SUPPLEMENTAL E-METHODS

Description of Participants

The recruiting clinician had to indicate if the diagnosis of COVID-19 was “confirmed”, “probable” or “suspected” based on the definitions of the World Health Organisation.[1] Importantly, at the beginning of the pandemic COVID-19 testing was not widely available; thus, many cases worldwide were "probable/suspected”. Additional details were recorded, including primary mitochondrial disease (PMD) genotype-phenotype, demographic information (age, sex, ethnicity), smoking status, coexisting comorbidities (respiratory dysfunction, mitochondrial diabetes, hypertension and other cardiovascular diseases, obesity, and neurological involvement), and outcome following COVID-19 infection. Patient status was assessed using: 1) the modified Rankin scale[2] (mRS), a six-point disability scale applied to evaluate stroke patients but proven effective also in neuromuscular patients,[3] at baseline (retrospectively, before the COVID-19 infection) and after the acute phase of COVID-19; and 2) the Newcastle Mitochondrial Disease Scale for Adults[4] (NMDAS) and the Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) at baseline.[5] The NMDAS is a validated method to monitor the clinical expression of mitochondrial disease and to measures progression in adult patients over 16 years. The NPMDS provides a similar assessment tool for pediatric patients (although no NPMDS value was provided for the four pediatric subjects of this study, therefore this scale has not been considered in the data analysis). NMDAS and NPMDS can be used in patients with mitochondrial disease of any genetic cause. The NMDAS rating scale includes the following three subscales: Current Function; System Specific Involvement; Current Clinical Assessment. It consists of 29 questions; each question has a possible score from 0 (no involvement) to 5 (severe involvement). The higher the score the more severe the disease. Patients have been stratified according with the severity of their PMD in mild (overall NMDAS score from 1 to 5), moderate (score from 6 to 20), and severe (score above 20).[6, 7]

Technical Information

The "International Neuromuscular COVID-19 Database" is available to clinicians worldwide (https://www.ucl.ac.uk/centre-for-neuromuscular-diseases/news/2020/may/international-neuromuscular-covid-19-database) and is hosted by University College London (UCL), London, United Kingdom (UK). The registry remains open; however, the current study utilizes data entered between 1st May 2020 and 31st May 2021. The database was originally designed to capture COVID-19 symptoms and outcomes for all neuromuscular diseases.[8] An additional module targeted to PMDs was created to capture disease-relevant information.

The database was developed and hosted at UCL, London, UK, but cases were registered worldwide. It was only through a global collaborative effort that it was possible to recruit 79 patients with genetically and/or clinicopathologically confirmed mitochondrial disease, which represents the largest cohort ever reported. The survey was clinician-reported; patient information related to the PMDs and COVID-19 were provided by specialists in the field. Clinician-reported databases have been used as a source of information in other similar studies on COVID-19 [9-13] and provide more precise information compared to coded data or medical records.[14]

Health care professionals were encouraged to report all cases of COVID-19 in patients with neuromuscular diseases, regardless of severity. A minimum of seven days was required between diagnosis of COVID-19 and reporting to enable sufficient time to observe the disease course through resolution of the acute phase of the illness and/or hospitalization. Only anonymized patient data was recorded; the only identifiable information captured was that of the primary care provider registering the patient (name, specialty, hospital, city, country, and email address) so that further details could be obtained from the reporter following data analysis, if required.

Standard Protocol Approvals, Registrations, and Patient Consents

Full waiver of consent was granted by the UK Health Research Authority (HRA), given the anonymized nature of the patient data and retrospective design of the study, and review by an NHS Research Ethics Committee (REC) was not required. The project was submitted as a "Service Evaluation" to the "Clinical Audit and Quality Improvement Subcommittee (CAQISC)". Local guidelines were followed for non-UK sites. Core study data were collated from medical records with a case report form designed using the Research Electronic Data Capture software (REDCap, Vanderbilt University, Nashville, TN, USA). Multisite access and data curation was coordinated by UCL, London, UK. All data was handled in accordance with General Data Protection Regulation (GDPR); UCL was the data controller and processor under GDPR and only authorized UCL staff had access to the database.

Statistics

Continuous data are expressed as mean (± SD), while categorical data as number and percentage (%). In univariable analysis, chi-square test was used to compare differences in demographic and PMD-specific features according to hospitalization status. If the cell counts were less than five, Fisher's exact test was used instead. Multivariable-adjusted logistic regression was used to test the independent association between demographic and PMD specific features with the odds of hospitalization. Data are reported as odds ratio (OR) and 95% confidence intervals (95%CIs).

References

1. World Health Organization. (2020). Coronavirus disease 2019 (COVID-19): situation report, 61. World Health Organization. Updated March 20, 2020. Accessed August 1, 2021. https://apps.who.int/iris/handle/10665/331605.

2. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.

3. Farrugia ME, Carmichael C, Cupka BJ, Warder J, Brennan KM, Burns TM. The modified rankin scale to assess disability in myasthenia gravis: Comparing with other tools. Muscle Nerve 2014;50:501-507.

4. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. Neurology 2006;66:1932-1934.

5. Phoenix C, Schaefer AM, Elson JL, et al. A scale to monitor progression and treatment of mitochondrial disease in children. Neuromuscul Disord 2006;16:814-820.

6. de Laat P, Koene S, van den Heuvel LP, Rodenburg RJ, Janssen MC, Smeitink JA. Clinical features and heteroplasmy in blood, urine and saliva in 34 Dutch families carrying the m.3243A > G mutation. J Inherit Metab Dis 2012;35:1059-1069.

7. Custers JAE, de Laat P, Koene S, Smeitink J, Janssen MCH, Verhaak C. Fear of disease progression in carriers of the m.3243A > G mutation. Orphanet J Rare Dis 2018;13:203.

8. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barre syndrome. Brain 2021;144:682-693.

9. Izadi Z, Brenner EJ, Mahil SK, et al. Association Between Tumor Necrosis Factor Inhibitors and the Risk of Hospitalization or Death Among Patients With Immune-Mediated Inflammatory Disease and COVID-19. JAMA Netw Open 2021;4:e2129639.

10. Strangfeld A, Schafer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930-942.

11. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859-866.

12. Pinato DJ, Tabernero J, Bower M, et al. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. Lancet Oncol 2021.

13. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. Lancet 2021;398:1230-1238.

14. In: th, Gliklich RE, Leavy MB, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Rockville (MD)2020.

eTable 1: Presence and absence of respiratory dysfunction for each patient

Patient n°	Obstructive lung disease	Obstructive Sleep Apnoea (OSA)	Restrictive lung disease	Non-invasive ventilation	Tracheostomy
1	No	No	No	No	No
2	No	No	No	No	No
3	No	No	Yes	No	No
4	No	No	No	No	No
5	No	No	No	No	No
6	No	No	Yes	No	No
7	No	No	No	No	No
8	No	No	No	No	No
9	No	No	No	No	No
10	No	No	No	No	No
11	No	No	Yes	No	No
12	No	No	No	No	No
13	No	No	No	No	No
14	No	No	No	No	No
15	No	No	Yes	No	Yes
16	No	No	No	No	No
17	No	No	No	No	No
18	No	No	No	No	No
19	No	No	No	No	No
20	No	No	Yes	No	No
21	No	No	No	No	No
22	Yes	Yes	No	Yes	No
23	Yes	Yes	Yes	Yes	No
24	No	No	No	No	No
25	No	No	No	No	No
26	No	No	No	No	No
27	Yes	No	No	Yes	No
28	No	No	No	No	No
29	No	No	No	No	No
30	No	No	No	No	No
31	Yes	No	No	No	No
32	No	No	No	No	No
33	Yes	No	No	No	No
34	No	No	No	No	No
35	No	No	No	No	No
36	No	No	No	No	No
37	No	No	No	No	No
38	No	No	No	No	No
39	No	No	No	No	No

40	No	No	No	No	No
41	No	No	No	No	No
42	No	No	No	No	No
43	No	No	No	No	No
44	No	Yes	Yes	Yes	No
45	No	No	No	No	No
46	No	No	Yes	No	No
47	No	No	No	No	No
48	No	No	No	No	No
49	No	No	No	No	No
50	No	No	No	No	No
51	No	No	No	No	No
52	No	No	No	No	No
53	No	No	No	No	No
54	No	No	Yes	No	No
55	No	No	No	No	No
56	No	No	No	No	No
57	No	No	No	No	No
58	No	No	No	No	No
59	No	No	No	No	No
60	No	No	No	No	No
61	No	No	No	No	No
62	Yes	No	No	No	No
63	No	No	Yes	No	Yes
64	No	No	No	No	No
65	No	No	No	No	No
66	No	No	No	No	No
67	No	No	No	No	No
68	No	No	No	No	No
69	No	No	No	No	No
70	No	No	Yes	No	No
71	No	No	No	No	No
72	No	No	No	No	No
73	No	No	No	No	No
74	No	No	No	No	No
75	No	No	Yes	Yes	No
76	No	No	Yes	No	No
77	No	No	No	No	No
78	No	No	No	No	No
79	No	No	Yes	Yes	No

eTable 2: Presence and absence of neurological involvement for each patient

Patient n°	Dysphagia	Skeletal muscle weakness	Polyneuropathy	Epilepsy	Learning disability	Stroke/ stroke-like episodes
1	No	No	No	No	No	No
2	No	No	No	No	No	No
3	Yes	Yes	Yes	No	No	No
4	No	No	No	No	No	No
5	No	No	No	No	No	No
6	No	No	No	Yes	No	Yes
7	No	Yes	No	No	No	No
8	No	No	No	No	No	No
9	No	Yes	No	No	No	No
10	Yes	Yes	No	No	No	No
11	Yes	Yes	No	No	Yes	No
12	No	No	No	Yes	Yes	No
13	No	No	Yes	No	No	No
14	No	Yes	No	No	No	No
15	Yes	Yes	No	No	Yes	No
16	No	Yes	No	No	No	No
17	No	No	No	No	No	No
18	No	Yes	No	No	No	No
19	Yes	Yes	No	Yes	No	No
20	Yes	Yes	No	No	Yes	No
21	No	Yes	Yes	Yes	No	Yes
22	No	Yes	No	No	No	No
23	No	Yes	Yes	No	No	No
24	No	Yes	Yes	Yes	Yes	No
25	No	No	No	No	No	No
26	No	Yes	No	No	No	No
27	No	No	No	No	No	No
28	No	No	No	No	No	No
29	Yes	Yes	No	Yes	Yes	No
30	No	No	No	Yes	No	No
31	Yes	No	No	No	No	No
32	No	No	No	No	No	No
33	Yes	No	No	Yes	No	No
34	No	No	No	No	No	No
35	No	No	No	Yes	No	Yes
36	No	No	No	No	No	No
37	No	No	Yes	No	No	No
38	No	No	No	No	No	No

39	No	No	No	No	No	No
40	No	No	No	No	No	No
41	No	No	No	No	No	No
42	No	No	No	No	No	No
43	No	No	No	No	No	No
44	Yes	Yes	Yes	No	Yes	No
45	No	No	No	No	No	No
46	No	Yes	Yes	No	No	No
47	No	No	No	No	No	No
48	Yes	Yes	No	No	No	No
49	No	Yes	No	No	No	No
50	No	No	No	No	Yes	No
51	No	No	No	No	No	No
52	No	No	No	No	No	No
53	No	Yes	No	No	Yes	Yes
54	Yes	Yes	No	Yes	Yes	No
55	No	Yes	No	No	No	No
56	No	No	No	No	No	No
57	No	No	No	No	No	No
58	Yes	No	No	No	No	No
59	Yes	Yes	No	No	No	No
60	Yes	Yes	No	No	No	No
61	Yes	Yes	No	Yes	Yes	No
62	No	No	No	No	No	No
63	Yes	Yes	No	Yes	Yes	Yes
64	No	Yes	No	No	No	No
65	No	No	No	No	No	No
66	No	No	No	No	No	No
67	No	No	No	No	No	No
68	No	No	No	No	No	No
69	No	No	No	No	No	No
70	Yes	Yes	No	Yes	No	Yes
71	No	No	No	No	No	No
72	Yes	Yes	No	Yes	No	Yes
73	No	Yes	No	Yes	No	Yes
74	No	No	No	No	No	No
75	No	Yes	No	Yes	No	No
76	Yes	No	No	No	No	No
77	No	Yes	No	No	No	No
78	No	Yes	No	No	No	No
79	Yes	Yes	No	No	No	No