syndromic JH to hEDS and passing through HSD [4]. The assumption of a clinical continuity between hEDS and HSD emerges from the early observation of a nearly complete overlap between hEDS and joint hypermobility syndrome (JHS), an obsolete term previously used to define aspecific phenotypes of symptomatic/clinically relevant JH [5]. Accordingly, the recent literature exploring the clinical ramifications of hEDS and HSD groups together these conditions in a single phenotype termed hEDS/HSD [6–9].

The introduction of more selective diagnostic criteria for hEDS and recognition of a continuous spectrum of JH-related phenotypes with an unknown molecular basis are prompting the scientific community to explore the clinical and biological boundaries of hEDS/HSD. One of the most common misconceptions around hEDS/HSD is that the new hEDS criteria produce a more severe diagnosis compared with HSD. In contrast, the new hEDS criteria were conceived to simplistically recognize patients with more convincing structural systemic involvement and/or Mendelian transmission within a wider spectrum of JH-related phenotypes [10]. The 2017 classification also placed an emphasis on the various JH-related co-morbidities as the most likely determinants of quality of life (QoL) in hEDS/HSD [4]. Accordingly, the 2017 classification of EDS and related disorders admits the coexistence of relatively healthy individuals respecting the hEDS criteria and severely affected individuals with a diagnosis of HSD.

Identification of severity classes within the hEDS/HSD heterogeneity is one of the greatest challenges of this research field. An exploratory study on 89 JHS children identified five subphenotypes, namely joint affected, athletic, systemic, soft tissue affected and high BMI [11]. These categories were recognized by the prevalence of selected items, such as BMI by age and number of painful joints. Some correlations with selected QoL determinants also emerged, as patients with the high BMI subphenotype experienced more pain while those with the soft tissue affected subphenotype reported more fatigue [11]. The same group also traced the trajectories of functional impairment of a similar cohort of 81 patients in a subsequent 3 year longitudinal study [12]. In this work, they found that JHS children with a higher incidence of multisystemic involvement and poor postural control more commonly present a deteriorating trajectory with increased functional impairment [12]. No similar study has been carried out in adults with hEDS/HSD and accumulated data have not yet been explored with the aim to subclassify patients in a clinical setting.

Here we interrogated a set of multidimensional data on QoL from 105 adults with hEDS/HSD in order to separate them by severity classes and to identify reliable markers predicting patients' inclusion in these classes. We also tried to configure an algorithm to translate this patient subclassification into clinical practice and to aid future studies.

## Methods

This work was conceived as the final part of a large, two-branch study aimed at exploring the non-canonical manifestations of JH and hEDS/HSD (or JHS/hEDS, as previously termed according to the past Villefranche nosology and Brighton criteria [5, 13]) in children and adults. The first branch of the study focussed on the neurodevelopmental profiling of children with various forms of syndromic JH compared with children primarily assessed for developmental coordination disorder [8]. The second branch assessed the clinical impact of coordination troubles in adults with hEDS/HSD [6]. Rough data obtained from the latter were further explored in search of multidimensional connections and possibly discrete subphenotypes, stratified by severity of QoL deterioration. All enrolled individuals gave their consent to the study, which is in accordance with the revised version of the Helsinki Declaration. This study was approved by the local ethics committee (protocol no. 250/CE Lazio 1).

### Patient selection and assessment

Patients were enrolled from February 2016 to February 2017 through a collaboration between the two major Italian reference centres for the diagnosis of EDS and related disorders (i.e. Unit of Clinical Genetics at the San Camillo-Forlanini Hospital in Rome and Center for Diagnosis and Management of EDS and Hereditary Connective Tissue Disorders at the Spedali Civili University Hospital in Brescia, Italy). This study was carried out before the publication of the revised classification of EDS and related disorders, in which an entirely novel set of stricter diagnostic criteria of hEDS was included, as

well as the introduction of HSD and the spectrum concept [1, 4]. Therefore all patients were originally diagnosed as JHS, hEDS or JHS/hEDS according to the Villefranche nosology for hEDS [13] and the Brighton criteria for JHS [5]. After publication of the 2017 international classification of EDS and related disorders, the clinical files of all enrolled patients were reviewed and the original diagnoses (i.e. JHS, hEDS and JHS/hEDS) were changed to hEDS (2017 hEDS criteria met) or HSD (2017 hEDS criteria not met). All enrolled patients underwent a systematic evaluation as previously described [14]. In case of a suspected overlap with other acquired or hereditary connective tissue disorders, the differential diagnosis was extended to include autoimmune rheumatologic screening, heart ultrasound, bone densitometry and other selected supplementary evaluations. When necessary, other sets of criteria, such as the revised Ghent criteria for Marfan syndrome [15], were applied, as well as the use of appropriate molecular studies. No patients had evidence of cognitive impairment.

The range of motion of selected joints or a group of joints was assessed by the ability of the patient to perform specific movements and/or passively with an orthopaedic goniometer. Attention was focussed on joints included in the Beighton score (BS), which is, at the moment, considered the best tool for the assessment of generalized JH [16] (supplementary material, section Methods, available at *Rheumatology* online).

Symptomatology and QoL were screened by using a set of validated questionnaires selected to explore a wide array of multisystemic involvement. Although all tools are conceived as self-administered questionnaires, all patients were assisted by a physician, who helped patients in case of a lack of understanding of items/sentences. These tools included the brief pain inventory (BPI), composite autonomic symptom score (COMPASS-31), functional difficulties questionnaire (FDQ-9), 20-item multidimensional fatigue inventory (MFI-20), part A of the attention deficit hyperactivity disorder self-report version 1.1 (ASRS-V1.1) and the 36-item Short Form (SF-36) (supplementary material, section Methods, available at *Rheumatology* online).

### Statistical analysis

The patients' baseline demographic and clinical characteristics were reported as frequency and percentage or as mean and S.D. for categorical and continuous variables, respectively. Hierarchical clustering on principal components (HCPC) analysis was performed to divide patients into two heterogeneous subsamples with different disease severity according to the scores of the 48 items (only continuous variables) from the six different administered questionnaires reported above.

The HCPC combines three standard methods used in multivariate data analyses: principal component analysis (PCA), hierarchical clustering and partitioning clustering (in particular, the *k*-means method). Given the large number of continuous variables (i.e. 48 items), our strategy was first based on the PCA as an exploratory method to reduce the dimensions into few continuous variables (i.e. factors) containing the most important information. Obtained PCA outputs were then scrutinized with the other two HCPC methods. Following this procedure, we were able to obtain more stable clusters, since PCA can be considered a denoising step.

To minimize subjectivity in choosing a cluster solution, we serially performed hierarchical clustering followed by *k*-means portion clustering upon the regression-based factors directly derived from PCA as follows. One factor represented one principal component and was obtained by linearly combining the variance shared by all measurable variables belonging to that principal component. Hierarchical clustering was then applied to these factor scores to distinguish patients' clusters without pre-specifying a fixed number of clusters. The number of clusters was then imposed upon the *k*-means method, which is a non-hierarchical learning algorithm that assigns each case to one cluster to minimize within-cluster dispersion and to maximize between-clusters variability [17]. Cluster comparisons were then performed using the two-sample unpaired *t* test and the standardized mean difference was reported as a measure of effect size. Given the sharp distribution of the variables' values in the two clusters (see Results section), they were arbitrarily named simplex (i.e. clustering of milder values) and complex (i.e. clustering of more severe values).

Considering this classification, we performed a conditional tree analysis to categorize patients by using all items from the six different administered questionnaires as potential splitting variables [18, 19]. This tree algorithm allowed the identification of subgroups of patients at different risk to be complex (= severe) according to the items' values observed when the six questionnaires are administrated. The probability of belonging to the complex cluster was also modelled with multivariable logistic regression with a backward variable selection and by including only those items with a standardized mean difference (SMD)$>$1.6. A numerical score measuring the risk of belonging to the complex cluster was built as a weighted linear combination of the observed values of item results significantly and independently associated by using the logistic regression coefficients as weights. To measure the diagnostic performances of this severity score, we performed a receiver operating characteristics (ROC) curve analysis. The optimal cut-off was estimated by jointly maximizing sensitivity and specificity. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at the optimal cut-off were reported along their 95% CIs.

Two-sided *P*-values $<$0.05 were considered statistically significant. All statistical analyses were performed with SAS software release 9.4 (SAS Institute, Cary, NC, USA) and R (version 3.4.4, R Project for Statistical Computing, Vienna, Austria).

## Results

A total of 105 patients were enrolled in this study. The mean age was 36.9 years (S.D. 12.1), with 9 males (8.6%)

and 96 females (91.4%). Sixty-nine individuals met the Villefranche criteria (72.4%) and 36 met the Brighton criteria (27.6%). By retrospectively applying the 2017 classification on previously gathered data, 58 (55.2%) met the 2017 hEDS, while the others were classified as HSD (44.8%). The mean BS value was 4.5 (S.D. 2.0); the full distribution of the BS values in this cohort was previously reported in Morlino *et al.* [6]. PCA analysis was performed on 48 continuous items (after scaling data to unit variance) from the six administrated questionnaires. Three main components accounting for 50% of the total amount of variability were identified. The full HCPC strategy identified two sharply separated clusters of patients (Fig. 1). Sixty-three (60.0%) patients were classified as complex (i.e. severe) and 42 (40.0%) were classified as simplex (i.e. milder). These two clusters did not differ in terms of age and clinical characteristics (BS, prevalence of Villefranche criteria and 2017 criteria), while they showed statistically and clinically significant differences in almost all items from the six questionnaires. There was also an excess of males in the simplex cluster (Table 1).

We then performed a conditional classification tree analysis using all items from the six different questionnaires as potential splitting variables, in order to identify the profiles that were at higher risk of belonging to the complex (severe) cluster. The classification tree analysis was carried out by selecting three of the four items that showed a SMD >1.6. Accordingly, the COMPASS-31 total score, BPI current intensity (of pain) and SF-36 physical fatigue were considered the more discriminating markers to predict inclusion in the complex (severe) cluster (Fig. 2).

With the aim of providing a parsimonious, easy-to-use and clinically useful tool to identify complex patients, we performed a multivariable logistic regression with a backward variable selection and included only those items with an SMD >1.6. The regression coefficients were then used as weights to compute a numerical severity score measuring the risk of belonging to the severe class as follows:

Severity score = (0.39305 × COMPASS-31 total score) − (0.04429 × SF-36 physical health) + (0.71451 × BPI current intensity).

**FIG. 1** Hierarchical clustering of patients in two separate classes by principal components analysis

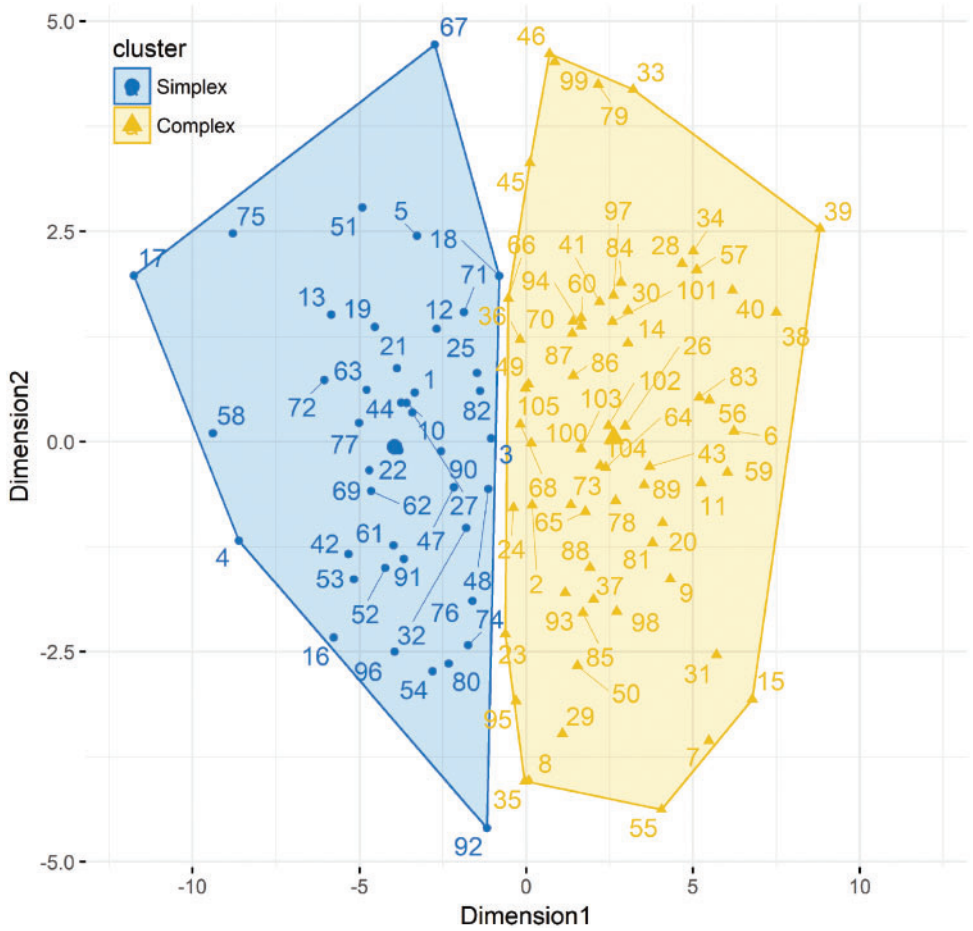
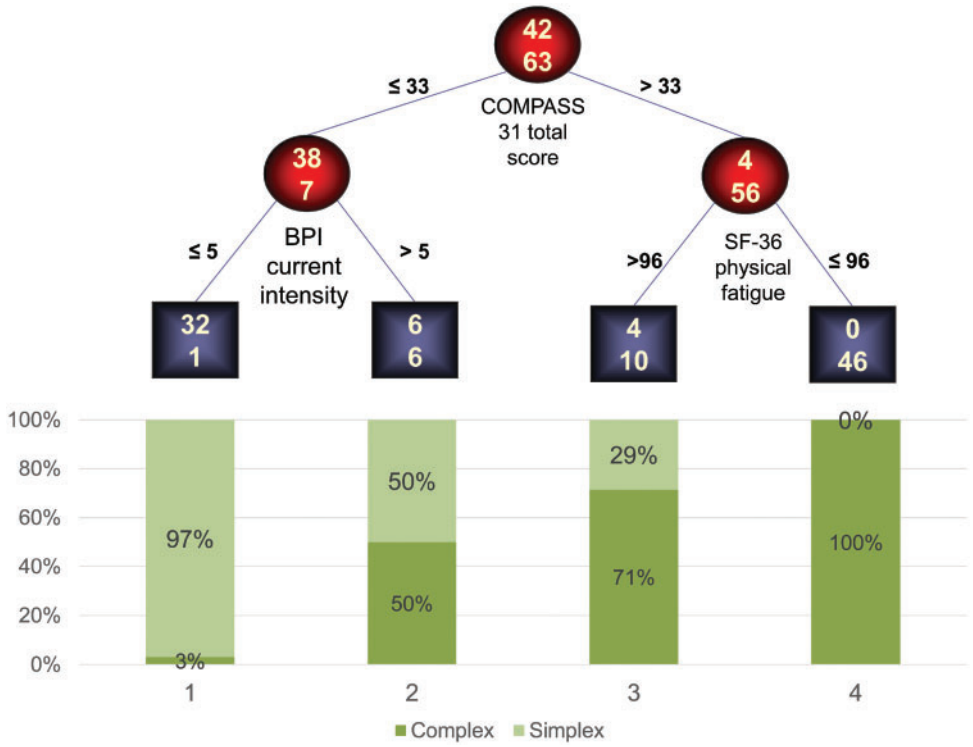


**Table 1** Distribution of patients' characteristics in the two identified clusters

| Characteristics | Simplex (milder) cluster | Complex (severe) cluster | *P*-value | SMD |
|---|---|---|---|---|
| Number of patients | 42 | 63 | | |
| Beighton score, mean (S.D.) | 4.95 (2.04) | 4.27 (1.95) | 0.088 | 0.342 |
| Villefranche criteria, *n* (%) | 29 (69.0) | 40 (63.5) | 0.706 | 0.118 |
| 2017 hEDS criteria, *n* (%) | 25 (59.5) | 33 (52.4) | 0.603 | 0.144 |
| Age, years, mean (S.D.) | 35.74 (12.71) | 37.65 (11.69) | 0.43 | 0.157 |
| Males/females, *n*/*n* (%/%) | 7/35 (16.7/83.3) | 2/61 (3.2/96.8) | **0.039** | 0.463 |
| ASRS-V1.1 positive, *n* (%) | 11 (26.2) | 44 (69.8) | <**0.001** | 0.971 |
| ASRS-V1.1, total score, mean (S.D.) | 2.81 (1.58) | 4.08 (1.22) | <**0.001** | 0.899 |
| BPI, bodily pain, mean (S.D.) | 5.76 (4.53) | 11.08 (5.84) | <**0.001** | 1.018 |
| BPI, current intensity, mean (S.D.) | 3.19 (2.30) | 6.57 (1.89) | <**0.001** | 1.607 |
| BPI, headache, *n* (%) | 9 (21.4) | 20 (31.7) | 0.349 | 0.235 |
| BPI, interference (general activities), mean (S.D.) | 3.55 (2.61) | 7.32 (1.90) | <**0.001** | 1.653 |
| BPI, interference (mood), mean (S.D.) | 3.43 (2.85) | 6.98 (2.17) | <**0.001** | 1.406 |
| BPI, interference (rowing), mean (S.D.) | 3.71 (2.80) | 7.08 (2.33) | <**0.001** | 1.307 |
| BPI, interference (sleeping), mean (S.D.) | 3.88 (2.89) | 7.62 (2.48) | <**0.001** | 1.387 |
| BPI, interference (social relations), mean (S.D.) | 2.50 (2.16) | 6.08 (2.77) | <**0.001** | 1.441 |
| BPI, interference (will of life), mean (S.D.) | 2.48 (2.34) | 6.40 (2.92) | <**0.001** | 1.481 |
| BPI, interference (working activities), mean (S.D.) | 4.29 (2.79) | 7.78 (1.84) | <**0.001** | 1.48 |
| BPI, joint pain, mean (S.D.) | 2.62 (2.51) | 5.71 (3.36) | <**0.001** | 1.045 |
| BPI, local drug use, *n* (%) | 0 ( 0.0) | 2 ( 3.2) | 0.662 | 0.256 |
| BPI, maximum intensity, mean (S.D.) | 5.02 (2.26) | 7.92 (1.59) | <**0.001** | 1.484 |
| BPI, mean intensity, mean (S.D.) | 3.79 (1.83) | 6.54 (1.63) | <**0.001** | 1.588 |
| BPI, minimum intensity, mean (S.D.) | 2.50 (1.53) | 4.60 (2.08) | <**0.001** | 1.152 |
| BPI, physical therapy use, *n* (%) | 9 (21.4) | 15 (23.8) | 0.962 | 0.057 |
| BPI, systemic drug use, *n* (%) | 21 (50.0) | 48 (76.2) | **0.01** | 0.564 |
| BPI, therapeutic efficacy, mean (S.D.) | 26.90 (30.96) | 29.52 (24.46) | 0.63 | 0.094 |
| BPI, question no. 1[a], *n* (%) | 25 (59.5) | 41 (65.1) | 0.711 | 0.115 |
| COMPASS-31, bladder functions, mean (S.D.) | 1.24 (1.36) | 3.29 (2.37) | <**0.001** | 1.062 |
| COMPASS-31, gastrointestinal functions, mean (S.D.) | 8.76 (3.73) | 14.68 (3.74) | <**0.001** | 1.584 |
| COMPASS-31, orthostatic intolerance, mean (S.D.) | 4.26 (2.02) | 6.75 (1.92) | <**0.001** | 1.26 |
| COMPASS-31, pupillomotor functions, mean (S.D.) | 8.24 (2.80) | 10.95 (2.39) | <**0.001** | 1.043 |
| COMPASS-31, secretomotor functions, mean (S.D.) | 2.55 (1.38) | 4.21 (1.52) | <**0.001** | 1.144 |
| COMPASS-31, total, mean (S.D.) | 26.76 (6.75) | 42.78 (8.02) | <**0.001** | 2.161 |
| COMPASS-31, vasomotor functions, mean (S.D.) | 1.67 (1.78) | 2.90 (2.00) | **0.002** | 0.655 |
| FDQ-9, item 1, mean (S.D.) | 2.14 (0.87) | 2.33 (1.00) | 0.317 | 0.203 |
| FDQ-9, item 2, mean (S.D.) | 2.40 (0.70) | 2.83 (0.93) | **0.014** | 0.513 |
| FDQ-9, item 3, mean (S.D.) | 2.52 (0.83) | 2.54 (0.91) | 0.928 | 0.018 |
| FDQ-9, item 4, mean (S.D.) | 2.64 (0.76) | 3.22 (0.63) | <**0.001** | 0.828 |
| FDQ-9, item 5, mean (S.D.) | 2.05 (0.91) | 2.41 (0.87) | **0.041** | 0.41 |
| FDQ-9, item 6, mean (S.D.) | 2.14 (0.61) | 2.81 (0.74) | <**0.001** | 0.987 |
| FDQ-9, item 7, mean (S.D.) | 2.07 (0.60) | 2.94 (0.76) | <**0.001** | 1.264 |
| FDQ-9, item 8, mean (S.D.) | 1.95 (0.79) | 2.68 (0.80) | <**0.001** | 0.916 |
| FDQ-9, item 9, mean (S.D.) | 2.29 (0.83) | 2.62 (0.81) | **0.044** | 0.405 |
| FDQ-9, total score, mean (S.D.) | 20.10 (3.63) | 24.32 (4.25) | <**0.001** | 1.067 |
| MFI-20, general fatigue, mean (S.D.) | 13.07 (3.08) | 14.94 (3.79) | **0.009** | 0.54 |
| MFI-20, mental fatigue, mean (S.D.) | 11.93 (2.51) | 12.71 (3.94) | 0.255 | 0.238 |
| MFI-20, physical fatigue, mean (S.D.) | 14.19 (2.44) | 15.38 (3.13) | **0.04** | 0.424 |
| MFI-20, reduction of activities, mean (S.D.) | 12.71 (2.48) | 14.06 (3.03) | **0.018** | 0.488 |
| MFI-20, reduction of motivations, mean (S.D.) | 12.10 (2.56) | 13.73 (2.46) | **0.001** | 0.651 |
| SF-36, emotional role limitations, mean (S.D.) | 59.33 (40.03) | 32.65 (38.94) | **0.001** | 0.676 |
| SF-36, general health, mean (S.D.) | 36.57 (17.74) | 18.11 (11.94) | <**0.001** | 1.221 |
| SF-36, general health + vitality, mean (S.D.) | 79.07 (31.30) | 40.97 (22.29) | <**0.001** | 1.402 |
| SF-36, mental health, mean (S.D.) | 63.14 (17.14) | 50.73 (20.93) | **0.002** | 0.649 |
| SF-36, physical activity, mean (S.D.) | 68.33 (16.74) | 38.33 (21.98) | <**0.001** | 1.536 |
| SF-36, physical health, mean (S.D.) | 146.93 (57.76) | 66.97 (39.81) | <**0.001** | 1.612 |
| SF-36, physical pain, mean (S.D.) | 44.67 (20.27) | 21.49 (13.52) | <**0.001** | 1.345 |
| SF-36, physical role limitations, mean (S.D.) | 33.93 (33.96) | 7.14 (15.83) | <**0.001** | 1.011 |
| SF-36, psycho-emotional health, mean (S.D.) | 181.48 (60.01) | 118.10 (65.51) | <**0.001** | 1.009 |
| SF-36, social activities, mean (S.D.) | 59.00 (21.40) | 34.71 (22.58) | <**0.001** | 1.104 |
| SF-36, vitality, mean (S.D.) | 42.50 (18.12) | 22.86 (15.21) | <**0.001** | 1.174 |

[a]'Have you had pain other than these everyday kinds of pain today?' Significant *P*-values are in bold.

FIG. 2 Identification of prognostic profiles at different risks of belonging to the complex/severe class by conditional classification tree analysis

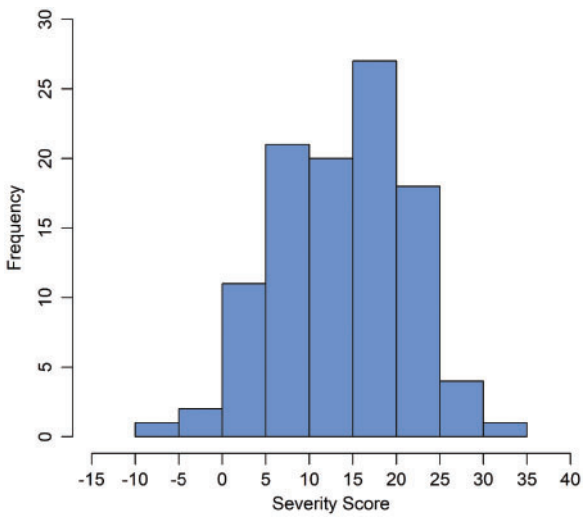



The tree-growing algorithm modelled the probability of belonging to the complex (severe) cluster by using all items from the six questionnaires as splitting variables. Splitting variable definitions are reported between branches, while the values of the corresponding binary categories sending patients to the left or right underlying tree class are reported on the branch. Circles indicate subgroups of patients. Squares indicate patient tree classes. Rectangles indicate percentage distributions of patients belonging to the complex and simplex severity classes within the same tree class. Numbers inside circles and squares represent the number of milder (top) and the number of more severe (bottom) patients, respectively.

The severity score distribution in our sample is shown in Fig. 3.

ROC curve analysis provided the diagnostic performances of the severity score. The analysis had an area under the ROC curve of 0.987 (95% CI 0.973, 1.000). At the optimal cut-off of 12.7, we observed a sensitivity of 0.94 (95% CI 0.85, 0.98), specificity of 0.95 (95% CI 0.84, 0.99), positive predictive value of 0.97 (95% CI 0.89, 1.00), negative predictive value of 0.91 (95% CI 0.78, 0.97) and an overall accuracy of 0.94 (95% CI 0.88, 0.98) (Fig. 4). Fig. 5 summarizes the distribution of our cohort according to the 2017 classification (hEDS *vs* HSD) and severity classes (complex cluster *vs* simplex cluster).

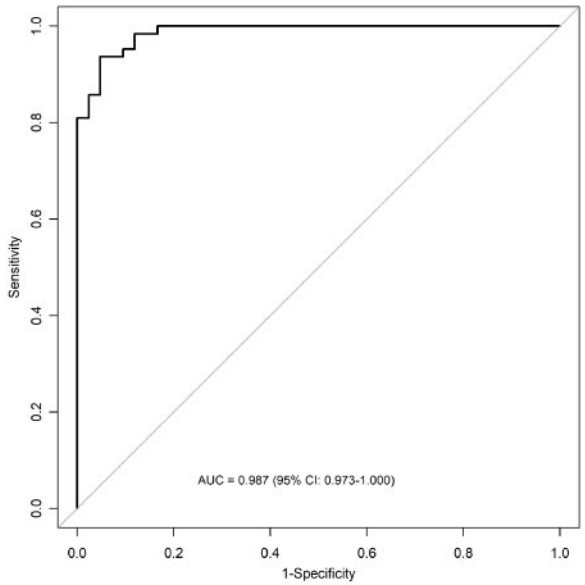
FIG. 3 Distribution of the severity score in our sample




## Discussion

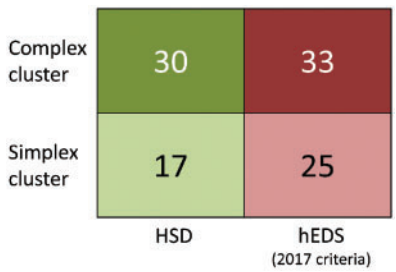
In this work we tried to identify discrete classes of severity within a group of 105 adults with hEDS/HSD. Disease severity was assessed with a set of validated questionnaires aimed at exploring QoL in general (SF-36), as well as other factors, in particular, coordination troubles (FDQ-9), attention and concentration difficulties (ASRS-V1.1), pain (BPI),

**Fig. 4** ROC curve analysis




AUC: area under the curve.

**Fig. 5** Bidimensional distribution of the cohort according to nosologic diagnosis and severity class




fatigue (MFI-20) and dysautonomic manifestations (COMPASS-31), potentially influencing QoL. The present work was generated as the natural prosecution of a previous study conceived to explore coordination troubles assessed with FDQ-9 in adults with hEDS/HSD [6]. We already demonstrated that a positive FDQ-9 score is associated with different features affecting QoL in adults with hEDS/HSD [6]. In the present study, we assumed that the 2017 hEDS criteria are useful to distinguish patients with a systemic connective tissue disease (in terms of structural anomalies) and/or families with Mendelian transmission of the disease within the spectrum, but they are probably inadequate to separate patients by severity, and hence medical needs. As admitted by most researchers, the presence of musculoskeletal complaints (the unique symptomatic item included in the 2017 criteria, i.e. criterion 2C) and the coexistence of JH-related co-morbidities are probably the leading biological factors affecting QoL in adults with hEDS/HSD [3, 4]. Fatigue, cardiovascular dysautonomia and functional gastrointestinal disorders are among the leading features that, although not included in the diagnostic criteria, affect the health status of adults with hEDS/HSD [20–22]. More recently, a set of neurodevelopmental features, including dyspraxia, learning disorder and attention deficit hyperactivity disorder, were demonstrated to relevantly contribute to QoL in both children and adults with symptomatic JH and hEDS/HSD [6, 8]. For all these reasons we considered coordination troubles, attention/concentration difficulties, pain, fatigue and dysautonomia the major domains for stratifying adults with hEDS/HSD.

Heterogeneity in terms of disease expression was put forward years ago by our group, when we approached the natural history of what was previously called JHS/hEDS [23, 24]. At that time, three possible different phases of disease progression were proposed: hypermobility (first phase), pain (second phase) and stiffness (third phase). Therefore patients could have been attributed to either phase by age, evidence/degree of JH, reported symptoms and limitations of daily living. Thus a hypothesis emerged from the unstructured experience of a single centre in which patients were followed under a yearly follow-up schedule. Although the first phase is observed in or self-described by most patients, not all individuals seem to have a disease course invariably progressing to the pain and stiffness phases. The predictable heterogeneity of JHS/hEDS was defined metatropism, a term that refers to 'the age-dependent evolution of the phenotype. . .which may present very differently in distinct life stages' [24]. In line with the concept that the hypermobility phase is typically observed among children and adolescents, other groups tried to search for elements that can predict disease progression once the diagnosis of hEDS/HSD is established in a paediatric patient [11, 12]. A more systematic approach to paediatric patients allowed the identification of different phenotypic profiles and distinguishable trajectories of distinct patterns of QoL deterioration in children with JHS/hEDS [11, 12]. Theoretically these predictions, if translated into clinically reliable tools and hence applicable to a single real case, could help the physician to personalize a patient's treatment using local health care system resources. Accordingly, we tried to generate a severity score to be applied to adult patients with hEDS/HSD in selected clinical backgrounds and to support future research.

This work identified two distinct classes of adults with hEDS/EDS. This clustering reasonably reflects a dichotomic distribution of the multidimensional deterioration of QoL, examined by the use of six heterogeneous questionnaires. More specifically, the worse and better values from the different questionnaires aggregated together in cluster one (complex or severe) and cluster two (simplex or milder), respectively. Among the 59 items used to separate these two clusters, 47 (79.7%) showed significant differences. These two groups were clearly distinguishable by the values of all items of the COMPASS-31, SF-36 and ASRS-V1.1,and most items of the BPI, MFI-20 and FDQ-9

(Table 1). Conversely, no significant differences were noted for the clinical diagnosis according to the old and new nomenclatures (i.e. no excess of hEDS 2017 and Villefranche criteria in the two clusters) and for age. This might suggest that the severity of hEDS/HSD is not significantly influenced by the 2017 criteria of hEDS and the aging process. This result also supports the concept that the distinction between hEDS and HSD according to the current nosology does not mirror any difference in severity. We also noted an excess of males in the simplex (milder) cluster (Table 1). Although the relatively small number of males may have negatively influenced the statistical power of the study, the difference in disease expression between sexes is well known in hEDS/HSD and may reflect the natural influence of sexual dimorphism on the eventual phenotype [25].

In a clinical context, the severity score might predict the full QoL profile by the administration of COMPASS-31, the 11-point numerical rating scale for current pain (BPI, current pain intensity) and the SF-36 physical health item. Translation into practice of the severity score might allow to place the patient in a low-intensity or high-intensity management programme according to the cluster (either complex/milder or complex/severe). A low-intensity programme could include periodic medical management for minor complications (e.g. cardiac valvular or aortic disease, reduction of the bone mass, orthopaedic trait, musculoskeletal injuries), lifestyle recommendations and medical treatment of manifesting minor complications. Conversely, a high-intensity programme should include all the above listed activities, as well as periodic multidimensional assessment of the residual functional activities and cyclic treatments by a multidisciplinary rehabilitation team.

Among the questionnaires used in this study, COMPASS-31 was the most reliable questionnaire for separating patients into the two identified severity classes. This is somewhat in contrast with the consolidated evidence that pain and fatigue are likely the most relevant determinants of QoL in EDS [26]. From a different perspective, our results confirmed the high impact of pain and fatigue on the QoL of adults with hEDS/HSD, but failed to identify them as the more sensible factors modulating QoL variability within the phenotypic heterogeneity of hEDS/HSD. In other words, patient stratification by severity does not seem determined by the primary features of hEDS/HSD (e.g. pain), but rather by a presumably coexistent additional pathomechanism.

Dysautonomia has been evoked as a clinically relevant manifestation of JHS [27]. More recently, cardiovascular autonomic abnormalities have been characterized in JHS/hEDS with a variety of profiles, including postural orthostatic tachycardia syndrome, orthostatic intolerance and neuromediated hypotension [28, 29]. In a single study, small-fibre neuropathy occurred with a very high rate in adults with EDS, including JHS/hEDS [30]. Interestingly, cardiovascular dysautonomia and a range of other functional symptoms commonly reported in hEDS/HSD are also considered typical manifestations of small-fibre neuropathy [31]. Therefore we speculate that the development of an underlying dysautonomia of potential neurogenic origin represents the leading factor determining the transition from the simplex to the complex cluster in adults with hEDS/HSD.

This study is explorative and has major limitations. We limited our investigation of the various QoL determinants to pain, fatigue, neurodevelopmental attributes and dysautonomic-related symptoms. Manifestations of psychological distress were not specifically included and therefore were limited to selected SF-36 items (e.g. psycho-emotional health). The number of included subjects might affect the power of the study, whose results remain preliminary and considering the presumed rarity of the investigated phenotype. Inclusion of adult patients only did not allow us to explore the impact of the developmental trajectories proposed by others [11, 12] on the resulting phenotype. Finally, this study was carried out on Italian patients and therefore we do not know if item values will distribute similarly in other populations. We hope that future studies will allow the development of a more complete tool for predicting severity class attribution of hEDS/HSD patients in a clinical setting and to validate the severity score in different populations.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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