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Original article

COVID-19 in Multiple Sclerosis: Clinically reported outcomes from the UK Multiple Sclerosis Register

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A B S T R A C T

Background: In March 2020, the United Kingdom Multiple Sclerosis Register (UKMSR) established an electronic case return form, designed collaboratively by MS neurologists, to record data about COVID-19 infections in people with MS (pwMS).
Objectives: Examine how hospital admission and mortality are affected by disability, age and disease modifying treatments (DMTs) in people with Multiple Sclerosis with COVID-19.
Methods: Anonymised data were submitted by clinical teams. Regression models were tested for predictors of hospitalisation and mortality outcomes. Separate analyzes compared the first and second 'waves' of the pandemic.
Results: Univariable analysis found hospitalisation and mortality were associated with increasing age, male gender, comorbidities, severe disability, and progressive MS; severe disability showed the highest magnitude of association. Being on a DMT was associated with a small, lower risk. Multivariable analysis found only age and male gender were significant. Post hoc analysis demonstrated that factors were significant for hospitalisation but not mortality. In the second wave, hospitalisation and mortality were lower. Separate models of the first and second wave using age and gender found they had a more important role in the second wave.
Conclusions: Features associated with poor outcome in COVID-19 are similar to other populations and being on a DMT was not found to be associated with adverse outcomes, consistent with smaller studies. Once in hospital, no factors were predictive of mortality. Reassuringly, mortality appears lower in the second wave.

1. Background

Following the global pandemic of the novel SARS-CoV2 (WHO. Statement on the Second Meeting of the International Health Regulations 2005) infection (COVID-19), the UK population was required to 'lock-down', in the first instance from the 23rd March 2020 and eased on 14th August 2020 and again from the 5th November 2020 until the 2nd December 2020 in England (IfG, 2021a). People with MS (pwMS), some of whom experience chronic disability and/or receive immune-suppressing disease modifying drugs, have ongoing concerns and uncertainty around their risk of COVID-19. Given these uncertainties, there is an ongoing need to explore the impact of COVID-19 on people with MS. The UK Multiple Sclerosis Register (UKMSR) has been capturing longitudinal clinical and patient reported outcomes in

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since 2011 (Middleton et al., 2018). In March 2020, a platform was established to allow clinicians to record data about pwMS, both admitted to hospital and treated at home, due to COVID-19. The UKMSR provided an electronic case return form (eCRF), designed collaboratively by the UK MS research community and with reference to a similar initiative in Italy (Sormani, 2020), capturing data about the COVID-19 features, and the MS history. This form was made available, securely over the internet, to all MS neurologists in the UK. Given the rapid evolution of the symptomatology of the virus, it was important to capture a broad spectrum of measures, both about the COVID-19 infection and essential data specific to MS. There are a number of published clinical studies from the United States (Salter et al., 2021), Iran (Sahraian et al., 2020), Italy (Sormani, 2020), the Netherlands (Loonstra et al., 2020) and Scotland (Fernandes et al., 2020), but given differences in the impact of COVID-19, and the management of MS, throughout the world, it is helpful to understand how the infection impacts pwMS in different countries where different health systems operate and more specifically within the UK and how this has evolved over the pandemic.

2. Objectives

To report on hospitalisation and death in people with MS infected with COVID-19 in the UK, as recorded by MS specialist neurology centres through two peaks of disease in March 2020 and February 2021.

3. Methods

The UK MS Register has ethical approval from South-West Central Bristol Research Ethics Committee (16/SW/0194). All study data was anonymous. An eCRF was distributed to UK neurologists via email, social networks, and the UK Multiple Sclerosis Society.

The requirement for data entry was a confirmed diagnosis of MS by a UK Neurologist and that the patient must be resident in the UK. For the purposes of analysis, we excluded those without a confirmed COVID-19 infection, or with missing values for hospital admission status and outcome. The eCRF provided three options for confirmation of COVID-19 infection: a positive PCR test, positive SARS-CoV2 antibody test, or clinical confirmation based on presenting symptoms and other investigations e.g. typical chest imaging findings (Islam et al., 2021).

The eCRF was created using REDCap (Harris et al., 2009) and data were analyzed using the R language (R Core Team, 2018). Validation was integrated into the eCRF (Appendix 1), with few response options being made mandatory, to allow for the difficulties of clinical data capture during the ongoing pandemic and not limit data capture. For the purposes of pre-analysis, some sub-categories of data were aggregated, in accordance with clinical advice. MS types were combined into either 'progressive' (primary progressive MS and secondary progressive MS) or 'not progressive' (relapsing remitting MS). The Expanded Disability Status Scale (EDSS) scores were categorised as 'Mild' (EDSS 0–2.5), 'Moderate' (EDSS 3–5.5), and 'Severe' (EDSS $\geq$ 6). Details on the following comorbidities were collected: cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, other chronic lung disease, hypertension, cancer, stroke, chronic renal diseases, and chronic liver diseases. For analysis, these were aggregated into three categories of 'Cardiovascular' (cardiovascular diseases, hypertension and stroke), 'Respiratory' (asthma, chronic obstructive pulmonary disease and other chronic lung disease), and 'Other' (diabetes, cancer, chronic renal disease or chronic liver disease). Comorbidities were further aggregated into one yes/no measure of having 'Any Comorbidity' for some analyzes. A complete data dictionary is available on request.

Hospital admission (yes/no) and final recorded outcome (deceased/alive) were combined into a status variable of "not admitted to hospital, now alive/recovering" to "admitted to hospital, now alive/recovering" to "admitted to hospital, now deceased" to summarise serious events. This was treated as a sliding scale of serious events (1 - "not hospitalised, alive" - 2 ("hospitalised, alive") - 3 ("hospitalised, deceased") to perform univariable and multivariable ordinal logistic regression for demographic and clinical factors. The assumption of proportionality of odds was confirmed and Variance Inflation Factor (VIF) was calculated by converting the logistic model to a linear one, and t-tests, analysis of variance (ANOVA) and Pearson's correlation were used to further explore interactions between independent variables. Variables were excluded from the multivariable model in a step-wise backwards fashion.

Treating the three levels ("not hospitalised, alive", "hospitalised, alive", "hospitalised, deceased") as nominal categories instead, further standardised hypothesis testing was conducted with the null hypothesis being that there was no association between the variable and the three potential outcomes. Chi-Squared and ANOVA were used in the first instance, with Fisher's Exact substituted for Chi-Squared where expected values were small, and Kruskal-Wallis substituted for ANOVA where results were non-normal. Post-hoc pairwise comparisons using Bonferroni adjustment were calculated for factors achieving statistical significance (Table 2).

The demographic and clinical factors chosen for inclusion were sex, age, MS type, EDSS, DMT treatment, comorbidities, and lymphocyte count prior to COVID-19 infection. With regards to DMT treatment, serious events were primarily assessed in terms of whether or not a patient was receiving a DMT at the time of infection.

Some event-specific variables were examined separately for serious events of hospitalisation and death. For hospital admission, these included reasons for admission to hospital, duration of hospital stay, and signs and symptoms of infection. For mortality, signs and symptoms of infection, as well as severity, and respiratory support, were assessed.

Certain features of the approach to COVID-19 diagnosis and treatment changed over the course of the pandemic (of particular relevance here, given our inclusion/exclusion criteria, is that PCR tests became more readily available over time). To better understand the effects of these changes on our data, standard hypothesis tests (with a null hypothesis assuming no association) were used to compare population demographics and clinical features from the 'first wave' (defined here as 3rd March 2020 – 20th August 2020) and 'second wave' (21st August 2020–16th March 2021 – as the end of this study). An ordinal logistic regression, using the independent variables chosen previously, was modeled on the first wave data and used to predict outcomes in the second wave data, and vice versa. The models were then used to compare the predictions of each model to both sets of data.

4. Results

4.1. Demographics

Data on 292 individual pwMS (England: 232, Wales: 41, Northern Ireland: 15, unspecified location: 4) were entered by clinicians between 27th March 2020 and 16th March 2021. Median age was 50 with an interquartile range (IQR: 42, 60), 68.5% were female. One hundred and seventy-three (59.3%) had relapsing-remitting MS, 103 (35.3%) had progressive (primary or secondary) and 16 (5.5%) had unknown MS type. Two hundred and twenty-four had last known EDSS scores prior to COVID-19 infection; 78 (34.8%) were 'Mildly', 51 (22.8%) 'Moderately', and 95 (42.4%) 'Severely' disabled.

One hundred and sixty-eight (57.5%) pwMS had a positive polymerase chain reaction (PCR) test, 5 (1.7%) had a positive antibody test and 23 (7.9%) were clinically confirmed based on presenting symptoms and other investigations. Ninety-six (32.9%) pwMS were excluded because they did not have confirmed COVID-19 according to the methods specified. A further 3 patients were excluded because they had missing values for either hospital admission status or outcome. Demographics and clinical features for the 193 included pwMS are provided in Table 1.

Table 1
Clinical features of people with MS with confirmed COVID-19, with known hospital admission and outcome status. One person with MS who died at home was included in the 'Deceased, Hospitalised' category.

Characteristic (*denotes reference category for analysis)	Confirmed by Test (n = 193) Deceased, Hospitalised n = 16	Alive, Hospitalised n = 70	Alive, Not Hospitalised n = 107	*Univariable Analysis: Odds Ratio [95% CI], p-value*
Gender: Female*/ Male, missing	9/7, 0	39/31, 0	86/21, 0	2.93 [1.61, 5.37], <0.001
Age (Years): Median (IQR), missing	66 (58, 73), 0	58 (50, 72), 0	44 (36, 52), 0	1.10 [1.07, 1.13], <0.001
MS Type: progressive/not progressive*, missing	12/1, 3	45/21, 4	17/90, 0	14.17 [7.17, 29.38], <0.001
EDSS Group: mild*/ moderate/ severe, missing	0/1/13, 2	9/7/41, 13	51/30/20, 6	1.55 [0.53, 4.47], 0.416 15.94 [6.97, 39.97], <0.001
DMT: yes/no*, missing	2/13, 1	24/43, 3	81/24, 2	0.13 [0.07, 0.25], <0.001
Comorbidities:				
Cardiac: yes/ no*	9/7	24/46	5/102	9.67 [4.57, 21.73], <0.001
Respiratory: yes/no*	5/11	13/57	6/101	
Other: yes/no*	4/12	15/55	2/105	4.19 [1.84, 9.81], <0.001
Any Comorbidity: yes/no*	11/5	36/34	11/96	6.45 [2.73, 15.86], <0.001 9.26 [4.77, 18.77], <0.001
Lymphocyte Count Prior to Covid-19 Infection ($10^{\wedge}9$/ microliter): Median (IQR), missing	2.05 (1.58, 2.83), 8	1.30 (0.80, 1.86), 24	1.27 (0.92, 1.72), 37	1.13 [0.83, 1.55], 0.426

4.2. Clinical features of hospitalised COVID-19 people with MS

In the case of 85 pwMS who were hospitalised, 54 (63.5%) were due to COVID-19, 7 (8.2%) for reasons associated with MS, 4 (4.7%) for social reasons (where the patient was unable to be supported at home) and 20 (23.5%) for 'other' or 'unknown' reasons. A median 9 days in hospital was recorded and this duration of stay was the same for all admissions regardless of survival. Levels of respiratory support for those in hospital were divided into low-dependency ('face mask' or 'nasal cannulae') and high-dependency ('high flow oxygen', 'non-invasive ventilation' or 'intubated and ventilated'), with a significant difference in survival rates between the two different intensity treatment levels (Fisher's Exact test; CI 0.03, 0.48, $p = 0.001$). Symptoms of infection associated with admission included respiratory problems (χ^2 13.17, df = 1, $p < 0.001$) and high temperature (χ^2 13.98, df = 1, $p < 0.001$).

Increasing age (t −8.88, df 159.71), male gender (χ^2 10.95, df = 1), having any comorbidity (χ^2 39.83, df = 1), increased disability (χ^2 54.17, df = 2) and progressive MS (χ^2 57.73, df = 1) were associated with being hospitalised ($p < 0.001$), while being on a DMT was associated with a lower likelihood of being admitted to hospital (χ^2 35.05, df = 1, $p < 0.001$).

4.3. Clinical features of people with ms dying as a result of COVID-19

One person with MS with COVID-19 died at home. Of those hospitalised, 15 out of 85 (17.7%) died; 11 of those (73.3%) had either 'critical' or 'severe' COVID-19 symptoms recorded compared to those who were admitted to hospital but survived (20%, $p < 0.01$)). 11 out of 15 (73.3%) of those who died in hospital had required some form of ventilatory support, compared to 31 out of 70 (44.3%) who were admitted but recovered. In the group that died, respiratory symptoms were found to be amongst the most significant (χ^2 3.74, df = 1, $p = 0.05$).

4.4. Outcome analysis: hospitalisation and death

Univariable ordinal logistic regression of serious events showed that male gender, older age, progressive disease, not being on active DMT treatment, and the presence of comorbidities were all significant (Table 1, $p < 0.01$), with age the most significant. In terms of disability, only severe disability was found to be significant. Lymphocyte count values prior to COVID-19 infection were not found to be significant.

When multivariable modeling was used there was high (>2.5) VIF for progressive MS type and EDSS. Standardised hypothesis tests found that these, as well as DMT treatments, the 'cardiac' and 'other' and 'any' comorbidity categories were all significantly associated with age at a level of $p < 0.01$; younger pwMS were more likely to be on a DMT, more likely to not have progressive disease, and to not have comorbidities. Respiratory comorbidities were associated with higher age at a level of $p = 0.02$ ($t - 2.48$, df = 29.46). Removing these due to the high levels of interaction, as well as lymphocyte counts, left only age and gender in the multivariable model, both showing significance at $p < 0.01$, Residual Deviance 261.71, AIC 269.71.

Treating the combined serious events as nominal categories, standardised hypothesis testing found significance in all factors at $p < 0.01$ except for lymphocyte counts prior to infection (Table 2, column 1). Post-hoc pairwise comparisons (Table 2, columns 2–4) found that significant differences were primarily found between the groups of those Alive, Hospitalised/Alive, Not Hospitalised, and Alive, Not Hospitalised/Deceased, Hospitalised, with no significant differences between the Alive, Hospitalised/Deceased, Hospitalised groups.

4.5. Differences between first and second wave

For this analysis, a further 21 pwMS from the confirmed COVID-19 group were excluded due to missing values for estimated infection date. The likelihood of being hospitalised due to COVID-19 decreased in the second wave ($\chi^2 = 35.40$, df = 1, $p < 0.001$), as did the likelihood of death (Fisher test; CI 0.02, 0.91, $p = 0.02$). As presented in Table 3, in the second wave pwMS were more likely to be younger (t −2.85, df 153), not have progressive MS ($\chi^2 = 8.50$, df = 1), have lower disability ($\chi^2 = 8.67$, df = 2) and more likely to be on a DMT ($\chi^2 = 5.03$, df = 1).

An ordinal logistic regression, again using age and gender as independent variables, was modeled on the first wave data, with age (OR 1.08, CI [1.04, 1.12]) and gender (OR 0.19, CI [0.06, 0.55]) both found to be significant at $p < 0.01$, Residual Deviance 109.18, AIC 117.18. This was able to predict outcomes in the first wave with an accuracy of 70.273% (CI 58.52%, 80.34%). Inaccurate predictions were a mixture of 13 better and 9 worse outcomes. Applying this model to the second wave found it to be 57.14% accurate (CI 46.75%, 67.10%), and 39/42 of the inaccurate predictions were for worse outcomes. Thus the model that fits the first wave predicted many more worse outcomes than occurred in the second wave. Repeating the process in reverse, using the second wave data for the model showed age (OR 1.11, CI [1.06, 1.17], $p < 0.01$) and gender (OR 0.29, CI [0.09, 0.94], $p = 0.04$) were again significant with an accuracy of 83.67% (CI 74.84%, 90.37%), Residual Deviance 86.46, AIC 94.46. 13/16 of the incorrect predictions were for better outcomes than happened. Applying this model to the first wave data gave an accuracy of 55.41 (CI 43.49%, 66.98%) and all predicted

Table 2
Standard hypothesis testing for nominal serious event categories, with post-hoc pairwise results for significant variables. Tests were conducted using Chi Squared and analysis of variance (ANOVA). Kruskal-Wallis test was substituted for ANOVA where results were non-normal, and Fisher's Exact test was substituted for Chi Squared where expected values were small. Post-hoc pairwise comparisons using Bonferroni adjustment were calculated for factors achieving statistical significance.

Characteristic	n	Standard hypothesis test: p-value	Post-hoc pairwise association tests, using Bonferroni adjustment: p-value		
			Alive, Not Hospitalised/Alive, Hospitalised	Alive, Hospitalised/ Deceased, Hospitalised	Alive, Not Hospitalised/ Deceased, Hospitalised
Gender: Female/Male, missing	134/59, 0	0.001	0.002	1.000	0.153
Age (Years) Mean, Standard Deviation, missing	50.75, 14.90, 0	<0.001	<0.001	0.200	<0.001
MS Type: progressive/not progressive, missing	74/112, 7	<0.001	<0.001	0.293	<0.001
EDSS Group: mild/moderate/severe, missing	60/38/ 74, 21	<0.001	<0.001	0.708	<0.001
DMT: yes/no, missing	107/80, 6	<0.001	<0.001	0.381	<0.001
Comorbidities:	38/155	<0.001	<0.001	0.459	<0.001
Cardiac: yes/no	24/169	0.002	0.034	0.930	0.017
Respiratory: yes/no	21/172	<0.001	<0.001	1.000	0.008
Other: yes/no	58/135	<0.001	<0.001	0.810	<0.001
Any Comorbidity: yes/no					
Lymphocyte Count Prior to Covid-19 Infection (10^9/microlitre), Mean, Standard Deviation, missing	1.58, 1.14, 69	0.134	–	–	–

Table 3
Population demographics and clinical features of the first ($n = 74$) and second waves ($n = 98$). Tests were conducted using Chi Squared and analysis of variance (ANOVA). Kruskal-Wallis test was substituted for ANOVA where results were non-normal, and Fisher's Exact test was substituted for Chi Squared where expected values were small.

Characteristic	First wave $n = 74$	Second Wave $n = 98$	Standard Hypothesis test: p-value
Gender: Female/Male, missing	48/26, 0	72/26, 0	0.294
Age (Years): Median (IQR), missing	54 (44, 64), 0	46 (37, 54), 0	0.005
MS Type: progressive/not progressive, missing	36/33, 5	28/70, 0	0.003
EDSS Group: mild/ moderate/severe, missing	18/10/35, 11	38/24/29, 7	0.013
DMT: yes/no, missing	35/35, 4	67/31, 0	0.025
Hospitalised: yes/no, missing	51/23, 0	22/76, 0	<0.001
Deceased: yes/no, missing	8/66, 0	2/96, 0	0.020

outcomes were better than the observed outcomes: 25 predictions were for the person would be alive without needing hospitalisation when in reality they were hospitalised, 4 predictions were for the person being alive but hospitalised when in reality they died, and 4 predictions were for the person being alive and not hospitalised when in reality they died.

5. Discussion

We present an overview of COVID-19 in pwMS from England, Wales and Northern Ireland, showing that the features associated with poor outcome in confirmed COVID-19 infection are similar to other non-MS populations reported around the world. We found a range of MS and non-MS factors appeared to be relevant to COVID-19 outcome, but in multivariable analysis only older age and male gender remained as significant predictors of poor outcome. We also demonstrated that these factors were associated with hospitalisation, but once hospitalised, none were associated with mortality. This implies that once in hospital factors, not quantified here, are predictive of mortality.

Our findings are consistent with our community-based self-reported study in the UK where there were fewer pwMS self-reporting as being hospitalised (Evangelou et al., 2020), and with other Register-based studies (Louapre et al., 2020), which also found that pwMS on a DMT were not at an increased risk of a poor outcome, but contrasts with international data on increased risks with some DMTs (Simpson-Yap et al., 2021). However, in common with our findings they did not find that DMTs were associated with a higher mortality (Simpson-Yap et al., 2021). This is perhaps because those on DMTs are generally younger and have lower levels of disability than those not on DMTs, would be less at risk of serious COVID outcomes and were also advised to self-isolate (IfG 2021b). Thus, it seems likely in the UK that the behavior of people on DMTs is potentially an important factor.

Reassuringly, we see that the outlook for COVID-19 in pwMS has improved in the second wave, as we observed younger, less progressive people having improved survival rates, in keeping with UK and other international results (IfG, 2021b; Griffin, 2020; James et al., 2021). Age and gender provided a better fit for the second wave model than the first, suggesting that the higher hospitalisation and mortality in the first wave may be attributed to other factors not accounted for in this data. Certainly, during the first wave there remains a concern about how decisions regarding treatment were made for those at-risk populations e.g. those above a certain age but also those with prior disabilities. These decisions were managed more cohesively following guidance for the second wave (Williamson et al., 2021; IfG, 2021).

Limitations of our study largely relate to the fact that the data capture tool was devised at the outset of the pandemic; the understanding of the COVID-19 infection has evolved over the course of the pandemic. As a result, we did not capture ethnicity (Garjani et al., 2021) or body mass index (Razieh et al., 2020), which have subsequently been shown to be factors associated with increased mortality.

Another factor was the limited availability of PCR testing in the first few weeks of the pandemic; this was eventually resolved through wider more effective testing, but it may have affected our analysis as several pwMS were excluded due to inconclusive COVID-19 status.

As with all studies we have to be mindful of reporting bias (McGauran et al., 2010), particularly in a study such as this where data is 'volunteered' by interested clinicians. Despite this, 46 different sites across England, Northern Ireland and Wales contributed data to this study across all time points. Reporting bias may also mean the most serious cases were reported, and milder community cases more likely to be missed. Additionally, pwMS on DMTs were potentially over-reported due to having a higher likelihood of being reviewed by neurologists due to their treatment regimen but ultimately the sample size as with other studies may have limited our ability to draw conclusions on DMTS.

6. Conclusion

Increasing age was the most significant factor for risk of hospitalisation and mortality in pwMS infected with COVID-19. Male gender, increasing disability, progressive MS, and the presence of comorbidities were also found to be associated with a higher risk whereas being on a disease modifying therapy was associated with a lower risk of hospitalisation and mortality. Once in hospital none of these factors were predictive of mortality.

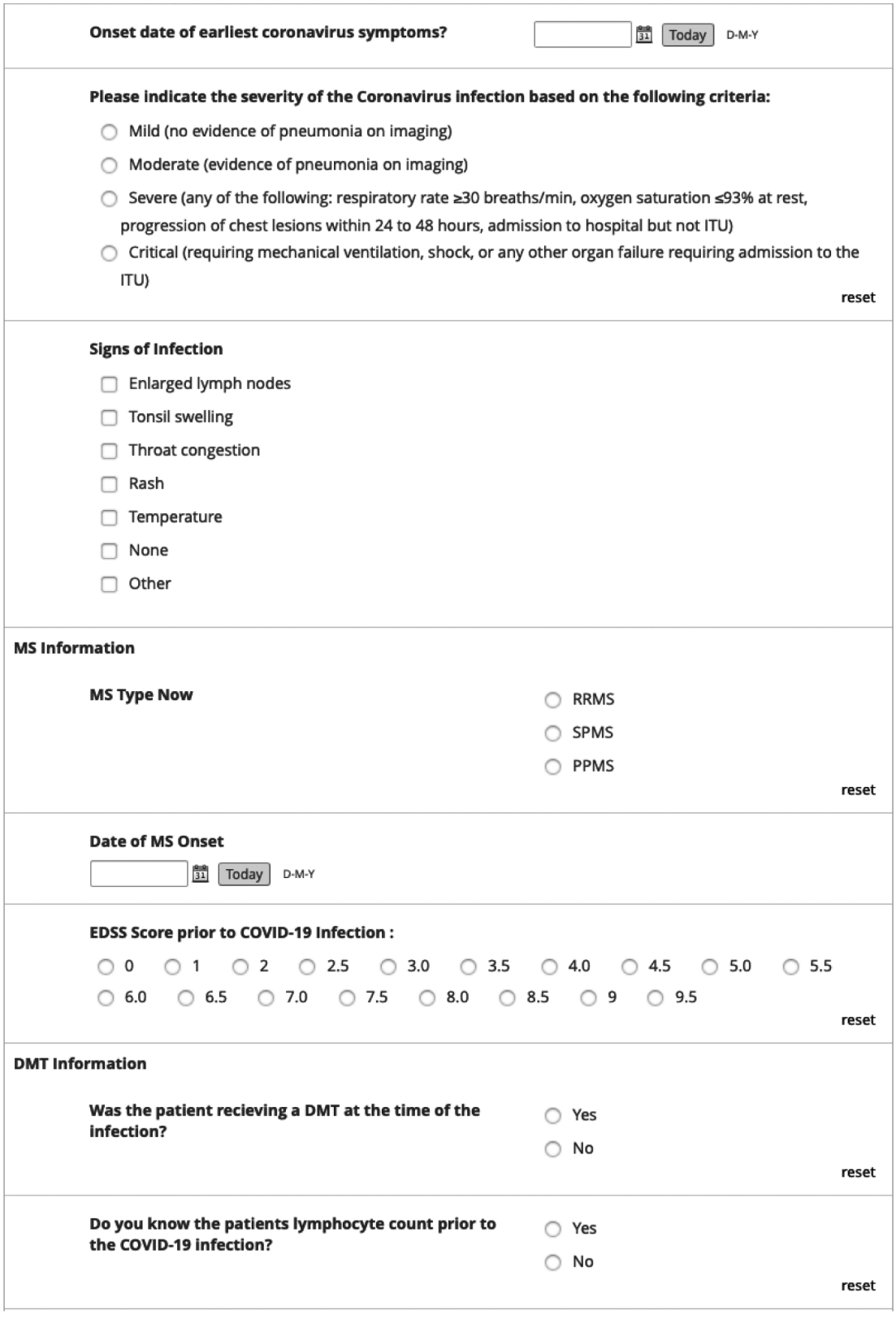

Fig. A1. Appendix 1: Example electronic case return form section.

CRediT authorship contribution statement

RM Middleton: Conceptualization, Writing – original draft, Methodology, Resources. **EM Craig:** Methodology, Software, Data curation, Formal analysis. **WJ Rodgers:** Methodology, Formal analysis. **K Tuite-Dalton:** Validation. **A Garjani:** Writing – review & editing, Data curation. **N Evangelou:** Writing – review & editing, Data curation. **R das Nair:** Writing – review & editing, Data curation. **R Hunter:** Writing – review & editing, Data curation. **EC Tallantyre:** Writing – review & editing, Data curation. **M Cauchi:** Data curation. **C Cairn:** Data curation. **D Paling:** Data curation. **S Fuller:** Data curation. **G McDonnell:** Data curation. **K Petheram:** Data curation. **B Liu:** Data curation. **U Nock:** Data curation. **G Ingram:** Data curation. **W Brownlee:** Writing – review & editing, Data curation. **J Taylor:** Data curation. **R Nicholas:** Writing – review & editing, Methodology, Supervision.

Conflicts of Interest

RMM, EMC, WJR, and KT-D, as part of the UK MS Register, have received grants from the MS Society. RdN has received research funding from the UK MS Society, National Institute for Health Research, & Medical Research Council, as well as funding (speakers' bureau) from Novartis, Biogen, and Merck. ECT had received honoraria, speaker fees or travel expenses for educational meetings from Biogen, Merck, Novartis, Roche and Takeda, unrelated to this work. DP is local principal investigator for commercial trials funded by Novartis and Janssen Pharmaceuticals, reports an investigator grant from Sanofi Genzyme, and reports advisory boards/consultancy and speakers fees from Biogen, Celgene, Janssen, MedDay, Merck, Novartis and Roche. WB received honoraria for educational activities and/or participated in advisory boards for Biogen, Celgene, Mylan; Novartis, Roche, Sanofi. RN reports support from advisory boards and travel expenses from Novartis, Roche and Biogen. He has grant support from the UK MS Society and is a member of a NICE HTA committee.This study was funded by Multiple Sclerosis Society (https://doi.org/10.13039/501100000381) and grant number: MSREG-001The UK MS Register has ethical approval from South-West Central Bristol Research Ethics Committee (16/SW/0194).

Appendix

Fig. A1

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