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Natural history of Becker muscular dystrophy: *DMD* gene mutations predict clinical severity

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Becker muscular dystrophy (BMD) is an X-linked neuromuscular disease attributable to mutations in *DMD*, leading to a deficient and less functional dystrophin, mainly in skeletal and cardiac muscle. Understanding the natural history of BMD is crucial for optimizing patient care and developing targeted treatments.

Retrospective data were collected from 943 patients diagnosed with BMD based on a combination of clinical, biochemical and genetic criteria followed by 17 Italian neuromuscular centres. Patients' demographics, main signs and symptoms at BMD onset, neuropsychiatric comorbidities, age at loss of ambulation, cardiac left ventricular ejection fraction, pulmonary forced vital capacity and *DMD* mutations were collected. Disease milestones were analysed in specific *DMD* mutational groups.

The median age at the last assessment was 26.0 (16.6–41.9) years, with a median age at diagnosis of 7.5 (4.0–14.0) years. In 55% of patients, the diagnosis was prompted by the incidental finding of hyperCKaemia. At the last assessment, 13.5% of patients had lost the ability to walk at a median age estimated by Kaplan–Meier analysis of 69 years. Thirty per cent of patients exhibited left ventricular impairment and 2.7% respiratory involvement. Ten per cent of patients carried out-of-frame mutations, 4% nonsense mutations and 86% in-frame deletions/duplications. The subset of in-frame deletions was classified further based on the specific mutations. Patients carrying del45–49 compared with del45–47 were associated with an earlier loss of ambulation ($P = 1 \times 10^{-4}$), whereas patients with del45–55 ($P = 0.005$), del48 ($P = 0.02$) and del48–49 ($P = 0.02$) were correlated with a later loss of ambulation compared with del45–47.

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Both del45–55 ($P = 0.002$) and del48 ($P = 0.003$) were significantly associated with decreased odds of developing a pathological left ventricular ejection fraction compared with del45–47.
Our results contribute to a better understanding of the natural history of BMD and capture precious data in the era of emerging therapies. The knowledge of the specific *DMD* mutation might help to define a prognosis in a subset of BMD patients and will serve as a model for the design of future therapies.

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Introduction

Becker muscular dystrophy (BMD, OMIM #300376) is an X-linked, rare inherited disease caused by mutations in *DMD*, which encodes dystrophin, a pivotal constituent of the dystrophin–glycoprotein complex.[1]

The absence of dystrophin, usually caused by out-of-frame mutations, causes the severe Duchenne muscular dystrophy (DMD, #310200) phenotype.[1,2] If dystrophin is produced in muscle cells, albeit reduced in quantity and/or with abnormal molecular weight,[3,4] as mostly occurring with 'in-frame' mutations, the resulting phenotype is BMD. BMD patients show a variable clinical picture,

including myalgias, limb-girdle weakness[1] leading to wheelchair dependency usually after the age of 16 years,[2,5] or isolated elevation of serum creatine kinase (CK) without overt muscle weakness.[6] Some individuals may also be asymptomatic, with calf pseudohypertrophy, or affected by dilated cardiomyopathy (XLCM or CMD3B; OMIM #302045) only.[7] Dilated cardiomyopathy can occur in 70% of BMD patients, representing the leading cause of death,[8] whereas respiratory insufficiency is uncommon and mostly restricted to non-ambulatory patients.[9] The role of dystrophin extends to the brain. Loss of *DMD*-related brain functions causes intellectual disability, learning difficulties or behavioural problems, which are frequent in DMD and BMD.[10]

The most common BMD mutations are deletions (60%–70%) and duplications (5%–10%), involving one or more exons. Single nucleotide variants, frameshift small deletions–insertions and splice site variants account altogether for 20% of mutations.[5] Two main mutational hot spots are recognized in *DMD* in exons 45–55 and 1–10.[1,2]

Currently, there is no definitive cure for BMD. The high clinical variability, slow progression and rarity of the disease represent barriers to drug development. We present retrospective clinical data from a large cohort of BMD patients to define disease milestones better in specific mutational subgroups.

Materials and methods

Enrolment and ethics statement

We included BMD patients from 17 Italian neuromuscular centres, according to the following clinical, biochemical and genetic criteria: confirmed diagnosis of BMD defined as: male AND confirmed *DMD* mutation (in-frame mutations) or out-of-frame or nonsense mutations (exception-to-the-rule) with BMD phenotype (milder clinical picture inconsistent with DMD) and with evidence of dystrophin expression by immunohistochemistry/immunofluorescence/western blot; alternatively, dystrophin protein of abnormal molecular weight and quantity in skeletal muscle assessed by western blot without *DMD* testing (patients included in the overall cohort description but excluded from genotype–phenotype correlation).

Muscle biopsy was available in 369 patients (39% of the cohort). In all muscle biopsies, dystrophin, assessed by western blot or immunofluorescence, was present above the level of traces, and the clinical phenotype was consistent with a diagnosis of BMD. Muscle biopsy was reviewed further only in the cases where it served as support to the diagnosis.

Clinical investigations adhered to the Declaration of Helsinki, and written informed consent, approved by institutional review boards, was obtained from all participants or their guardians in accordance with ethical requirements. The coordinating centre institutional review board protocol number is 5310/AO/22.

Clinical data

Family and medical history and disease end points, including age at diagnosis, age at loss of ambulation (LoA) defined as continuous wheelchair use, and age at loss of ability to run (LoR), were recorded for each participant. The principal signs and symptoms at onset were documented.

When available, left ventricular ejection fraction (LVEF) as an indicator of left ventricular systolic function, and forced vital capacity (FVC) as a marker of respiratory muscle function were recorded. Impaired LVEF was defined as <55%, whereas impaired FVC as <50% of predicted values. Information regarding glucocorticoid (GC) therapy, cardiological drugs, implantable cardioverter–defibrillator or pacemaker implantation, cardiac transplantation and non-invasive ventilation were recorded. Neuropsychiatric comorbidities, including epilepsy, seizures, neurodevelopmental and psychiatric disorders, were also noted.

Genetic data

DMD mutation data were collected from genetic reports at each centre. Detailed information on the genetic tests used was available for 212 (22.5%) patients. Multiplex ligation-dependent probe amplification (MLPA) was used in 170, next generation sequencing (NGS)/Sanger sequencing in 25, and multiplex PCR followed by confirmation of the boundaries of the deletion/duplication in 17. Mutations were grouped by single/multiple exon deletions or duplications, and small mutations: nonsense, missense, pathogenic synonymous, frameshifting and splicing site. Mutational groups specifically analysed were nonsense, in-frame (IF) and out-of-frame (OF) mutations.

Statistical analyses

Categorical values were described as frequencies/percentages, and continuous values were described as the mean [±standard deviation (SD)], with 95% confidence interval (CI) and median [interquartile range (IQRs)], as appropriate. Categorical comparisons were conducted using Fisher's exact test where applicable. We performed time-to-event analyses for LoA/LoR, with age as a time variable (Kaplan–Meier method), and compared subgroups by log-rank test or Cox regression as appropriate. Odds ratios (ORs) for pathological LVEF% were calculated by multivariate logistic regression, and significance was estimated by Wald's test. We used multivariate linear regression to estimate effects of age at last assessment and *DMD* mutations on the FVC%. The significance level was set at $P < 0.05$. Analyses were performed using R v.4.2.2.

Results

Description of the cohort

We collected data from 943 BMD patients from 17 Italian neuromuscular centres. We identified 152 familial cases belonging to 71 families. Demographic data were available for 890 (94.4%) patients: the age at last assessment ranged from 1.6 to 86.2 years, with a mean age of 30.0 (±17.0) years and a median age of 26.0 (16.6–41.9) years. Three hundred and nineteen (35.8%) patients had an age at last assessment <20 years, 319 (35.8%) between 20 and 40 years, 196 (22.0%) between 40 and 60 years, and 56 (6.3%) >60 years. Age at diagnosis was available for 589 (62.5%) patients, with a mean of 12.6 (±14.4) years and a median of 7.5 (4.0–14.0) years. Symptoms or signs at onset were known for 593 (62.9%) patients. The most frequently observed sign was an incidental finding of elevated serum CK present in 325 (54.8%) patients; followed by myalgia/cramps in 71 (12.0%) patients. Seven patients (1.2%) reported delayed acquisition of motor milestones. Gait abnormalities were observed in 38 (6.4%) individuals, difficulties in running in 26 (4.4%), difficulties in climbing stairs in 24 (4.1%), frequent falls in 10 (1.7%), and difficulties in getting up from the floor in nine (1.5%). Rhabdomyolysis or myoglobinuria was reported in 15 (2.5%), dilated cardiomyopathy in three (0.5%), and behavioural problems in two (0.3%). Other unspecified symptoms were present in 63 individuals (10.6%). Several patients presented with multiple symptoms at onset.

Table 1 Mutation frequencies

	n (%)		*n* (%)
Mutation group			
Exon deletions	775 (85.8)	–	–
Exon duplications	50 (5.5)	–	–
Small mutations	78 (8.6)	Frameshift indel	7 (9.0)
		In-frame indel	7 (9.0)
		Missense	10 (12.8)
		Nonsense	35 (44.9)
		Splicing mutations/deep intronic mutations	16 (20.5)
		Pathogenic synonymous	3 (3.8)
Reading frame group			
In-frame	779 (86.3)	–	–
Nonsense	35 (3.9)	–	–
Out-of-frame	89 (9.9)	–	–

Neuropsychiatric comorbidities

Out of the 552 (58.5%) patients for whom data was available, 55 (10.0%) had reported learning deficits. Information about behavioural disorders was obtained in 583 (61.8%) patients: 17 (2.9%) patients were reported to be diagnosed with attention-deficit/hyperactivity disorder, one (0.2%) with obsessive–compulsive disorder, five (0.9%) with autism spectrum disorder, and one patient had the co-occurrence of autism spectrum disorder and obsessive–compulsive disorder (0.2%). Thirty (5.2%) individuals were affected by unspecified behavioural issues.

Other behavioural/psychiatric disorders were collected in 517 (54.8%) patients, including: generalized anxiety disorder in 10 (1.9%), major depression in five (1.0%), low mood in five (1.0%), co-occurrence of major depression and low mood in one (0.2%), bipolar disorder in three (0.6%), eating disorders in two (0.4%), personality disorders in two (0.4%), schizophrenia in two (0.4%), and unspecified psychiatric disease in nine (1.7%) patients.

Information regarding medical history of epilepsy and febrile seizures status was available for 169 of 943 patients in the cohort (17.9%). Among these 169 patients, epilepsy was reported in 12 (7.1%), febrile seizures in four (2.4%), and two patients (1.2%) had seizures that were not specified further.

DMD mutation analyses

DMD mutations were known for 903 (95.8%) patients: 775 (85.8%) had deletions, 50 (5.5%) duplications and 78 (8.6%) small variants (Table 1). The latter included seven (9.0%) frameshifting mutations, seven (9.0%) non-frameshifting indel mutations, 10 (12.8%) missense mutations, 35 (44.9%) nonsense mutations, 16 (20.5%) splicing sequences mutations affecting the splicing process or deep intronic mutations, and three (3.8%) pathogenic synonymous mutations (Table 1). Frequencies of individual exon deletions and duplications are reported in Figs 1 and 2. For further analyses, we grouped deletions from exon 1 to exon 9 as deletions at the N-terminal domain (delN-term).

We also grouped the *DMD* mutations according to the maintenance of the reading frame: 86.3% of patients (779) carried IF mutations, 3.9% (35) nonsense mutations and 9.9% (89) OF mutations (Table 1).

Analyses of loss of ambulation and loss of ability to run

Information about LoA was known for 822 (87.2%) patients; of these, 111 (13.5%) patients had lost the ability to walk at the time of data collection, with a mean age at LoA of 35.3 (±15.0) years (Table 2 and Supplementary Table 1). Information about LoR was available for 552 (58.5%) patients. One hundred and forty (25.4%) had experienced the loss of their ability to run at the time of data collection. The mean age at which LoR occurred was 24.4 (±12.3) years (Table 3 and Supplementary Table 1). We estimated a median age at LoA of 69 years and a median age at LoR of 40 years (Figs 3A and 4A and Tables 2 and 3) by the Kaplan–Meier method.

Glucocorticoid information was collected for 597 (63.3%) patients whose ambulatory status was known; of these, 38 (6.4%) underwent GC treatment ≥1 year before LoA. When comparing patients who underwent GC treatment with those who did not, we observed median ages at LoA of 43 versus 77 years ($P = 2 \times 10^{-8}$; Fig. 3B, Table 2 and Supplementary Table 2).

Comparing patients carrying nonsense, IF and OF mutations, we observed that OF mutation carriers experienced significantly earlier LoA in comparison to patients with IF mutations, with median ages estimated by the Kaplan–Meier method of 42 versus 70 years ($P = 9 \times 10^{-12}$; Fig. 3C and Table 2). The worse outcome of OF mutations on the age at LoA was supported further by the Cox regression analysis (HR: 5.1, 95% CI: 3.1–8.4, $P = 1 \times 10^{-10}$; Table 2).

Within the subset of patients carrying in-frame exon deletions of *DMD*, we conducted a comparative analysis between the patients carrying deletions of exons 45–47 (del45–47) versus patients with del45–48, del48, del48–51, del45–55, del45–51, del45–53, del48–49, del45–49, delN-term and the 'other' subgroup, including the remaining in-frame deletions (Fig. 3D and Table 2).

No patients with del45–55, del48, del48–49 and del48–51 experienced loss of walking ability. The patients with del45–55 ($P = 0.005$), del48 ($P = 0.02$) and del48–49 ($P = 0.02$) showed a statistically significant later median at LoA. In contrast, patients with del45–49 exhibited a statistically significant earlier median age at LoA in comparison to patients with del45–47 ($P = 1 \times 10^{-4}$).

Cox regression analysis confirmed that patients carrying del45–49 had a significantly higher risk of LoA in comparison to individuals with del45–47 (HR: 4.1, 95% CI: 1.8–9.2, $P = 7 \times 10^{-4}$; Table 2).

We applied a similar approach to assess the LoR (Fig. 4B–D and Table 3). Patients with the del45–47 mutation showed a significantly earlier median at LoR in comparison to the 'other' group (HR: 0.1, 95% CI: 0.0–0.2; $P = 2 \times 10^{-6}$). Del45–51 (HR: 0.1, 95% CI: 0.0–0.6; $P = 0.01$), del45–55 (HR: 0.1, 95% CI: 0.0–0.3; $P = 2 \times 10^{-4}$), del48 (HR: 0.03, 95% CI: 0.00–0.25; $P = 9 \times 10^{-4}$) and del48–51 (HR: 0.1, 95% CI: 0.0–0.3; $P = 0.003$) were associated with a longer retention of the ability to run (Fig. 4D and Table 3).

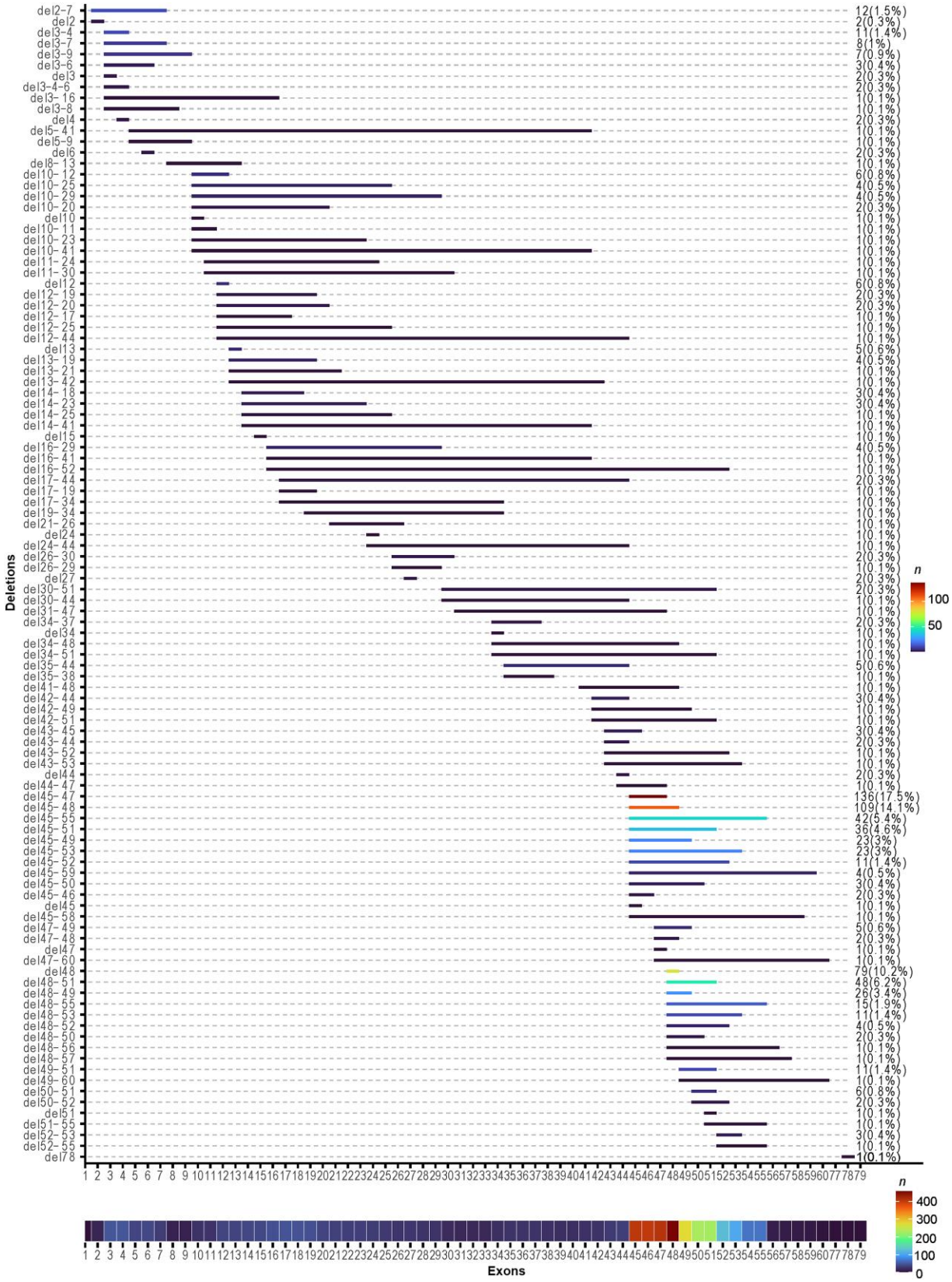

Figure 1 All exon deletions present in our cohort and exons deleted. Each exonic deletion is represented as a segment extending along the length of the deletion section. The colour is assigned based on the number of patients sharing the same mutation (indicated on the right with relative frequency), according to the colour code shown in the key. At the bottom, each exon is coloured based on the number of times it is deleted, according to the adjacent key.

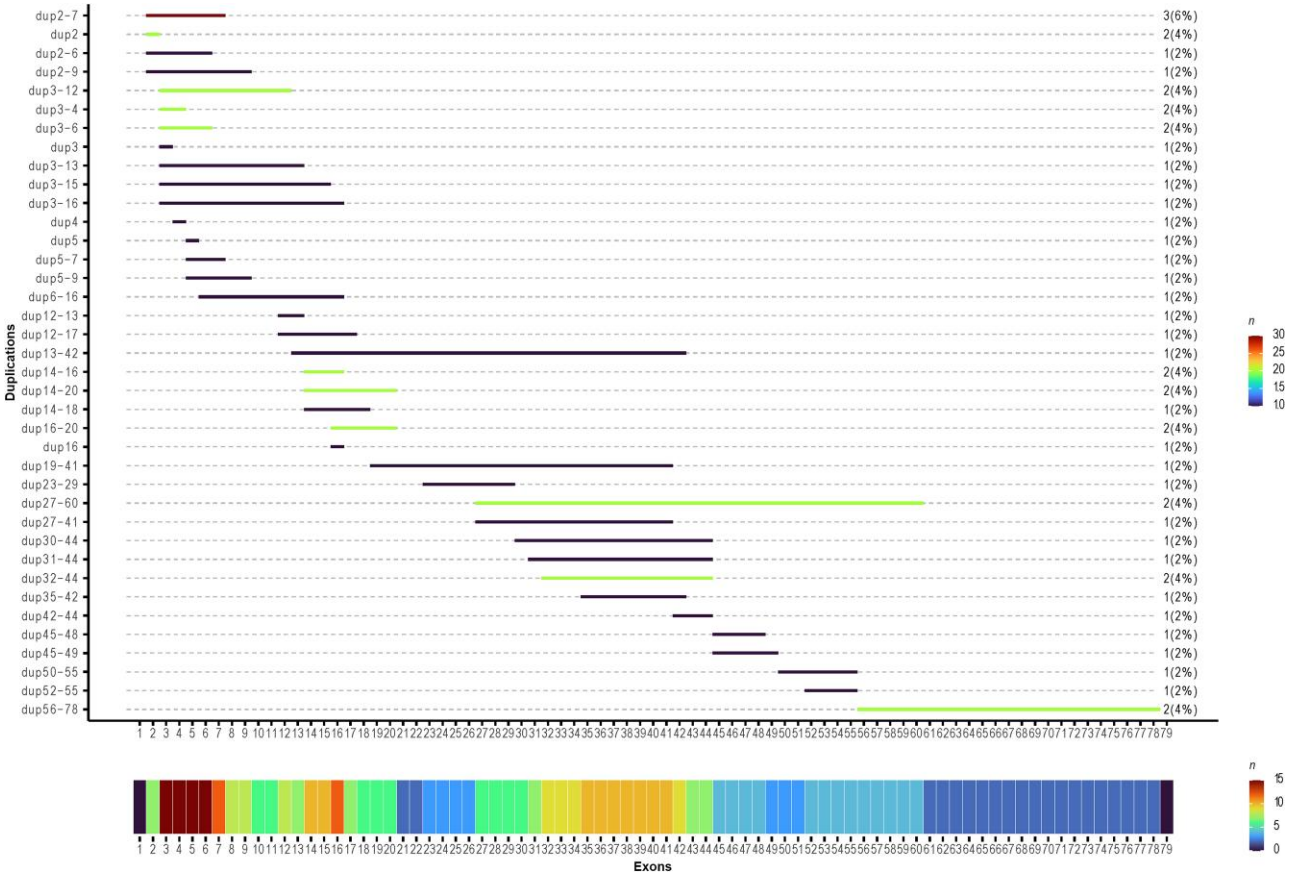

Figure 2 All exon duplications present in our cohort and exons duplicated. Each exonic duplication is represented as a segment extending along the length of the duplication section. The colour is assigned based on the number of patients sharing the same mutation (indicated on the right with relative frequency), according to the colour code shown in the legend. At the bottom, each exon is coloured based on the number of times it is duplicated, according to the adjacent legend.

Table 2 Proportions of ambulant patients in the Becker muscular dystrophy cohort and hazard ratios calculated by cox regression to compare different subgroups

Patients[a]		Events[b]	Median age[c], years	Proportion of ambulant patients at			HR (95% CI)	*P*-value
				20 years	40 years	60 years		
Total cohort ($n = 822$)		111 (13.5)	69	0.97	0.83	0.59	–	–
GC pre-LoA ($n = 597$)	No ($n = 559$)	55 (9.8)	77	0.99	0.87	0.68	–	–
	Yes ($n = 38$)	12 (31.6)	43	0.90	0.54	0.00	5.3 (2.8–10.1)	4×10^{-7}
Reading frame ($n = 789$)	In-frame ($n = 686$)	68 (9.9)	70	0.98	0.88	0.66	–	–
	Nonsense ($n = 29$)	5 (17.2)	NA	0.96	0.77	0.58	1.7 (0.7–4.3)	0.23
	Out-of-frame ($n = 74$)	22 (29.7)	42	0.90	0.53	0.40	5.1 (3.1– 8.4)	1×10^{-5}
Mutation groups ($n = 622$)	del45–47 ($n = 124$)	19 (15.3)	66.3	1.00	0.88	0.53	–	–
	del45–48 ($n = 95$)	16 (16.8)	66	1.00	0.90	0.57	0.8 (0.4–1.5)	0.46
	del45–49 ($n = 21$)	9 (42.9)	41	0.94	0.62	0.00	4.1 (1.8–9.2)	7×10^{-4}
	del45–51 ($n = 31$)	1 (3.2)	NA	1.00	1.00	0.75	0.5 (0.1–3.8)	0.51
	del45–53 ($n = 20$)	1 (5.0)	NA	1.00	0.90	0.90	1.1 (0.2–8.5)	0.91
	del45–55 ($n = 40$)	0 (0.0)	NA	1.00	1.00	1.00	–	–
	del48 ($n = 68$)	0 (0.0)	NA	1.00	1.00	1.00	–	–
	del48–49 ($n = 23$)	0 (0.0)	NA	1.00	1.00	1.00	–	–
	del48–51 ($n = 42$)	0 (0.0)	NA	1.00	1.00	1.00	–	–
	delN-term ($n = 33$)	4 (12.1)	NA	0.91	0.85	0.64	1.5 (0.5–4.4)	0.48
	Other ($n = 125$)	7 (5.6)	77	1.00	0.88	0.78	0.6 (0.2–1.5)	0.27

CI = confidence interval; GC = glucocorticoids; HR = hazard ratio; LoA = loss of ambulation; NA = not applicable.
[a]Number of patients for whom information about LoA was available.
[b]Number (percentage) of events, considering the loss of the ability to walk as an event.
[c]Median age estimated by Kaplan–Meier method.

Table 3 Proportion of patients able to run in the Becker muscular dystrophy cohort and hazard ratios calculated by Cox regression to compare different subgroups

Patients[a]		Events[b]	Median age[c], years	Proportion of patients able to run at			HR (95% CI)	P-value
				20 years	40 years	60 years		
Total cohort ($n = 552$)		140 (25.4)	40	0.82	0.49	0.32	–	–
GC pre-LoA ($n = 472$)	No ($n = 448$)	122 (27.2)	40	0.83	0.49	0.34	–	–
	Yes ($n = 24$)	8 (3.3)	30	0.68	0.48	0.48	1.6 (0.8–3.3)	0.19
Reading frame ($n = 789$)	In-frame ($n = 476$)	112 (0.2)	45.0	0.85	0.51	0.33	–	–
	Nonsense ($n = 23$)	8 (0.4)	32.2	0.80	0.50	0.33	1.2 (0.6–2.5)	0.56
	Out-of-frame ($n = 44$)	16 (0.4)	30.0	0.63	0.22	0.22	2.0 (1.2–3.4)	0.01
Mutation groups ($n = 425$)	del45–47 ($n = 75$)	35 (46.7)	25.0	0.65	0.21	0.00	–	–
	del45–48 ($n = 55$)	24 (43.6)	30.0	0.79	0.35	0.17	0.7 (0.4–1.1)	0.11
	del45–49 ($n = 11$)	7 (63.6)	25.0	0.67	0.00	0.00	1.7 (0.7–3.8)	0.21
	del45–51 ($n = 23$)	1 (4.3)	NA	1.00	0.75	0.75	0.1 (0.0–0.6)	0.01
	del45–53 ($n = 12$)	2 (16.7)	NA	1.00	0.67	0.67	0.3 (0.1–1.4)	0.13
	del45–55 ($n = 33$)	2 (6.1)	NA	0.95	0.87	0.87	0.1 (0.0–0.3)	2×10^{-4}
	del48 ($n = 54$)	1 (1.9)	NA	1.00	0.83	0.83	0.03 (0.0–0.3)	9×10^{-4}
	del48–49 ($n = 14$)	7 (50.0)	38.0	1.00	0.29	0.00	0.5 (0.2–1.2)	0.15
	del48–51 ($n = 33$)	1 (3.0)	NA	0.97	0.97	0.97	0.1 (0.0–0.3)	0.003
	delN-term ($n = 27$)	10 (37.0)	40.0	0.72	0.27	0.13	0.7 (0.4–1.5)	0.37
	Other ($n = 88$)	5 (5.7)	80.6	0.94	0.88	0.88	0.1 (0.0–0.2)	2×10^{-6}

CI = confidence interval; GC = glucocorticoids; HR = hazard ratio; LoR = loss of ability to run; NA = Not Applicable.
[a]Number of patients for whom information about LoR was available.
[b]Number (percentage) of events, considering the loss of the ability to run as event.
[c]Median age estimated by Kaplan–Meier method.

Analyses of left ventricular systolic function

LVEF% was known for 621 (65.9%) patients. LVEF% ranged from 15% to 84%, with a mean of 55.9% (±11.1%) and a median of 60% (51%–63%) at a mean age of 30.0 (±16.5) years. One hundred and eighty-seven (30.1%) patients showed LVEF% of <55% (Supplementary Fig. 1A and Table 4).

Among these 621 patients, 206 (33.2%) were or had been under cardiac pharmacological treatment, and eight (1.3%) patients underwent a cardiac transplant. However, it should be noted that two of them underwent transplants before the recorded LVEF% value; hence, they have been excluded from the further analyses. In our cohort, one (0.2%) patient had a pacemaker implant and 24 (3.9%) used implantable cardioverter–defibrillators.

Multivariate logistic regression, incorporating the age at last assessment as a covariate, was used to calculate the adjusted odds ratios (adj.ORs) in patients with a specific deletion in comparison to patients with del45–47. Del45–55 (adj.OR: 0.1, 95% CI: 0.0–0.5, $P = 0.002$), del48 (adj.OR: 0.1, 95% CI: 0.0–0.5, $P = 0.003$) and 'other' in-frame deletions (adj.OR: 0.2, 95% CI: 0.1–0.5, $P = 4 \times 10^{-4}$) are associated with decreased odds of having pathological values of LVEF%. On the contrary, the odds of having a pathological LVEF% seem to increase slightly with age at the last assessment (adj.OR: 1.1, 95% CI: 1.0–1.1, $P = 9 \times 10^{-10}$; Supplementary Table 2).

Analyses of respiratory function

FVC% values at the last respiratory assessment were obtained for 441 (46.8%) patients, ranging from 20% to 174%, with a mean FVC% of 91.8% (±19.4%) and a median of 94.0% (81.0%–103.0%) at a mean age of 28.9 (±16.1) years. Only 12 patients (2.7%) had FVC% values of <50%, and all of them were non-ambulant (Supplementary Fig. 1B and Table 4). Twenty-eight of 559 (5.0%) patients used non-invasive ventilation.

Multivariate linear regression was used to calculate the effect of specific deletions with respect to del45–47 on FVC%, incorporating the age at last assessment as a covariate. None of the examined deletions showed a significant effect (Supplementary Table 3).

Analyses of discordant familiar phenotypes

Phenotypic divergence among related patients with the same *DMD* mutation was observed in 29 of 71 families (40.8%). In 20 of these families (28.2%), only one family member exhibited neuropsychiatric conditions. However, in two families (2.8%), both brothers were affected by different neuropsychiatric conditions. For example, in a pair of twins with the p.(Glu1343*) nonsense mutation, one had attention-deficit/hyperactivity disorder and generalized anxiety disorder, while the other was diagnosed with autism spectrum disorder, learning deficits and bipolar disorder.

Significant differences in LoA were reported in 4 of 71 families (5.6%). For instance, in one family with three siblings carrying a three-nucleotide in-frame deletion, p.(Lys226del), the youngest and oldest brothers remained ambulant at 63.9 and 57.8 years, whereas the middle brother lost ambulation at 22 years. In another case, involving three brothers with the del45–47, the oldest lost ambulation at 34 years, whereas the other two become non-ambulant at 40 and 41 years, respectively. Differences in cardiac function were also observed in 6 of 71 families (8.5%). For example, in a set of three brothers, the youngest displayed more severe left ventricular dysfunction, with an LVEF of 18% at 44 years, in comparison to the LVEF values of 47% and 51% in his brothers at 45 and 46 years, respectively.

No comparisons were conducted among familial and isolated cases in terms of outcome measures or frequency of the *DMD* mutations observed.

Incidental finding of elevated serum creatine kinase and *DMD* mutations

In order to verify whether BMD diagnosis initiated by hyerCKaemia was associated with 'milder' *DMD* mutations, we compared the

subset of patients with del45–47 with each mutational group by assessing the number of patients whose diagnosis was prompted by incidental findings of elevated serum CK and the number of patients with other symptoms or signs at onset. We observed a significantly higher number of patients with del45–51 ($P < 0.001$), del45–55 ($P = 0.04$), del48 ($P = 0.001$) and del48–51 ($P < 0.001$) in the hyperCKaemia subset of patients (Supplementary Table 4).

Discussion

We present here the relevant disease milestones and genotype–phenotype correlations in a cohort of >900 BMD patients, the largest reported to date. BMD is part of the dystrophinopathy spectrum, which ranges from the severe Duchenne muscular dystrophy to asymptomatic BMD cases. Diagnosis BMD can be particularly challenging, especially in younger patients, and often requires a comprehensive approach that integrates clinical, biochemical and molecular data.

Symptoms/signs at onset reflected the clinical heterogeneity of BMD. HyperCKaemia, followed by several muscular symptoms, were the most common presenting features (~55%) in our cohort. There are few large studies reporting symptoms at BMD onset: in a recent Japanese multicentre study of 225 patients, skeletal muscle symptoms were the most common symptoms that triggered patient diagnoses (60%), followed by asymptomatic hyperCKaemia (~32%), CNS (~5%) and cardiac complications (~2%),[11] whereas in a smaller cohort of 67 European BMD patients calf pain was the main symptom at onset (27.5%), followed by abnormal motor performances in 67%.[12] In Italy, CK levels are routinely assessed before surgery or in children with vomiting, diarrhoea or prolonged fever,[13,14] accounting for frequent incidental findings of elevated CK.

Mutation distribution was confirmative of the literature data. Deletions were the most common mutations (~86%) and clustered within the mutational hot spot in exons 45–55, consistent with prior studies.[2,5,15] Forty-three per cent of mutations (392 of 903) shared a 5′ breakpoint in intron 44, with del45–47 and del45–48 being the most frequent. Duplications were predominantly located in the 5′ hot spot. Small mutations were a minority (~9%), with nonsense mutations being the most common (~45%).[16] Among these, six mutations were located in OF exons at either the N-terminal or C-terminal end of the gene (exons 1, 2, 12 and 75).

It has been suggested that nonsense mutations occurring in OF exons might lead to more severe phenotypes owing to the inability to restore the open reading frame through alternative splicing.[17,18] However, nonsense codons located at the N- or C-terminal of the gene might allow expression of low levels of dystrophin through translational re-initiation or expression of distally truncated, but functional dystrophin. Among patients carrying nonsense mutations in OF exons, only one (exon 75) exhibited a severe phenotype, with LoA at 16 years, dilated cardiomyopathy and respiratory failure.

LoA is a rare and late occurrence in BMD. In this cohort, the rate of LoA was ~14%, with an estimated median age at LoA of 69 years and only 3% experiencing LoA before the age of 20 years.

Given that GCs have shown benefits in DMD,[19] we investigated whether ≥1 year of treatment might also delay LoA in BMD. The minority of BMD treated with corticosteroids showed an earlier LoA than those who were not treated, but this was probably attributable to the increased prescription of glucocorticoids in those patients with more severe disease (ascertainment bias).

Out-of-frame mutations in BMD are rare (~10%) and represent exceptions to the Monaco rule.[17,18,20,21] Among the proposed dystrophin rescue mechanisms, translational re-initiation in the N-terminal domain and escape from nonsense RNA-mediated decay of C-terminal mutations are notable. If the mutation occurs in the rod domain, alternative splicing might restore the open reading frame.

Patients with out-of-frame mutations, as expected, experienced significantly earlier LoA (median 42 years), probably owing to lower dystrophin quantity because of reduced transcript stability. Unfortunately, dystrophin quantity data are not readily available to confirm this.

We observed ~25-year earlier median LoA with del45–49 in comparison to del45–47, consistent with previous studies.[2,22,23] This deletion leads to a double coiled-coil 'T' shape rather than the triple coiled-coil spectrin repeat, resulting in a decrease in flexibility of the rod domain and the creation of a hydrophobic centre, in addition to reduced phospholipid membrane binding, resulting in a severe BMD phenotype.[22]

Conversely, del45–55, del48–49 and del48 appeared to be associated with milder phenotypes.[24,25] Among these, del48–49 was relatively more severe, as shown by LoR in most patients after the age of 30 years, whereas running ability was mostly preserved with del45–55 and del48, despite some variability. Neuronal nitric oxide synthase might explain this variability in del45–55,[26] because it binds to spectrin repeats 16–17, which are partly removed by this deletion. In severe phenotypes, neuronal nitric oxide synthase localizes exclusively to the cytosol, whereas in mild cases it is present in both the cytosol and the sarcolemma. Mislocalization can lead to inflammation, protein degradation and altered calcium homeostasis.[26]

It is interesting to note that mutations associated with milder phenotypes (del45–51, del45–55, del48 and del48–51) were enriched in the subset of patients whose diagnosis was prompted by incidental findings of elevated serum CK, underlying the importance of ruling out a BMD diagnosis in hyperCKaemia patients.

Cardiac involvement in BMD varies and is not correlated with skeletal muscle involvement.[8,27] We used LVEF% as a measure of overall heart function and found a negative correlation between LVEF% values and the age at the last assessment. It is important to emphasize that cardiomyopathy can manifest early in the disease course, as demonstrated by the youngest patient in our cohort, who exhibited impaired ejection fraction at 13 years of age. Consequently, regular cardiac monitoring in BMD patients, potentially from early adolescence, is crucial.

We observed that patients with del48, del45–55 and those categorized in the 'other' group tended to have better LVEF% values in comparison to patients with del45–47. These findings align with previous reports, in which the isolated deletions of exon 48 and del45–55 are associated with mild BMD.[24,28,29] Nonetheless, rare cases of isolated XLCM are linked to the deletion in exons 45–55. An explanation for this phenomenon has yet to be determined, but two hypotheses have been proposed: loss of a protein domain specific for cardiac function and/or loss of specific intronic sequences involved in transcriptional regulation.[23] Instead, del45–47 is often associated with severe phenotypes, possibly owing to modification in dystrophin hydrophobicity and increases lipid-binding properties.[22,23]

Although *DMD* mutations might serve as possible predictors of clinical outcomes, our study of familial cases highlights the potential role of genetic modifiers in BMD, as has already been well established in DMD. This adds another layer of complexity to predicting prognosis in BMD.[30] In contrast to DMD, respiratory failure is uncommon in BMD. The mean FVC% in our cohort was 91.8%, similar to the findings in the case series described by Mori-Yoshimura *et al.*[31] It is noteworthy that all patients with severe respiratory

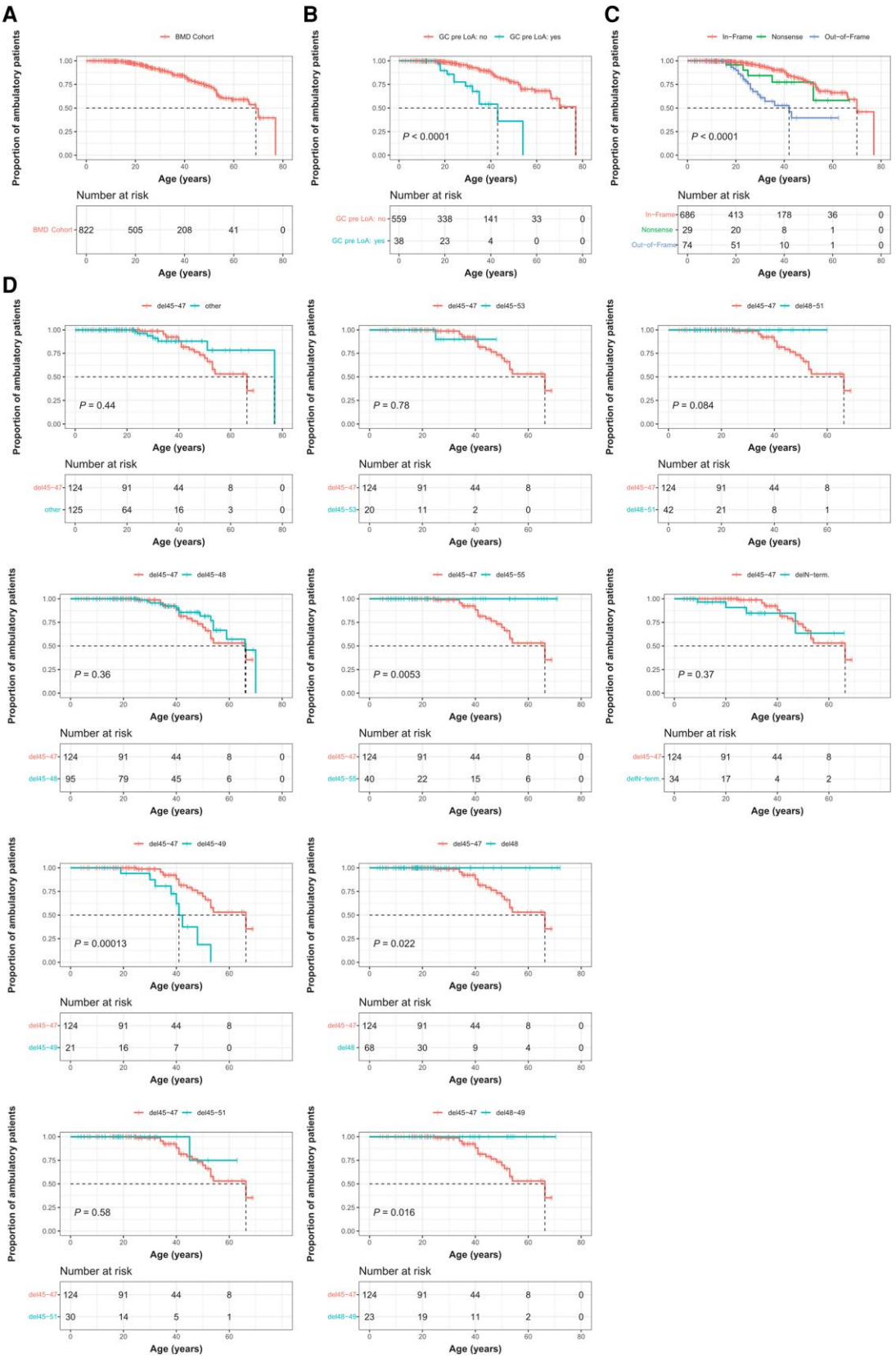

Figure 3 Kaplan–Meier plots of loss of ability to walk. Kaplan–Meier plots showing the proportion of ambulatory patients at different ages (**A**); the proportion of ambulatory patients at different ages by glucocorticoid (GC) treatment (**B**), by reading-frame and nonsense groups (**C**) and subdivided into mutational subgroups and compared with del45–47 (**D**). The *P*-value indicates the statistical significance of the log-rank test, evaluating the differences in Kaplan–Meier curves among the groups. BMD = Becker muscular dystrophy; LoA = loss of ambulation.

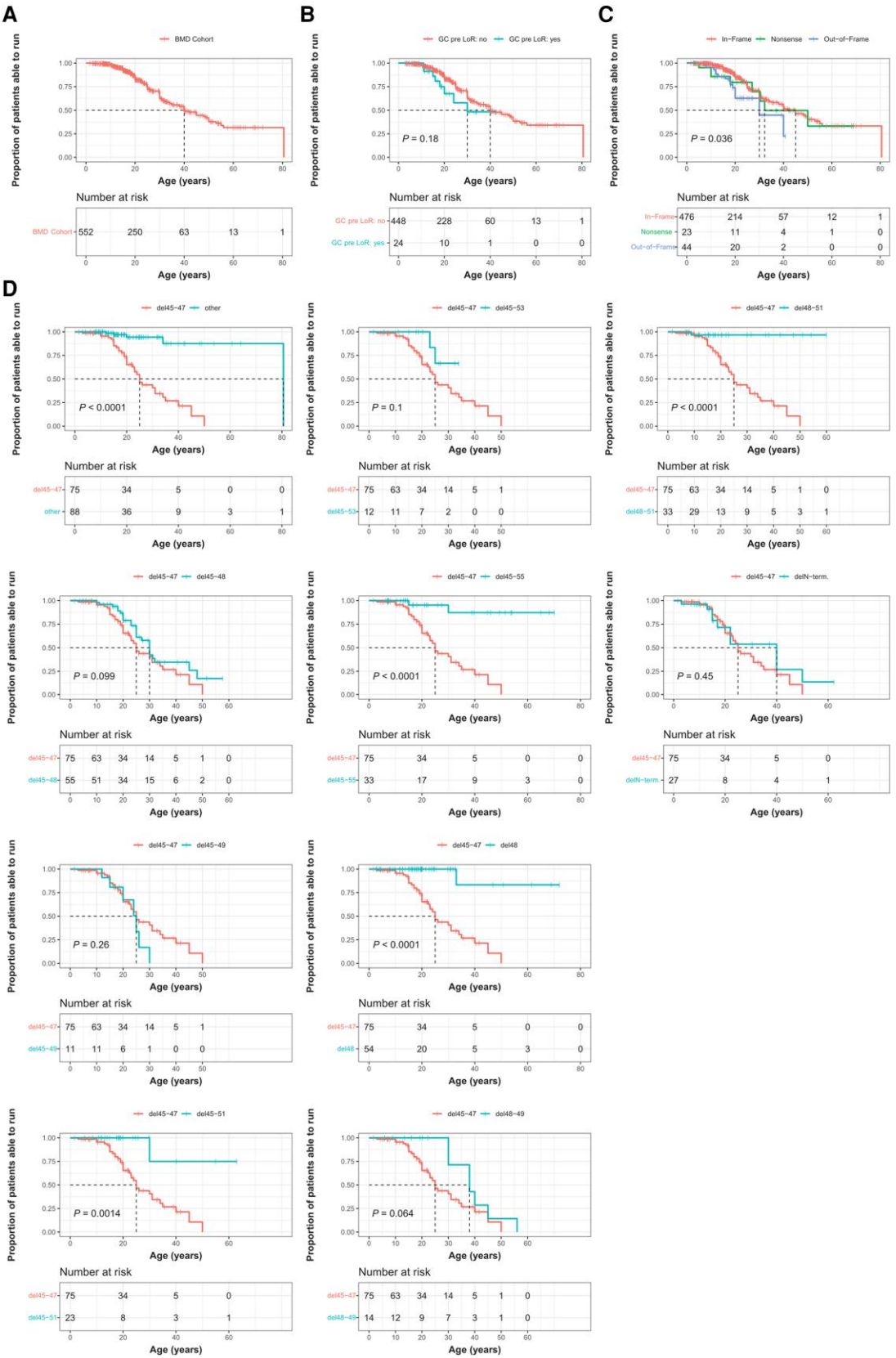

Figure 4 Kaplan–Meier plots of loss of ability to run. Kaplan–Meier plots showing the proportion of patients able to run at different ages (**A**); the proportion of patients able to run at different ages by glucocorticoid (GC) treatment (**B**), by reading-frame and nonsense groups (**C**) and subdivided into mutational subgroups and compared with del45–47 (**D**). The *P*-value indicates the statistical significance of the log-rank test, evaluating the differences in Kaplan–Meier curves among the groups. BMD = Becker muscular dystrophy; LoR = loss of ability to run.

Table 4 Left ventricular ejection fraction percent of predicted and forced vital capacity percent of predicted at last assessment by age groups

Parameter	Age at last assessment, years				
	<20	20–40	40–60	≥60	Total
LVEF, % predicted					
n (%)	215 (34.6)	239 (38.5)	126 (20.3)	41 (6.6)	621 (100)
Mean (SD)	61.7 (6.8)	53.4 (11.4)	52.5 (11.9)	50.2 (12.8)	55.8 (11.1)
95% CI	60.7–62.6	52.0–54.8	50.4–54.6	46.3–54.1	55.0–56.7
Median (IQR)	62.0 (59.0–65.0)	56.0 (48.0–61.0)	55.0 (47.0–60.0)	55.0 (45.0–59.0)	60.0 (51.0–63.0)
Range	27–84	15–73	18–73	20–65	15–84.
n < 55% (%)	16 (7.4)	94 (39.3)	57 (45.2)	20 (48.8)	187 (30.1)
FVC, % predicted					
n (%)	171 (38.8)	161 (36.5)	85 (19.3)	24 (5.4)	441 (100.0)
Mean (SD)	92.1 (14.4)	92.2 (20.5)	88.5 (25.2)	99.2 (18.8)	91.8 (19.4)
95% CI	89.9–94.2	89.1–95.4	83.1–93.9	91.7–106.7	90.0–93.6
Median (IQR)	93.0 (82.0–100.0)	95.0 (83.0–105.0)	92.0 (74.0–104.0)	101.5 (90.3–108.3)	94.0 (81.0–103.0)
Range	52–130	20–134	22–174	56–130	20–174
n < 50% (%)	0 (0.0)	8 (5.0)	4 (4.7)	0 (0.0)	12 (2.7)

CI = confidence interval; FVC = forced vital capacity; IQR = interquartile range; LVEF = left ventricular ejection fraction; SD = standard deviation.

impairment (12 patients with FVC% < 50%) were not ambulant; hence, motor deterioration could be a significant contributing factor to respiratory impairment.[9]

We acknowledge several limitations to our study. Firstly, it is a retrospective study, and some information relies on patient recall. Secondly, our study is a multi-centric Italian study, with different clinical evaluators and different equipment to perform the cardiac and pulmonary function analyses. These factors could limit the inter-rater reliability of data.

In our study, neurocognitive features appear to be underestimated,[32-34] whereas epilepsy and febrile seizures seem to be overestimated. Neurocognitive issues are more frequently assessed in paediatric patients, but if symptoms are mild they often go unaddressed as patients transition to adult care. The higher-than-expected rate of epilepsy might be skewed by a reporting bias, whereby cases were more likely to be documented when present, and might not represent the true prevalence accurately. A deeper understanding is crucial, because they might significantly influence the design and outcomes of clinical trials.

However, the strength of our study lies in the large cohort of BMD patients included and in the completeness of the patients' data available and described.

Conclusion

In conclusion, this large sample size enabled us to analyse subsets with homogeneous *DMD* mutations, facilitating the correlation of specific genetic variants with clinical features and driving evidence-based conclusions. Given the emergence of new therapies for BMD, natural history data and robust genotype–phenotype correlations are of pivotal relevance. These data might help to define inclusion criteria for new clinical studies and serve as a historical control to assess the effectiveness of new treatments. Moreover, they offer valuable insights for dystrophin-restoring therapies, using BMD as an exemplary *in vivo* model.

Data availability

The data that support the findings of this study are not publicly accessible owing to their clinical nature, because they contain sensitive and confidential patient information that could compromise patient privacy. These data are available only upon request, from the corresponding author, and a formal data sharing agreement must be completed before any data can be shared.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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