Clinical Rheumatology (2022) 41:2213–2223
https://doi.org/10.1007/s10067-022-06087-1

ORIGINAL ARTICLE

Prevalence and risk of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis

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Received: 17 August 2021 / Revised: 3 January 2022 / Accepted: 29 January 2022 / Published online: 30 March 2022

Abstract

Objectives COVID-19 pandemic has already had a tremendous impact on the process of human society; the survival of mankind and the healthy living environment deterioration with the influence will last for many years. This meta-analysis aims to assess the risk of COVID-19 in patients with rheumatic diseases.

Methods PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) were systematically searched with no language restriction up to July 5, 2021. The pooled rates were synthesized by fixed effect model or random effect model depending on heterogeneity.

Results A total of 83 articles were included in this meta-analysis. The incidence of COVID-19 in patient with rheumatic diseases was 0.0190 (95% *CI*: 0.0136-0.0252), and the hospitalization rate, intensive care unit admission rate, mechanical ventilation rate, and case fatality rate of patients with rheumatic diseases infected with COVID-19 were 0.4396 (95% *CI*: 0.3899-0.4898), 0.0635 (95% *CI*: 0.0453-0.0836), 0.0461 (95% *CI*: 0.0330-0.0609), and 0.0346 (95% *CI*: 0.0218-0.0493), respectively.

Conclusions Our research shows that patients with rheumatic diseases have great risk of COVID-19. Differences in COVID-19 incidence, hospitalization rates, and mortality rates in regions were statistically significant. We still need to pay attention to the risk of COVID-19 in patients with rheumatic diseases.

Key Points

- *Although the risk of COVID-19 in patients with rheumatic diseases has been discussed in previous meta-analysis, their research directions were inconsistent, and few studies focus on prevalence or serious outcomes of COVID-19 in patient with rheumatic diseases, while the quality of these articles was variable.*
- *The incidence of COVID-19 and serious clinical outcomes in patients with rheumatic diseases were still high along with differential risks in most regions.*
- *The use of glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs did not affect the hospitali zation rate and mortality in rheumatism patients with COVID-19.*

Keywords COVID-19 · Meta-analysis · Prevalence · Rheumatic disease

Feier Wang and Yubo Ma contributed equally to this work and should be considered co-first authors.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by novel coronavirus has been a destructive worldwide medical crisis. As of August 5, 2021, the global death toll resulted from COVID-19 has reached 4.2 million [1]. The main clinical manifestations of the disease include dry cough, fever, dyspnea, fatigue, and acute lung injury [2–4]. Patients with comorbidities like hypertension and lung diseases were associated with increased risk of severe pneumonia, which eventually leads to acute respiratory distress syndrome (ARDS) and respiratory failure [2, 5, 6]. In December, 2020, WHO officially notified the main mutations of COVID-19 since its emergence [7] and confirmed that as the epidemic continues, more mutations will be discovered. At present, four worrying mutant viruses dominate the global epidemic, especially the rapidly spreading "Delta" mutant virus. The Delta strain, was firstly discovered in India, has 15 gene mutations, and partially avoids the neutralizing antibodies in the human body and easily invades human cells. Moreover, after entering the human body, the viral loads of Delta infections were greater compared to infections during initial epidemic wave in early 2020, resulting in faster virus replication ability and stronger infectivity, which is currently the main epidemic strain worldwide [8].

Rheumatic diseases characterized with the pathological invasion of bones, muscles, blood vessels, and related soft tissues or connective tissues, most of which are autoimmune diseases, and the underlying inflammatory reactions could cause various tissues and organ damage, which seriously affect normal physiological function. Common rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis, systemic sclerosis, gout, and Sjogren's syndrome, were the main cause of physical disability and decline in life quality of these patients and social burden to health care systems. Evidence shows that, in China, the prevalence of rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis, and gout are approximately 0.28%, 0.29%, 0.03%, 0.27%, and 0.09% [9, 10]. Autoimmune diseases affect 3-5% of the global populations [11, 12], representing tens of millions of patients with impaired immune systems worldwide. Rheumatic diseases have the characteristics of slow onset, long course of disease, and genetic predisposition. Incidence of rheumatoid arthritis has been declined in recent decades [13–15]. Compared with the general populations, RDs patients are still facing greater risk of viral and bacterial infection as well as complications [16–18]. The possibility that immunosuppression due to biologics and DMARDs drug treatment could increase the sensitivity of COVID-19 infection was the reason for patients with rheumatic disease discontinued treatment these days [19–22].

It is necessary to explore the risk of COVID-19 among patient with RDs, and we conducted this study to determine the risk of COVID-19 infection and its clinical outcome by integrating the epidemiological data. We analyzed the impact of individual risk factor associated with the prevalence and clinical outcomes of RDs like age, gender, living habit, comorbidities, and medications.

Materials and methods

This research was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [24].

Literature search

According to PICOs scheme, the aim of this meta-analysis was to describe the risk of COVID-19 infection, hospitalization, and clinical treatment outcomes (death, intensive care unit admission, mechanical ventilation) in RDs patients.

The electronic databases of PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) were systematically searched up to July 5, 2021. The keywords and search strategy were listed as follows: ("rheumatic disease" or "autoimmune disease" or "connective tissue disease" or "musculoskeletal disease" or "ankylosing spondylarthritis" or "rheumatoid arthritis" or "systemic lupus erythematosus" or "vasculitis" or "psoriatic arthritis" or "systemic sclerosis" or "Sjogren's syndrome") and "COVID-19" and ("infection" or "prevalence" or "mortality" or "death" or "need to be hospitalized" or "need for ICU/mechanical ventilation"). We also manually searched references of the relevant articles.

Inclusion and exclusion criteria

The commonly used data contained the total number of RDs observation cohort, COVID-19 confirmed cases, or number of hospitalizations or death. Articles with no data available were excluded. The Global Rheumatology Community, which created remarkable achievement, calls on all rheumatology community to conduct timely communication, collect data, and plan and disseminate accurate and comprehensive knowledge to promote rheumatism care in the COVID-19 pandemic. Articles using public data from the COVID-19 Global Rheumatology Alliance [25] were excluded for result comparison and data overlap reduction. Correspondences,

letters, comments, and replies were excluded for stable conclusion.

Data extraction

Each of the enrolled article was extracted by two researchers independently for the following information: author's name, area of research, rheumatic disease clinical diagnosis, demographic characteristics for study population (age, gender, body mass index (BMI), comorbidities), study time, disease duration, and outcome indicators including morbidity, inpatient number, deaths, intensive care unit (ICU) admission, number of persons subjected to mechanical ventilation, and medications. Characteristics about the patient's age and the duration of the underlying disease are uniformly adjusted by showing in mean with standard deviation (SD) [26, 27]. Some research articles collecting data from multiple countries were grouped into cooperation research. Drugs for patients with rheumatic diseases were divided into the following categories: nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic or targeted synthetic DMARDs (b/tsDMARDs), and glucocorticoids (GC).

Methodological quality assessment

The methodological quality assessment of each literature was assessed based on the standardized Joanna Briggs Institute meta-analysis of Statistics Assessment and Review Instrument (JBI MAStARI) critical appraisal tools for descriptive or case series studies. The two reviewers calculated the overall score of each study based on the numbers of answers of "yes," ranging from 0 to 9. Studies with score among 0 to 3 were categorized as low quality, 4 to 6 as medium quality, and 7 to 9 as high quality. All the discrepancies from the two reviewers about the results of study selection, data extraction, and quality assessment were resolved by discussing with consensus.

Statistical analysis

We calculated the combined rate and 95% confidence interval (*CI*) to estimate the incidence of COVID-19, hospitalization rate, and mortality in patient with rheumatic diseases by Freeman-Tukey double arcsine transform [28]. The I^2 test and Cochran's Q statistic were used to assess the statistic heterogeneity between studies [29]. When $I^2 > 50\%$ or $P < 0.05$, the heterogeneity is considered as statistically significant. If heterogeneity existed, the pooled rate and 95% *CI* were estimated by random effects model, and, if not, assessed by fixed effect model [30, 31]. The Z test was used to evaluate the statistical significance of the pooled rate, and $P < 0.05$ was considered significant. In order to explore the potential sources of heterogeneity, subgroup analysis was performed according to study area. Meta-regression was adopted to detect the source of heterogeneity when data about potential variables were provided by more than 10 articles and cumulative meta-analysis based on sample size was used to test the stability of results. All analysis and statistics are done in R.

Result

Study characteristic

Searched on online databases, Fig. 1 shows the retrieval process of this meta-analysis. Overall, candidate publications were initially screened (PubMed ($n = 3133$), Web of Science ($n = 1093$), CNKI database ($n = 322$), CBM database ($n = 50$), Embase($n = 503$)). After removal of duplicates, a total of 3841 full-test literatures were assessed for eligibility using title and abstract, and then we reviewed the bibliography abstract and full text in necessary. Eventually, 83 eligible studies were enrolled in the current meta-analysis from Asia, Europe, North America, and South America. The main characteristics of each article are presented in Table S1.

Methodological quality assessment, evaluated by JBI MAStARI critical appraisal tools, showed that the methodological qualities of all literatures were considered acceptable (Tables S2 and S3).

Prevalence of COVID-19 in rheumatic diseases

The meta-analysis of 44 observational studies with the number of 181,133 individuals showed that the prevalence of COVID-19 was 0.0190 (95% *CI*:0.0136-0.0252). Analysis of subgroups according to the region of study conduction showed the prevalence of COVID-19 was ranged from 0.0115 to 0.0499 (Fig. 2). Researches from North America showed the prevalence of COVID-19 in patients with RDs was 0.0499 (95% *CI*: 0.0246-0.0830). Heterogeneity was significant in overall study ($I^2 = 98.5\%$) which probably due to the difference in research scale. No publication bias was detected by Begg's and Egger's tests (Fig. S1 Egger's: $P = 0.0635$; Begg's: $P = 0.1886$). In addition, no significant variation of heterogeneity was detected when each study was omitted (Fig. S2).

Meta-regression was then conducted to explore the source of heterogeneity, data about potential variables were provided by more than 10 articles, and thus the factors tested by the univariate model were methodological quality, age, gender, smoking status, and comorbidities. However, no any significant heterogeneity was detected in meta-regression analysis for each factor (Table 1). It can be considered that age, gender, smoke, and comorbidities

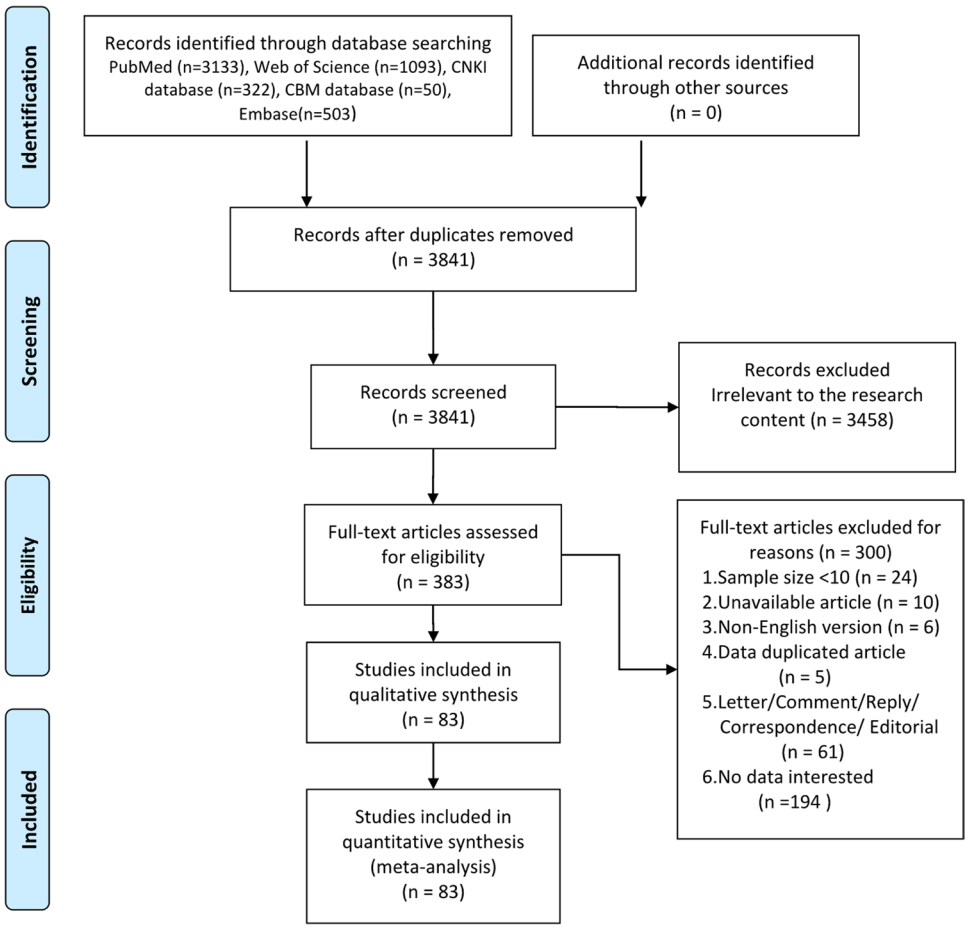


Fig. 1 Flow chart of the literature search and study selection in the meta- analysis

did not contribute to the risk of COVID-19 in patients with rheumatic diseases ($P > 0.05$). We also conducted cumulative meta-analysis according to sample sizes, and a total of 44 studies were included in this analysis. In general, the incidence rate was relatively stable, without big reversal (Fig. S3).

Hospitalization rate of COVID-19 in rheumatic diseases

A meta-analysis based on hospitalization data provided by 55 studies with 16,451 cases of coronavirus disease displayed that the total hospitalization rate was 0.4396 (95% *CI*: 0.3899-0.4898) (Fig. 2). Analysis of subgroups showed the hospitalization rates of COVID-19 in rheumatic diseases ranged from 0.3293 to 0.4848, with the highest hospitalization rate in Asia. There was considerable heterogeneity in both the overall ($I^2 = 94.3\%$) and subgroup analysis. The asymmetric funnel plot suggested there was small study effect or publication bias (Fig. S4 Egger's: $P = 0.0099$; Begg's: $P = 0.6162$). Sensitivity analysis did not find fluctuations in the stability of the result (Fig. S5).

The meta regression tested by the univariate model found that gender and comorbidities (hypertension, cardiovascular disease, and kidney disease) of confirmed cases were the source of heterogeneity (Table 1). Meta regression analysis showed that higher proportion of male sex, hypertension, and cardiovascular or kidney disease patients (male: regression coefficient: 0.5429, 95% *CI*: 0.1359-0.9498, $P < 0.05$; hypertension: regression coefficient: 0.3727, 95% *CI*: 0.0299-0.7154, $P < 0.05$; cardiovascular disease: regression coefficient: 0.9316, 95% *CI*: 0.1618-1.7014, $P < 0.05$) was associated with higher risk of hospitalization due to COVID-19. In this study, we collected the medication usage of rheumatic disease patient cohort and rheumatic disease patients with COVID-19-confirmed cohort. However, the medication data, classified by drug name in most articles and described without specific situation of single use or combined, cannot be obtained in overlapping and non-interference. Therefore, meta-regression on drug treatment was performed in a small volume. GC and csDMARD were not related to hospitalization rate ($P > 0.05$). Cumulative meta-analysis performed according to sample size with 55 articles showed stable result (Fig. S6).

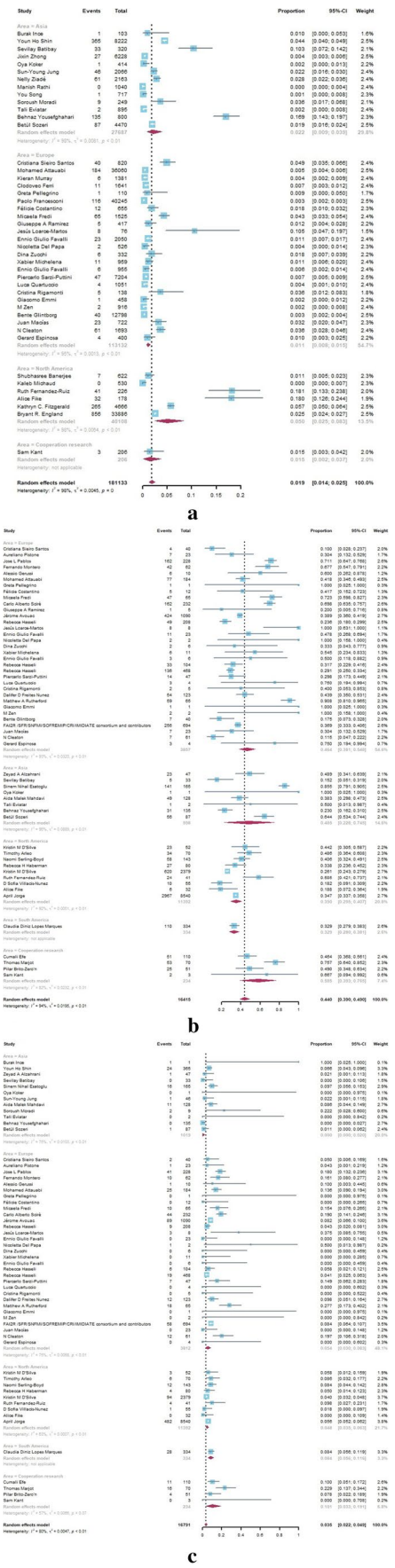


Fig. 2 **a** Meta-analysis to assess the prevalence of COVID-19 in patients with rheumatic diseases. **b** Meta-analysis to assess the hospitalization rate of COVID-19 in patients with rheumatic diseases. **c** Meta-analysis to evaluate the mortality rate of COVID-19 in patients with rheumatic diseases

Risk of death in rheumatic diseases with COVID-19

Meta-analysis of the mortality rate based on 57 studies showed the mortality rate caused by COVID-19 was 0.0346 (95% *CI*: 0.0218-0.0493) for rheumatism population (Fig. 2). We observed differences in both the mortality rate caused by coronavirus disease among different regions ($P < 0.05$). The mortality rates of Asia, Europe, North America, and South America were 0.0000 (95% *CI*: 0.0000-0.0202), 0.0539 (95% *CI*: 0.0295-0.0828), 0.0477 (95% *CI*: 0.0345-0.0627), and 0.0838 (95% CI: 0.0563-0.1161); Begg's ($P = 0.6346$) and Egger's ($P = 0.0222$) test suggested publication bias, and the funnel plot was not asymmetric of death risk in cohort of rheumatic patients (Fig. S7). In addition, sensitivity analysis was performed to assess the stability and liability by assessing whether the mortality rate was stable when any single study was excluded, and no significant variation of heterogeneity was detected when each study was omitted (Fig. S8).

Overall heterogeneity in above analyses was considerable ($I^2 = 80.0\%$) but limited in most subgroups. Meta regression still conducted to analyze sources of heterogeneity in mortality rate The average age of confirmed case comorbidity (cardiovascular disease) was the source of heterogeneity in calculation of mortality in rheumatism cohort (Table 1). Older age (regression coefficient: 0.0045, 95% *CI*: 0.0007-0.0083, $P < 0.05$) and a higher proportion of cardiovascular disease (regression coefficient: 0.5579, 95% *CI*: 0.1999-0.9159, $P < 0.05$) were associated with higher mortality rate due to COVID-19. Meanwhile, GC and csDMARD were not found to have an impact on the mortality of confirmed patients ($P > 0.05$). Cumulative meta-analysis showed the mortality rate caused by COVID-19 was stable (Fig. S9).

Clinical measures to patients with COVID-19 and rheumatic diseases

Data collection was also conducted on the number of ICU admission and mechanical ventilation from 33 and 26 articles, respectively. The ICU admission rate and mechanical ventilation rate caused by COVID-19 were 0.0635 (95% *CI*: 0.0453-0.0836) and 0.0461 (95% *CI*: 0.0330-0.0609). Patients from Asia and North America had high ICU admission rate and mechanical ventilation rate relatively (Fig. 3). However, the results of subgroup analysis showed no statistically significant difference in mechanical ventilation rate across different areas ($P > 0.05$). Meta regression showed

Table 1 Meta- regression of the variables potentially associated with prevalence of COVID-19 and clinical outcomes of COVID-19 in patients with rheumatic diseases

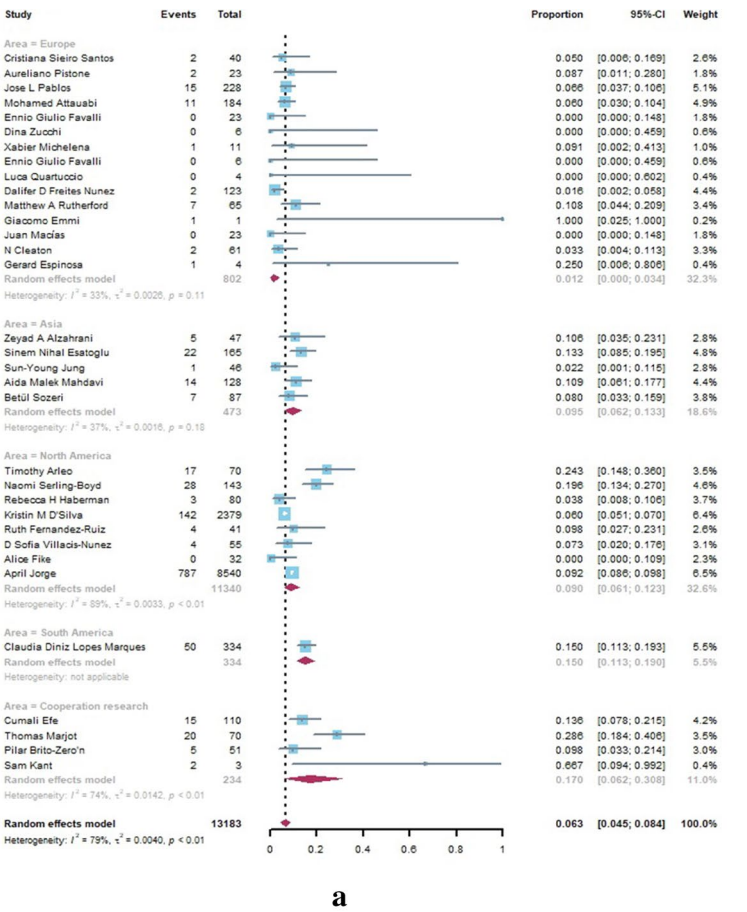
Study objectives	Variables	Number of studies	Coefficient	SE	Lower 95% *CI*	Upper 95% *CI*	*Z* value	*P* value
Prevalence	Male (%)	33	−0.1262	0.1214	−0.3642	0.1118	−1.039	0.2988
	Age (mean)	23	0.0008	0.0012	−0.0015	0.0032	0.6974	0.4856
	Smoke (%)	11	−0.1762	0.18	−0.529	0.1766	−0.9789	0.3277
	Hypertension (%)	19	−0.3615	0.1861	−0.7263	0.0033	−1.9422	0.0521
	Diabetes mellitus (%)	20	−0.0019	0.2778	−0.5464	0.5427	−0.0068	0.9946
	Pulmonary disease (%)	13	−0.3653	0.2408	−0.8373	0.1066	−1.5171	0.1292
	methodological quality	44	−0.0012	0.0143	−0.0292	0.0268	−0.0821	0.9346
	Other factors*	< 10						NA
Hospitalization	Male (%)	46	0.5429	0.2076	0.1359	0.9498	2.6145	**0.0089**
	Age (mean)	36	0.0061	0.0034	−0.0006	0.0128	1.7819	0.0748
	Smoke (%)	20	0.105	0.2608	−0.4061	0.6161	0.4026	0.6872
	Comorbidities (%)	15	0.0296	0.2875	−0.5338	0.5931	0.1031	0.9179
	Hypertension (%)	36	0.3727	0.1749	0.0299	0.7154	2.1309	**0.0331**
	Diabetes mellitus (%)	34	0.45	0.4766	−0.484	1.3841	0.9443	0.345
	Obesity (%)	21	−0.151	0.4293	−0.9924	0.6903	−0.3518	0.725
	Cardiovascular disease (%)	21	0.9316	0.3927	0.1618	1.7014	2.372	**0.0177**
	Pulmonary disease (%)	25	0.6525	0.3408	−0.0155	1.3206	1.9144	0.0556
	Kidney disease (%)	21	0.8672	0.3097	0.2603	1.4742	2.8004	**0.0051**
	Malignancy (%)	18	−0.3798	0.5265	−1.4117	0.6522	−0.7213	0.4707
	Glucocorticoid (%)	17	−0.0000	0.0000	−0.0001	0.0001	−0.5519	0.5810
	csDMARD (%)	13	−0.0002	0.0003	−0.0008	0.0003	−0.8919	0.3725
	methodological quality	55	0.0036	0.0291	-0.0533	0.0606	0.1244	0.9010
	Other factors*	< 10						NA
Death	Male (%)	46	0.133	0.1352	−0.1319	0.3979	0.9841	0.325
	Age (mean)	36	0.0045	0.0019	0.0007	0.0083	2.3391	**0.0193**
	Smoke (%)	20	0.0341	0.1254	−0.2117	0.2799	0.2721	0.7856
	Comorbidities (%)	13	0.2845	0.1577	−0.0246	0.5936	1.8039	0.0712
	Hypertension (%)	35	0.1691	0.1095	−0.0455	0.3838	1.5445	0.1225
	Diabetes mellitus (%)	33	0.159	0.2509	−0.3328	0.6509	0.6338	0.5262
	Obesity (%)	21	0.1334	0.214	−0.286	0.5529	0.6234	0.5331
	Cardiovascular disease (%)	21	0.5579	0.1827	0.1999	0.9159	3.0542	**0.0023**
	Pulmonary disease (%)	24	0.1297	0.207	−0.276	0.5354	0.6266	0.5309
	Kidney disease (%)	21	0.3184	0.1672	−0.0092	0.6461	1.9048	0.0568
	Malignancy (%)	17	−0.1178	0.2275	−0.5637	0.328	−0.518	0.6045
	Glucocorticoid (%)	16	−0.0000	0.0000	−0.0001	0.0000	−0.7862	0.4317
	csDMARD (%)	13	−0.0001	0.0001	−0.0003	0.0002	−0.5454	0.5855
	methodological quality	57	0.0222	0.0162	−0.0095	0.0540	1.3731	0.1697
	Other factors*	< 10						NA

*When fewer articles (< 10) provided univariate information for meta-regression, variables were excluded from univariate analysis, like some kinds of comorbidities or medication data. %: represents the percentage of the characteristic in the population

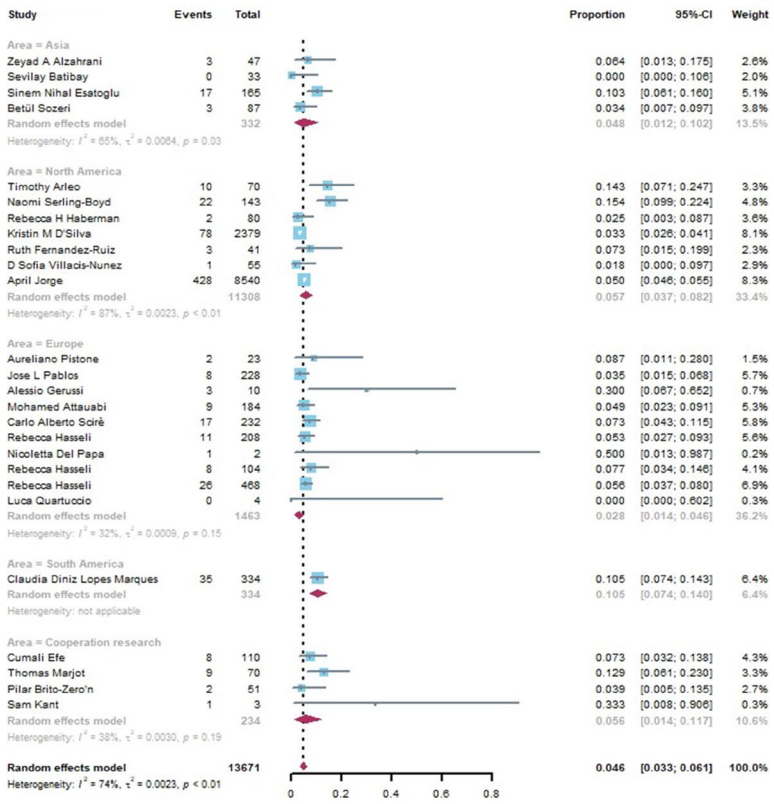
that no variable contributed to mechanical ventilation rate caused by COVID-19, while methodological quality could be a source of heterogeneity about ICU admission in patients with COVID-19 and rheumatic diseases (Table 2).

Data from WHO and the COVID-19 GRA

Under the premise that the interfering factors such as age, gender, and comorbidities do not match, the case fatality rate of this meta-analysis is 0.0346 (95% CI:0.0218-0.0493) between WHO reported (2.13%) and the COVID-19 GRA reported (5.60%). But the hospitalization rate is higher



a



b

Fig. 3 **a** Meta-analysis to identify the ICU admission rate of COVID-19 in patients with rheumatic diseases. **b** Meta-analysis to identify the mechanical ventilation rate of COVID-19 in patients with rheumatic diseases

Table 2 Meta- regression of the variables potentially associated with clinical measures of COVID-19 in patients with rheumatic diseases

Study objectives	Variables	Number of studies	Coefficient	SE	Lower 95% *CI*	Upper 95% *CI*	*Z* value	*P* value
ICU	Male (%)	28	0.0556	0.1486	−0.3468	0.2357	−0.3738	0.7085
	Age (mean)	23	−0.0007	0.0025	−0.0056	0.0043	−0.2679	0.7888
	Smoke (%)	15	−0.0484	0.2007	−0.4417	0.3449	−0.2413	0.8093
	Hypertension (%)	22	0.1339	0.1419	−0.1442	0.412	0.9436	0.3454
	Diabetes mellitus (%)	21	0.5011	0.3308	−0.1473	1.1494	1.5147	0.1298
	Obesity (%)	13	0.1052	0.2598	−0.4041	0.6145	0.4048	0.6857
	Cardiovascular disease (%)	10	−0.2649	0.3844	−1.0183	0.4885	−0.6892	0.4907
	Pulmonary disease (%)	15	−0.2809	0.3606	−0.9876	0.4258	−0.7791	0.4359
	Kidney disease (%)	15	0.2055	0.1939	−0.1746	0.5857	1.0599	0.2892
	Malignancy (%)	11	0.2504	0.4269	−0.5863	1.0871	0.5866	0.5575
	methodological quality	33	0.0557	0.0260	0.0046	0.1067	2.1371	**0.0326**
	Other factors*	< 10						NA
Mechanical ventilation	Male (%)	24	−0.0928	0.1406	−0.3684	0.1828	−0.6601	0.5092
	Age (mean)	18	0.0018	0.0024	−0.0028	0.0064	0.7641	0.4448
	Smoke (%)	12	0.0093	0.1225	−0.2308	0.2494	0.0761	0.9394
	Hypertension (%)	19	0.1157	0.1195	−0.1186	0.3499	0.9679	0.3331
	Diabetes mellitus (%)	18	−0.0666	0.2337	−0.5246	0.3915	-0.2849	0.7757
	Obesity (%)	14	0.0989	0.2188	−0.3299	0.5278	0.4521	0.6512
	Cardiovascular disease (%)	11	0.0459	0.3001	−0.5424	0.6341	0.1528	0.8786
	Pulmonary disease (%)	12	−0.3979	0.2108	−0.8111	0.0153	−1.8876	0.0591
	Kidney disease (%)	14	0.1996	0.2763	−0.342	0.7412	0.7222	0.4702
	Malignancy (%)	12	0.2718	0.3017	−0.3195	0.8631	0.9009	0.3676
	methodological quality	26	0.0198	0.0193	−0.0181	0.0577	1.0237	0.3060
	Other factors*	< 10						NA

*When fewer articles (< 10) provided univariate information for meta-regression, variables were excluded from univariate analysis, like some kinds of comorbidities or medication data. %: represents the percentage of the characteristic in the population

than European Alliance of Associations for Rheumatology (EULAR) COVID-19 Registry monthly report [32] (28%) and the COVID-19 GRA (30.87%).

Discussion

At present, the meta-analysis has reported the morbidity, hospitalization rate, death risk of total cohort of patients with rheumatic diseases and inpatients, and serious clinical treatment rates (ICU admission rate and mechanical ventilation rate) of patients with RD, 0.0190 (95% *CI*: 0.0136-0.0252); 0.4396 (95% *CI*: 0.3899-0.4898); 0.0346 (95% *CI*: 0.0218-0.0493); 0.1418 (95% *CI*: 0.1161-0.1690); 0.0635 (95% *CI*: 0.0453-0.0836); and 0.0461 (95% *CI*: 0.0330-0.0609), correspondingly.

Since the COVID-19 spread, whether patients with rheumatic diseases have an additional risk of COVID-19-related morbidity or mortality was a concern for many rheumatologists. Fifteen months after the pandemic, the published data consistently showed that the main drivers of poor clinical outcomes were age, male sex and cardiovascular disease, and other comorbidities in general population as well as patients with rheumatic diseases [33].

We found that male sex and comorbidities like hypertension, cardiovascular disease, and kidney disease were associated with an increased risk of hospitalization caused by COVID-19; older age or cardiovascular disease was associated with an increased risk of death. At the same time, the drug use of csDMARD or GC has not been found to be related to the risk of hospitalization or death from COVID-19 in confirmed cases. For other factors potentially affecting COVID-19 prognosis in RD patients, conclusions could not be drawn due to limited data. Our results are not completely consistent with published studies, for example, older age was no longer a significant risk factor for hospitalization, which was similar to the results of Wang Q et al. [34] and Montero et al. [35] but contradictory with some other articles [36–38]. Although the regional differences exist, we conclude that the prevalence, hospitalization, and mortality rates caused by COVID-19 in patients with rheumatic

diseases have remained at a high level. Xu's [39] research also reported clinical results of patients with COVID-19 and rheumatic diseases. It suggests high ICU admission rate and case fatality rate, which were 0.09 (95% *CI* 0.05–0.15) and 0.07 (95% *CI* 0.03–0.11).

Akiyama [36] published a meta-analysis on the prevalence and clinical outcome of COVID-19 in patients with autoimmune diseases in October 2020. They believed that GC and csDMARDS were risk factors for hospitalization and death for rheumatism patient during the COVID-19 pandemic. It was also analyzed the use status of b/tsDMARDS-csDMARDS combination or b/tsDMARDS monotherapy, which displayed the hospitalization risk and mortality, has changed in the final even if drug dose did not stratify. In particular, anti-tumor necrosis factor (TNFα) therapy has a protective effect, related to the reduction of hospitalization risk and mortality. A scoping review identified that the use of glucocorticoids, JAK inhibitors (especially high-dose), TNF inhibitors (TNFi), and anti-IL-17 agents may be associated with an increased frequency of respiratory viral events [40]. Both csDMARDs and bDMARDs linked with a higher risk of serious infections [41]. These drugs target key molecules involved in the immune response against infectious antigens and therefore may increase susceptibility to viruses and bacteria [42]. It has been confirmed in multiple studies, in which medium-dose and above (> 5mg) glucocorticoids (GC) have increased risk of hospitalization in rheumatic patients who develop COVID-19 [43, 44]. However, studies have also reported no influence from anti-rheumatic drugs on risk of severe COVID-19 outcomes, although the accuracy of data for partial drugs was unstable [45, 46]. In more details, it has been suggested that no substantial risk was detected csDMARDS [42] as we show.

Interpretation of different results should be cautious. In the development of the COVID-19 epidemic in different periods, many changes fed back on changes in clinical data. The emergence and spread of virus variants like Delta, the improvement of prevention measures, the refinement of drug types and dosages in medical research, and the changes in the supply and demand relationship of medical resources may cause contradictions in researches. A unified viewpoint in the past will accept the challenge from new ones. Viral genomes in Europe and America are different from those in Asia, which suggests that the racial difference in the prognosis of patients with COVID-19 may be a reason for study heterogeneity [47, 48]. Our article conducted subgroup analysis based on the area, which showed differentiation in the prevalence and clinical characteristics of COVID-19 in rheumatism group. Hypertension was generally considered to be related to the prognosis of severe COVID-19 [2, 6, 49], and a new study denies it [50]. The incomplete coincidence of conclusions between studies may also be due to the following: the lag and deviation in voluntary data reporting and the lack of detailed information on the countries or continents from which these data are sourced. It is worth noting that medical load explosion at the beginning of the epidemic may cause confirmed cases reported to be smaller than real world data, due to testing measures that are unreachable.

Our study excluded communications, replies, comments, or letters and vigorously avoided data overlap. This research also has limitations. The meta-analysis of observational studies on the prevalence and hospitalization rates of COVID-19 was quite heterogeneous possibly due to differences in the scale of the study, inclusion of different diseases, and study location. Therefore, we conducted a subgroup analysis and performed meta-regression to assess the impact of each potential risk factor on individual outcomes. Meta-regression on drug treatment performed with a small number of articles resulted in analysis which is not stable enough. Most of the cases in the study came from Europe, particularly, the high proportion of articles from Italy. There is no doubt with certain study population crossover. On the other side, there was one report from South America, which showed high hospitalization rate and mortality rate. This is due to unbalances in epidemic trends and reporting efficiency within different regions.

In summary, we believed that there were differences in the risk and clinical outcome of COVID-19 in different regions for rheumatic diseases. Male, older, and underlying comorbidities are risk factors for hospitalization or death. In our analysis on glucocorticoid or csDMARDs use, without categorization of the drugs in their doses, we found no adverse effects on hospitalization and clinical outcomes. Larger studies can explain more risk factors to protect vulnerable people.

Abbreviations COVID-19: coronavirus disease 2019; DMARDs: disease modifying anti-rheumatic drugs; PsA: psoriatic arthritis; AS: ankylosing spondylitis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; SS: Sjogren's syndrome; AD: autoimmune diseases; RDs: rheumatic diseases; NSAIDs: nonsteroidal anti-inflammatory drugs; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; b/tsDMARDs: biologic or targeted synthetic DMARDs; GC: glucocorticoids; TNFα: antitumor necrosis factor; TNFi: TNF inhibitors; CI: confidence interval; ICU: intensive care unit; BMI: body mass index; PCR: polymerase chain reaction

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06087-1.

Acknowledgements We really appreciate the efforts of all the researchers whose articles were included in this study.

Funding This study was supported by grants from the National Natural Science Foundation of China (81273169, 81573218, 81773514) and the funds for academic and technical leaders in Anhui province (2017D140).

Declarations

Ethics approval Not required.

Consent to participate Not required.

Consent for publication This article has been carefully prepared, unpublished, and does not consider applying for other journals. All the authors meet the Uniform Requirements for Manuscripts Submitted to Biomedical Journals criteria for authorship and approved the manuscript.

Disclosures None.

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