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SYSTEMATIC REVIEW

Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis

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Abstract

Patients with rheumatic diseases are often more susceptible to different bacteria and viruses because of immune impairment, but it is not clear whether there is a higher risk of infection and a more serious course of disease for novel coronavirus (SARS-CoV-2). We performed this systematic review and meta analysis to assess the risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population. We searched PubMed, EMBASE, Scopus and Web of Science databases from January 1, 2020 to October 20, 2020 to determine epidemiological information related to patients with rheumatic diseases and COVID-19, including clear risk estimate or data that could be converted and extracted. We included 26 observational studies, totaling about 2000 patients with rheumatic diseases of whom were infected with COVID-19. Meta-analysis showed that the risk of COVID-19 infection in rheumatic patients was significantly higher than that in the general population (OR = 1.53, 95% CI 1.24–1.88, $P = 0.000$). In terms of hospitalization and severe clinical outcomes associated with COVID-19, we found that rheumatic patients showed similar results to the reference population (hospitalization OR = 1.36, 95% CI 0.81–2.29, $P = 0.247$; admitted to ICU OR = 1.94, 95% CI 0.88–4.27, $P = 0.098$; death OR = 1.29, 95% CI 0.84–1.97, $P = 0.248$). The presence of comorbidities, hypertension, lung diseases were significantly associated with the increased risk of COVID-19-related hospitalization in rheumatic patients and anti-TNF drugs were associated with lower hospitalization risk. Older age was related to severe COVID-19. Our meta-analysis indicated that rheumatic patients were at a higher risk of COVID-19 infection but might not lead to a more serious disease process.

Keywords Rheumatic diseases · COVID-19 · Risk · Systematic review · Meta analysis

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by highly transmitted novel coronavirus (SARS-CoV-2), has brought great medical challenges and caused tremendous deaths and socioeconomic losses [1]. Recently, a second wave of COVID-19 outbreaks has occurred in some European countries due to imported cases and deregulation [2]. Patients with rheumatic diseases (RD) may have a higher risk of infection due to dysregulated and excessive innate immune responses and disease activity [3–5]. However, it is not clear whether this population has a higher risk of COVID-19 and a more serious disease progression. It is generally believed that RD patients' risk of COVID-19 and their disease progression are similar to those in the general population [6–8]; however, there is very limited data on this topic, and some results are contradictory due to differences in region and sample size. In addition, individual risk factors

that may lead to more severe COVID-19 disease progression have aroused widespread concern among patients and rheumatologists. According to recent data, advanced age, male sex, and comorbidities in hospitalized patients were significant risk factors for severe COVID-19 in the general population. The presence of inflammatory markers was most strongly associated with poor clinical prognosis [9–11]. The purpose of this systematic review and meta-analysis is to integrate data on the epidemiology of COVID-19 in the RD population and to analyze the risk of COVID-19 infection and its complications in RD patients compared with the general population. We also analyzed the impact of individual risk factors associated with severe COVID-19, including age, sex, drug therapy, comorbidities, and different RD categories.

Methods

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and has been registered on PROSPERO (CRD: 42020214220).

Search strategy

We conducted a comprehensive search of the PubMed, EMBASE, Web of Science and Scopus databases, including all relevant articles from January 1, 2020 to October 20, 2020 [13]. To supplement any omissions in our online searches, we manually searched the reference lists of related articles, including reviews, guidelines, and statements. Search was limited to articles published in English. The following terms were searched in comprehensive free text. For PubMed: ("Rheumatic Diseases" OR "rheumatic disease" OR "rheumatism" OR "osteoarthritis" OR "arthritis" OR "lupus" OR "systemic sclerosis" OR "vasculitis" OR "ankylosing spondylitis" OR "gout") AND ("COVID-19" OR "COVID19" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019-nCoV" OR "2019nCoV" OR "2019 novel coronavirus" OR "novel coronavirus pneumonia" OR "SARS-CoV-2" OR "SARSCoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "corona virus" OR "new coronavirus"). See Supplemental Appendix S1–S4.

Study selection

We adopted the following inclusion criteria: original research describing COVID-19 infection risk in RD patients compared with reference population and research on hospitalization and severe COVID-19 outcomes. From original research, we extracted estimation of unadjusted effect (odds

ratios, ORs) and 95% confidence interval (CI) or event number and sample size. Risk factor analysis extracted adjusted ORs and 95% CI from multivariable logistic regression model, and combined them only when the study contained at least two items. There were no restrictions based on gender, age, geographical distribution or study duration. We excluded the following: review articles, case reports, case, studies with sample sizes of less than 10, studies from which data could not be obtained, studies with inconsistent content or without reference population data, and any publications in languages other than English or for which we could not obtain the full text. For studies containing duplicate data from the same database, we chose the study with the largest sample size. When necessary, we contacted authors to obtain as much data as possible from missing reports. For each article, two researchers (QXW and RXS) independently filtered the title and abstract, identified the full text relevant to the study, and further reviewed the study to determine if it met the inclusion criteria. Disagreements were resolved through discussion or negotiation with a third reviewer (XPH).

Data extraction and quality assessment

The data were pre-extracted by two authors (QXW and RXS), and then the calibrated data extraction table was used to extract the data independently. The following data were collected: author, year of publication, country, type of study, sample size, patient gender and age, diagnosis of disease, anti-rheumatic treatment drugs, number of patients diagnosed or suspected COVID-19 and outcome indicators.

The Newcastle–Ottawa Scale (NOS) was applied for assessing the quality of cohort and case–control studies [14]. Using the tool, each study was awarded stars based on 8 items, 1–3 stars were of low quality, 4–6 stars were of moderate quality, and 7 or more stars were classified as high quality [15]. For cross-sectional studys, the Agency for Healthcare Research and Quality (AHRQ) (https://www.ncbi.nlm.nih.gov/books/NBK35156/) was applied. Each item was worth 1 point: 0–3 = low quality; 4–7 = moderate quality; 8–11 = high quality [16]. The JBI key assessment tool was used to evaluate case series studies, which included 10 questions relating to the internal validity and risk of bias [17]. Each question could be answered with "yes", "no", "unclear" or "not applicable", and the answers to "yes" > 7 were regarded as high quality (low risk of bias).

Outcome assessment

The primary outcome of the study was to determine the risk of diagnosed or suspected COVID-19 in RD patients with SARS-COV-2 exposure, relative to the reference population. The "reference population" refers to the non-rheumatic group matched with the rheumatic group according to

clinical characteristics, or the general population in the same community. Confirmed patients were positive for SARS-CoV-2 as measured by real-time PCR. Suspected patients met the following conditions: (1) close contact history; (2) symptoms related to COVID-19; (3) with or without typical imaging features of COVID-19; (4) PCR test was negative or not tested. The secondary results were: (1) hospitalization, (2) admission to intensive care unit (ICU), (3) death and (4) analysis of individual risk factors associated with hospitalization and severe COVID-19. "Severe COVID-19" was defined as ICU admission/ mechanical ventilation and death related to COVID-19 infection.

To perform subgroup analyses for the diagnosis of different diseases, we classified RD as follows: (a) inflammatory rheumatic disease included rheumatoid arthritis (RA), psoriatic arthritis (PsA), spondylo arthritis (SpA), juvenile idiopathic arthritis and autoinflammatory syndrome; (b) non-inflammatory rheumatic disease included osteoarthritis, osteoporosis and fibromyalgia. We divided the routine drug use of RD patients prior to COVID-19 diagnosis into the following four categories: (a) conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs); (b) targeted synthetic/biologic DMARDs (ts/bDMARDs); (c) glucocorticoids (GCs); (d) non-steroidal anti-inflammatory drugs (NSAIDs). csDMARDs included methotrexate, cyclophosphamide, azathioprine, cyclosporine, leflunomide, mycophenolate mophetilo, antimalarials (chloroquine and hydroxychloroquine), colchicine, sulfasalazine; ts/bDMARDs included anti-TNF drugs (infliximab, etanercept, adalimumab, golimumab and certolizumab) and non-anti-TNF drugs (anti-IL6, anti- IL-17, anti-IL-17/23, rituximab, belimumab, abatacept, Janus kinase inhibitors).

Statistical analysis

We used Stata software (version15.1, Statacorp, College Station, TX, USA) for statistical analysis of the data. Due to the expected heterogeneity of the included studies, we used a random effects model to pool the data related to infection risk and clinical outcomes of COVID-19 in RD patients. Cochran's Q test (P value < 0.1 indicates significant) and I^2 statistics were used to evaluate the heterogeneity between studies, and I^2 value of > 50% indicates significant heterogeneity [18, 19]. Subgroup analyses were performed based on disease diagnosis, geographical distribution and research design, all of which were decided a priori, and subgroups could be further grouped if necessary. When 5 or more studies were included, we used the funnel chart to evaluate potential publication bias. When more than 10 studies were included, we used Begg's test and Egger's test to determine the funnel chart asymmetry. Sensitivity analysis detected the stability of the results by removing each study [20]. All statistical tests used a bilateral P value of 0.05 for significance.

Results

Literature search and research features

The initial search identified 2534 records, and the manual search identified another one [21]. 1361 articles were obtained once duplicate records were removed. After screening titles and abstracts, 1271 articles were excluded and 90 were further assessed for eligibility. Ultimately, 26 articles met all eligibility criteria (Fig. 1).

A total of 26 observational studies were included [21–46], reporting on a total of 101,124 RD patients, including about 2000 of whom were infected with COVID-19. The studies were conducted in China (2), the United States (3), Italy (10), Spain (9), Germany (1), and also included a study with data of the first 600 patients presented to the COVID-19 Global Rheumatology Alliance (C19-GRA) registry [22]. The systematic review and meta-analysis included 4 cohort studies, 1 case–control study, 14 cross-sectional studies and 7 case series studies, of which 5 were of high quality, 11 were of medium quality, and 10 were of low quality. A detailed description of the included studies is presented in Table 1 (see Supplemental Table S1–S3 for quality assessment).

Risk of COVID-19 infection in rheumatic diseases

Meta-analysis of fourteen studies [23–36] showed that patients with RD had a significantly higher risk of developing COVID-19 than the general population (OR = 1.53, 95% CI 1.24–1.88, $P = 0.000$; $I^2 = 62.4\%$, $P = 0.001$) (Fig. 2). Subgroup analysis according to different disease diagnoses showed that each subgroup showed similar results to the whole, and the heterogeneity was not significant ($I^2 = 0$–28.7%). There was a higher risk of COVID-19 infection in inflammatory rheumatic disease subgroup when compared with RD (OR = 1.87, 95% CI 1.27–2.76 vs. OR = 1.28, 95% CI 1.04–1.58) (Supplemental Fig. S1a). Subgroup analysis based on geography showed that each subgroup had moderate heterogeneity ($I^2 = 48.5\%$ with Asia, and $I^2 = 66.3\%$ with Europe). Compared with the reference population, European countries had an increased risk of COVID-19 (OR = 1.54, 95% CI 1.24–1.93, $P = 0.000$), while Asia did not show any remarkable differences (OR = 1.38, 95% CI 0.61–3.09, $P = 0.438$) (Supplemental Fig. S1b). Further grouping of Europe subgroup according to country showed that Italy had the highest risk of COVID-19 infection (OR = 1.73, 95% CI 1.07–2.79, $P = 0.024$; $I^2 = 64.5\%$, $P = 0.010$) (Supplemental Fig. S1c). The funnel chart drawn was visually symmetrical, indicating that there was no publication bias.

Fig. 1 PRISMA flow diagram of literature search and screening
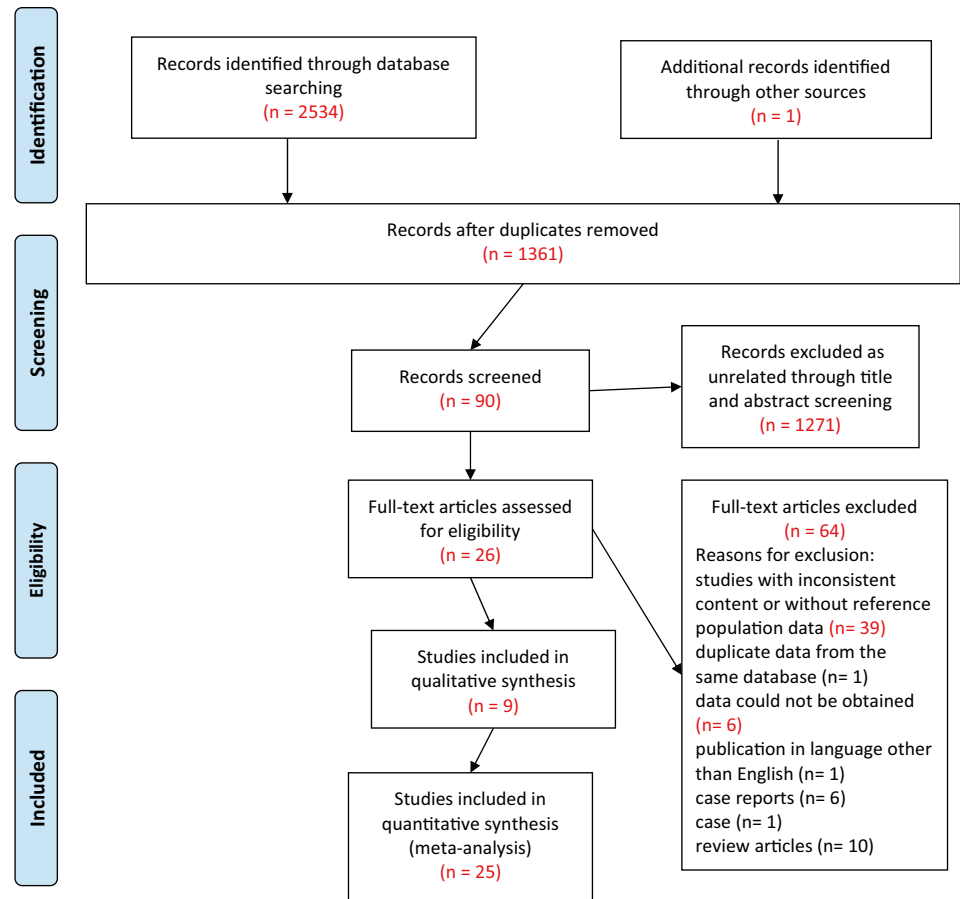
This was supported by Egger's test ($P = 0.470$) and Begg's test ($P = 0.913$). Sensitivity analysis showed that the combined effect estimate varied between 1.37 and 1.62 when individual studies were removed in turn (Supplemental Fig. S2a–c).

Hospitalization risk of COVID-19 in rheumatic diseases

Meta-analysis of six observational studies [21, 34, 35, 37–39] showed that there was no difference in the risk of hospitalization of RD patients due to COVID-19 compared with reference group (OR = 1.36, 95% CI 0.81–2.29, $P = 0.247$; $I^2 = 61.7\%$, $P = 0.023$) (Fig. 3). The subgroup analysis according to the study design showed the conclusion consistent with the whole and the heterogeneity was not significant ($I^2 = 20.6\%$ with cohort study, and $I^2 = 41.3\%$ with cross-sectional study). The funnel plot was not asymmetric. When each of the six included studies was removed in turn, the combined effect estimate remained within the overall confidence interval (OR 1.03–1.63) (Supplemental Fig. S3a–c).

ICU admission risk of COVID-19 in patients with rheumatic diseases

Meta-analysis of four studies [27, 34, 38, 39] showed that there was no higher risk of ICU admission related to COVID-19 in RD population compared with reference population (OR = 1.94, 95% CI 0.88–4.27, $P = 0.098$; $I^2 = 45.3\%$, $P = 0.140$) (Fig. 4). Sensitivity analysis showed that the effect estimate varied within the overall range when studies were eliminated one by one (Supplemental Fig. S4a).

Risk of death from COVID-19 in rheumatic patients

Seven studies assessed the risk of death from COVID-19 in RD patients and included a quantitative synthesis [27, 34–36, 38–40]. The results showed that there was no higher risk of death due to COVID-19 in patients with RD compared with reference population (OR = 1.29, 95% CI 0.84–1.97, $P = 0.248$; $I^2 = 0\%$, $P = 0.495$) (Fig. 5). The resulting funnel chart was visually asymmetric, indicating the possibility of publication bias. Sensitivity analyses showed that effect estimate ranged from 0.98 to 1.37 upon removal of individual studies (Supplemental Fig. S4b and c).

Table 1 Characteristics of the included studies

Authors, year	Country	Study type	Sample size	Age (years) Mean ± SD [e]	Male (%)[e]	Disease diagnosis	Anti-rheumatic drugs	Confirmed/ suspected COVID-19 cases[e]	Quality grading
Michelena et al., 2020 [26]	Spain	Cross-sectional study	959	45 (30–63)[a]	337 (35.1)	IRD	ts/bDMARD	11/NA	Moderate
Pablos et al., 2020 [38]	Spain	Matched cohort study	228	63 (54–78)[a]	87 (38.2)	RD	csDMARD + ts/bDMARD	228/NA	Moderate
Nuño et al., 2020 [43]	Spain	Case series	122	58.3 ± 16.3	42 (34.4)	RD	csDMARD + ts/bDMARD	100/22	Low
Benucci et al., 2020 [32]	Italy	Cross-sectional study	295	NR	NR	RD	bDMARD	4/NA	Moderate
Haberman et al., 2020 [45]	USA	Case series	103	52.7 (28–88)[b]	29 (28.2)	IRD	csDMARD + ts/bDMARD	80/23	Low
Fredi et al., 2020 [40]	Italy	Matched case–control study	26	NR	NR	RD	csDMARD + bDMARD	26/NA	Moderate
Pablos et al., 2020 [31]	Spain	Cross-sectional study	26,131	65 (53–78)[a]	11,497 (44.0)	RD	csDMARD + ts/bDMARD	199/NA	Low
Damiani et al., 2020 [34]	Italy	Cross-sectional study	1193	55 ± 12.7	811 (68.0)	PsO	bDMARD	22/NA	Low
D'Silva et al., 2020 [39]	USA	Matched cohort study	52	62.5 ± 15.1	16 (30.8)	RD	csDMARD + ts/bDMARD	52/NA	Moderate
Scirè et al., 2020 [46]	Italy	Case series	232	62.2 ± 13.9	83 (35.8)	RD	csDMARD + ts/bDMARD	232/NA	High
Zen et al., 2020 [29]	Italy	Cross-sectional study	916	53.6 ± 14.3	196 (21.4)	RD	csDMARD + bDMARD	2/NA	Moderate
Freites Nuñez et al., 2020 [42]	Spain	Case series	123	59.9 ± 14.9	37 (30.1)	RD	csDMARD + ts/bDMARD	58/65	Low
Quartuccio et al., 2020 [28]	Italy	Cross-sectional study	1051	58.4 ± 14.6	348 (33.1)	RD	bDMARD	4/NA	Moderate
Favalli et al., 2020 [25]	Italy	Cross-sectional study	955	53.7 ± 14	311 (32.6)	RD	csDMARD + ts/bDMARD	6/NA	High
Aries et al., 2020 [27]	Germany	Cross-sectional study	11,771	NR	NR	RD	csDMARD + ts/bDMARD	30[c]	Low
Jovani et al., 2020 [37]	Spain	Cross-sectional study	1037	NR	NR	RD	csDMARD + ts/bDMARD	NR	Low
Gianfrancesco et al., 2020 [22]	C19-GRA	Case series	600	56 (45–67)[a]	177 (29.5)	RD	csDMARD + ts/bDMARD	437/163	Low
Montero et al., 2020 [41]	Spain	Case series	62	60.9 ± 13.9	36 (58.1)	RD	csDMARD + bDMARD	51/11	High

Table 1 (continued)

Authors, year	Country	Study type	Sample size	Age (years) Mean ± SD [e]	Male (%)[e]	Disease diagnosis	Anti-rheumatic drugs	Confirmed/ suspected COVID-19 cases[e]	Quality grading
Zhong et al., 2020 [24]	China	Retrospective cohort study	43	49·2 ± 11·6	10 (23.3)	RD	csDMARD + bDMARD	20/7	High
Ferri et al., 2020 [23]	Italy	Prospective cohort study	1641	60 ± 13	385 (23.5)	RD	csDMARD + ts/bDMARD	11/NA	Moderate
Fernandez-Ruiz et al., 2020 [44]	USA	Case series	226	NR	16 (7.1)	SLE	csDMARD	41/NA	High
Gisondi et al., 2020 [21]	Italy	Cross-sectional study	5206	53.2 ± 11.2	2383 (45.8)	PsO	bDMARD	NR	Low
So et al., 2020 [33]	China	Cross-sectional study	39,835	NR	NR	RD	csDMARD + ts/bDMARD	5/NA	Moderate
Mena Vázquez et al., 2020 [36]	Spain	Cross-sectional study	5020	60.8 ± 13.5	7 (30.4)	IRD	csDMARD + ts/bDMARD	15/NA	Moderate
Blanch-Rubió et al., 2020 [30]	Spain	Cross-sectional study	2102	66.4 ± 13.3	409 (19.5)	non-IRD	Anti-osteoporosis therapy + DMARD	109[d]	Low
Salvarani et al., 2020 [35]	Italy	Cross-sectional study	1195	NR	523 (43.8)	RD	ts/bDMARD	9/NA	Moderate

COVID-19 coronavirus disease 2019, *C19-GRA* COVID-19 Global Rheumatism Alliance, *RD* rheumatic diseases, *IRD* inflammatory rheumatic disease, *non-IRD* non-inflammatory rheumatic disease, *PsO* psoriasis, *SLE* systemic lupus erythematosus, *csDMARD* conventional synthetic disease-modifying anti-rheumatic drug, *ts/bDMARD* targeted synthetic/biologic disease-modifying anti-rheumatic drug, *NR* not reported, *NA* not applicable

[a]Represented as median (interquartile range)

[b]Represented as median (range)

[c]Represented as clinical symptoms and SARS- CoV-2 PCR and/or IgG positive

[d]Represented as confirmed or highly suspected COVID-19 cases

[e]Unless otherwise specified

Risk factors for hospital admissions related to COVID-19 in rheumatic patients

From six studies, we extracted twenty-seven variables related to the risk of hospitalization in COVID-19 [22, 41–45], of which ten potential risk factors were identified and were quantitatively described (Table 2, Supplemental Table S4). Seventeen of these were considered routinely collected (Supplemental Table S4). In the meta-analysis, the presence of comorbidities (OR = 2.41, 95% CI 1.04–5.61, $P = 0.041$), hypertension (OR = 3.69, 95% CI 1.41–9.69, $P = 0.008$) and lung diseases (OR = 2.93, 95% CI 1.64–5.23, $P = 0.000$) were significantly associated with the increased risk of hospitalization in patients with RD and COVID-19 and anti-TNF drugs were associated with lower hospitalization risk (OR = 0.38, 95% CI 0.19–0.81, $P = 0.005$). Heterogeneity was low in each variable ($I^2 = 0$–6.5%). Increased age, female sex, glucocorticoids, NSAIDs, csDMARD and antimalarial drugs had no significant correlation with hospitalization risk, and each variable had a low to considerable heterogeneity ($I^2 = 0$–84.3%). Race (non-white vs. white) (OR = 7.78, 95% CI 1.13–53.58), diabetes (OR = 2.61, 95% CI 1.39–4.88), chronic renal insufficiency/end- stage renal disease (OR = 3.02, 95% CI 1.21–7.54), systemic autoimmune conditions (chronic inflammatory arthritis = reference)
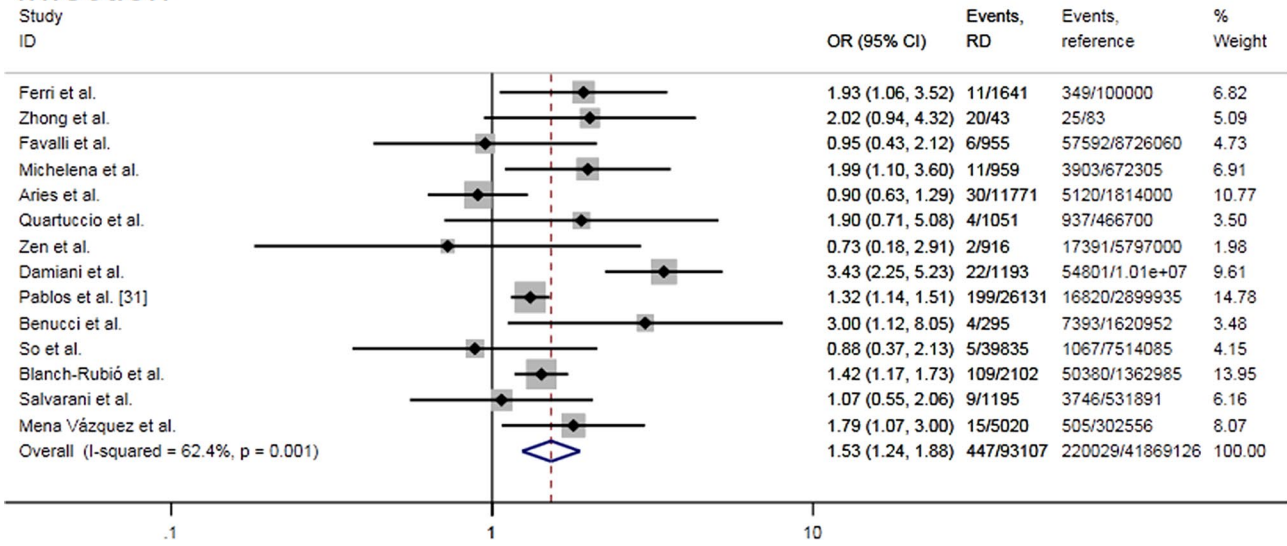
Infection

Fig. 2 Forest plot of the risk of COVID-19 infection in rheumatic patients
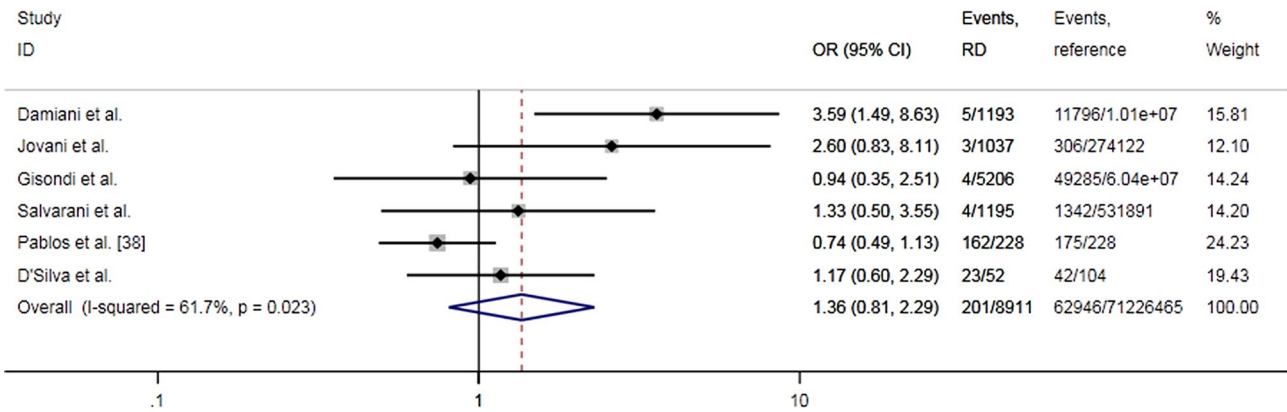
Hospitalization

Fig. 3 Forest plot of the COVID-19-related hospitalization risk in rheumatic patients
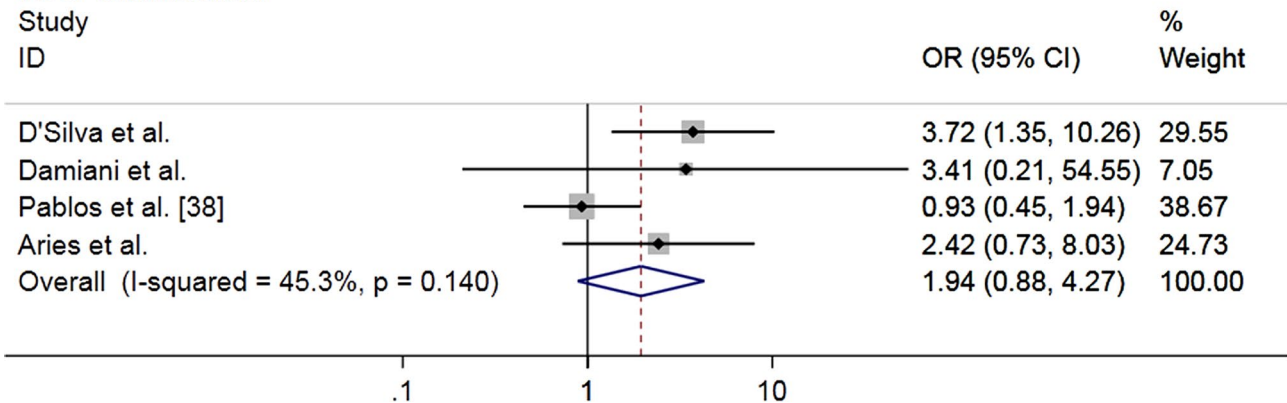
ICU admission

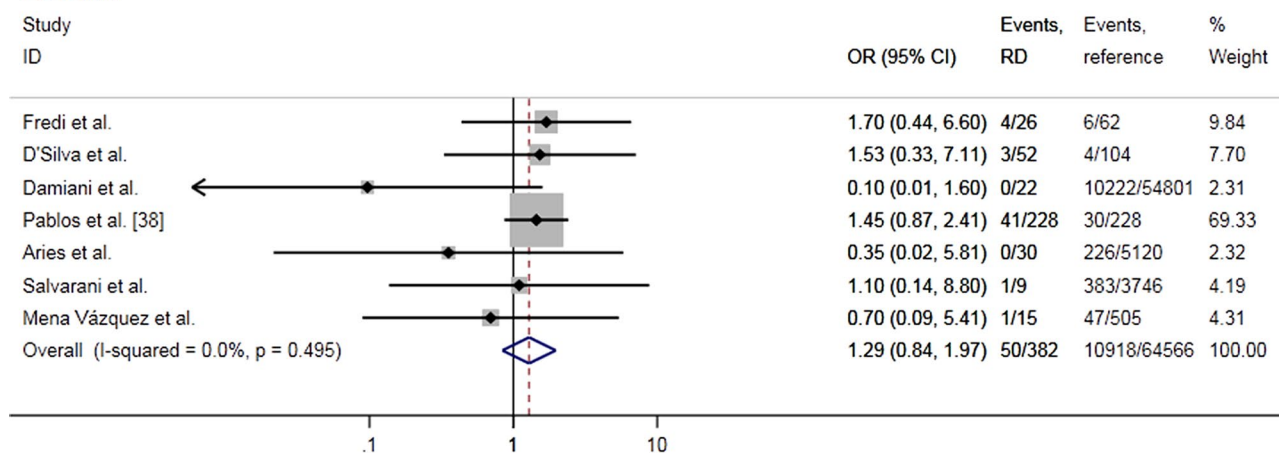Fig. 4 Forest plot of ICU admission risk related to COVID-19 in patients with rheumatic diseases

Death

Fig. 5 Forest plot of the risk of death from COVID-19 in rheumatic patients

Table 2 Meta-analysis of hospital admission risk factors related to COVID-19 in patients with rheumatic diseases

Variable	No. of studies	Heterogeneity		Meta-analysis	
		I^2 (%)	P value	OR (95% CI)	P value
Age (years)	2	84.3	0.011	1.17 (0.97–1.42)	0.093
Gender, women	3	63.8	0.063	0.47 (0.19–1.17)	0.106
Comorbidities (yes)	2	4.5	0.306	2.41 (1.04–5.61)	0.041
Hypertension	2	0	0.638	3.69 (1.41–9.69)	0.008
Lung disease	3	6.5	0.343	2.93 (1.64–5.23)	0.000
Glucocorticoids	2	82.2	0.018	6.23 (0.50–77.55)	0.155
NSAIDs	2	32.9	0.222	0.79 (0.39–1.64)	0.532
csDMARD	2	0	0.652	1.15 (0.71–1.88)	0.570
Antimalarial drugs	3	51.3	0.129	1.21 (0.53–2.79)	0.646
Anti-TNF drugs	2	0	0.739	0.38 (0.19–0.81)	0.005

COVID-19 coronavirus disease 2019, *NSAIDs* non-steroidal anti-inflammatory drugs, *csDMARD* conventional synthetic disease-modifying anti-rheumatic drug

(OR = 3.55, 95% CI 1.30–9.67), methotrexate (OR = 2.06, 95% CI 1.01–5.29) and Janus kinase inhibitors (OR = 10.23, 95% CI 1.88–55.51) showed an increased risk of hospitalization but only present in one study each. Another study showed that ts/bDMARD (OR = 0.46, 95% CI 0.22–0.93) was associated with a lower risk of hospitalization. Body mass index (BMI), obesity, smoking, cardiovascular diseases, systemic lupus erythematosus, PsA, SpA, vasculitis, csDMARD + ts/bDMARD and non-anti-TNF drugs were not associated with hospitalization risk in the separate study they included (all P values > 0.05).

Analysis of risk factors related to severe COVID-19

We included three studies [36, 38, 46], including eleven variables associated with severe COVID-19 (Supplemental Table S4). Not all variables were included in the meta-analysis as not all studies presented data that could be used in models. Two studies described that older age was a risk factor for severe clinical outcomes in patients with RD and COVID-19 (OR = 1.13, 95% CI 1.01–1.27; OR = 4.83, 95% CI 2.78–8.37). One study described that male sex (OR = 1.93, 95% CI 1.21–3.07), connective tissue disease (OR = 1.82, 95% CI 1.00–3.30) and antivirals (OR = 2.05, 95% CI 1.30–3.23) significantly increased the risk of poor prognosis. In two studies, obesity, diabetes, heart failure, ts/bDMARD, csDMARD and csDMARD + ts/bDMARD were not statistically significant risk factors for severe COVID-19 (all P values > 0.05). Two studies reported that use of hormones (any dose) was not associated with poor COVID-19 outcomes (all P values > 0.05).

Discussion

In this systematic review and meta-analysis of 26 observational studies, we showed that patients with RD had an increased risk of developing COVID-19 compared with the general population. This was reflected in the whole and subgroup analysis of European countries and was especially true in Italy. The risk of hospitalization due to COVID-19 among RD patients was similar to that in the control population. We found that the presence of comorbidities, hypertension, and lung diseases were related to the increased risk of hospitalization caused by COVID-19. Anti-TNF might be a protective factor for hospitalization related to COVID-19.

In our combined results, age was no longer a statistically significant risk factor for hospitalization. This was similar to the findings from Montero et al. [41] (OR = 2.6, 95% CI 0.42–16.21, P = 0.30) but disagreed with another study [22]. In this study, individuals age > 65 had an increased risk of COVID-19-related hospitalization (OR = 2.56, 95% CI 1.62–4.04, P < 0.01). Our meta-analysis also did not find that hormones increased the risk of hospitalization, which contradicts previously published findings. A study on the C19-GRA registry [22] described that patients taking glucocorticoids ≥ 10 mg/day had a higher risk of hospitalization (OR = 2.05, 95% CI 1.06–3.96, P = 0.03), and Montero et al. [41] also found that glucocorticoids dose ≥ 5 mg/day was associated with increased risk of hospitalization (OR = 5.00, 95% CI 1.08–23.15, P = 0.04). Our meta-analysis showed that the risk of severe COVID-19 in the RD population was similar to that observed in the reference population. Older age might be a risk factor for severe COVID-19 among RD patients. We did not find the role of hormones in the progression of serious disease. For other factors potentially affecting COVID-19 prognosis in RD patients, conclusions could not be drawn due to limited data.

This study is the first comprehensive meta-analysis of COVID-19 risk assessment in the RD population, and it consolidated data from different countries and different time periods. The study also had limitations. On the one hand, the studies were mainly distributed in European countries affected at the early stage of the epidemic, especially in Italy (38.5%) and Spain (34.6%) [47–49]. Therefore, these findings best reflected the European RD population during the COVID-19 pandemic. In addition, many studies occurred in the same city, which made it difficult to rule out the possibility of overlapping patients. On the other hand, the combined results showed significant heterogeneity. Thus, we undertook subgroup analyses to explore possible sources of heterogeneity. The cause of heterogeneity regarding the infection and hospitalization risk results could be potentially explained by different disease diagnoses and study design, respectively. Furthermore, due to shortages of medical resources at the peak of the epidemic, some patients might have been unable to seek medical treatment, resulting in an underestimation of serious patients. Moreover, if patients with RD took preventive measures (masks, hand hygiene) for fear that they had a higher risk of infection, it would lead to an underestimation of the risk of this population. Finally, taking into account the differences in SARS-CoV-2 PCR testing between countries and the scope of availability, as well as the sensitivity of the test, which would also affect the results of the study [50].

Our results showed that people with RD were potentially at high risk of SARS-CoV-2 infection. However, as in previous coronavirus outbreaks, RD patients were not at increased risk of serious complications [5]. We suggest that patients with RD should strengthen their own protection, avoid exposure to SARS-CoV-2, and strictly follow health guidelines such as wearing masks, washing hands, and restricting social distancing. Additionally, the rapid spread of SARS-CoV-2 is closely linked to travel. Therefore, policymakers should monitor incoming travelers and mandate quarantines [47, 51]. Our data were not sufficient to recommend medication for RD patients, but we recommended following the guidelines issued by the European League Against Rheumatism (EULAR), which suggested that patients should continue immunosuppressive therapy and immediately seek further healthcare advice of an expert as COVID-19 symptoms worsened [52]. The data on COVID-19 in RD population were still very limited, so our conclusions were unsafe. We hope to see additional future large-scale population-based studies that integrate multiple data sources to further confirm our conclusions.

Conclusions

This systematic review and meta-analysis showed that RD patients were more likely to be infected with SARS-CoV-2 than the general population, but we did not find that RD patients had higher hospitalization risk or more serious clinical outcomes related to COVID-19. The presence of comorbidities, hypertension, lung diseases were significantly associated with the increased risk of COVID-19-related hospitalization in rheumatic patients and anti-TNF drugs were associated with lower hospitalization risk. Older age was associated with worse clinical prognosis.

Compliance with ethical standards

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