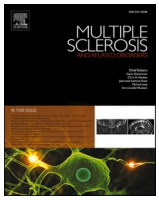
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 57 (2022) 103358

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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



Review article

Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Multiple Sclerosis
Covid-19 Severity
Ocrelizumab
Rituximab
Anti-CD-20 therapies

ABSTRACT

Background: COVID-19 may spread through various ways ranging from asymptomatic to severe forms, until respiratory failure, critical conditions and death occurs. There is a particular concern for patients affected by multiple sclerosis, especially for those under disease-modifying treatments. Some studies have found an association between anti-CD20 therapies (especially rituximab) and severe COVID-19. However, results were not always clear and thus a systematic review was helpful.

Methods: A systematic literature search was performed independently by two authors on the main search tools considering as key inclusion criterion the presence of data on patients under ocrelizumab or rituximab positive to COVID-19. The quality of the included studies was evaluated based on a modified version of the Dutch Cochrane center critical review checklist proposed by MOOSE and in case of missing data an email was sent to the corresponding authors asking for missing information. After excluding case-reports, a random effects meta-analysis of proportions was conducted using the continuity correction and the I^2statistic was calculated to measure heterogeneity.

Results: 29 articles were included in the analysis and the median quality of the articles reached 4/5 after having integrated the additional details provided by the authors. The articles included 5173 patients, of whom 770 (14.8%) and 455 (8.8%) were, respectively, under ocrelizumab and rituximab. Pooled estimates of hospitalization, pneumonia and intensive care unit admission were 18.1%, 14.8% and 3.3%, respectively, while pooled estimate for death was 1.8% overall and 1.6% and 4.5%, respectively, for patients under ocrelizumab and rituximab.

Conclusion: Patients treated with rituximab seem to be at higher risk of severe COVID-19 outcomes compared to patients under other treatments.

1. Introduction

Even if most of the COVID-19 cases are classified as mild, disease course can be severe or critical, possibly leading to serious pneumonia, hospitalization, admission to intensive care unit (ICU), and death (Wu and McGoogan, 2020). Furthermore, there is a particular concern for patients affected by multiple sclerosis (MS) and especially for those who take disease-modifying treatments (DMTs) that impact on the immune system and that can increase the risk of infections (Winkelmann et al., 2016).

Several studies have investigated associations between the use of DMTs and COVID-19 severity among patients with MS. A pooled analysis from an Italian and French cohort found a significant relationship of anti-CD20 therapies (rituximab and ocrelizumab) with COVID-19 severity, confirming previous results from a smaller Italian cohort (Sormani et al., 2021; Sormani et al., 2021). Consistently, in a North American study, both ocrelizumab and rituximab were associated with hospitalization, but association was stronger for rituximab (Salter et al., 2021).

However, the role of anti-CD20 treatments in the COVID-19 severity were not always confirmed (Bsteh et al., 2021; Louapre et al., 2020). Therefore, it is relevant to undertake a comprehensive systematic review

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https://doi.org/10.1016/j.msard.2021.103358
Received 30 September 2021; Received in revised form 20 October 2021; Accepted 28 October 2021
Available online 5 November 2021

Table 1
- Search strategy.

SOURCE	STRING
Scopus	(TITLE-ABS-KEY (coronavirus OR covid) AND TITLE-ABS-KEY (rituximab OR ocrelizumab) AND TITLE-ABS-KEY (ms OR multiple AND sclerosis)) AND NOT DOCTYPE (re) AND (LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020))
Web of Science	TOPIC: (Covid or coronavirus) AND TOPIC: (rituximab or ocrelizumab) AND TOPIC: (MS or multiple sclerosis) NOT DOCUMENT TYPES: (Review) Refined by: PUBLICATION YEARS: (2021 OR 2020)
PubMed	Search: (((MS or multiple sclerosis) AND (Covid OR coronavirus)) AND (rituximab OR ocrelizumab)) NOT (Review[Publication Type]) NOT (Meta-Analysis[Publication Type]) NOT (Systematic Review[Publication Type]) Filters: from 2020 to 2021 Sort by: Most Recent
Ectrims 2020	Search: (Covid OR coronavirus) AND (rituximab OR ocrelizumab) NOT (Review[Publication Type]) NOT (Meta-Analysis[Publication Type]) NOT (Systematic Review[Publication Type])

for estimating the mortality rate among patients under these therapies, for exploring all their available characteristics and in general for estimating their rates of severe COVID-19 events.

2. Methods

2.1. Article selection

A systematic literature search covering studies published until 31st July 2021, was performed in Scopus, Web of Science, PubMed and among the abstracts presented at the 2020 ECTRIMS meeting.

Search strategy is detailed in Table 1.

The key inclusion criterion was that the study presented data on COVID-19 course for MS patients treated with ocrelizumab or rituximab.

Two authors independently conducted the literature search and screened titles and abstracts based on the criteria reported above. They also collected the full texts and evaluated the eligibility of each study. Duplicated manuscripts among the sources, with clearly or suspicious overlapping patients, and those out of topic were excluded. The following data were extracted from the identified studies: authors, title, country, sample size, number of suspected/confirmed COVID-19 cases, number of males/females, mean age with range, number of patients with progressive MS, number of patients with relapsing MS, median last EDSS, mean MS duration with range, use and frequencies of MS treatments (cladribine, alemtuzumab, azathioprine, glatiramer acetate, daclizumab, dimethyl fumarate, fingolimod, interferon, methotrexate, mitoxantrone, natalizumab, ocrelizumab, rituximab, teriflunomide,

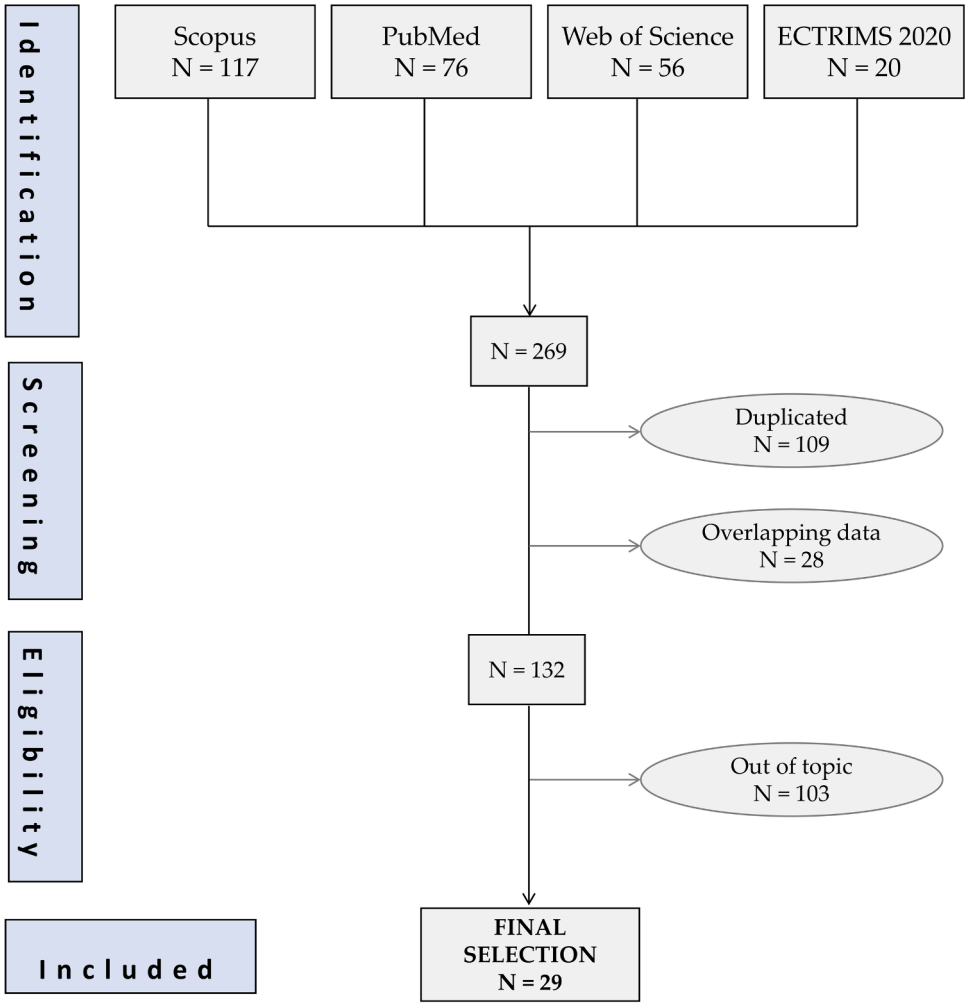

Fig. 1. Flow diagram for study selection.

Table 2
Titles of the included studies.

Nr	First Author	Title
01	*Arrambide G.*	SARS-CoV-2 Infection in Multiple Sclerosis (Arrambide et al., 2021)
02	*Barzegar M.*	Characteristics of COVID-19 disease in multiple sclerosis patients (Barzegar et al., 2020)
03	*Bsteh G.*	COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: Insights from a nation-wide Austrian registry (Bsteh et al., 2021)
04	*Bose G.*	Reactivation of SARS-CoV-2 after Rituximab in a Patient with Multiple Sclerosis (Bose and Galetta, 2021)
05	*Chaudhry F.*	COVID-19 in multiple sclerosis patients and risk factors for severe infection (Chaudhry et al., 2020)
06	*Ciampi E.*	COVID-19 in MS and NMOSD: A multicentric online national survey in Chile (Ciampi et al., 2020)
07	*Conte WL.*	Attenuation of antibody response to SARS-CoV-2 in a patient on ocrelizumab with hypogammaglobulinemia (Conte, 2020)
08	*Czarnowska A.*	Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies-the Polish experience (Czarnowska et al., 2021)
09	*D'Abramo A.*	Prolonged and severe SARS-CoV-2 infection in patients under B-cell-depleting drug successfully treated: A tailored approach (D'Abramo et al., 2021)
10	*Devogelaere J.*	Coronavirus disease 2019: favorable outcome in an immunosuppressed patient with multiple sclerosis (Devogelaere et al., 2020)
11	*Fernandez-Diaz E.*	Real-world experience of ocrelizumab in multiple sclerosis in a Spanish population (Fernandez-Diaz et al., 2021)
12	*Fragoso J.*	Coronavirus disease 2019 in Latin American patients with multiple sclerosis (Fragoso et al., 2021)
13	*Gibson EG.*	Prolonged SARS-CoV-2 Illness in a Patient Receiving Ocrelizumab for Multiple Sclerosis (Gibson et al., 2021)
14	*Hervás-García JV.*	Seroprevalence of sars-cov-2 in multiple sclerosis patients under immunomodulatory treatment in Lleida (study emcovid-19) (Hervas-Garcia et al., 2020)
15	*Louapre C.*	Clinical Characteristics and Outcomes in Patients with Coronavirus Disease 2019 and Multiple Sclerosis (Louapre et al., 2020)
16	*Loonstra FC.*	COVID-19 in multiple sclerosis: The Dutch experience (Loonstra et al., 2020)
17	*Montero-Escribano P.*	Anti-CD20 and COVID-19 in multiple sclerosis and related disorders: A case series of 60 patients from Madrid, Spain (Montero-Escribano et al., 2020)
18	*Olivares Gazca JC.*	Mélange intéressante: COVID-19, autologous transplants and multiple sclerosis (et al., 2020)
19	*Sadeghi M.*	Types of pharmaceutical intervention in patients with multiple sclerosis (ms): a fine line between immunosuppressive and risk of covid-19 infection (Sadeghi Maryam et al., 2021)
20	*Sahraian MA.*	Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis (Sahraian et al., 2020)
21	*Salter A.*	Outcomes and Risk Factors Associated With SARS-CoV-2 Infection in a North American Registry of Patients With Multiple Sclerosis (Salter et al., 2021)
22	*Sen S.*	The outcome of a national MS-COVID-19 study: What the Turkish MS cohort reveals? (Sen et al., 2021)
23	*Sormani MP.*	Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis (Sormani et al., 2021)
24	*Spelman T.*	Increased rate of hospitalization for COVID-19 among rituximab-treated multiple sclerosis patients: A study of the Swedish multiple sclerosis registry (Spelman et al., 2021)
25	*Suwanwongse K.*	Benign course of COVID-19 in a multiple sclerosis patient treated with Ocrelizumab (Suwanwongse and Shabarek, 2020)
26	*Thornton JR.*	Negative SARS-CoV-2 Antibody Testing Following COVID-19 Infection in Two MS Patients Treated with Ocrelizumab (Thornton and Harel, 2020)
27	*Woo MS.*	Control of SARS-CoV-2 infection in rituximab-treated neuroimmunological patients (Woo et al., 2021)
28	*Wurm H.*	Recovery from COVID-19 in a B-cell-depleted multiple sclerosis patient (Wurm et al., 2020)
29	*Wallach A.*	The presence of SARS-CoV2 antibodies in MS patients (Armstrong et al., 2021; Arrambide et al., 2021; Barzegar et al., 2020, 2021; Bose and Galetta, 2021; Bsteh et al., 2021; Chaudhry et al., 2020; Ciampi et al., 2020; Conte, 2020; Czarnowska et al., 2021; D'Abramo et al., 2021; Devogelaere et al., 2020; Fernandez-Diaz et al., 2021; Fragoso et al., 2021; Garg et al., 2020; Hervas-Garcia, 2020; Loonstra et al., 2020; Louapre et al., 2020; Montero-Escribano et al., 2020; Olivares Gazca et al., 2020; Sahraian et al., 2020; Salter et al., 2021; Sen et al., 2021; Sormani et al., 2021b,a; Spelman et al., 2021; Stroup et al., 2000; Suwanwongse and Shabarek, 2020; Thornton and Harel, 2020; Wallach and Picone, 2021; Winkelmann et al., 2016; Woo et al., 2021; Wu and McGoogan, 2020; Wurm et al., 2020; The Multiple Sclerosis International Federation 2020; Gibson et al.2021; Sadeghi Maryam et al., 2021)

Table 3
Assessment of the quality of included studies by a modified MOOSE criteria.

Nr (study)	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Clear definition of study population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clear definition of outcomes and outcome assessment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No*	Yes	Yes	No*	Yes	No*	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Independent assessment of outcome parameters	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No*	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Important confounders and prognostic factors identified	Yes	Yes	No	No*	No*	Yes	No	Yes	Yes	Yes	No	No*	Yes	No*	No	No*	No*	No*	No*	No	Yes	Yes	Yes	Yes	No	No*	Yes	Yes	No
Quality Score on published data	4	3	3	3	3	3	3	4	4	4	3	3	4	1	3	3	1	2	2	2	4	4	4	3	3	3	4	4	2
Quality Score revised with data provided by authors	4	3	3	4	4	3	3	4	4	4	3	4	4	3	3	4	3	4	4	2	4	4	4	3	3	4	4	4	2

*Data provided by the authors but not published.

other), number of hospitalizations, number of patients admitted to the ICU, number of patients with pneumonia, number of deaths, number of deceased patients treated with ocrelizumab, number of deceased patients treated with rituximab. In case of missing data, an email was sent to the corresponding authors asking to complete the missing information.

2.2. Quality assessment

All selected articles were rigorously appraised by two authors according to a modified version of the Dutch Cochrane center critical review checklist proposed by MOOSE (Stroup et al., 2000). Key domains assessed by the MOOSE tool include: (I) Clear definition of study population; (II) Clear definition of outcomes and outcomes assessment; (III) Independent assessment of outcome parameters; (IV) Sufficient

Table 4
Baseline characteristics.

Nr	First Author	Demography			MS data			Disease Modifying Treatments				
		Sample	Females/ Males	Age, yrs (range)	Progressive /RR	Last EDSS	MS duration, yrs (range)	Un treated	Cladribina	Alemtuzumab	Azathioprine	Glatiramer Acetate
01	*Arrambide G.*	326	221/105		63/263	2		59	6	18	0	13
02	*Barzegar M.*	9	8/1	29 - 50	2/6	0	1 - 27	2	0	0	0	1
03	*Bsteh G.*	126	90/36	21–79	28/98	2		36	2	2	1	11
04	*Bose G.*	1	1/0	32 - 32	0/1	1.5	12 - 12	0	0	0	0	0
05	*Chaudhry F.*	40	24/16	28 - 84	9/30	2	1 - 31	8	0	1	0	3
06	*Ciampi E.*	14	10/4	17 - 57	0/14	1	2 - 14	0	0	2	0	0
07	*Conte WL.*	1	1/0	48 - 48				0	0	0	0	0
08	*Czarnowska A.*	396	282/114	18 - 68	24/372	2	0 - 33	0	5	1	0	42
09	*D'Abramo A.*	1	1/0	54–54		1.5		0	0	0	0	0
10	*Devogelaere J.*	1	1/0	33 - 33	0/1	8	16 - 16	0	0	0	0	0
11	*Fernandez-Diaz E.*	3	0/3	32 - 49	2/1	6		0	0	0	0	0
12	*Fragoso J.*	73	50/23	17–72	4/69	2	0–26	3	1	1	0	10
13	*Gibson EG.*	1	1/0	46–46	0/1			0	0	0	0	0
14	*Hervás-García JV.*	19	12/7	41 - 67	1/18	2	3 - 24	0	1	1	0	0
15	*Louapre C.*	347	249/98		65/276	2		63	3	1	0	33
16	*Loonstra FC.*	86	60/26	20 - 71	14/69	3	6.8 - 32.8	12	0	1	0	4
17	*Montero-Escribano P.*	9	7/2	41 - 55	4/4		5 - 30	0	0	0	0	0
18	*Olivares Gazca JC.*	4	3/1	39 - 54	1/3	5.8	3 - 21	0	0	0	0	0
19	*Sadeghi M.*	371	235/136	39 - 43.5	104/267		1 - 13	7	0	0	0	0
20	*Sahraian MA.*	68	56/12		3/60			2	0	0	1	5
21	*Salter A.*	1626	1202/421		280/1255			237	14	9	0	84
22	*Sen S.*	309	219/90	18–66	32/277	1.5	0.2–31	26	0	1	0	27
23	*Sormani MP.*	844	593/251	18–82	135/676	2		151	11	14	10	70
24	*Spelman T.*	476	340/136	19–78	67/407	2	0.0–40.7	18	8	5	0	9
25	*Suwanwongse K.*	1	0/1	31 - 31				0	0	0	0	0
26	*Thornton JR.*	2	1/1	39 - 42	0/2	1.5	4 - 5	0	0	0	0	0
27	*Woo MS.*	1	1/0	44 - 44	0/1	2	21 - 21	0	0	0	0	0
28	*Wurm H.*	1	1/0	59 - 59	1/0	6	4 - 4	0	0	0	0	0
29	*Wallach A.*	17	13/4	32 - 67				2	0	0	0	1

follow-up; (V) No selective loss during follow-up; and (VI) Important confounders and prognostic factors identified. Each domain could be filled in with "yes", "no" or "unclear" and rated as follows: yes (1 point), no/unclear (0 points) based on published data.

However, since two domains (IV and V) were considered irrelevant for the purpose of this study, only four (I, II, III, VI) were combined in an overall reporting quality score (ranging from 0 to 4 points). A study was defined of highest quality if all criteria were rated as "yes" because free from intra-study bias.

2.3. Statistical analysis

To estimate the mortality rate among patients treated with ocrelizumab and rituximab and to evaluate the overall rate of mortality, hospitalization, and ICU admission, a random effects meta-analysis of proportions using the continuity correction was conducted, with the I^2statistic to measure heterogeneity. Case reports were excluded from the meta-analysis to avoid misleading results and to not overestimate the rate of severe outcomes (case reports usually describe more serious cases rather than mild disease courses).

Meta-analysis was performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

3. Results

Out of 269 articles retrieved from investigated databases, 29 were included in the final analysis (Fig. 1) (Table 2).

The quality of selected studies ranged from 1 to 4 points (median = 3) by considering original published data, whereas with implemented details provided by authors the total quality score of manuscripts improved to 2 to 4 points (median = 4) (Table 2) (Table 3).

These studies involved 5173 patients (81% with confirmed COVID-19), with an age ranging from 17 to 84 years, and 71% of the participants were females. The sample size for the included studies ranged from 1 (single case report) to 1626 cases. As about MS history, 80.6% of the sample presented a relapsing remitting form of disease, 770 (14.8%) patients were in treatment with ocrelizumab and 455 (8.8%) with rituximab (Table 4).

Frequencies of COVID-19 outcomes and results from the meta-analysis are reported in Table 5. A total of 888 patients were hospitalized (pooled estimate: 18.1%; 95%CI = [14.5%;21.6%]), 436 cases reported pneumonia (pooled estimate: 14.8%; 95%CI = [9.6%;20.1%]); 200 patients were admitted to ICU and 115 died. Fifteen (1.9%) and ten (2.2%) fatal events occurred respectively among patients on ocrelizumab and on rituximab.

4. Discussion

The pooled estimate of the hospitalization rate was 18.1%, slightly lower compared to the rate observed in a systematic review which included studies on MS and COVID-19 without restrictions based on the treatment type (20.7%) (Barzegar et al., 2021).

In general, hospitalization rates were found to vary widely depending on several characteristics, including age, gender, presence of comorbidities, residence area and reference period under study (Garg et al., 2020). For a deeper analysis of these results, it is important to consider that MS population differ from the general population in distribution of several characteristics, such as age, gender, and presence of comorbidities (The Multiple Sclerosis International Federation, 2020). In addition, the high heterogeneity (88%) found in this meta-analysis can be partially explained by the fact that data are collected from different Countries, referred to different periods of pandemic and based on different study designs. Similar considerations can be made to explain the high heterogeneity for the pneumonia rate, with lower and upper confidence interval ranged from 9.6 to 20.1%. Furthermore, pneumonia data were not always available, probably due to the

Disease Modifying Treatments									
Dimethyl fumarate	Fingolimod	Interferon	Methotrexate	Mitoxantrone	Natalizumab	Ocrelizumab	Rituximab	Teriflunomide	Other
41	27	36	0	0	26	23	33	37	7
0	1	4	0	0	0	0	1	0	0
19	16	6	0	0	10	0	0	2	0
0	0	0	0	0	0	0	1	0	0
6	2	2	0	0	2	12	0	3	1
2	5	1	0	0	1	2	0	2	0
0	0	0	0	0	0	1	0	0	0
164	16	82	0	3	35	20	0	25	3
0	0	0	0	0	0	1	0	0	0
0	0	0	0	0	0	0	1	0	0
0	0	0	0	0	0	3	0	0	0
15	14	10	0	0	6	5	3	5	0
0	0	0	0	0	0	1	0	0	0
5	2	3	0	0	2	3	2	0	0
35	42	20	1	0	57	38	17	33	4
18	15	5	0	0	5	19	0	5	2
0	0	0	0	0	0	2	7	0	0
0	0	0	0	0	0	0	4	0	0
0	41	125	0	0	0	3	0	0	195
2	4	10	0	0	2	1	38	2	1
208	106	53	2	0	170	484	77	82	42
30	68	62	0	0	7	43	1	43	1
174	94	73	1	1	85	89	5	64	0
48	20	18	0	0	57	7	262	11	13
0	0	0	0	0	0	1	0	0	0
0	0	0	0	0	0	2	0	0	0
0	0	0	0	0	0	0	1	0	0
0	0	0	0	0	0	0	1	0	0
0	0	1	0	0	1	10	1	1	0

Table 5
Outcomes.

Nr	First Author	Hospitalization	Pneumonia	ICU Admission	Death		
					Overall	OCR	RTX
01	*Arrambide G.*	69/326(21%)	NA/326 (NA)	7/326(2%)	7/326(2%)	0/23(0%)	1/33(3%)
02	*Barzegar M.*	2/9 (22%)	2/9 (22%)	1/9 (11%)	1/9 (11%)	—	1/1 (100%)
03	*Bsteh G.*	12/126(10%)	NA/126(NA)	NA/126(NA)	4/126(3%)	NA/NA(NA)	NA/NA(NA)
04	*Bose G.^*	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	—	0/1 (0%)
05	*Chaudhry F.*	20/40 (50%)	17/40 (43%)	5/40 (13%)	4/40 (10%)	NA/12 (NA)	—
06	*Ciampi E.*	3/14 (21%)	2/14 (14%)	0/14 (0%)	0/14 (0%)	0/2 (0%)	—
07	*Conte WL.^*	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	—
08	*Czarnowska A.*	27/396 (7%)	1/396 (0.3%)	NA/396 (NA)	1/396 (0.3%)	1/20 (5%)	—
09	*D'Abramo A.^*	1/1(100%)	1/1(100%)	0/1(0%)	0/1(0%)	0/1(0%)	—
10	*Devogelaere J.^*	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	—	0/1 (0%)
11	*Fernandez-Diaz E.*	1/3 (33%)	NA/3 (NA)	0/3 (0%)	0/3 (0%)	0/3 (0%)	—
12	*Fragoso J.*	15/73(21%)	20/73(27%)	6/73(8%)	2/73(3%)	1/5(20%)	1/3(33%)
13	*Gibson EG.^*	1/1(100%)	1/1(100%)	0/1(0%)	0/1(0%)	0/1 (0%)	—
14	*Hervás-García JV.*	1/19 (5%)	1/19 (5%)	0/19 (0%)	0/19 (0%)	0/3 (0%)	0/2 (0%)
15	*Louapre C.*	73/347 (21%)	NA/347 (NA)	4/347 (1%)	12/347 (3%)	0/38 (0%)	1/17 (6%)
16	*Loonstra FC.*	22/86 (26%)	4/86 (5%)	3/86 (3%)	4/86 (5%)	1/19 (5%)	—
17	*Montero-Escribano P.*	1/9 (11%)	1/9 (11%)	0/9 (0%)	0/9 (0%)	0/2 (0%)	0/7 (0%)
18	*Olivares Gazca JC.*	1/4 (25%)	NA/4 (NA)	0/4 (0%)	0/4 (0%)	—	0/4 (0%)
19	*Sadeghi M.*	38/371 (10%)	89/371 (24%)	4/371 (1%)	0/371 (0%)	0/3 (0%)	—
20	*Sahraian MA.*	17/68 (25%)	NA/68 (NA)	NA/68 (NA)	2/68 (3%)	0/1 (0%)	2/38 (5%)
21	*Salter A.*	320/1626 (20%)	112/1626 (7%)	104/1626 (6%)	54/1626 (3%)	11/484 (2%)	3/77(4%)
22	*Sen S.*	85/309 (28%)	81/309 (26%)	9/309 (3%)	3/309(1%)	0/43 (0%)	0/1 (0%)
23	*Sormani MP.*	96/844 (11%)	99/844 (12%)	38/844 (5%)	13/844 (2%)	1/89 (1%)	1/5 (20%)
24	*Spelman T.*	73/476(15%)	NA/476 (NA)	19/476(4%)	8/476(2%)	NA/7 (NA)	NA/262 (NA)
25	*Suwanwongse K.^*	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	—
26	*Thornton JR.^*	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	—
27	*Woo MS.^*	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	—	0/1 (0%)
28	*Wurm H.^*	1/1 (100%)	1/1 (100%)	NA/1 (NA)	0/1 (0%)	—	0/1 (0%)
29	*Wallach A.*	5/17 (29%)	NA/17 (NA)	0/17 (0%)	0/17 (0%)	0/10 (0%)	0/1 (0%)
	Pooled estimate						
	% (95% IC)	18.1% (14.5%−21.6%)	14.8% (9.6%−20.1%)	3.3% (1.8%−4.7%)	1.8% (1.0%−2.6%)	1.6% (0.6%−2.6%)	4.5% (0.8%−8.1%)
	I^2	88.4%	97.5%	77.1%	76.9%	0.0%	11.8%

^ Case reports excluded from the meta-analysis.

difficulty in assessing its presence in retrospective studies. Concerning ICU admissions, the highest percentages of occurrence were observed from two studies (13 and 11%), but in half of the studies there were no patients admitted in ICU. However, it is relevant that for many patients included in this work ($N = 591$) information on ICU admissions were not available or unclear. ICU admissions should be more investigated and reported due to their relevance in COVID-19 mortality. Indeed, a meta-analysis conducted on the general population showed an ICU COVID-19 mortality rate of 35.5% (Armstrong et al., 2021). On the other hand, clear and complete information on deaths were reported in all the studies, almost always with details regarding assumed treatments. Specifically, only 115 out of 5173 (2.2%) patients presented a fatal event, resulting in a pooled estimate of 1.8% and in a heterogeneity of 77%. The frequency of deaths was lower than the one observed in a previous study on MS and COVID-19 (3.0%) (Barzegar et al., 2021) but regarding patients on rituximab, there were 10/455 (2.2%) fatal events compared to 15/770 (1.9%) on ocrelizumab, with estimates of 4.5 and 1.6%. This higher rate of deaths among patients under rituximab is consistent with the stronger association with hospitalization already found in a previous work (Salter et al., 2021).

Patients treated with rituximab seem to be at higher risk of severe COVID-19 outcomes compared to patients under other treatments. The reason for this difference has been suggested by a sensitivity analysis from the Italian work (Sormani et al., 2021) which revealed a trend of an increased risk of anti-CD20 agents with therapy duration. In particular, as compared to patients treated with other therapies, patients on anti-CD20 therapy for less than six months had an OR = 1.65 (95% CI = 0.56–4.90, $p = 0.36$), patients on anti-CD20 therapy between six and twelve months had an OR = 2.24 (95% CI = 0.91–5.55, $p = 0.08$), and patients on anti-CD20 therapy for more than twelve months had an OR = 2.98 (95% CI = 1.37–6.46, $p = 0.006$).

Therefore, the increased risk of patients in Rituximab can be due to their longer therapy duration compared to that of patients in Ocrelizumab.

Declaration of Competing Interest

Schiavetti I, Ponzano M, Signori A, Bovis F, Carmisciano L have nothing to disclose. Sormani MP received consulting fees from Merck, Biogen, Novartis, Sanofi-Genzyme, Roche, Celgene, Geneuro, GSK, Medday, Immunic.

Acknowledgments

We really thank authors which have provided some additional data of their samples or have confirmed some unclear measures.

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