Respiratory involvement in FSHD patients: a retrospective study

F. Pace, E.Lees, R. Muni Lofra, C. Marini-Bettolo, V. Straub, E. Robinson, G. Tasca

The John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE
NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust
Newcastle University

Aims:

To retrospectively investigate respiratory function in a large cohort of FSHD patients, to support and enhance current patient management and clinical practice guidelines.

Introduction:

- Facioscapulohumeral muscular dystrophy (FSHD) affects 870,000 individuals globally.
- It is a rare autosomal dominant muscle disorder. It is associated with an epigenetic derepression of the D4Z4 macrosatellite repeat on chromosome 4 allowing the ectopic expression of the DUX4 retrogene

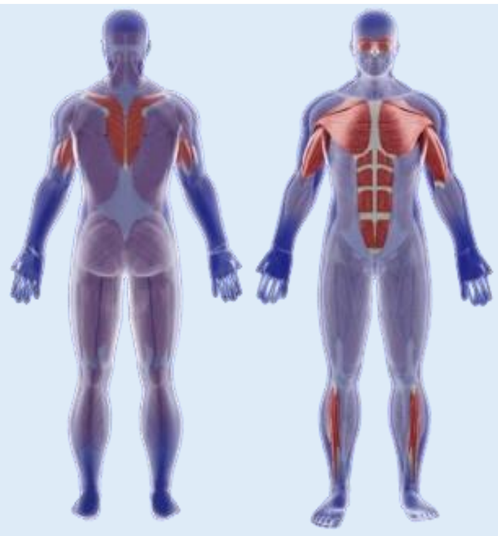

Figure 1: Muscles affected by FSHD[1]

- Clinically, FSHD is characterized by a gradual, asymmetrical and predominant muscle weakness of the face upper arms and shoulder girdle muscles.
- While FSHD's impact on skeletal muscles is well-documented, respiratory function in FSHD patients has primarily been described through cross sectional studies, often limited to the most severely affected patients or smaller cohorts of either adults and children, with relatively short follow up periods of up to 5 years. This has the potential to hinder comprehensive patient care and result in incomplete clinical guidelines.

Methods:

- Data from 191 FSHD patients visited at the John Walton Muscular Dystrophy centre between 1990 and 2024 was gathered about genetic diagnosis, age and signs at disease onset and FSHD typical features (scoliosis, scapular winging, facial and abdominal involvement).
- Severity of the disease was recorded. This was assessed both genetically, via D4Z4 fragment length from genetic tests, and clinically, using clinician-reported measurements of motor performance: the SOFT, summary of functional test and NSAD (The North Star Assessment for limb-girdle type muscular dystrophies) scales. Patient ambulatory status was also recorded (0 non ambulant, 1 walking with aids, 2 ambulant).
- Patient respiratory status was recorded and assessed through Forced Vital Capacity (FVC), recorded in sitting and lying, forced expiratory volume in 1 second (FEV1) and Peak Cough Flow in liters per minute (PCF).
- Forced vital capacity (FVC), peak cough flow (PCF) and ambulatory status were correlated via a two-tailed t test carried out using IBM SPSS Statistics

Results:

- A total of 1011 respiratory data points was recorded. The data was spread over a disease duration range of 83.76 years.

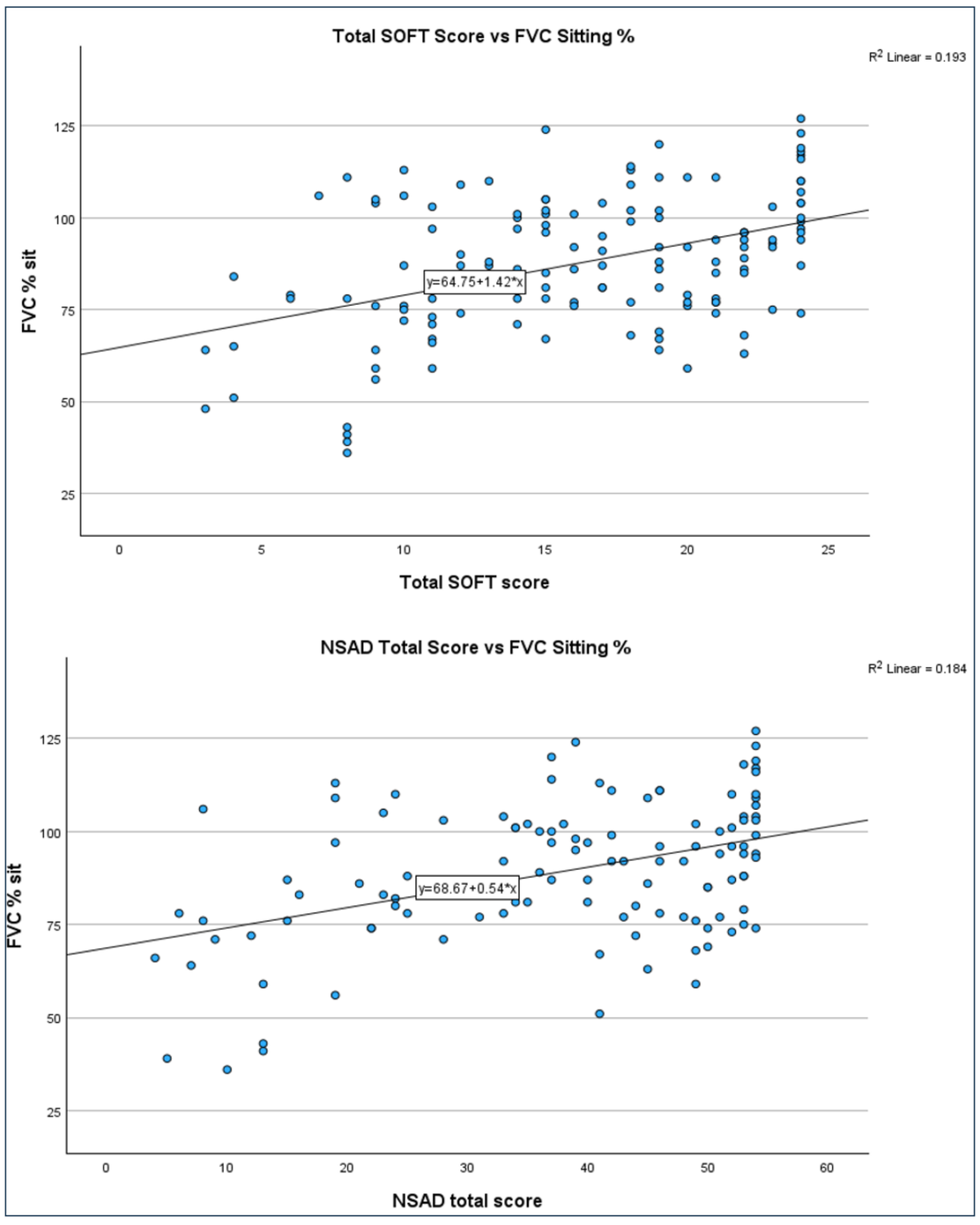

Figure 2: Scatterplot of Total SOFT and NSAD scores vs FVC % recorded sitting

- The mean age of disease onset (n=139) was 25.83 ± 15.04 years and the mean disease duration (n=139) was 24.33 ± 14.8 years
- A moderate positive correlation between the total SOFT score and sitting FVC % was recorded (n=139, r=0.439, significant at p<0.01) . A similar relationship was found between total NSAD score and sitting FVC % (n=116, r=0.429) . See figure 2.
- A moderately postive correlation was also seen between FVC% and Ambulatory status and PCF and ambulatory status (figure 3, respectively r=0.469 and r=0.370)
- All the results mentioned above were significant at p<0.01

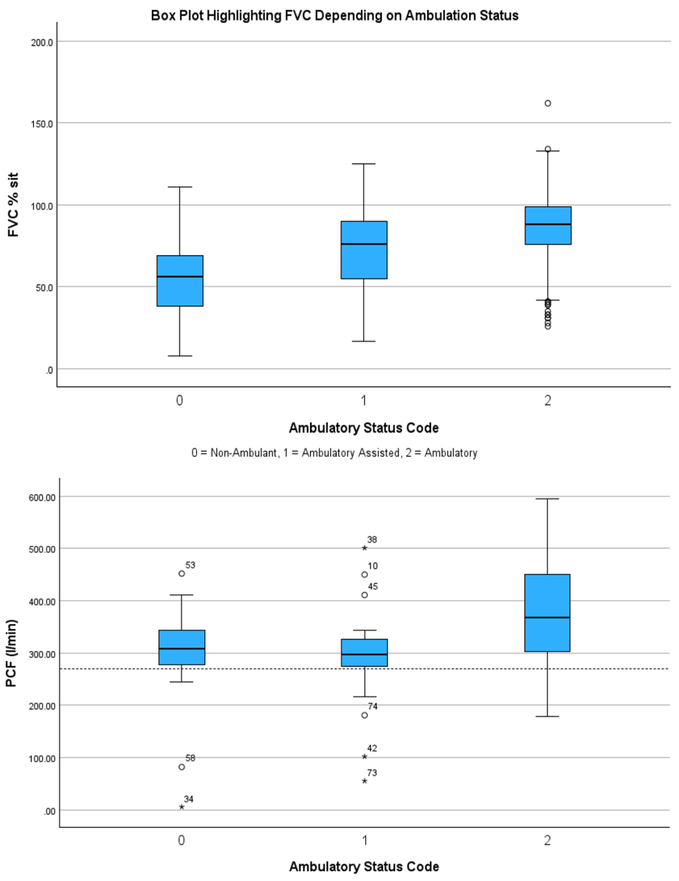

Figure 3: Boxplot of FVC and PCF measured against Ambulatory status

Discussion:

- This research analyzes the largest FSHD cohort, who have undergone respiratory evaluation, to date. In summary, a notable decline in respiratory function was observed as disease severity progressed, with non-ambulatory patients being the most affected. This can be seen in figure 2, where respiratory muscle function, assessed through FVC%, worsened as SOFT and NSAD scores (measuring motor performance) decreased. These results were further validated by Forced vital capacity and Peak cough flow also decreasing as ambulatory status worsened (figure 3). This is consistent with the existing literature[2,3]
- The wide disease duration range of 83.76 years indicates substantial variability within the sample. Further research is warranted to explore whether this variability introduces any confounding factors or influences the observed correlations.
- While a total of 1011 respiratory data points were collected, the participant pool (n=139 individuals for mean age, disease duration and total SOFT and n=116 for NSAD score) could be considered rather limited. This could affect the extent to which the findings can be generalized and the strength of statistical analyses, particularly concerning correlations.
- Study limitations encompassed a relatively small cohort size, variability in the data collected for each patient over time despite standardized assessment protocols, and potential influence from co-morbidities.
- Going forward, a prospective data collection approach could be adopted, allowing for the inclusion of a control group and ensuring a more consistent and comprehensive standardized assessment protocol. Additionally, employing advanced statistical methods like regression analysis or structural equation modeling could provide deeper insights into the relationships between variables.

References: 1)https://www.vitatx.com/fshd 2)Henke, C. *et al.* (2019) 'Respiratory muscle weakness in facioscapulohumeral muscular dystrophy', *Muscle & Nerve*, 60(6), pp. 679–686. doi:10.1002/mus.26717. 3)Respiratory involvement in ambulant and non-ambulant patients with facioscapulohumeral muscular dystrophy