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Clinical Heterogeneity in Myotonic Dystrophy Type 1

Identifying Phenotype Categories Using Unsupervised Clustering

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Abstract

Background and Objectives

Myotonic dystrophy type 1 (DM1) is a genetic multisystem disorder with a wide variability in symptom severity and symptom co-occurrence. This study aimed to identify homogeneous patient subgroups in DM1 with distinct disease characteristics, determine key features underlying these subgroups, and evaluate their potential to inform clinical care and individualized therapy.

Methods

Adult patients with genetically confirmed DM1 were assessed during annual visits to the Dutch DM1 expert center using standardized examinations and questionnaires to characterize disease burden. K-means cluster analysis was conducted on 10 baseline parameters that reflect the multisystemic disease impact of DM1. External validation was conducted using baseline data from the END-DM1 natural history study.

Results

Six hundred fifty-eight Dutch patients with DM1 were included, with a mean age of 45.33 ± 14.30 years and a mean disease duration of 13.24 ± 10.42 years. Four clusters were identified, including 166, 169, 149, and 174 patients. Cluster 1 included patients with severe myotonia, gastrointestinal complaints, fatigue and daytime sleepiness, and reduced ability to perform daily activities. Cluster 2 included patients severely affected across all domains except for myotonia. Cluster 3 showed reduced respiratory functioning and reduced ability to perform daily activities. Cluster 4 included patients with minimal symptoms. Clustering of 581 patients in the external data set resulted in similar cluster profiles.

Discussion

Four distinct clinical subgroups with characteristic multisystemic profiles were identified and independently validated. These findings demonstrate that DM1 heterogeneity reflects qualitatively different disease patterns rather than a simple severity continuum and provide foundation for more targeted patient stratification in clinical trials and health care.

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Supplementary Material

Introduction

Myotonic dystrophy type 1 (DM1) is a hereditary multisystem disorder with an estimated clinical prevalence between 5 and 20 per 100,000 individuals.[1] DM1 is caused by an expansion of the cytosine-thymine-guanine (CTG) triplet in the 3′ untranslated region of the dystrophia myotonica protein kinase gene on chromosome 19.[2] The CTG trinucleotide repeat is naturally

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Glossary

DM1 = myotonic dystrophy type 1; **FDSS** = Fatigue and Daytime Sleepiness Scale; **GSRS** = Gastrointestinal Symptoms Rating Scale; **MICE** = multiple imputations by chained equation; **MIRS** = Muscular Impairment Rating Scale; **MRC** = Medical Research Council; **PCA** = Principal component analysis.

polymorphic, in healthy individuals typically ranging from 5 to 37 repeats, whereas in affected DM1 patients the repeat ranges between 50 and 5,000.[3] The length of CTG trinucleotide repeat expansion is moderately correlated with disease severity, as larger expansions are associated with a more severe disease phenotype and earlier onset of symptoms.[4] In successive generations, anticipation occurs, which results in an increased severity of symptoms, and a decrease in age at onset.[5] Paternal transmission is generally associated with greater intergenerational instability of smaller CTG repeat alleles, while maternal transmission more frequently involves transmission of larger expansions and is more strongly associated with the congenital form of the disease.[6] Patients with DM1 typically experience progressive muscle weakness and myotonia, alongside many multisystemic manifestations.[7] These include amongst others respiratory insufficiency, cardiac abnormalities, cataracts, gastrointestinal complaints, and reduced cognitive performance.[8-12] Alongside this large variability in co-occurrence and severity of symptoms, there is wide variability in individual patient disease burden.[13,14]

The variability in phenotypic expression poses significant challenges for disease management and the development of disease modifying therapies.[15] Patients with similar CTG repeat lengths or ages can differ markedly in symptom patterns, progression rate, and overall disease burden. This heterogeneity complicates prognosis and hinders the development of disease modifying therapies. However, little is known about how specific symptoms co-occur across domains, and previous studies addressing this have not considered the magnitude of symptoms that co-occur.[16]

Clustering algorithms offer a promising computational approach to disentangle complex heterogeneous disease populations and to identify subgroups within a population.[17] In DM1, such clustering may reveal natural groupings of patients who share common multisystem profiles, thereby uncovering patterns that are not visible when each symptom is studied in isolation. Defining these subgroups could facilitate more precise disease monitoring, improve prognostic accuracy, and support stratified trial design by reducing group variability. The objective of this study was therefore to identify distinct DM1 patient clusters with relatively homogenous multisystem profiles, and to explore the co-occurrence of symptoms within this population.

Methods

Study Design

This analysis is part of an ongoing observational natural history study (MYODRAFT) conducted by the Dutch DM1 expertise center (Radboud University Medical Center (Radboudumc) and Maastricht University Medical Center+ (MUMC+)). This data set is used as the discovery cohort for cluster analysis. Recruitment and follow-up are ongoing.

Genetically confirmed patients with DM1 were examined according to a predefined protocol during their yearly routine visit to the outpatient clinic. The length of CTG repeats was measured from patient blood samples by PCR, followed by Southern blot hybridization and triplet-primed PCR. In the context of this study, tripled primed PCR is applied only for diagnostic detection of repeat expansions and does not allow for reliable sizing beyond approximately 150 repeats. As a result, CTG repeat lengths were divided into 2 categories, namely between 50 and 150 and over 150 repeats. Baseline data from a single study visit of patients enrolled in the study between March 2017, and September 2024 was extracted for this analysis. All patients under 18 years old at enrollment in the registry were excluded from the analysis. This age cutoff was applied because the clinical assessment protocol differs between pediatric and adult participants in the registry, resulting in several of the variables used for the present cluster analysis not being available in patients enrolled before the age of 18 years.

Clinical Examination

Demographic data, general medical data, disease duration (time interval between onset of first symptoms and age at study inclusion) and symptomatology were recorded. Patients were classified into 4 clinical subtype categories based on the age at first symptom onset, namely the congenital-onset, childhood-onset, adult-onset, and late-onset subtype.[18] The ordinal Medical Research Council (MRC) sum score was used to test muscle strength.[19] Neck flexors and neck extensors were scored separately on a 0–5 scale. The following muscle groups were examined bilaterally using the MRC scale (0–5 per side): finger flexors, wrist extensors, elbow flexors, elbow extensors, shoulder abductors, hip flexors, knee flexors, knee extensors, foot flexors, and foot extensors. A total score of 110 represents normal muscle strength. The Muscular Impairment Rating Scale (MIRS) was used to categorize participants based on the MRC sum score. The MIRS is a 5-point scale used to assess the overall severity of muscle weakness, with higher scores indicating greater impairment.[20] The Martin-Vigori meter was used to measure hand grip strength quantitatively. This device was applied in accordance with recommendations from the American Society of Hand Therapists.[21] The Martin-Vigori meter gauges the pressure expressed in kilo Pascals, inside a rubber bulb connected to a manometer through a rubber junction tube. The medium-sized bulb was used for all participants. An average of 3

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maximum voluntary squeezes were recorded, with an approximate 30-second rest period between each attempt. Scores in kilopascals of the participants were converted to a percentage of the predicted value based on normative data for their respective sex and age groups.[22] The average score of the left and right hand combined was used for analysis, as previous research did not show significant differences between dominant and nondominant hands.[23] Hand grip action myotonia was measured, defined as difficulty with relaxing finger flexor muscles after forceful contraction. Patients were instructed to tightly squeeze their hands into a fist for 5 seconds while keeping the back of their hand resting on a table. Patients were subsequently instructed to quickly open their hands as fast as they could. The time was recorded from the command to open the hand until all fingertips of digits II–V had reached the surface of the table.

Respiratory symptoms and pulmonary function were assessed during routine clinical evaluation. All pulmonary function tests met appropriate standards of the European Respiratory Society and American Thoracic Society.[24] The forced vital capacity of patients in supine and seated position was recorded and compared with the predicted normal values and expressed as a percentage of the normal value.[25,26] In addition, the use of noninvasive ventilation was recorded.

A 12-lead ECG was evaluated by a qualified cardiologist for the following cardiac parameters: cardiac rhythm, heart rate in beats per minute, PR interval in ms, QRS interval in ms, and QTc time in ms.

Questionnaires

The DM1-Activ^{C} is a questionnaire on activity and social participation for patients with DM1. It is a Rasch-built, 25-item interval measurement scale that captures the ability to perform daily activities.[27] The Fatigue and Daytime Sleepiness Scale (FDSS) is a Rasch-built, 11-item interval scale used to measure symptoms of fatigue and daytime sleepiness.[28] Both for the DM1-Activ^{C} and the FDSS, the raw score was converted to a centile metric. For the DM1-Activ^{C}, a higher score indicates better ability to perform daily activities. For the FDSS, a higher score indicates more fatigue and daytime sleepiness. The Gastrointestinal Symptoms Rating Scale (GSRS) is a 15-item questionnaire that measures 5 symptoms of gastrointestinal complaints, namely, reflux, abdominal pain, indigestion, diarrhea, and constipation.[29] A higher score indicates more gastrointestinal complaints.

External Validation Cohort

To assess the robustness and generalizability of the identified clusters, external validation was performed using baseline measurements of the END-DM1 data set ("validation cohort"). Further details regarding the study population, procedures, and outcome measures of the END-DM1 study are provided in the published protocol.[30] For the external validation, the same variables were used as the discovery data set, except for the GSRS and the FDSS, as they were not available. Instead, the Myotonic Dystrophy Health Index subscales for fatigue, daytime sleepiness, and gastrointestinal symptoms were used.[31] The external validation cohort was solely used to assess the robustness and reproducibility of the clustering structure identified in the discovery cohort, rather than to independently characterize this population.

Statistical Analyses

All analyses were conducted using R version 4.2.0. GPT-5 (OpenAI, 2026) was used to assist with language and analysis code. All analysis code was reviewed and tested before implementation. All scientific content, study design, statistical analyses, interpretation of the results, and final manuscript revision were approved by all authors. The analysis code is publicly available in Zenodo.[32] Two data sets were used, the data from the MYODRAFT registry were used as a discovery data set ("discovery cohort"), and the END-DM1 data set was used for validation (validation cohort). Identical procedures were used for both analyses. To impute missing data, multiple imputations by chained equation (MICE) was used with predictive mean matching with 50 imputations. Imputed data were only used for cluster allocation, not for the description of the clusters. The stability of the imputation process was assessed using trace plots. Density plots were used to examine the distributions of imputed values compared with the observed values. In addition, correlation matrices were used to determine the similarity of imputed values against the observed values. Box-cox transformation was applied to the input variables used for clustering, with the optimal lambda selected through maximum likelihood estimation. Then, the input variables were standardized using Z-score normalization, whereby each variable was centered by subtracting its mean and scaled by dividing by its SD.

K-means clustering was used to identify subgroups. Clustering stability was evaluated by repeating the k-means clustering 100 times and calculating the adjusted Rand index for each run compared with the reference solution. An adjusted Rand[33] index of 1 indicates perfect agreement, and 0 means agreement expected by chance. The number of clusters was based on clinical interpretation, cluster size, and the R-square value. To find potential clusters of patients, cluster analysis was conducted on parameters that reflect the multisystemic disease burden. As a result, 10 continuous variables were chosen for the discovery cohort: myotonia, hand grip strength, MRC sum score, DM1-Activ^{C}, FDSS, GSRS, FVC% in supine and seated position, PR interval, and QRS duration. Outcome measures in this study were selected based on recommendations of the 222nd ENMC Workshop.[34] Principal component analysis (PCA) and biplots were used to visualize the clusters.

Descriptive statistics are presented as mean and SD or median and interquartile range in case of non-normally distributed data. The normality of data was determined by the Shapiro-Wilk test. Categorical variables are expressed as frequencies and percentages. Continuous variables were compared between clusters

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using one-way analysis of variance for normally distributed data and the Kruskal-Wallis test for non-normally distributed data. p values were adjusted for multiple comparisons using the Benjamini-Hochberg correction. Differences between categorical data were determined by the χ^2 test. The level of statistical significance was set at 0.05.

For external validation in the END-DM1 cohort, the same data imputation and analysis procedures were used as the discovery cohort. Furthermore, cluster centroids derived from the validation data set were compared with those from the original data set using the Euclidean distance between centroids as a quantitative measure of similarity. Clusters across data sets were then matched based on minimal centroid distance. Clusters were matched using the Hungarian algorithm. This approach allows us to evaluate whether clusters representing comparable presentation of symptoms could be identified across independent cohorts.

Standard Protocol Approvals, Registration, and Patient Consents

The study protocol adheres to principles of the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee (METC-16-4-001, approved on March 18, 2016). Written informed consent was obtained from all patients.

Data Availability

Deidentified individual participant data underlying this study will be made available on reasonable request from qualified investigators for scientifically valid research purposes, subject to applicable ethical and institutional approvals.

Results

Sample Characteristics

Data were extracted as of September 25, 2024. The discovery cohort included 658 patients between the ages of 18 and 86 years, with a mean age of 45.3 years and a mean disease duration of 13.2 years. Baseline data were obtained at a single study visit, with enrollment taking place between March 2017 and September 2024. Baseline characteristics of the discovery cohort are presented in Table 1. The cohort consisted of the DM1 onset subtypes within the registry, namely, childhood-onset, adult-onset, and late-onset disease, together with a small number of congenital patients who were 18 years or older at enrollment. The distribution of onset subtypes across the clusters is presented in Table 1.

Cluster Analysis

Frequency of missing data per cluster was analyzed to determine if missing data were associated with cluster allocation (eTable 1). The trace plots were stable without significant trends or drifts (eFigure 1). The density plots (eFigure 2) indicated that the imputed values have a similar distribution compared with the observed values. The correlation matrix of the observed values (eFigure 3) and the correlation matrix of the imputed values (eFigure 4) were similar. eFigures 5 and 6 show the distribution of the variables before and after normalization.

K-means clustering of the discovery cohort with the best tradeoff between R-square value, cluster size, and clinical interpretation resulted in 4 clusters of 166, 169, 149 and 174 patients, respectively (eFigure 7). The average adjusted Rand index was 0.81. Figure 1 shows the separation of the 4 clusters in a PCA score plot. Biplots comparing principal components 1 to 4 are presented in eFigures 8–13. Figure 2A shows an overview of disease characteristics of the 4 clusters for the discovery and validation cohort. Demographic and clinical characteristics of patients in each cluster are presented in Table 1. Patients of the 4 different clusters had significantly different muscular, respiratory, and cardiac characteristics, as presented in Tables 2-4. Moreover, patients in the 4 different clusters reported significant differences in fatigue and daytime sleepiness, gastrointestinal symptoms, and limitations in daily activities (Table 5).

Cluster 1 (n = 166) consisted of middle-aged patients (mean 43.9 years) with a relatively short disease duration of on average 12.6 years. This cluster predominantly had the adult-onset phenotype with MIRS category III. Compared with other clusters, this group of patients exhibited mild to moderate muscular weakness, within an overall profile characterized by reduced ability to perform daily activities, alongside relatively severe myotonia, gastrointestinal complaints, fatigue, and daytime sleepiness.

Cluster 2 (n = 169) consisted of older patients on average (mean 50.3 years), with a mean disease duration of 20.9 years. Most had the adult-onset phenotype with MIRS category IV and the highest proportion of maternal inheritance (34.3%). This cluster of patients had a high overall disease severity across muscular and multisystem domains but limited myotonia.

Cluster 3 (n = 149) consisted of middle-aged patients (mean 42.0 years) with a relatively short disease duration of 11.4 years. Most had the adult-onset phenotype with MIRS category III. Compared with other clusters, this group of patients exhibited mild to moderate muscular weakness, within an overall profile characterized by reduced ability to perform daily activities, as well as reduced respiratory capacity and diminished hand grip strength.

Cluster 4 (n = 174) consisted of middle-aged patients (mean 44.8 years) with a relatively short disease duration of 8.1 years. The highest propertion had the adult-onset subtype with MIRS category I, although late-onset disease was relatively common. This group showed a low overall disease burden with little multiorgan involvement and a high prevalence of short CTG repeat lengths.

External Validation

The validation cohort included 581 patients with a mean age of 43.6 years and a mean disease duration of 18.9 years. K-means cluster analysis on the validation cohort resulted in 4 clusters with 114, 141, 165, and 161 patients, respectively, within each cluster. The average adjusted Rand index was

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Table 1 Demographic and Clinical Characteristics of the 4 Clusters in the Discovery Data Set

Variable	Baseline cohort (n = 658)	Cluster 1 (n = 166)	Cluster 2 (n = 169)	Cluster 3 (n = 149)	Cluster 4 (n = 174)	Adjusted *p* value
Sex, n (%)						<0.001
Female	373 (56.7)	107 (64.5)	91 (53.8)	77 (51.7)	98 (56.3)	
Male	285 (43.3)	59 (35.5)	78 (46.2)	72 (48.3)	76 (43.7)	
Age, y (SD)	45.3 (14.3)	43.9 (13.6)	50.3 (11.9)	42.0 (14.5)	44.8 (15.7)	<0.001
Disease duration, y (SD)	13.2 (10.4)	12.6 (9.6)	20.9 (10.6)	11.4 (8.8)	8.1 (8.0)	<0.001
CTG repeat category, n (%)						<0.001[a]
50–150	212 (32.2)	56 (33.7)	21 (12.4)	34 (22.8)	101 (58.1)	
>150	344 (52.3)	90 (54.2)	98 (58.0)	101 (67.8)	55 (31.6)	
Unknown	102 (15.5)	20 (12.1)	50 (29.6)	14 (9.4)	18 (10.3)	
Inheritance pattern, n (%)						0.454[a]
Maternal	204 (31.0)	49 (29.5)	58 (34.3)	44 (29.4)	53 (30.5)	
Paternal	393 (59.7)	100 (60.2)	103 (70.0)	89 (59.7)	101 (58.0)	
Unknown	61 (9.3)	17 (10.3)	8 (4.7)	16 (10.7)	20 (11.5)	
Phenotype, n (%)						<0.001[a]
Congenital	19 (2.9)	5 (3.0)	7 (4.1)	3 (2.0)	4 (2.3)	
Childhood	118 (17.9)	37 (22.3)	34 (20.1)	34 (22.8)	13 (7.5)	
Adult	406 (61.7)	104 (62.7)	128 (75.7)	87 (58.4)	87 (50.0)	
Late-onset	115 (17.5)	20 (12.0)	0 (0.0)	25 (16.8)	70 (40.2)	

[a] χ^2 test.

0.68. After centroid matching using the Hungarian algorithm, clusters in the validation cohort corresponded closely to clusters in the discovery cohort. The cluster profiles in the validation data set demonstrated a similar pattern of disease severity across the different domains as the discovery data set (Figure 2B).

Figure 1 Principal Component Analysis Score Plot Indicating K-Means Cluster Membership as Indicated in the Legend

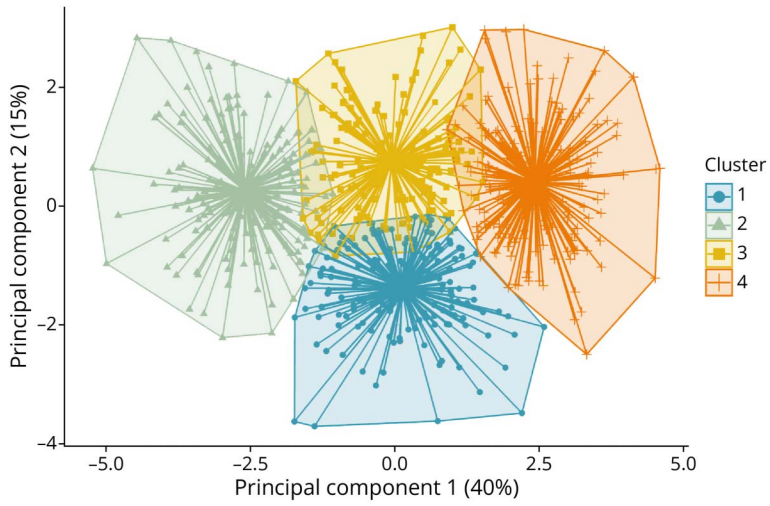

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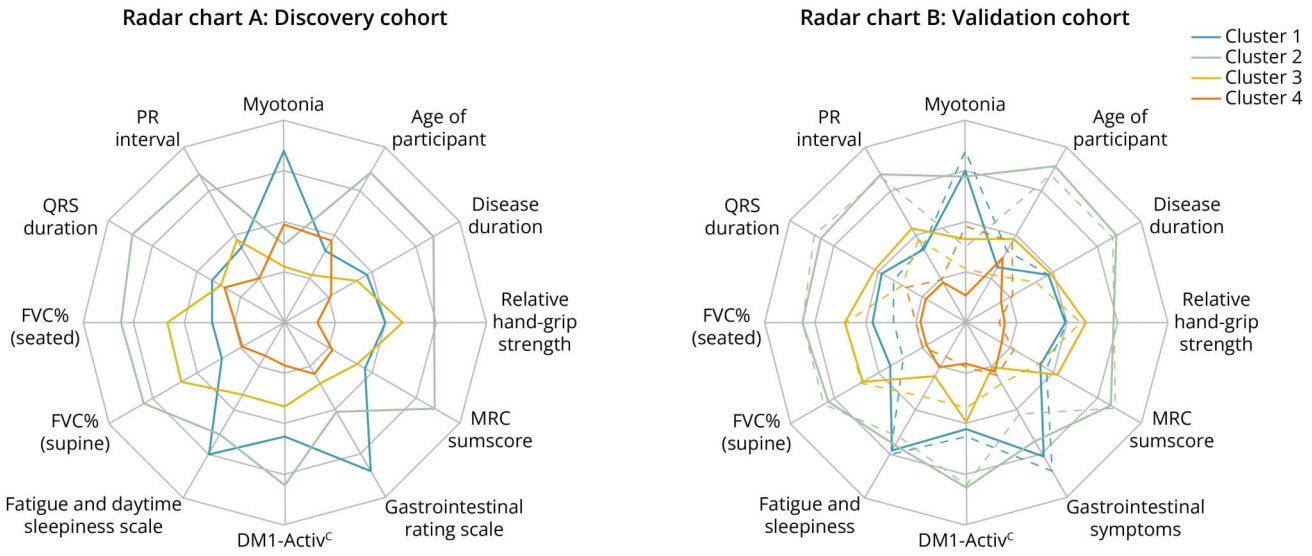
Figure 2 Radar Chart of Disease Characteristics per Cluster in the Discovery and Validation Cohort



Note: For Figure 2B, the discovery cohort is shown as dotted lines for ease of comparison. For the radar chart visualization, variables were recoded such that values closer to the center of the chart represent more favorable disease outcomes, a shorter disease duration or younger age. This transformation was applied to ensure consistent interpretation. Z-score scaling was used for visualization. FVC = Forced Vital Capacity, MRC = Medical Research Council.

Discussion

In this study, we identified 4 reproducible clinical subgroups of DM1 with distinct disease characteristics. The consistency of these clusters across 2 independent data sets supports their robustness and suggests that they reflect clinically meaningful phenotypes rather than statistical artefacts.

Clustering captured the known spectrum of mild and severe disease manifestations, as exemplified by clusters 2 and 4. These clusters show substantial overlap to phenotypes already familiar to clinicians. Cluster 2 predominantly comprises adult-onset patients with severe disease manifestations across the multisystemic spectrum and higher CTG repeats, whereas cluster 4 predominantly comprises patients with milder disease manifestations and lower CTG repeats. The overlap with clinically recognized phenotypic patterns supports the clinical relevance of this clustering approach. However, the clusters were derived using a data-driven approach based on similarity between input variables and therefore do not represent a one-

Table 2 Motor and Muscle Characteristics of the 4 Clusters in the Discovery Data Set

Variable	Baseline cohort (n = 658)	Cluster 1 (n = 166)	Cluster 2 (n = 169)	Cluster 3 (n = 149)	Cluster 4 (n = 174)	Adjusted *p* value
Myotonia, s (SD)[a]	4.14 (4.4)	7.1 (6.8)	3.3 (2.8)	2.4 (2.5)	4.1 (3.9)	<0.001
Percentage predicted hand grip strength (SD)[a]	37.1 (30.3)	37.46 (22.38)	11.6 (10.7)	28.6 (17.6)	71.9 (27.9)	<0.001
MRC sum score (SD)[a]	101.0 (10.8)	102.1 (7.4)	87.6 (12.5)	103.7 (5.0)	108.6 (2.5)	<0.001
MIRS category (%)						<0.001[b]
I	89 (13.5)	11 (6.6)	0 (0.0)	9 (6.0)	69 (39.7)	
II	140 (21.3)	41 (24.7)	11 (6.5)	41 (27.5)	47 (27.0)	
III	194 (29.5)	50 (30.1)	50 (29.6)	67 (45.0)	27 (15.5)	
IV	117 (17.8)	35 (21.1)	65 (38.5)	12 (8.1)	5 (2.9)	
V	29 (4.4)	3 (1.8)	25 9 (14.8)	1 (0.7)	0 (0.0)	
Unknown	89 (13.5)	26 (15.7)	18 (10.6)	19 (12.7)	26 (14.9)	

Abbreviations: MRC = Medical Research Council, MIRS = Muscular Impairment Rating Scale.
[a] Variables were used as input variables for cluster analysis.
[b] χ^2 test.

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Table 3 Respiratory Characteristics of the 4 Clusters in the Discovery Data Set

Variable	Baseline cohort (n = 658)	Cluster 1 (n = 166)	Cluster 2 (n = 169)	Cluster 3 (n = 149)	Cluster 4 (n = 174)	Adjusted *p* value
FVC%, sitting/standing position (SD)[a]	76.4 (19.0)	85.0 (10.5)	54.3 (13.8)	69.9 (11.2)	92.9 (10.4)	<0.001
FVC%, supine position (SD)[a]	70.3 (21.4)	80.2 (12.9)	44.7 (15.5)	61.7 (12.1)	89.5 (9.5)	<0.001
ΔFVC % of predicted, sitting/standing to supine (SD)	6.5 (7.3)	5.2 (7.2)	10.8 (7.2)	7.5 (8.1)	3.1 (4.4)	<0.001
Noninvasive ventilation, n (%)						<0.001[b]
No	403 (61.2)	109 (65.7)	94 (55.6)	91 (61.1)	109 (62.6)	
Yes	138 (21.0)	33 (19.9)	64 (37.9)	34 (22.8)	7 (4.0)	
Unknown	117 (17.8)	24 (14.4)	11 (6.5)	24 (16.1)	58 (33.4)	

Abbreviations: FVC = Forced Vital Capacity.
[a] Variables were used as input variables for cluster analysis.
[b] χ^2 test.

to-one correspondence with congenital, childhood-onset, adult-onset, and late-onset subgroup classifications. Therefore, this clustering approach also enabled the identification of intermediate subgroups that are less well characterized in the literature, each defined by a unique combination of multisystemic involvement. These intermediate clusters showed comparable levels of muscular involvement, but they differed substantially in other aspects of disease manifestations. Specifically, cluster 1 showed the highest burden of gastrointestinal symptoms, fatigue and daytime sleepiness, and myotonia among all clusters, whereas cluster 3 showed more respiratory involvement. Patients in cluster 3 also reported better functional ability as reflected by scores in the DM1-Activ^C and worse hand grip strength than cluster 1. This pattern suggests that heterogeneity in DM1 is not a continuum of skeletal muscle impairment because patients with similar skeletal muscle impairment may present with different multisystemic manifestations. Cardiac abnormalities further illustrate this: Conduction disorders were found in most clusters and the presence of cardiac implants in all clusters, including those with relatively mild muscular impairment. This highlights the necessity for routine cardiac assessment in all patients, regardless of their skeletal muscle involvement, as stated in previous research.[35] Together, these results indicate that even when muscular involvement is (relatively) mild, thorough assessment and management of multisystemic issues are required.

The magnitude of myotonia observed across clusters suggests that myotonia does not progress linearly with overall disease severity. Specifically, the cluster with the greatest muscle impairment exhibited only mild myotonia, whereas the cluster with the most severe myotonia had relatively preserved muscular impairment. This observation is consistent with previous research that showed that severity of myotonia and muscle weakness do not correlate linearly.[36] This pattern indicates that myotonia may increase during earlier stages of disease progression but become less prominent with more

Table 4 Cardiac Characteristics of the 4 Clusters in the Discovery Data Set

Variable	Baseline cohort (n = 658)	Cluster 1 (n = 166)	Cluster 2 (n = 169)	Cluster 3 (n = 149)	Cluster 4 (n = 174)	Adjusted *p* value
ECG: PR interval, ms (SD)[a]	185.1 (38.9)	180.7 (30.0)	208.0 (42.7)	183.6 (41.8)	169.1 (30.6)	<0.001
ECG: QRS interval, ms (SD)[a]	109.1 (25.1)	105.2 (19.3)	125.2 (33.2)	103.0 (18.9)	102.2 (17.2)	<0.001
ECG: QTc interval, ms (SD)	425.5 (41.1)	424.6 (49.1)	437.6 (37.1)	421.6 (34.6)	418.8 (41.3)	0.012
Cardiac implant (%)						<0.001[b]
No	539 (81.9)	142 (85.6)	106 (62.7)	133 (89.3)	158 (90.8)	
Yes	89 (13.5)	16 (9.6)	56 (33.2)	9 (6.0)	8 (4.6)	
Unknown	30 (4.6)	8 (4.8)	7 (4.1)	7 (4.7)	8 (4.6)	

Abbreviations: ECG = electrocardiography, ms = milliseconds.
[a] Variables were used as input variables for cluster analysis.
[b] χ^2 test.

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Table 5 Gastrointestinal Symptoms Rating Scale, Fatigue, and Daytime Sleepiness Scale, and DM1-Activ^{C} of the 4 Clusters of the Discovery Data Set

Variable	Baseline cohort (n = 658)	Cluster 1 (n = 166)	Cluster 2 (n = 169)	Cluster 3 (n = 149)	Cluster 4 (n = 174)	Adjusted *p* value
Gastrointestinal Symptoms Rating Scale (SD)[a]	17.0 (14.0)	27.1 (15.0)	17.0 (12.7)	12.3 (11.2)	10.7 (10.5)	<0.001
Fatigue and Daytime Sleepiness Scale sum score (SD)[a]	36.4 (13.2)	47.8 (10.1)	41.6 (10.3)	33.1 (10.0)	24.9 (11.1)	<0.001
DM1-Activ^{C} sum score (SD)[a]	71.5 (21.1)	66.6 (13.5)	48.2 (13.9)	77.81 (14.2)	93.3 (10.0)	<0.001

[a] Variables were used as input variables for cluster analysis.

muscle weakness. This cluster profile suggests a nonlinear progression of myotonia, although the cross-sectional nature of the data does not allow for a direct assessment of longitudinal trajectory. Together, these findings indicate that myotonia may be driven by distinct pathophysiologic mechanisms.

Myotonia also tended to co-occur with gastrointestinal issues and fatigue. The mechanisms underlying the association between these variables remain unclear. Gastrointestinal symptoms are common in DM1 and may arise from multiple disease mechanisms, but how these relate to specific symptoms such as myotonia is not well established. However, similar constellations of symptoms have been reported previously, with studies reporting that that hand stiffness, fatigue and daytime sleepiness, and gastrointestinal problems co-occur frequently.[16]

Notably, fatigue and daytime sleepiness were present across all clusters, consistent with their high overall prevalence in DM1.[37] Their manifestation in different constellations, such as the combination of gastrointestinal complaints with more pronounced fatigue and sleepiness in cluster 1, suggests that these symptoms are not simply secondary to disease severity but may reflect shared underlying mechanisms. Several pathways may account for these associations. Sleep disturbances and excessive daytime sleepiness have been linked to functional gastrointestinal disorders such as irritable bowel syndrome and dyspepsia.[38-40] In DM1, autonomic dysfunction may impair gastrointestinal motility and sleep-wake regulation.[41,42] In addition, gastrointestinal disturbances such as small intestinal bacterial overgrowth, could reduce nutrient availability and therefore exacerbate fatigue.[43] Overall, this cluster analysis supports the notion that sleep, fatigue, and gastrointestinal complaints are interconnected and may arise from overlapping multisystemic processes.

An important consideration when interpreting the specificity of clusters is the role of sex differences in symptoms expression. For example, cluster 1 includes predominantly women, raising the possibility that the prominence of gastrointestinal complaints and fatigue in this group may partly reflect sex-related factors.[44] Similarly, cluster 3, which showed a higher degree of respiratory involvement, exhibited a slight predominance of male participants. This finding is consistent with earlier reporting suggesting more frequent pulmonary complications among males with DM1.[44] However, this pattern might also be shaped by broader contextual influences, such as occupational exposures and or lifestyle factors, rather than disease specific mechanisms alone. Similarly, differences in age, disease duration, and subtype may also contribute to the observed cluster characteristics. Like sex, these variables were not used to define the cluster profiles. These findings suggest that biological sex or other demographic variables may modulate the multisystemic expression of DM1 and may contribute to the observed heterogeneity.

The findings from this study have several important clinical and translation implications. Functional limitations in DM1 are multifactorial, arising from a combination of multisystemic manifestations, which underscore the need for multidisciplinary assessment and care. The identification of distinct clinical clusters offers a framework for patient stratification, enabling more personalized management tailored to the predominant symptoms and disease burden of each subgroup. These clusters also highlight the importance of using multidimensional outcome measures in clinical trials because conventional end points focusing on a single latent domain may fail to capture meaningful changes.

A key implication relates to patient selection for therapeutic trials. Many ongoing industry-led trials require prominent myotonia to serve as a proof of concept and relatively limited organ involvement. Our results indicate that this trial population corresponds largely to only one of several clinically meaningful clusters (primarily cluster 1). This mismatch has 2 major consequences: (1) it restricts the pool of eligible participants, making recruitment more challenging, and (2) it limits the generalizability of trial results to the broader DM1 population. In addition, cardiac involvement was observed across all clusters in this study, suggesting that exclusion based on cardiac manifestations may further reduce generalizability to the broader DM1 population. The clusters identified here therefore argue for broader, phenotype-informed inclusion criteria or, when appropriate, cluster-based stratification to ensure that trial populations better reflect real-world heterogeneity. These clusters are not intended to restrict eligibility criteria for trial participation or to exclude patients that do not fit into a specific subgroup. Rather, cluster-based stratification

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can enhance study design by creating more homogeneous patient subgroups, reducing variability and increasing the likelihood of detecting meaningful treatment effects. For example, trials could choose to align end points with the dominant symptoms of a cluster. This approach also informs the selection of appropriate outcome measures. Moreover, cluster information can serve as the basis for predictive models of disease progression and therapeutic responses, supporting more efficient and targeted clinical trials. An important consideration is whether these clusters represent relatively stable disease phenotypes or whether patients transition between these identified clusters over time as disease manifestations evolve. The identification of similar clusters profiles in an independent validation cohort indicate that the findings are reproducible. Nevertheless, the cross-sectional setup of the study precludes conclusions regarding the stability of cluster membership over time. Therefore, longitudinal studies are required to determine whether patients remain within these clusters or transition between them as disease manifestations evolve.

This study also has limitations. First, DM1 displays numerous potential disease manifestations involving many different organs and tissues. This study attempted to cluster patients using frequently reported disease outcomes. However, no information was available on neurocognitive symptoms (such as executive cognitive functioning, social functioning, information processing speed, and episodic memory), urogenital symptoms, and endocrine symptoms because these variables were not available in the registry. Including these variables could have resulted in different cluster allocations. Alternative clustering approaches and variable selections may therefore reveal different subgroup structures and warrant further investigation. Approaches anchored on a specific disease domain, such as cardiac, muscular, or cognitive involvement, may be complementary to the unsupervised strategy used here and could be particularly informative for risk stratification and therapeutic targeting. Second, patients were recruited at the neurology outpatient clinic, which may limit representativeness of the entire patient population. Possibly, the included patients are more severely affected because minimally affected patients may not seek medical care. Conversely, patients with a high disease burden might decline participation, also introducing potential bias. Similarly, this study excluded patients younger than 18 years. As a result, individuals with the congenital form of DM1 were mostly excluded from this study. Therefore, these findings cannot be extrapolated to patients with congenital DM1. Third, data imputation may introduce inaccuracies as the data missingness pattern are not well understood. Nevertheless, the impact of imputation is likely minimal: The MICE algorithm was deemed appropriate because the trace plots, density plots, and similarity between the correlation matrices of observed and imputed values did not indicate issues with the imputation process.

In conclusion, this study delineates distinct and clinically relevant DM1 subgroups, demonstrating that functional limitations arise from diverse multisystemic patterns rather than a simple severity continuum. These findings provide a foundation for more precise patient stratification and highlight the need for trial designs and outcome measures that better reflect the full spectrum of DM1 phenotypes.

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Author Contributions

L.A. la Fontaine: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J.W.T.M. de Kok: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Imkamp: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D. Van As: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J.E. Bruijnes: drafting/revision of the manuscript for content, including medical writing for content. P.A.C. 't Hoen: drafting/revision of the manuscript for content, including medical writing for content. B.A.H. Vosse: drafting/revision of the manuscript for content, including medical writing for content. S.M.J. van Kuijk: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I.-S.J. Merkies: drafting/revision of the manuscript for content, including medical writing for content. C.G. Faber: drafting/revision of the manuscript for content, including medical writing for content. K. Mul: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data.

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Disclosure

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/NG.

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