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ORIGINAL ARTICLE

Phenotypic Clusters and Multimorbidity in Hypermobile Ehlers-Danlos Syndrome

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Abstract

Objective: To perform a retrospective clinical study in order to investigate phenotypic penetrance within a large registry of patients with hypermobile Ehlers-Danlos syndrome (hEDS) to enhance diagnostic and treatment guidelines by understanding associated comorbidities and improving accuracy in diagnosis.

Patients and Methods: From May 1, 2021 to July 31, 2023, 2149 clinically diagnosed patients with hEDS completed a self-reported survey focusing on diagnostic and comorbid conditions prevalence. K-means clustering was applied to analyze survey responses, which were then compared across gender groups to identify variations and gain clinical insights.

Results: Analysis of clinical manifestations in this cross-sectional cohort revealed insights into multimorbidity patterns across organ systems, identifying 3 distinct patient groups. Differences among these phenotypic clusters provided insights into diversity within the population with hEDS and indicated that Beighton scores are unreliable for multimorbidity phenotyping.

Conclusion: Clinical data on the phenotypic presentation and prevalence of comorbidities in patients with hEDS have historically been limited. This study provides comprehensive data sets on phenotypic presentation and comorbidity prevalence in patients with hEDS, highlighting factors often overlooked in diagnosis. The identification of distinct patient groups emphasizes variations in hEDS manifestations beyond current guidelines and emphasizes the necessity of comprehensive multidisciplinary care for those with hEDS.

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The Ehlers-Danlos syndromes (EDSs) encompass a group of 14 heritable connective tissue disorders (CTDs).[1,2] Although each subtype is defined by specific phenotypes and genetic markers, hypermobile Ehlers-Danlos syndrome (hEDS), the most prevalent subtype of EDS, currently lacks a clear genetic marker. Patients typically exhibit musculoskeletal pathologies as a consequence of generalized joint hypermobility (GJH) and mild skin involvement. Although most subtypes of EDS can be diagnosed through genetic testing, a clinical diagnosis of hEDS relies on specific criteria. These criteria include GJH assessed by the Beighton score, systemic manifestations of a CTD, and absence of signs or symptoms indicative of other established CTDs.[3] hEDS often presents with symptoms that go beyond the current diagnostic criteria. Patients may present with functional disorders of the gut-brain axis, sleep disturbances, anxiety, depression, fatigue, dysautonomia, mast cell activation syndrome (MCAS), and spinal instabilities.[4-9] Variability in clinical presentation, presence or absence of comorbidities, and severity of symptoms can vary. Although no direct treatments or cures for hEDS exist, symptom management involves physical and occupational therapy, pain management, medications for comorbidities, the use of mobility aids and bracing, and surgical interventions when necessary. Despite increasing awareness and knowledge, data sets defining more comprehensive clinical findings in patients

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with hEDS have remained scarce. This cross-sectional clinical study, comprising 2149 clinically diagnosed patients with hEDS, seeks to unveil the prevalence of hEDS phenotypes and comorbid conditions while investigating potential interrelationships among them. This study represents an initiative to harness a clinical cohort spanning the United States. Its overarching aim was to establish novel clinical criteria aimed at providing a relevant and accurate streamlined diagnosis process for patients with hEDS.

PATIENTS AND METHODS

From May 2021 to July 2023, participant self-reported responses were recorded by clinical research coordinators in REDcap (N=2491) for patients enrolling in an hEDS genetic research study.[10] Ethical approval was obtained from the Medical University of South Carolina institutional review board; Pro00098399), and all participants provided written informed consent. Those who met inclusion criteria for the study were aged older than 12 years, had a clinical diagnosis, and reside in the United States. Having an hEDS diagnosis from a physician was a requirement of the prescreen process and was additionally asked in the informed consent process. The selection criterion was outlined in our prescreening consent process and in the informed consent obtained during telehealth or in-person consultations by diagnosing physicians or research study coordinators. Our institutional review board approved only inclusion of hEDS and not individuals with significant phenotypic overlap such as hypermobility spectrum disorder.[11] Data from individuals without an hEDS diagnosis (N=240) and those reporting that they have been diagnosed with another subtype of EDS (N=52) or another type of CTD (N=50) were excluded from the survey. This resulted in 2149 participants who answered all questions and were included in the study (Figure 1A). Understanding that many patients may not have undergone diagnostic evaluations for these conditions, questions included basic demographic characteristics and hEDS signs and symptoms based on the 2017 hEDS diagnostic criteria (diagnostic phenotypes and Beighton score criteria) and previously reported comorbidities in patients with hEDS (Supplemental Table, available online at http://www.mcpiqojournal.org).[4-9] The Beighton score is a screening tool for GJH included in the hEDS diagnostic criteria, ranging from 0-9. A higher score reflects the extent of hypermobility across assessed joints.[12,13] Depending on age, the Beighton score must be greater than 4 (older adults), 5 (adults), or 6 (children) to qualify as GJH.[12,13] The Beighton score, generated by the diagnosing physician, was provided by the patients through our survey.

Nonhierarchical k-means cluster analysis was conducted to identify distinct patient subgroups as reported previously.[14,15] K-means clustering was conducted to find similar groupings among the patients with hEDS enrolled in our study. This approach is a multivariate statistical technique to identify similarities and differences among numeric data. This analysis groups the numeric data into k-clusters with the goal of identifying clusters that are meaningful to interpret. Thus, k-means clustering was conducted to identify whether the patient cohort with hEDS could be stratified into meaningful subgroups. The number of clusters, k, was chosen through graphical assessment, and the analysis was conducted and assessed through descriptive statistics and linear discriminant analysis as previously described. The optimal number of clusters was chosen by plotting the total within-cluster sum of squares (WSSs) as a function of the number of clusters. The optimal number of clusters is the point on the graph where the curve appears to flatten, indicating that additional clusters would have little effect on the total WSSs. For this analysis, 3 clusters were chosen. When the demographic characteristics, Beighton score, and clinical data were used in the WSSs, the plot had no elbow. However, when variables were included for multimorbidity, the WSS plot had an elbow indicating that 3 clusters were optimal and that inclusion of Beighton criteria resulted in a dissolution of these clusters. Thus, this k-means clustering with 3 clusters identified subgroups with notable distinctions between the multimorbidity profiles of each cluster.

RESULTS

In total, 2491 participants initially completed registry intake as of July 2023. After excluding

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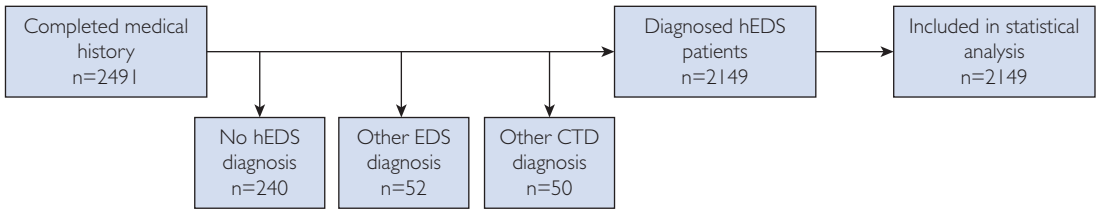

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	Female (n)	Female (%)	Male (n)	Male (%)	Nonbinary (n)	Nonbinary (%)	Total (n)	Total (%)
Participants	1967	91.53%	106	4.93%	76	3.54%	2149	100.00%
Average age (years)	37.98		32.85		30.47		37.46	
Ethnicity								
Not hispanic or latino	1819	84.64%	94	4.37%	68	3.14%	1981	92.18%
Hispanic or latino	99	4.61%	7	0.33%	8	0.37%	114	5.30%
Unknown/other/unreported	49	2.28%	5	0.23%	0	0.00%	54	2.51%
Race								
White	1848	85.99%	96	4.47%	66	3.05%	2010	93.53%
Asian	22	1.02%	0	0.00%	0	0.00%	22	1.02%
Black or African American	10	0.47%	0	0.00%	1	0.05%	11	0.51%
American Indian/Alaska Native	16	0.74%	1	0.05%	1	0.05%	18	0.84%
Unknown/other/unreported	71	3.30%	9	0.42%	8	0.37%	88	4.09%
Family history of hEDS								
Yes	1503	69.94%	87	4.05%	51	2.36%	1641	76.36%
No	464	21.59%	19	0.88%	25	1.16%	508	23.64%

B

FIGURE 1. Demographic characteristics and inclusion criteria. (A) 2491 patients completed registry intake; 240 were excluded owing to no hEDS diagnosis; 52 and 50 additional patients were excluded owing to other type of EDS diagnosis or other CTDs; 2149 patients were included in statistical analyses. (B) Participant demographic characteristics reporting total number and percentage of patients based on sex, ethnicity, race, and a family history of hEDS. Non-Hispanic, White women make up the majority of those with hEDS and 70% have a family history. CTD, connective tissue disorder; EDS, Ehlers-Danlos syndrome; hEDS, hypermobile Ehlers-Danlos syndrome.

individuals without a confirmed clinical diagnosis of hEDS or those diagnosed with other CTDs, the final cohort consisted of 2149 participants (Figure 1A). Among the 2149 participants, a majority (91.53%) identified as female, whereas 4.93% identified as male, and 3.54% identified as nonbinary. A large portion (94%) of the participants self-identified as White, and the average age of participants was 37 years (Figure 1B). Approximately 76% reported a family history of hEDS. Participants provided self-reported clinical information and were categorized based on gender, the presence or absence of hEDS symptoms, and common comorbidities (Supplemental Table).

Phenotypic presentations and comorbid conditions were categorized under 7 medical specialties with the following color representations: orthopedics (green), dermatology (light blue), internal medicine (gray), cardiology (orange), neurology/neurosurgery (dark blue), immunology (yellow), and psychiatry (pink) (Figure 2A). Participant responses were tabulated based on gender (Figure 2B). Among female participants, the most-reported diagnostic phenotypes included chronic pain and joint subluxations, both exceeding 90%. These were closely followed by abnormal scarring (70.16%), stretchy skin (67.97%), poor wound healing (62.48%), and joint dislocations (60.09%). Valvular heart disease was notably prevalent in this cohort, with approximately one-fourth of patients reporting issues with 1 or more heart valves. Abdominal hernias and pelvic organ prolapse were observed in nearly 20% of the female cohort.

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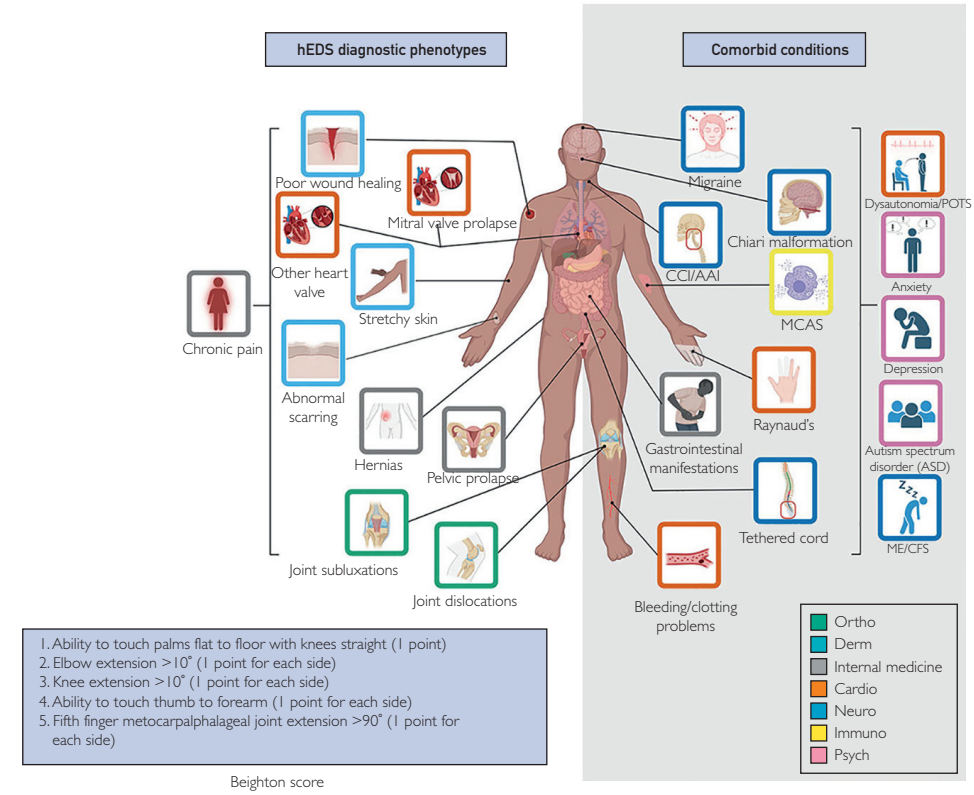

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hEDS diagnostic phenotypes	Female		Male		Nonbinary		Total	
	n	%	n	%	n	%	n	%
Joint subluxations	1771	90.04%	88	83.02%	68	89.47%	1927	89.67%
Chronic pain	1773	90.14%	74	69.81%	70	92.11%	1917	89.20%
Abnormal scarring	1380	70.16%	58	54.72%	58	76.32%	1496	69.61%
Abnormally stretchy skin	1337	67.97%	70	66.04%	54	71.05%	1461	67.99%
Poor wound healing	1229	62.48%	51	48.11%	47	61.84%	1327	61.75%
Joint dislocations	1182	60.09%	61	57.55%	55	72.37%	1298	60.40%
Mitral valve prolapse	465	23.64%	17	16.04%	19	25.00%	501	23.31%
Abdominal hernia(s)	414	21.05%	25	23.58%	15	19.74%	454	21.13%
Pelvic organ prolapse	391	19.88%	5	4.72%	9	11.84%	405	18.85%
Other heart valve conditions	278	14.13%	15	14.15%	13	17.11%	306	14.24%

C

Comorbid conditions	Female		Male		Nonbinary		Total	
	n	%	n	%	n	%	n	%
Gastrointestinal manifestations	1601	81.39%	76	71.70%	63	82.89%	1740	80.97%
Anxiety	1487	75.60%	71	66.98%	67	88.16%	1625	75.62%
Dysautonomia/POTS	1411	71.73%	56	52.83%	56	73.68%	1523	70.87%
Migraine	1386	70.46%	59	55.66%	59	77.63%	1504	69.99%
Depression	1228	62.43%	60	56.60%	58	76.32%	1346	62.63%
Raynaud's phenomenon	873	44.38%	29	27.36%	39	51.32%	941	43.79%
Mast cell activation	797	40.52%	27	25.47%	35	46.05%	859	39.97%
ME/CFS	630	32.03%	30	28.30%	27	35.53%	687	31.97%
CCI/AAI	628	31.93%	24	22.64%	27	35.53%	679	31.60%
Bleeding or clotting problems	437	22.22%	21	19.81%	18	23.68%	476	22.15%
Autism spectrum disorder	148	7.52%	16	15.09%	26	34.21%	190	8.84%
Chiari malformation	155	7.88%	5	4.72%	10	13.16%	170	7.91%
Tethered cord	133	6.76%	5	4.72%	7	9.21%	145	6.75%

D

Additional demographics	Female	Male	Nonbinary	Total
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of conditions	11.22 (3.39)	9.41 (3.68)	12.37 (3.56)	11.17 (3.44)
Mean age (years)	37.98 (12.87)	32.85 (14.92)	30.47 (8.98)	37.46 (12.98)
Beighton score	7.45 (1.40)	7.07 (1.64)	7.62 (1.18)	7.44 (1.40)
Total count	1967	106	76	2149

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Reported prevalence for most conditions was notably lower in the male cohort compared with the female group. Joint subluxations were the most common diagnostic phenotype (83.02%), followed by chronic pain (69.81%), stretchy skin (66.04%), joint dislocations (57.55%), abnormal scarring (54.72%), and poor wound healing (48.11%). Pelvic organ prolapse (4.72%) and mitral valve prolapse (16.04%) were observed at lower frequencies in males than those in females, whereas abdominal hernias and other heart valve conditions were similar between the genders. The nonbinary cohort closely resembled the female patients in all diagnostic phenotypes, except for a reduced frequency of pelvic organ prolapse (11.84% and 19.88%, respectively).

Individuals with hEDS frequently have other comorbid health conditions that are not considered in the syndrome's diagnostic criteria. Among the 13 comorbidities included, the most frequently observed across all genders was gastrointestinal issues, with a prevalence of 81.39% among females, 71.70% among males, and 82.89% among nonbinary patients. (Figure 2C). Dysautonomia, postural tachycardia syndrome (POTS), anxiety, migraines, and depression were more prevalent in population with hEDS than most diagnostic phenotypes, with females and nonbinary patients exhibiting higher rates compared with those in males. Gender-related differences were also observed in slightly less-common comorbid conditions, such as Raynaud phenomenon, MCAS, and craniocervical instability/atlantoaxial instability, with females and nonbinary patients with hEDS reporting higher prevalence. Bleeding or clotting issues appeared to be similar across patients regardless of gender. Neurologic conditions, such as Chiari malformation were nearly twice as common in females compared with those in males and 3 times as common in nonbinary individuals. A similar trend was observed for tethered cord syndrome, with a 2-fold increase in occurrence among nonbinary patients with hEDS. Notably, the prevalence of autism spectrum disorder was twice as high in males compared with that in females and nearly 5 times higher in nonbinary individuals. Patients in our study had an average reported Beighton score of 7.4 across all genders (range, 7.1-7.6) and age groups (range, 7.0-7.6) (Figure 2D). We did not observe a correlation between the Beighton score and the number of comorbid conditions reported by the patients, gender, or age. On average, participants reported 11 conditions, and 98.6% of patients had at least 4 comorbid conditions (Figure 2D).

To explore whether the spectrum of hEDS phenotypes and comorbidities tend to group together within our patient population, we conducted cluster variant analyses. These k-means cluster analyses, encompassing both hEDS criteria and comorbid conditions, revealed the presence of 3 distinct clusters among patient cohort with hEDS and were found to be independent of patient age (Figure 3A). Clusters 1 (gray) and 3 (blue) comprised patients with more than 11 conditions, whereas Cluster 2 (orange) represented patients with fewer than 11 conditions (Figure 3B). Violin plots provide visual insights into these clusters, delineating them based on diagnostic phenotype, comorbid conditions, or the total number of conditions (Figure 3C-E).

The differences observed among the phenotypic clusters provided valuable insights into the diversity within our patient population with hEDS (Figure 4). Patients within Cluster 1 exhibited a higher prevalence of most diagnostic and comorbid phenotypes than those in the other 2 clusters. Conversely, patients with hEDS within Cluster 2 reported a lower prevalence of most phenotypes, whereas those in Cluster 3 represented an intermediate phenotype presentation (Figure 4A, B). The most pronounced distinctions within the

FIGURE 2. Phenotypes and comorbid conditions with hEDS. (A) hEDS diagnostic phenotypes are conditions based on 2017 hEDS diagnostic criteria. Comorbid conditions are not included in the 2017 hEDS diagnostic criteria. Beighton criteria are presented. Color outlines of boxed phenotypes represent distinct clinical specialties. (B, C) Prevalence of diagnostic conditions and comorbidities by gender. Note that females are more frequently affected compared with males, except in the case of autism and abdominal hernia. (D) Additional demographic characteristics reporting females are affected by more conditions. Nonbinary individuals appear to have more conditions and are diagnosed earlier than those who designate as females or males.

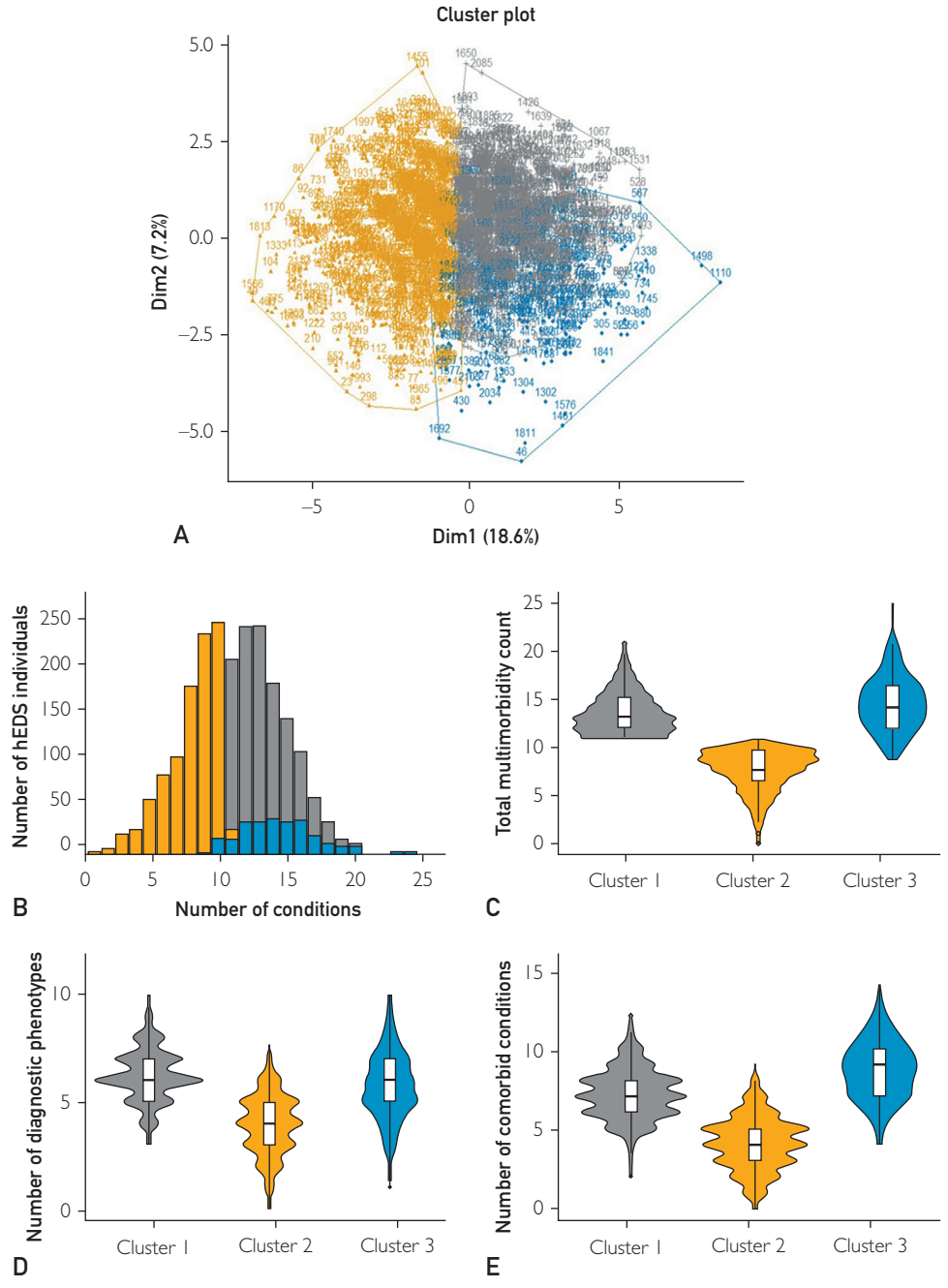

FIGURE 3. K-means clusters and multimorbidity profiles for hEDS. (A) K-means cluster plot illustrating the grouping of all patients with hEDS based on their reported clinical demographic characteristics. The plot reveals the presence of 6 distinct and independent clusters within the patient population with hEDS. (B) Graphical representation of the distribution and frequency of chronic conditions reporting differences between each cluster. (C-E) Prevalence of total multimorbidity, diagnostic phenotypes, and comorbid conditions per cluster.

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hEDS diagnostic phenotypes	Cluster 1		Cluster 2		Cluster 3		Total	
	n	%	n	%	n	%	n	%
Chronic pain	951	97.44%	725	78.21%	241	97.97%	1917	89.20%
Joint subluxations	943	96.62%	751	81.01%	233	94.72%	1927	89.67%
Abnormal scarring	837	85.76%	471	50.81%	188	76.42%	1496	69.61%
Poor wound healing	787	80.64%	373	40.24%	167	67.89%	1327	61.75%
Abnormally stretchy skin	768	78.69%	519	55.99%	174	70.73%	1461	67.99%
Joint dislocations	748	76.64%	390	42.07%	160	65.04%	1298	60.40%
Mitral valve prolapse	310	31.76%	112	12.08%	79	32.11%	501	23.31%
Abdominal hernia(s)	264	27.05%	112	12.08%	78	31.71%	454	21.13%
Pelvic organ prolapse	250	25.61%	103	11.11%	52	21.14%	405	18.85%
Other heart valve conditions	195	19.98%	70	7.55%	41	16.67%	306	14.24%

B

Comorbid conditions	Cluster 1		Cluster 2		Cluster 3		Total	
	n	%	n	%	n	%	n	%
Gastrointestinal manifestations	889	91.09%	629	67.85%	222	90.24%	1740	80.97%
Anxiety	844	86.48%	598	64.51%	183	74.39%	1625	75.62%
Migraine	823	84.32%	476	51.35%	205	83.33%	1504	69.99%
Dysautonomia/POTS	807	82.68%	498	53.72%	218	88.62%	1523	70.87%
Depression	744	76.23%	450	48.54%	152	61.79%	1346	62.63%
Raynaud's phenomenon	568	58.20%	235	25.35%	138	56.10%	941	43.79%
Mast cell activation	496	50.82%	194	20.93%	169	68.70%	859	39.97%
ME/CFS	423	43.34%	144	15.53%	120	48.78%	687	31.97%
CCI/AAI	365	37.40%	129	13.92%	185	75.20%	679	31.60%
Bleeding or clotting problems	322	32.99%	86	9.28%	68	27.64%	476	22.15%
Autism spectrum disorder	109	11.17%	43	4.64%	38	15.45%	190	8.84%
Chiari malformation	0	0.00%	20	2.16%	150	60.98%	170	7.91%
Tethered cord	0	0.00%	9	0.97%	136	55.28%	145	6.75%

C

Additional demographics	Cluster 1	Cluster 2	Cluster 3	Total
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of conditions	13.37 (1.93)	8.00 (1.93)	14.39 (2.65)	11.17 (3.44)
Mean age	38.30 (12.42)	36.03 (13.73)	39.56 (11.68)	37.46 (12.98)
Total count	976	927	246	2149

FIGURE 4. Subgroups and prevalence of chronic conditions per hEDS cluster. (A, B) Percentage prevalence of each chronic condition per cluster and totals across all clusters. Note that lower prevalence of diagnostic and comorbid conditions in Clusters 1 and 2 compared with Cluster 3, which has a high prevalence of neurologic conditions. (C) Mean number of conditions, age and total number of patients within each cluster. Note that Cluster 2 individuals have a lower prevalence of nearly all diagnostic and comorbid conditions, whereas Cluster 3 has the highest prevalence.

clusters were related to neurologic comorbid conditions (Figure 4B). Clusters 1 and 2 exhibited a low prevalence of conditions such as craniocervical instability/atlantoaxial instability, Chiari malformation, and tethered cord syndrome. In contrast, Cluster 3 reported a notably higher rate of these specific comorbidities in addition to increased prevalence of MCAS. We further examined the number of conditions within each cluster (Figure 4C). Cluster 3 patients reported the highest number of conditions, exceeding 14 in many cases. These disparities in chronic diagnostic conditions and comorbidities served as distinguishing features between the 3 clusters. Interestingly, integrating Beighton scores into the clustering analysis resulted in the dissolution of the established clusters and indicated that Beighton criteria might not be a reliable clinical criterion for hEDS multimorbidity phenotyping.

DISCUSSION

This study offers new insights into the diverse range of phenotypes and coexisting health conditions within the patient population

with hEDS. Despite hEDS typically following an autosomal dominant inheritance pattern, our data underscore a bias toward White females, consistent with previous reports.[8] This observation raises questions of whether women bear a greater disease burden, are more proactive in seeking diagnosis, or if underlying biological/genetic factors influence disease susceptibility, penetrance, or severity in females.

In our cohort with hEDS, we found mitral valve prolapse, abdominal hernias, pelvic organ prolapse, and other heart valve conditions to be the least prevalent of the 2017 diagnostic criteria. However, there is still an enrichment of these conditions when compared with population data sets.[16] Several symptoms and conditions, not encompassed in the 2017 hEDS diagnostic criteria, such as gastrointestinal manifestations and dysautonomia, exhibit high prevalence among individuals diagnosed with hEDS. Aside from joint subluxations and chronic pain, the phenotypic symptoms included in the 2017 criteria were less prevalent in the hEDS patient registry compared with the top 4 common comorbidities (gastrointestinal manifestations, anxiety, dysautonomia/POTS, and migraine). This finding raises questions about the adequacy of the 2017 criteria in capturing the full spectrum of hEDS manifestations, calling for further research to refine diagnostic guidelines. A data point of note is the prevalence of conditions, such as MCAS and dysautonomia/POTS among individuals diagnosed with hEDS. Although these conditions have previously been linked to hEDS, our study provides valuable prevalence data, offering insights into their impact on a broader population with hEDS.[17] It should be noted that comorbid conditions, such as MCAS and POTS are likely underdiagnosed in the population with hEDS, and therefore, our data represent a conservative estimate.

Recognizing the prevalence of such conditions is needed for enhancing patient care and diagnostic accuracy. A major outcome of our studies is to advocate for the expansion of the hEDS diagnostic criteria based on our findings, which can more appropriately guide clinical decision making while guiding future research endeavors. Our investigation revealed 3 distinct disease clusters, organized based on the prevalence of comorbid conditions and diagnostic phenotypes. In broad strokes, Cluster 2 appears to encompass individuals with a milder clinical presentation, characterized by reduced phenotype prevalence and comorbid conditions, resulting in an overall lower count of conditions. In contrast, patients who fall within Cluster 3, comprising 246 of 2149 individuals (11.5%), exhibit spinal and neurologic involvement and a total disease burden exceeding 14 conditions.

The identification of distinct clusters within the patient cohort with hEDS, especially when considering comorbid conditions, suggests that traditional diagnostic approaches may not fully capture the diversity within the population with hEDS. These findings also emphasize the likelihood of genetic diversity contributing to the variable expression and penetrance of hEDS phenotypes. By combining large survey data sets, such as the one presented in this study, with whole-genome sequencing or genome-wide association studies, there is potential to discover new molecular maps with diagnostic/prognostic value for identifying and managing patients across disease phenotypes. This prompted us to investigate whether the extent of GJH, as evaluated by the Beighton score, correlates with specific clinical manifestations. However, integrating Beighton scores into the clustering analysis resulted in the dissolution of the established clusters. This observation indicates that the Beighton score may not be the most reliable tool for predicting patient phenotypes and suggests that GJH may not necessarily align with disease presentation.

This study explores the relationship between multimorbidity and hEDS, shedding light on the clinical findings of this condition. This report offers a broad understanding of the phenotypic spectrum observed in patients with hEDS. The adoption of multidisciplinary and well-coordinated approaches holds promise for improving screening, diagnosis, and treatment. In the absence of valid diagnostic criteria, patients will continue to be underdiagnosed or improperly diagnosed. With a prevalence that is likely more common in the population than recognized, these approaches could lead to substantial enhancements in patient outcomes and reduce the burden on the health care system.

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CONCLUSION

Our findings provide fresh insights into the clinical spectrum of hEDS, underscore the presence of multimorbidity within the cohort, and emphasize the importance of considering these clinical associations in research, cross-screening, and patient care. Moreover, this study results reveal the capacity to group patients with hEDS into subclusters based on their clinical phenotypes, suggesting potential divergent genetic and/or environmental influences. Identifying these subclusters can empower physicians with innovative clinical approaches and the possibility of predictive diagnostic tools. Currently, patients with hEDS see multiple specialists at numerous institutions to treat singular symptoms. This study serves to reinforce the essential collaboration among physician specialists, patients, and researchers to break down the barriers of siloed health care for this patient population. Through these efforts, we are poised to not only elevate patient care but also markedly enhance the overall quality of life for individuals with hEDS. Leveraging data from the largest cross-sectional clinical registry to date, the revision of clinical guidelines for diagnosing patients with hEDS based on these data sets should now be considered.

Limitations

Although our study provides valuable insights into hEDS, it is important to acknowledge limitations of self-reported surveys. Self-reported data may be impacted by recall bias and selection bias as those who participated may have different responses from those who chose not to participate. Another important consideration is that our study recorded gender identity but not biological sex. The average age of participants was 37 years but included children as young as 13 years, who may present with a different phenotype or fewer comorbidities than they will as adults as previously indicated.[18] Health disparities and limited access to care pose additional challenges, thus the percentages of patients with specific comorbidities are likely conservative estimates. Regardless, our study provides novel insights into the clinical presentation and multimorbidity in hEDS and can serve as a guide for clinical care and future research studies.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CTD,** connective tissue disorder; **EDS,** Ehlers-Danlos syndrome; **hEDS,** hypermobile Ehlers-Danlos syndrome; **GJH,** generalized joint hypermobility

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