Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 52 (2021) 103004

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Registry of patients with multiple sclerosis and COVID-19 infection in Saudi Arabia

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ARTICLE INFO

Keywords:
Multiple sclerosis
COVID-19
Saudi Arabia

ABSTRACT

Background: The outbreak of coronavirus disease 2019 (COVID-19) has rapidly spread and developed as a pandemic threatening global health. Patients with multiple sclerosis (MS)–an autoimmune demyelinating inflammatory disease of the central nervous system (CNS)–are predominantly treated with immunomodulatory/immunosuppressive disease-modifying therapies (DMTs), which can increase the risk of infection. Therefore, there is concern that these patients may have a higher risk of COVID-19. In response to growing concerns of neurologists and patients, this study aimed to determine the prevalence, severity, and possible complications of COVID-19 infection in patients with MS in Saudi Arabia (SA).

Methods: In this prospective cohort study, demographic and clinical data were obtained from patients residing in SA with MS who had a positive result for COVID-19 per reverse transcription-polymerase chain reaction test or viral gene sequencing, using respiratory or plasma samples. Comparison of COVID-19 severity groups was performed using one-way ANOVA or Kruskal-Wallis test for numerical variables and Chi-squared test for categorical variables.

Results: Seventy patients with MS and COVID-19 (71% female) were included in this analysis. Of the 53 (75.7%) patients receiving a DMT at the time of COVID-19 infection, the most frequently used DMTs were fingolimod (25%) and interferon-beta (25%). Nine (13%) patients had MS relapse and were treated with intravenous methylprednisolone in the four weeks before COVID-19 infection. The most common symptoms at the peak of COVID-19 infection were fever (46%), fatigue (37%), and headache (36%). Symptoms lasted for a mean duration of 8.7 days; all symptomatic patients recovered and no deaths were reported. COVID-19 severity was categorized in three groups: asymptomatic ($n = 12$), mild–not requiring hospitalization ($n = 48$), and requiring hospitalization ($n = 10$; two of whom were admitted to the intensive care unit [ICU]). Between the three groups, comparison of age, body mass index , Expanded Disability Severity Score , MS disease duration, and DMT use at the time of infection showed no significant differences. A higher percentage of patients who were admitted to hospital or the ICU (40%; $p = 0.026$) presented with an MS relapse within the prior four weeks compared with those who were asymptomatic or had a mild infection (both 8.3%).

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https://doi.org/10.1016/j.msard.2021.103004
Received 12 February 2021; Received in revised form 13 April 2021; Accepted 29 April 2021
Available online 7 May 2021

Conclusion: These findings present a reassuring picture regarding COVID-19 infection in patients with MS. However, patients with MS who have had a relapse in the preceding four weeks (requiring glucocorticoid treatment) may have an increased risk of severe COVID-19.

1. Introduction

Coronaviruses are structurally enveloped pathogens containing a large plus-strand RNA genome that can cause a variety of severe diseases, including respiratory tract illnesses and gastroenteritis in amphibians, birds, and mammals (van der Hoek et al., 2004). To date, several human coronaviruses have been identified, including severe acute respiratory syndrome coronavirus (SARS-CoV) (Drosten et al., 2003) and, most recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered, which causes the coronavirus disease named COVID-19 (Hartenian et al., 2020).

The outbreak of the highly-transmissible COVID-19, first reported on December 31, 2019, in Wuhan, China (World Health Organization, 2020), has since spread rapidly, becoming a pandemic in March 2020, threatening global health (Khot and Nadkar, 2020). As of 31 January 2021, there have been over 102 million cases reported worldwide, more than 367,000 of which in Saudi Arabia (SA) ((COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2021; Dong et al., 2020; Saudi Center for Disease Prevention and, 2021). In the era of COVID-19, there are significant concerns for individuals with pre-existing co-morbidities, such as cardiovascular, pulmonary, and immune-mediated diseases (Laroni et al., 2020). Occasionally, coronaviruses can result in neuroinvasion due to their tropism for the central nervous system (CNS), resulting in potential neurological damage, which may carry heightened implications for patients with pre-existing neurological diseases with associated demyelination (Boziki et al., 2020; Carod-Artal, 2020).

One such disease is multiple sclerosis (MS), an autoimmune demyelinating inflammatory disorder of the CNS (Alshamrani et al., 2020), affecting over 2.8 million people worldwide in a 2:1 female to male ratio (Coetzee and Thompson, 2020). Patients with MS are predominantly treated with immunomodulatory/immunosuppressive disease-modifying therapies (DMTs), which alter the immune response, potentially increasing the risk of infection (Laroni et al., 2020; Luna et al., 2020). Thus, there is concern that these patients may be at an increased risk of COVID-19 infection or severe outcomes. Alongside neurologists' concern for their patients, a Saudi Arabian study of 176 patients with MS reported 46% of participants had anxiety over taking their DMT medication, and a further 32% had missed hospital appointments, highlighting the significant impact of the COVID-19 pandemic on the healthcare of patients with MS (Alnajashi and Jabbad, 2020).

In response to the growing uncertainty and anxiety of health care professionals and patients alike, this study aimed to determine the prevalence, severity, and possible complications of COVID-19 infection in patients with MS in SA.

2. Methods

2.1. Study design

This was a prospective cohort study conducted across twelve hospitals in SA. Demographic and clinical data, including gender, age, type of MS diagnosed, type of DMT prescribed, symptoms of COVID-19 infection, and hospital admissions (including those to the ICU) were obtained from medical records and patients through a face-to-face interview process, conducted at the respective hospitals. This study was approved by the ethics committee or institutional review board of each center involved. Informed verbal consent was obtained from all patients for inclusion in the study.

2.2. Patient selection

Patients residing in SA with relapsing-remitting MS, primary progressive MS, secondary progressive MS, or clinically isolated syndrome, per 2010 McDonald criteria, with a positive result for COVID-19 were considered for this study. COVID-19 was diagnosed based on a positive result of a reverse-transcription-polymerase chain reaction test or viral gene sequencing, using either respiratory or plasma samples. Individuals were discounted if they were pregnant, lactating, had a history of substance abuse, or there was the presence of another neurological disorder.

2.3. Statistical analysis

Prevalence-based sample size was determined using "Qualtrics" sample-size calculator; it quantified that a minimum of 40 patients with MS and COVID-19 infection were required to be recruited from the general population of SA. Confidence intervals of 95% with a 5% margin of error were used. Descriptive statistics for categorical variables used frequencies and relative frequencies. For numeric variables, mean and standard deviation (SD) were used when the variable was normally distributed, while median and range were used for expanded disability severity scale (EDSS) score. The severity of COVID-19 was categorized as either asymptomatic, mild (not requiring hospitalization) or requiring hospitalization. A one-way ANOVA or Kruskal-Wallis test was used to compare COVID-19 severity groups, and Chi-squared tests to compare categorical variables, with a p-value <0.05 considered statistically significant. The software IBM SPSS statistics, version 26, was used to compute data analysis.

3. Results

3.1. Demographics and patient characteristics

Across SA, 70 patients with MS and COVID-19 infection were included, of whom 50 (71%) were female (Table 1). Geographically, the highest percentage of patients were from the central region (47%), followed by the eastern region (24%) and the western region (23%). The mean (standard deviation [SD]) age of patients was 33.7 (11) years, and the mean (SD) body mass index (BMI) was 26 (4.8) kg/m^2. As for the types of MS included, most patients (n = 61 [87%]) had relapsing-remitting MS, five (7%) had secondary progressive MS, three (4%) had primary progressive MS, and one (1%) had clinically isolated syndrome. The mean (SD) disease duration was 5.4 (4.6) years and median EDSS score was 1.5 (range, 0–7).. Twelve (17%) patients required glucocorticoid treatment for demyelinating disease in the previous two months before COVID-19 infection. Nine (13%) patients presented with an MS relapse within four weeks before COVID-19 infection; all nine patients were treated with intravenous methylprednisolone. Of the 53 (76%) patients receiving a DMT at time of COVID-19 infection, the most frequently used drugs for MS were fingolimod (n = 13; 25%), interferon-beta (n = 13; 25%), and teriflunomide (n = 8; 15%).

3.2. Characteristics of COVID-19 infection

As presented in Table 2, the most common initial symptoms of COVID-19 among these patients with MS were fever (54%), headache (33%), and dry cough (30%), while the most common symptoms at the peak of infection were fever (46%), fatigue (37%), and headache (36%). The mean (SD) approximate duration of COVID-19 symptoms was 8.7 (9.3) days. Twenty-two (31.4%) patients visited the emergency room

Table 1
Demographics and characteristics of patients with MS diagnosed with COVID-19 infection

	Total ($N = 70$)
Age, mean (SD), years	33.7 (11)
Sex, n (%)	
Female	50 (71.4)
Male	20 (28.6)
Region, n (%)	
Central	33 (47.1)
East	17 (24.3)
West	16 (22.9)
South	3 (4.3)
North	1 (1.4)
BMI, mean (SD), kg/m^2	26.1 (4.8)
Smoking status, n (%)	
Current	3 (4.3)
Never	60 (85.7)
Past	7 (10.0)
Vaping status, n (%)	
Current	2 (2.9)
Never	68 (97.1)
Disease duration, mean (SD), years	5.4 (4.6)
Disease course, n (%)	
Relapsing remitting MS	61 (87.1)
Secondary progressive MS	5 (7.1)
Primary progressive MS	3 (4.3)
Clinical Isolated syndrome	1 (1.4)
Ambulatory status, n (%)	
Fully ambulatory	58 (82.9)
Non-ambulatory	3 (4.3)
Walk with Assistance	9 (12.9)
EDSS score, median (range)	1.5 (0–7)
MS relapse in the previous 4 weeks before **COVID-19 infection, n (%)**	
No	61 (87.1)
Yes	9 (12.9)
Taking DMT at time of COVID-19 infection, n (%)	
No	17 (24.3)
Yes	53 (75.7)
Fingolimod	13 (24.5)
Interferon-beta	13 (24.5)
Teriflunomide	8 (15.1)
Dimethyl fumarate	7 (13.2)
Natalizumab	4 (7.5)
Ocrelizumab	4 (7.5)
Rituximab	3 (5.7)
Cladribine	1 (1.9)
Glucocorticoid for demyelinating disease in the previous **2 months before COVID-19 infection, n (%)**	
No	58 (82.9)
Yes	12 (17.1)

BMI, body mass index; COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation.

and ten (14.3%) were admitted to the hospital. Of the ten hospitalized patients, five were not being treated with a DMT at time of COVID-19 infection (Fig. 1); the remaining five were receiving ocrelizumab ($n = 2$), rituximab ($n = 1$), fingolimod ($n = 1$) or teriflunomide ($n = 1$). Two of the hospitalized patients were admitted to the intensive care unit (ICU); both patients required mechanical ventilation and received systemic glucocorticoids for the treatment of COVID-19. One patient (age, 63 years) had a diagnosis of secondary progressive MS and was receiving the DMT ocrelizumab at the time of COVID-19 infection while the other patient (age, 34 years) had relapse-remitting MS and was not being treated with a DMT at the time of infection. Both patients had received glucocorticoids within the previous two months before COVID-19 diagnosis (Table S1). All symptomatic patients recovered and no deaths were reported.

3.3. Patient characteristics and severity of COVID-19

Of the 70 patients, there were twelve asymptomatic cases, 48 mild cases (not hospitalized), and ten hospitalized cases. There were no significant differences in age, BMI, EDSS score, or MS disease duration among the three COVID-19 severity groups (Table 3), nor between the three groups with regards to DMT use at time of COVID-19 infection

Table 2
Characteristics of the COVID-19 infection

	Total ($N = 70$)
Initial symptoms , n (%)	
Fever	38 (54.3)
Headache	23 (32.9)
Dry cough	21 (30.0)
Fatigue	18 (25.7)
Asymptomatic	13 (18.6)
Pain (joint, bone, muscle)	11 (15.7)
Sore throat	10 (14.3)
Anosmia	9 (12.9)
Chills	7 (10.0)
Diarrhea	5 (7.1)
Dizziness	5 (7.1)
Dyspnea	5 (7.1)
Asthenia	4 (5.7)
Shortness of breath	4 (5.7)
Nausea	3 (4.3)
Ageusia	2 (2.9)
Runny nose	1 (1.4)
Symptoms at the peak of infection, n (%)	
Fever	32 (45.7)
Fatigue	26 (37.1)
Headache	25 (35.7)
Dry cough	20 (28.6)
Anosmia	19 (27.1)
Sore throat	15 (21.4)
Asymptomatic	12 (17.1)
Shortness of breath	12 (17.1)
Asthenia	11 (15.7)
Pain (joint, bone, muscle)	10 (14.3)
Ageusia	10 (14.3)
Chills	9 (12.9)
Diarrhea	9 (12.9)
Neurological symptoms	7 (10.0)
Dyspnea	7 (10.0)
Dizziness	6 (8.6)
Nausea	4 (5.7)
Runny nose	0 (0.0)
Duration of symptoms, mean (SD), days	8.7 (9.3)
Isolation and hospital admission, n (%)	
Home isolation	62 (88.6)
Emergency Room visited	22 (31.4)
Hospital admission	10 (14.3)
ICU admission	2 (2.9)
Ventilation	2 (2.9)
Extracorporeal membrane oxygenation	0 (0.0)
Chest imaging, n (%)	
Abnormal	5 (7.1)
Normal	19 (27.1)
Not done	46 (65.7)
ECG, n (%)	
Normal or Not Clinically Significant	15 (21.4)
Not done	55 (78.6)
Echocardiogram. n (%)	
Normal or Not Clinically Significant	5 (7.1)
Not done	65 (92.9)
Last white blood cell count before COVID-19 diagnosis (within the past 6 months), n (%)	
Abnormal and Clinically Significant	6 (8.6)
Normal or Not Clinically Significant	53 (75.7)
Not done	11 (15.7)
Last lymphocyte count before COVID-19 diagnosis (within the past 6 months), n (%)	
Abnormal and Clinically Significant	8 (11.4)
Normal or Not Clinically Significant	51 (72.9)
Not done	11 (15.7)

BMI, body mass index; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; ICU, intensive care unit; MS, multiple sclerosis; SD, standard deviation.

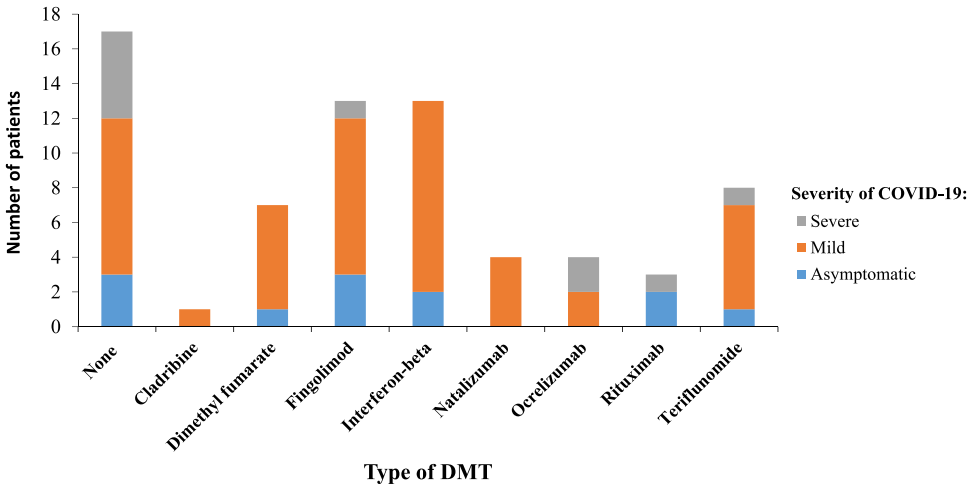

Fig. 1. Severity of COVID-19 infection, according to DMT taken at time of infection
DMT, disease modifying therapy; MS, multiple sclerosis.

Table 3
Patient characteristics and severity of COVID-19.

		N	Mean	SD	P-value
Age, years	Asymptomatic	12	32.9	11.9	0.332
	Mild symptoms	48	32.9	9.4	
	Hospital or ICU admission	10	38.5	16.0	
BMI, kg/m^2	Asymptomatic	12	26.9	3.7	0.678
	Mild symptoms	47	25.7	4.8	
	Hospital or ICU admission	9	26.8	6.0	
EDSS score	Asymptomatic	12	2.0	1.8	0.833
	Mild symptoms	48	2.0	2.0	
	Hospital or ICU admission	9	2.4	2.7	
MS disease duration, years	Asymptomatic	12	5.0	4.2	0.954
	Mild symptoms	48	5.3	4.2	
	Hospital or ICU admission	10	6.2	6.5	

BMI, body mass index; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; ICU, intensive care unit; MS, multiple sclerosis; SD, standard deviation.

Table 4
DMT use and severity of COVID-19 infection

			Taking DMT at time of COVID-19 Infection		P-value
			No	Yes	
COVID-19 severity	Asymptomatic	N	2	8	0.094
		%	20.0	80.0	
	Mild symptoms	N	8	33	
		%	19.6	80.4	
	Hospital or ICU admission	N	4	3	
		%	57.1	42.9	

COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; ICU, intensive care unit; MS, multiple sclerosis.

(Table 4). There were also no significant differences observed between patients who presented with symptomatic or asymptomatic COVID-19 infection (Table S2 and Table S3). However, it was noted that a higher percentage of patients who were admitted to hospital or the ICU (40%; $p = 0.026$) had presented with an MS relapse within four weeks prior to COVID-19 infection compared with those who were asymptomatic or had mild symptoms (both 8.3%; Table 5).

4. Discussion

In this cohort study of 70 patients with MS and COVID-19 infection residing in SA, the highest proportion of patients were from central SA, followed by east and west, with the fewest number of cases coming from the south and north of SA. These numbers appear proportionate based on the population distribution and geographical COVID-19 incidence rate in SA (Almofada et al., 2020; World Population Review, 2020). Most patients were being treated with a DMT at the time of COVID-19 infection. Similar to recent studies of MS patients in SA (Alnajashi and Jabbad, 2020, Alhazzani et al., 2019), the most commonly used DMTs were interferon-beta and fingolimod. The COVID-19 symptoms reported by patients with MS in this study reflected those described in the general population. Encouragingly, all patients in this cohort recovered or presented with no symptoms at all. The high recovery rate observed may have been influenced by the young age of MS patients, the high proportion of females, and the low incidence of comorbidities in such patient populations (Vishnevetsky and Levy, 2020), as well as the low rates of non-ambulatory status and low median EDSS score reported in this study cohort (Louapre et al., 2020). In this cohort, no significant associations between age or BMI and COVID-19 severity were observed. This contrasts with the numerous reports identifying age as a major risk factor of COVID-19, widely noted since the early stages of the pandemic (Chen et al., 2020; Chen et al., 2020). Other studies with larger patient groups have also indicated that obesity, defined asBMI >30, correlates with poor COVID-19 prognosis (Louapre et al., 2020; Gianfrancesco

Table 5
MS relapse within four weeks and severity of COVID-19 infection

			MS relapse in the four weeks prior to COVID-19 infection		P-value
			No	Yes	
COVID-19 severity	Asymptomatic	N	11	1	0.026
		%	91.7	8.3	
	Mild symptoms	N	44	4	
		%	91.7	8.3	
	Hospital or ICU admission	N	6	4	
		%	60.0	40.0	

COVID-19, coronavirus disease 2019; ICU, intensive care unit; MS, multiple sclerosis.

et al., 2020; Soeroto et al., 2020; Reder et al., 2021;).

MS disease duration and disability, assessed by EDSS, did not influence the severity of COVID-19 in this study. At the same time, EDSS has been identified as an independent risk factor of severe COVID-19 in patients with MS(Louapre et al., 2020; Simpson-Yap et al., 2020).

DMT use at the time of infection was not associated with COVID-19 severity in this cohort of patients with MS, which corresponds with other recent data showing no significant correlation between COVID-19 severity and the use of DMTs for the treatment of MS (Louapre et al., 2020,; Salama et al., 2020,; Barzegar et al., 2020,; Sormani et al., 2021). This lack of association between DMT type and COVID-19 severity supports a recent management consensus from experts in MS care from Saudi Arabia, which generally recommends continuing most DMTs during the COVID-19 era (Al Jumah et al., 2021). Consensus was not reached with regards to continuing ocrelizumab given that anti-CD20 therapies have been associated with an increased risk of severe COVID-19 infection (Reder et al., 2021; Sormani et al., 2021; Salter et al., 2021). Correspondingly, in our study, two of the four patients receiving ocrelizumab at the time of infection had severe disease, including one who required mechanical ventilation.

As was the case in this study, MS relapses are commonly treated with glucocorticoids, e.g., methylprednisolone. Nine patients treated with methylprednisolone following an MS relapse within four weeks before their diagnosis of COVID-19 were at a significantly higher risk of developing a more severe infection, requiring hospital or ICU admission and potentially mechanical ventilation. This is in line with findings from an Italian cohort of MS patients, which showed recent treatment with high-dose methylprednisolone was associated with increased risk (OR 5.2 95% CI 2.22-12.5; $p = 0.001$) of severe forms of COVID-19(Sormani et al., 2021). Therefore, broad immunosuppression with glucocorticoids before COVID-19 contraction may be associated with a more severe COVID-19 infection (Salter et al., 2021). These findings are also similar to observations with other autoimmune diseases. For example, a case series of 600 patients with rheumatic disease found that patients exposed to glucocorticoid $\geq$10 mg/day before COVID-19 infection were significantly more likely to require hospitalization (OR 2.1 [95% CI 1.1–4.0]) (Gianfrancesco et al., 2020). Interestingly, a study conducted in China found that two patients with neuromyelitis optica spectrum disorder (an autoimmune disease of the CNS (Sattar et al., 2020)), that had previously been treated with oral methylprednisolone, were diagnosed with more severe COVID-19 infection and associated pneumonia (Fan et al., 2020). Furthermore, it may be hypothesised that the dampening effect of methylprednisolone on the inflammatory cytokine cascade, activation of T cells, and extravasation of immune cells into the CNS could be factors leading to poorer outcomes of COVID-19 (Sloka and Stefanelli, 2005).

This study was limited by the relatively small sample size, especially in some subgroups. However, this was still more than the minimum sample of 40 patients required to be recruited.

5. Conclusions

These findings present a reassuring picture regarding COVID-19 infection in patients with MS. This study found no association between the severity of COVID-19 and age, BMI, EDSS, MS disease duration or DMT use at the time of infection. However, patients with MS treated with glucocorticoids for a relapse in the four weeks before COVID-19 infection may have an increased risk of developing a more severe case of COVID-19.

Credit statement

Foziah Alshamrani: Conceptualization, Methodology, Investigation, Formal Analysis, Writing - Review & Editing
Hind Alnajashi: Investigation, Formal Analysis
Mohammed Aljumah: Formal Analysis,
Mohammad Almuaigel: Conceptualization, Methodology, Investigation, Formal Analysis,
Yaser Almalik: Investigation, Formal Analysis
Seraj Makkawi: Investigation
Sadiq Alsalman: Investigation
Mousa Almejally: Investigation
Shireen Qureshi, Investigation
Salman Aljarallah: Investigation, Data Curation
Nuha AlKhawajah: Formal Analysis
Hanaa Kedah: Investigation
Hessa Alotaibi: Investigation
Jameelah Saeedi: Investigation
Abdulla Alamri: Investigation

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authorship

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article. All authors had access to the study data and take responsibility for the integrity of the data and the accuracy of the data analysis, and have given their approval for this version to be published.

Compliance with ethics guidelines

This study was approved by the ethics committee or institutional review board of each individual center involved. Informed verbal consent was obtained from all patients for inclusion in the study.

Funding

Medical writing support was funded by Merck KGaA, Darmstadt, Germany.

CRediT authorship contribution statement

Foziah Alshamrani: Conceptualization, Methodology, Investigation, Formal analysis, Writing - review & editing. **Hind Alnajashi:** . **Mohammed AlJumah:** . **Mohammad Almuaigel:** . **Yaser Almalik:** . **Seraj Makkawi:** . **Sadiq Alsalman:** . **Mousa Almejally:** . **Shireen Qureshi:** . **Salman Aljarallah:** . **Nuha AlKhawajah:** . **Hanaa Kedah:** . **Hessa Alotaibi:** . **Jameelah Saeedi:** . **Abdulla Alamri:** .

Acknowledgements

The authors would like to thank all the patients for their participation in this study alongside King Abdullah International Medical Research Center. Medical writing assistance was provided by Anna Khan of inScience Communications, Springer Healthcare Ltd, UK, and funded by Merck KGaA, Darmstadt, Germany.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103004.

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