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.

Autoimmunity Reviews 20 (2021) 102778

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Clinical outcomes of COVID-19 in patients with rheumatic diseases: A systematic review and meta-analysis of global data

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ARTICLE INFO

Keywords:
Rheumatic diseases
COVID-19
Outcomes
SARS-CoV-2

ABSTRACT

Objectives: The impact of rheumatic diseases on COVID-19 infection remains poorly investigated. Here we performed a systematic review and meta-analysis to evaluate the outcomes of COVID-19 in patients with rheumatic diseases.

Methods: We systematically searched PubMed, Embase, Cochrane Library, Scopus and preprint database up to 29th August 2020, for publications with confirmed COVID-19 infection in patients with rheumatic diseases. The primary outcomes were the rates of hospitalization, oxygen support, intensive care unit (ICU) admission and death. A meta-analysis of effect sizes using the random-effects models was performed, and meta-regression analyses were performed to explore heterogeneity. The data from the COVID-19 Global Rheumatology Alliance physician registry (the COVID-19 GRA) was used as a reference.

Results: A total of 31 articles involving 1138 patients were included in this systematic review and meta-analysis. The publications were from Europe, Asia and North America, but none from other continents. The overall rates of hospitalization, oxygen support, ICU admission and fatality among COVID-19 infected patients with rheumatic diseases were 0.58 (95% confidence interval (CI) 0.48–0.67), 0.33 (95% CI 0.21–0.47), 0.09 (95% CI 0.05–0.15) and 0.07 (95% CI 0.03–0.11), respectively. The rate of oxygen support in Europe (0.48, 95% CI 0.4–0.57) was higher than that in other continents. Among all hospitalized patients, the rates of oxygen support, ICU admission and fatality were 0.61 (95% CI 0.48–0.73), 0.13 (95% CI 0.07–0.21) and 0.13 (95% CI 0.09–0.18), respectively. The fatality rate was highest in Europe (0.19, 95% CI 0.15–0.24). The fatality rate was higher both in this meta-analysis and the COVID-19 GRA (7.0% and 6.7%, respectively) than that (3.4%) in WHO database, although the age, gender and comorbidity were not matched.

Conclusion: Patients with rheumatic diseases remain vulnerable with substantial rates of severe outcomes and a geographic variation. More studies were urgently needed to elucidate the risk factors of severe outcomes in this population.

1. Introduction

An outbreak of infection with the novel coronavirus (SARS-CoV2) since December 2019 has rapidly emerged as a pandemic [1]. Globally, more than 24 million confirmed cases of coronavirus disease 2019 (COVID-19) had been reported, with 833,951 confirmed death by 29th August 2020 [2]. COVID-19 does not only cause respiratory illness but also leads to uncontrolled inflammatory response and hypercoagulation through activating both the innate and adaptative immune system [3]. The presence of comorbidities, such as hypertension or diabetes mellitus, is a risk factor for disease severity and fatality [4]. It is imperative to evaluate the outcomes of COVID-19 in patients with rheumatic diseases. Firstly, patients with rheumatic diseases are vulnerable given the background of dysregulated immune response and the use of antirheumatic drugs with different degrees of immunosuppression. An exaggerated immune response may occur following an acute viral infection, for

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https://doi.org/10.1016/j.autrev.2021.102778
Received 11 December 2020; Accepted 20 December 2020
Available online 18 February 2021

instance, the uncontrolled type I interferon activation in patients with systemic lupus erythematosus (SLE). Secondly, multiple cytokine has been involved in the pathogenesis of severe COVID-19 [5–7]. Anti-rheumatic drugs may dampen the hyperinflammatory state, becoming a potential treatment for COVID-19. Hydroxychloroquine (HCQ) and tocilizumab were promising candidates [8], but subsequent studies did not demonstrate their efficacy to improve clinical outcomes in COVID-19 infected patients or for post-exposure prophylaxis of close contacts [9–11]. Glucocorticoids, which are widely used in rheumatic diseases, has remained controversial in the treatment of COVID-19 infected patients [12]. The RECOVERY trial, however, demonstrated the beneficial effect of dexamethasone resulting in lower mortality among those who were receiving either invasive mechanical ventilation or oxygen alone [13]. Although a sustained elevation of interleukin (IL)-6 are associated with worse outcomes of COVID-19 [14], the result from a recent trial was disappointing [11]. A systematic review and meta-analysis was recently published and showed that the effect of most anti-rheumatic disease therapies in COVID-19 remained inconclusive [15].

At present, the impact of COVID-19 on patients with rheumatic diseases is poorly understood. Whether a poorer outcome due to the immunocompromised status among patients with rheumatic disease, or better outcomes with anti-rheumatic therapies that mitigate the hyper-inflammation is unknown [16]. No specific rheumatic diseases was identified as risk factors for poor outcomes with COVID-19 in version 2 of American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic [17]. There is also a knowledge gap of the geographic differences in the severity and fatality rate among COVID-19 infected patients with rheumatic diseases. Recently, several studies reported the clinical and prognostic characteristics of COVID-19-infected patients with rheumatic diseases [18–23]. However, there were concerns about the limitations of small sample sizes, heterogeneity of methodology, and a lack of generalizability to the overall population of COVID-19 patients with rheumatic diseases. The COVID-19 Global Rheumatology Alliance physician registry (The COVID-19 GRA) has been making a great effort to collect information pertinent to COVID19 infection in patients with rheumatic diseases, but it is voluntary and predominantly from western countries [24]. Therefore, we conducted this systematic review and meta-analysis of observational studies on COVID-19 patients with rheumatic disease, to summarize the published and preprint literature that described the clinical characteristics and outcomes of COVID-19 patients with rheumatic diseases, and to provide a higher level of evidence for better clinical decision making.

2. Methods

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two reviewers (Ruyi Cai and Zixi Yi) undertook the literature search, assessment for eligibility and data extraction independently. A third reviewer (Chuanhui Xu) would adjudicate if there were any discordant findings between the two independent reviewers. The research was registered and approved in PROSPERO (CRD42020206279).

2.1. Search strategy

For a systematic and comprehensive search, we searched PubMed, Embase, Cochrane Library and Scopus for papers published up to 29th August 2020. Publications on preprint servers (medRxiv, bioRxiv and ChinaXiv) were also reviewed. Key/relevant MeSh terms and keywords included the following keywords: “2019-ncov”, “novel coronavirus”, “COVID-19”, “SARS-CoV-2”, “new coronavirus”, “coronavirus disease 2019”, “wuhan pneumonia”) AND (“rheumatic disease”, “rheumatic condition”, “autoimmune disease”, “autoimmune condition”, “connective tissue disease”, “musculoskeletal disease”, “muscle and skeletal disease”, “Arthritis”, “Systemic Lupus Erythematosus”, “Spondylarthritis”, “spondyloarthropathy”, “vasculitis”, “Sjogren’s Syndrome”, “Scleroderma”, “systemic sclerosis”, “Osteoarthritis”, “Antiphospholipid Syndrome”, “myositis”, “gout”. Detailed literature search strategies are shown in Supplementary Table 1–5. Two investigators (Ruyi Cai and Zixi Yi) screened titles and abstracts of identified articles independently. Full text of identified studies was then further reviewed by the two reviewers.

2.2. Study selection and data extraction

All studies containing the epidemiological and clinical information of COVID-19-infected rheumatic patients were identified. Inclusion criteria included: (1) studies reporting data on COVID-19 confirmed patients, survivors, or COVID-19 related death; (2) studies containing available epidemiological or clinical data of COVID-19-infected patients with rheumatic disease; (3) studies limited to humans; (4) had one of the following outcomes: hospitalization, requirement for oxygen support, intensive care unit (ICU) admission, or death; (5) only the latest study to be included in the analysis if duplicated studies from same population or database were reported. The exclusion criteria were as follows: (1) duplicated studies; (2) reviews, conference proceedings, commentaries, quality of life studies, cost-effectiveness analyses; (3) those in which the rheumatic disease data or COVID-19 data could not be ascertained; (4) rheumatic diseases induced by COVID-19; (5) small sample size ($\leq$3). The publications from the COVID-19 GRA were not included for the following reasons: (1) the data were voluntarily reported; (2) inability to ascertain whether the cases were also included in other studies; (3) lack of detail of the country/continent from which these data originated; (4) the data was used as a reference for this meta-analysis.

Two investigators (Ruyi Cai and Zixi Yi) independently reviewed potentially relevant articles, and disagreements were discussed and resolved with consensus and, if necessary, by involving the third reviewer (Chuanhui Xu).

The following information was extracted: country, continent, study design type, sample size, sex, age, rheumatological diagnosis, outcomes (hospitalization, oxygen support, ICU admission, death).

2.3. Endpoint setting and stratification strategy

Our primary outcomes were rates of hospitalization, oxygen support, ICU admission and fatality in COVID-19 infected patients with rheumatic diseases. The stratification strategy we adopted for the subgroup analysis was by continent: patient populations in Europe, Asia, and North America were analyzed respectively.

2.4. Data analysis

The pooled proportions with their corresponding 95% confidence intervals (CI) were calculated to estimate the rates of hospitalization, oxygen support, ICU admission and fatality in COVID-19 infected patients with rheumatic diseases. The Freeman-Tukey double arcsine transformation was used for pooled estimates to stabilize the variances. The I^2 statistic and Q test were used to measure the between-study heterogeneity. If $I^2 > 50\%$ and $P < 0.1$, the heterogeneity was considered high, and the summary rates were combined under with a random effects model; otherwise a fixed-effects model were used. The Z test was used to assess the statistical significance of pooled rates, and two-tailed $P < 0.05$ were considered significant. To explore potential sources of heterogeneity, subgroup analyses were performed based on the continent. Visual inspection of funnel plots and Egger’s regression asymmetry test were applied to assess potential publication bias. STATA 14.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analyses.

Table 1
The summary of characteristics of studies recruiting patients from community.

First author	Country	Continent	Study design	No. of patients	Age (years) mean ± sd,/median(range)	Sex	
						Male	Female
Wallace et al. [48]	America	North America	cohort	31	61 (28–82)	9	22
Haberman et al. [49]	America	North America	case series	59	50 (25–73)	7	7
Gartshteyn et al. [50]	America	North America	case series	10	44.3	1	9
Fernandez-Ruiz et al. [34]	America	North America	cohort	41	47 ± 17.19	3	38
Veenstra et al. [35]	America	North America	cohort	77	–	–	–
D'silva et al. [51]	America	North America	cohort	52	62.5 ± 15.1	16	36
Mathian et al. [52]	France	Europe	cohort	17	53.5 (26.6–69.2)	4	13
Aries et al. [44]	Germany	Europe	cross-sectional	30	–	–	–
Ansarin et al. [20]	Iran.	Asia	cross-sectional	30	55.1 ± 13.6	7	23
Scirè et al. [53]	Italy	Europe	cross-sectional	232	62.2 ± 13.9	83	149
Bozzalla Cassione et al. [54]	Italy	Europe	case series	4	52.5 (27–53)	0	4
Fredi et al. [19]	Italy	Europe	case-control	65	68 (55–76)	24	41
Favalli et al. [55]	Italy	Europe	cohort	6	49 ± 20.42	2	4
Monti et al. [56]	Italy	Europe	case series	4	58 ± 5	0	4
Quartuccio et al. [57]	Italy	Europe	cross-sectional	4	60.25 ± 12.6	2	2
Santos et al. [43]	Spain	Europe	cross-sectional	30	Female 61.8 (46.5–75) male 68 (48.5–72)	12	18
Pablos et al. [23]	Spain	Europe	cohort	228	63 (54–78)	87	141
Queiro Silva et al. [58]	Spain	Europe	cross-sectional	7	49.2 ± 6.8 (37–56)	4	3
Espinosa et al. [33]	Spain	Europe	cross-sectional	4	43.75 ± 5.54	0	4
Michelena et al. [59]	Spain	Europe	cross-sectional	11	45 (30,63)	6	5
Freites Nuñez et al. [60]	Spain	Europe	cohort	123	59.88 (14.90)	37	86

Table 2
The summary of characteristics of studies only recruiting hospitalized patients.

First author	Country	Continent	Study design	No. of patients	Age (years) mean + −sd,/ median(range)	Sex	
						Male	Female
Sharmeen et al. [37]	America	North America	case series	4	Male (78,49) Female (76,27)	2	2
Cheng et al. [36]	China	Asia	cross-sectional	5	66 (61–72)	1	4
Ye et al. [18]	China	Asia	case series	21	–		
Lin et al. [40]	China	Asia	cohort	11	55 (25,71)	1	10
Zhao et al. [61]	China	Asia	cross-sectional	29	Median 61	4	25
Huang et al. [41]	China	Asia	cross-sectional	17	64.0 (60.5–71.5)	3	14
Benucci et al. [62]	Italy	Europe	cross-sectional	4	60 ± 9.5	1	3
Teh et al. [39]	Malaysia	Asia	cross-sectional	5	42.8 ± 18.3	0	5
Wan et al. [42]	Malaysia	Asia	cross-sectional	4	–	0	4
Santos et al. [38]	Spain	Europe	cohort	38	Survivors 75.1 (69.3–75.8), Deceased 78.4 (74.5–83.5)	18	20

3. Results

3.1. Study selections

The initial search of databases yielded 1822 articles, which were narrowed down to 26 after removing 932 duplicated records, 716 unrelated publications by title and abstract screening, and 148 publications including reviews, case reports, data from Global Rheumatology Alliance registry and papers with small sample size (≤3), patients all admitted in ICU or without relevant outcome data. Five articles from preprint servers (medRxiv, bioRxiv and ChinaXiv) were added. The study selection flowchart was shown in Supplement Fig. 1.

3.2. Overall study characteristics

A total of 31 articles involving 1138 patients were assessed in this systematic review and meta-analysis. Characteristics of the included studies were shown in Tables 1 and 2. There were 16 articles ($n = 807$) from Europe, 8 articles ($n = 122$) from Asia and 7 articles ($n = 274$) from North America (all from the US), respectively. No publication from South America, Africa or Oceania. There were ten studies which only included hospitalized patients (Table 2). About 64% of the patients were female. Various rheumatological diseases were reported, including 32.8% patients with rheumatoid arthritis (RA), 15.3% SLE, 22.3% spondyloarthritis, 6.07% vasculitis, 2.76% Sjogren syndrome, 5.85% inflammatory myopathy, 1.77% systemic sclerosis, 0% gout and 13.1% others (Supplementary Table 6). However, the outcomes were reported as aggregated outcomes for the respective cohort of patients without further classification by rheumatic disease type.

3.3. Outcomes of COVID-19 infected patients with rheumatic diseases

The outcomes would be different between the patients recruited from the community and those only from hospitalized patients. We first analyzed all the data excluding the studies which only recruited hospitalized patients (data from Table 1, excluded data from Table 2 that only recruited hospitalized patients). The overall hospitalization rate among COVID-19 infected patients with rheumatic diseases was 0.58 (95% CI 0.48–0.67, Fig. 1A). The rates of oxygen support, ICU admission and fatality were 0.33 (95% CI 0.21–0.47), 0.09 (95% CI 0.05–0.15) and 0.07 (95% CI 0.03–0.11), respectively (Fig. 1B - D). Subgroup analysis among different continents showed no differences with regards to the rates of hospitalization(0.62 (95% CI 0.51–0.73) in Europe, 0.5 (95% CI 0.37–0.64) in North America and 0.60 (95% CI 0.41–0.77) in Asia) and ICU admission(0.07 (95% CI 0.02–0.13) in Europe, 0.11 (95% CI 0.03–0.24) in North America and 0.23 (95% CI 0.1–0.42) in Asia) (Fig. 1A and Fig. 1C). The rate of oxygen support was higher in Europe (0.48, 95% CI 0.4–0.57) than that in North American (0.20, 95% CI 0.10–0.33) (Fig. 1B). The fatality rate was higher in Asia(0.27, 95% CI 0.12–0.46) (Fig. 1D), but only one study was available from Asia (Iran, *n*

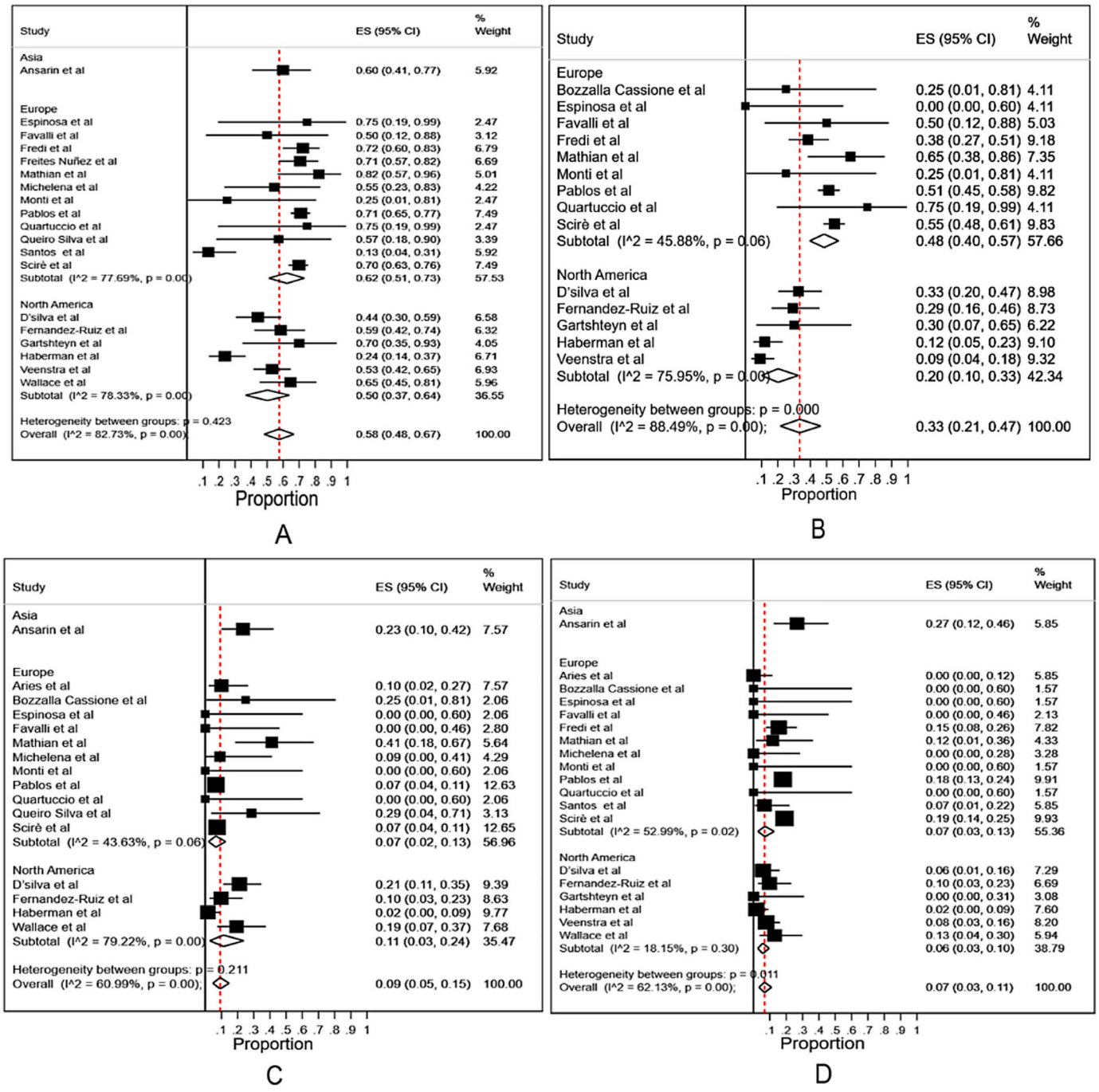


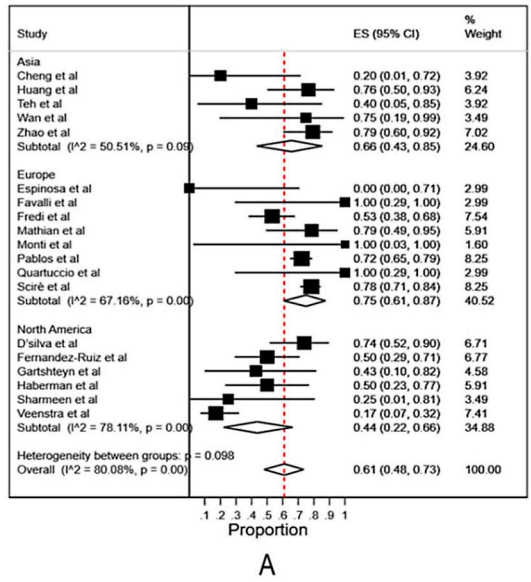
Fig. 1. Meta-analysis and subgroup analysis of the rates of hospitalization, oxygen support, ICU admission and fatality in COVID-19 infected patients with rheumatic diseases in different continents, excluding the studies only recruiting hospitalized patients.
A: the rates of hospitalization. B: the rates of oxygen support. C: the rates of ICU admission. D: the rates of fatality.
Overall: meta-analysis of the rates in Asia, Europe and North America.
Subtotal: subgroup meta-analysis of the rates in different continents.

= 30) [20] for subgroup analysis among different continents.

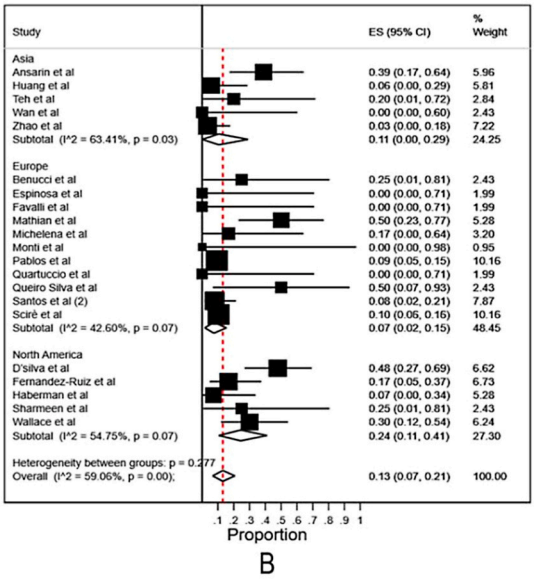
We then anlyzed the data among all hospitalized patients (data of hospitalized patients from Table 1 and all data from Table 2). The rates of oxygen support, ICU admission and fatality among all hospitalized patients were 0.61 (95% CI 0.48–0.73), 0.13 (95% CI 0.07–0.21) and 0.13 (95% CI 0.09–0.18), respectively (Fig. 2A - C). Subgroup analysis among different continents showed the rate of oxygen support was 0.66 (95% CI 0.43–0.85) in Asia, 0.75 (95% CI 0.61–0.87) in Europe, and 0.44 (95% CI 0.22–0.66) in North America, respectively, without significant difference (Fig. 2A). The rate of ICU admission was 0.11 (95% CI 0.00–0.29) in Asia, 0.07 (95% CI 0.02–0.15) in Europe, and 0.24 (95% CI 0.11–0.41) in North America, respectively, without significant difference (Fig. 2B). The fatality rate was higher in Europe (0.19, 95% CI 0.15–0.24) than that in North America (0.12, 95% CI 0.06–0.19) and Asia (0.11, 95% CI 0.02–0.23) (Fig. 2C).

3.4. Comparison with data from the COVID-19 GRA and WHO

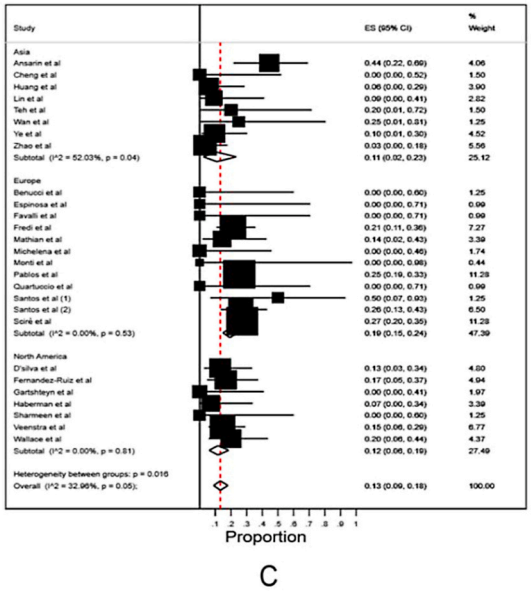
There could be differences between this meta-analysis and the data from the COVID-19 GRA as the latter was voluntarily reported. As shown



A



B



C

(caption on next column)

Fig. 2. Meta-analysis and subgroup analysis of the rates of oxygen support, ICU admission and fatality in COVID-19 infected patients with rheumatic diseases in different continents, including the studies only recruiting hospitalized patients. A: the rates of oxygen support. B: the rates of ICU admission. C: the rates of fatality.
Overall: meta-analysis of the rates in Asia, Europe and North America.
Subtotal: subgroup meta-analysis of the rates in different continents.

in Table 3, there was a difference in specific diseases but largely comparable. There were fewer female patients (64%) in this meta-analysis compared with that (75.9%) in the COVID-19 GRA (Table 3). The rate of hospitalization and death were higher in this meta-analysis than that in the COVID-19 GRA (58% vs 32.8% and 7.0% vs 6.7%, respectively) (Table 3) [25]. It was not possible to compare the rates of oxygen support and ICU admission because there were 11.9% of patients who required ventilation, but the type of ventilation used was unknown in the COVID-19 GRA [25]. The fatality rate was higher both in this meta-analysis and the COVID-19 GRA (7.0% and 6.7%, respectively) than that (3.4%) in WHO database [2], but the age, gender and comorbidities were not matched.

3.5. Publication bias analysis

Visual inspection of funnel plots and Egger's test were used to evaluate the publication bias. The funnel plot was displayed in Supplementary Fig. 2 and Supplementary Fig. 3. The statistical results showed there was no publication bias in our study (Egger's test $P = 0.439$ for hospitalization, $P = 0.661$ for oxygen support, $P = 0.446$ for ICU admission and $P = 0.172$ for fatality in COVID-19 infected patients with rheumatic diseases, excluding the studies only recruiting hospitalized patients; Egger's test $P = 0.295$ for oxygen support, $P = 0.394$ for ICU admission and $P = 0.141$ for fatality in COVID-19 infected patients with rheumatic diseases among all hospitalized patients, including the studies only recruiting hospitalized patients).

4. Discussion

This systematic review and meta-analysis of global data summarized the clinical outcomes of COVID-19 in patients with rheumatic diseases, including 1138 patients with various rheumatic diseases from 31 studies. Overall, the rates of hospitalization, oxygen support, ICU admission and fatality among COVID-19 infected patients with rheumatic diseases was 0.58 (95% CI 0.48–0.67), 0.33 (95% CI 0.21–0.47), 0.09 (95% CI 0.05–0.15) and 0.07 (95% CI 0.03–0.11), respectively. Among the patients hospitalized, the rates of oxygen support, ICU admission and fatality were 0.61 (95% CI 0.48–0.73), 0.13 (95% CI 0.07–0.21) and 0.13 (95% CI 0.09–0.18), respectively. The results imply that rheumatic disease is a risk factor for poor outcomes in patients with COVID-19. Of note, the fatality was higher in Europe among hospitalized patients.

We noted the heterogeneity of publications. Most cases were reported from Europe with a higher fatality. Fewer cases were reported from Asia, most of which only recruited hospitalized patients. The heterogeneity among different studies and different continents may be due to several reasons. Firstly, the capacity for screening and diagnosis of COVID-19 cases evolved over the course of the pandemic, limited initially by access to test kits and reagents, manpower and laboratory infrastructure. Over time, testing was gradually scaled up to include community testing with the increasing sophistication of test kits with rapid turnaround times, improving the accuracy of reporting. The cases may be under or not reported in some developing countries with challenges in access to testing and consolidated reporting of cases. Secondly, many countries implemented different policies during different stages of the pandemic. Some countries, such as China, South Korea, Singapore and New Zealand, adopted early intensive measures to contain COVID-19 with strict contact tracing, mandatory mask-wearing, safe social

Table 3
Comparison with data from The COVID-19 Global Rheumatology Alliance Global Registry.

	Meta-analysis	Global Registry
Female %	64%	76%
Rheumatoid arthritis	33.7%	38.4%
Spondyloarthritis[a]	22.0%	15.5%
Systemic Lupus Erythematosus	14.3%	20.7%
Vasculitis	5.5%	5.6%
Inflammatory myopathy	5.2%	2.4%
Sjogren syndrome	3.3%	3.8%
Systemic sclerosis	1.7%	3.4%
Gout	0%	2.4%
Others[b]	14.4%	5.7%
Hospitalized	56%	33%
Death	7.0%	6.7%

[a] Merged data of spondyloarthritis and psoriatic arthritis in the COVID-19 Global Rheumatology Alliance Global Registry.

[b] : merged data of other inflammatory arthritis, sarcoidosis and undifferentiated connective tissue disease in the COVID-19 Global Rheumatology Alliance Global Registry (accessed on 13rd November 2020).

distancing, early lockdowns and implementation of infectious disease legislations. In contrast, the restriction may have been more lenient among some countries in Europe and North America during the early days of the pandemic. Containment of milder cases in the form of home or community quarantine facilities, hospitalization only for more severe cases, and palliative care for nursing home residents without hospital transfers would also have impacted the profile and outcomes of non-hospitalized vs hospitalized patients. Notably, 13 out of 15 studies were from Spain and Italy (except 1 from Germany and one from France. Table 1) where were most severely affected by COVID-19 in Europe [26] Thirdly, the genotypes of SARS-CoV2 due to mutation may vary in different regions, or may have evolved over time, both for imported and community transmitted cases, which may explain the different severities of the disease. A previous study showed that the virus genomes in Europe and America were different from those in Asia [27]. Fourthly, the ethnic disparities of outcomes in COVID-19 patients may contribute to the heterogeneity. For instance, the mortality is lower among South Asian compared to White British patients from the study in Bradford [28]. Similarly, the disparities in the risk and outcomes of COVID-19 were also reported by Public Health England [29].

There were differences in terms of proportions of specific rheumatic diseases, gender and outcomes when this study was compared with the COVID-19 GRA data. The COVID-19 GRA was a commendable effort from the global rheumatology community. The results were mutually corroborated between our meta-analysis and the COVID-19 GRA, although differences exist. Furthermore, our meta-analysis added the data from Asia, which were scant in the COVID-19 GRA with only <5 out of 600 from the Asian region [24]. Our meta-analysis included eight studies (n = 122) from Asia, mainly from China and Malaysia. There were studies that showed no case of rheumatic disease contracted COVID-19 in Hong Kong [30], and the incidence of COVID-19 infection was low in the Asia Pacific Lupus Collaboration patient cohort [31]. Reporting on COVID-19 in patients with rheumatic diseases should be encouraged from other countries heavily burdened by COVID-19 infection, such as India, Indonesia and Philippine.

A meta-analysis on the prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases was published by Akiyama et al. [32]. However, the results should be interpreted with cautions. The fatality rate was higher (0.113, 95% CI 0.098 to 0.13) than our study (0.07, 95% CI 0.03–0.11) and the COVID-19 GRA data (0.067). There were total 16 publications included in our meta-analysis but not in the study by Akiyama et al. Three publications were missed [33–35], eight were excluded because only hospitalized patients were recruited [18,36–42], four published after 31st July 2020 when is the updated time of literature search by Akiyama et al. [19,20,43,44]. Furthermore, we were not certain whether the cases were duplicated in published data and the COVID-19 GRA data. Therefore, it would not have been appropriate to include COVID-19 GRA data for the meta-analysis.

The strengths of our systematic review and meta-analysis were the rigorous application of systematic review methodology and a comprehensive search of the literature, which included published and preprint archives. We distinguished whether the studies only recruited hospitalized patients, and compared with the COVID-19 GRA data. A few limitations existed in this study. Firstly, most publications included were small case series and cohort studies. Secondly, the criteria for hospitalization and ICU admission may differ in different countries, or different centres in the same country due to resource limitations, differences in healthcare and financing models of care. Nevertheless, it would have reflected the severity of the disease. Thirdly, the details of the outcomes were mostly unavailable for specific rheumatic disease and specific treatments. The immunomodulatory effects of conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) would be different from biologic synthetic DMARDs versus targeted therapies and immunosuppressants. Even though no robust data has shown that anti-rheumatic drugs were effective for the treatment of COVID-19 [15], including the most recently published randomized control trial of tocilizumab [11]. The use of anti-rheumatic drugs before the onset of COVID-19 infection may also have had an impact on COVID-19 rheumatology patients with bad prognostic factors and may be context-dependent [45]. For instance, accumulating data showed that methotrexate reduced the risk of cardiovascular events in patients with rheumatoid arthritis [46], but not in the general population with a high risk of cardiovascular events [47]. Therefore, researchers and the COVID-19 GRA are strongly encouraged to report the outcomes in specific rheumatic disease and with a specific treatment, which may shed light on the safety and effectiveness of anti-rheumatic drugs in COVID-19 patients with rheumatic diseases. We appreciate that the heterogeneity of treatments even among a certain rheumatic disease, let alone the less common diseases may still make interpretation of aggregated data challenging.

This systematic review and meta-analysis inform a comprehensive picture of the clinical outcomes of COVID-19 patients with rheumatic diseases. These patients remain vulnerable, given the significant rates of ICU admission with a high risk of fatality. This study emphasized the urgent need for more data with a larger sample size, more detailed treatment and disease-specific outcomes, longer-term follow-up, and sociodemographic and clinicopathological variables.

Declaration of Competing Interest

This work is not funded by any organization. The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2021.102778.

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