Late-Stage Outcomes in Patients with Limb-Girdle Muscular Dystrophy (LGMD) Sarcoglycanopathy Subtypes: A Systematic Review

Sharanya Murty,[1] Antoinette Cheung,[2] André Müller-York,[1] Lavanya Sudharshan,[1] Andrew R. Kennedy,[2] Shelagh M. Szabo[2]

[1] Sarepta Therapeutics, Inc., Cambridge, MA USA, [2] Broadstreet HEOR, Vancouver BC Canada

Introduction

- LGMD sarcoglycanopathy subtypes (LGMD2C/R5, LGMD2D/R3, LGMD2E/R4, LGMD2F/R6) are a group of rare, autosomal recessive diseases caused by pathogenic variants in sarcoglycan proteins (α-, β-, γ- or δ-), which are essential for maintaining muscle membrane integrity and signaling during muscle contraction[1,2]
- The occurrence of loss of ambulation (LOA) in LGMDs has been summarized previously;[3,4] however, late-stage clinical manifestations such as pulmonary and cardiac musculature involvement may also occur, including progression to respiratory failure and cardiomyopathy[2,5]
- The clinical course of sarcoglycanopathies is highly variable;[2,5] consequently, designing clinical and real-world studies is challenging
- A clearer understanding of sarcoglycanopathy natural history may help to characterize clinical trajectories and inform the management of patients living with LGMDs

Objective

- To summarize data on respiratory, cardiac, and survival outcomes among patients diagnosed with sarcoglycanopathies, overall and by subtype

Methods

- A published systematic literature review (SLR)[3,4] was refreshed to identify patient-level data on cardiac and respiratory status for patients with autosomal recessive LGMD subtypes; the present analysis focuses on sarcoglycanopathies
  - The search strategy was re-run on May 2023; full search details have been reported previously[3,4]
- Outcomes of interest, overall and by subtype, were median (interquartile range [IQR]) age at:
  - Symptom onset
  - Respiratory involvement
  - Cardiac involvement
  - Death (cause of death was noted where reported)
- Patients were categorized as having respiratory or cardiac involvement, as described by authors (**Figure 1A and 1B**)
- Age at (last) assessment was used as a proxy if age at involvement was not reported

Figure 1A: *Examples of descriptions used to categorize respiratory involvement*

Involvement	No involvement
• Abnormal pulmonary function • Mild restrictive respiratory function • Required (non-invasive) ventilation • Respiratory failure • Restrictive lung function	• Asymptomatic • Did not require respiratory support • No abnormal pulmonary function • No pulmonary involvement • Had no respiratory complications

Figure 1B: *Examples of descriptions used to categorize cardiac involvement*

Involvement	No involvement
• Arrhythmia (Lown grade 4b) • Cardiac involvement • Cardiac support therapy required • Cardiomyopathy[a] • Global hypokinesia[a]	• Absence of / no heart abnormalities • No abnormal doppler of ECG • No abnormal heart function • No cardiac involvement • No cardiomyopathy

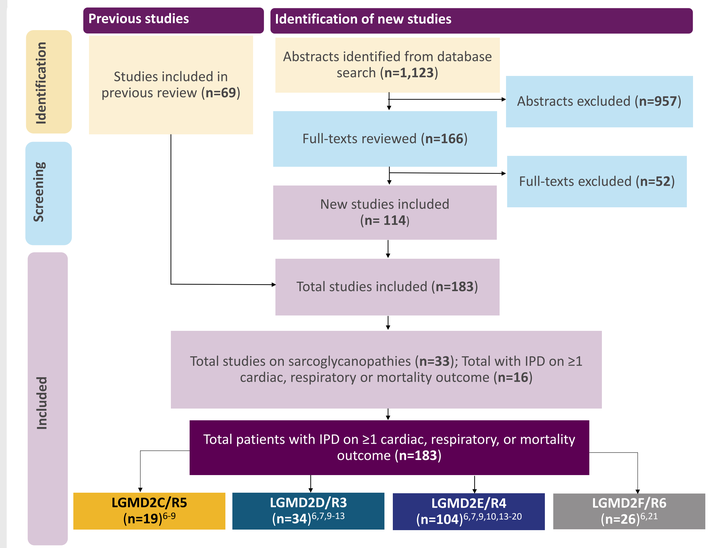
Abbreviations: ECG: electrocardiogram
Notes: [a]Included in the severe cardiac involvement analyses

Results

Data availability

- Overall, 183 sarcoglycanopathy patients had patient-level data describing at least one outcome of interest (**Figure 2**); 10 studies reported respiratory status, 14 reported cardiac status, 9 reported mortality
- Included studies were observational in design, including case reports and case series, and spanned multiple decades (publication years: 1996 to 2022)
- Studies represented populations from North and South America, Europe, and Asia; individual ethnic groups were also represented, such as Magdalen Islands Acadian[12], Pakhtun[20], and Taiwanese[11]

Figure 2: *PRISMA diagram*

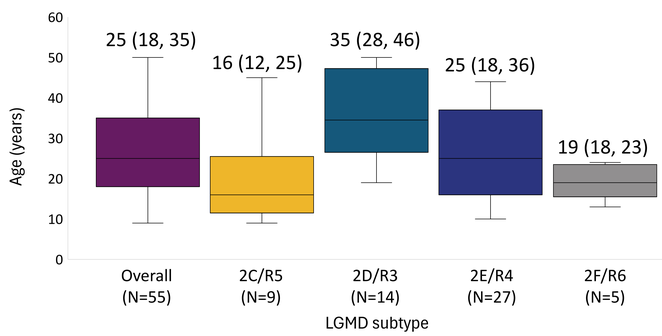


Abbreviations: IPD: individual patient data; LGMD: limb-girdle muscular dystrophy

Respiratory involvement

- Median (IQR) age at symptom onset was similar between patients with respiratory involvement (6 [4, 7] years; n=55) and those who did not yet have respiratory involvement (7 [4, 12] years; n=76), though variability was wider in the latter group
- Among patients with available data, age at respiratory involvement varied, but generally occurred in early adulthood across subtypes (**Figure 3**)

Figure 3: *Median (IQR) age at respiratory involvement, overall and by subtype[a]*

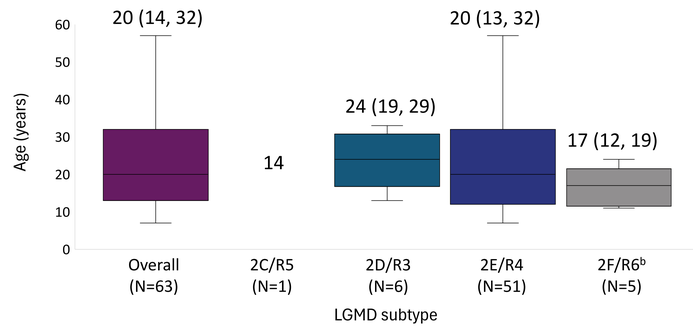


Abbreviations: IQR: interquartile range; LGMD: limb-girdle muscular dystrophy
Notes: [a]Among patients with age at respiratory involvement data (or proxy for this)

Cardiac involvement

- Median (IQR) age at symptom onset was similar between patients with cardiac involvement (5 [3, 9] years; n=63) and those who did not yet have cardiac involvement (6 [4, 9] years; n=96)
- Age at any cardiac involvement was limited except among those with LGMD2E/R4 (**Figure 4**)
- Severe cardiac involvement (e.g., cardiomyopathy, hypokinesia, and sudden cardiac death) was described in 34 sarcoglycanopathy patients, occurring at a median (IQR) age of 20 years (14, 32)

Figure 4: *Median (IQR) age at any cardiac involvement, overall and by subtype[a]*



Abbreviations: IQR: interquartile range; LGMD: limb-girdle muscular dystrophy
Notes: [a]Among patients with age at cardiac involvement data (or proxy for this); [b]All LGMD2F patients were from the same cohort

Mortality

- Overall, 14 patients with available data died; deaths were only noted among those with LGMD2D/R3 and LGMD2E/R4 (**Table 1**)
- All reported deaths were in patients who were non-ambulatory
- Where cause of death was specified (n=10), 7 were respiratory-related (respiratory failure or pneumonia) and the remainder were cardiac-related (cardiac failure or sudden death)

Table 1: *Summary of characteristics for patients who died*

	LGMD2D/R3 (n=6)	LGMD2E/R4 (n=8)
Male, n (%)	2 (33.3%)	7 (87.5%)
Age at symptom onset (years), Median [IQR]	7 [7, 9]	4 [2, 6]*
Age at death (years), Median [IQR]	39 [34, 48]	21 [16, 25]
Years from onset to death, Median [IQR]	33 [27, 42]	17 [13, 18]*
LOA, n (%)	6 (100.0%)	8 (100.0%)
Age at LOA (years), Median [IQR]	15 [12, 17]	12 [10, 16]**
Respiratory involvement, n with involvement / n with available data	6/6	2/3
Cardiac involvement, n with involvement / n with available data	0/1	3/5

Abbreviations: IQR: interquartile range; LGMD: limb-girdle muscular dystrophy; LOA: loss of ambulation
Notes: *Calculated using data from 5 patients with available data; **Calculated using data from 7 patients with available data

Conclusions

Findings from this review suggest that patients with sarcoglycanopathies have symptom onset in early childhood

Among those with reported late-stage outcomes, respiratory and cardiac involvement generally manifest by early adulthood

While studies reporting mortality were limited, available evidence suggests that respiratory and cardiac involvement are primary causes of premature mortality

Limitations of this review include potential publication biases from case reports or case series, and small sample sizes for individual subtypes

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