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Rheumatoid arthritis and COVID-19 outcomes: a systematic review and Meta-analysis

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Abstract

Objectives This study aimed to conduct a comprehensive systematic literature review and meta-analysis to assess the risk and outcomes of coronavirus disease 2019 (COVID-19) in patients with rheumatoid arthritis.

Methods A systematic search was performed across four electronic databases. The quality of the studies was assessed using the Newcastle–Ottawa quality assessment scale and the Joanna Briggs Institute critical appraisal checklist. Statistical analyses were conducted using STATA 14 software.

Results A total of 62 studies were included in the analysis. First, the meta-analysis revealed the following prevalence rates among rheumatoid arthritis patients: COVID-19, 11%; severe COVID-19, 18%; COVID-19-related hospitalization, 29%; admission to the intensive care unit (ICU) due to COVID-19, 10%; and death from COVID-19, 8%. Second, rheumatoid arthritis was associated with an increased risk of COVID-19 infection (OR 1.045(0.969–1.122), $p=0.006$), COVID-19-related hospitalization (OR 1.319(1.055–1.584), $p=0.006$), admission to the ICU due to COVID-19 (OR 1.498(1.145–1.850), $p=0.002$), and death from COVID-19 (OR 1.377(1.168–1.587), $p=0.001$). Third, no statistically significant association was found between rheumatoid arthritis and severe COVID-19 (OR 1.354(1.002–1.706), $p=0.135$).

Conclusions Rheumatoid arthritis patients have a significantly greater risk of COVID-19 infection, hospitalization, ICU admission, and death than individuals without rheumatoid arthritis. However, rheumatoid arthritis did not show a significant association with the risk of severe COVID-19. These findings underscore the need for tailored management strategies and vigilant monitoring of COVID-19 outcomes in rheumatoid arthritis patients.

Systematic Review Registration The study has been registered on PROSPERO [https://www.crd.york.ac.uk/PROSPERO/], and the registration number is CRD42024528119.

Keywords COVID-19, Rheumatoid arthritis, Systematic review, Meta-analysis

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Introduction

The global impact of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been profound over the past four years, significantly affecting global health and mortality [1]. Initially, identified in China in December 2019, COVID-19 swiftly spread worldwide, resulting in substantial morbidity and mortality. As of April 13, 2024, there were 704,753,890 confirmed cases globally, with 7,010,681 reported deaths [2]. Risk factors for severe disease include advanced age, male sex, ethnicity, obesity, and underlying conditions such as hypertension, diabetes mellitus, and cardiovascular diseases [3–8].

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by progressive joint damage and synovial inflammation, often leading to debilitating physical impairments and increased mortality [9–13]. Globally, rheumatoid arthritis incidence estimates indicate a pooled prevalence of 0.46% (95% CI 0.37–0.57%) between 1986 and 2014, with an estimated prevalence of approximately 460 per 100,000 people as of 2019 [14]. Studies have consistently shown that rheumatoid arthritis patients are at increased risk for various infections, which can be attributed to immune dysregulation and immunosuppressive therapies [15–23].

Given these considerations, it is hypothesized that rheumatoid arthritis patients may encounter the increased susceptibility to SARS-CoV-2 infection and more severe COVID-19 outcomes than the general population. However, the literature presents conflicting findings. While some clinical trials have suggested that certain immunosuppressive treatments for rheumatoid arthritis might improve COVID-19 outcomes [24], other studies have reported no significant differences in COVID-19 incidence or hospitalization rates between rheumatoid arthritis patients and the general population [25–27]. Previous studies had been performed in the initial stages of the pandemic and there are additional studies published after the two reviews [28, 29], so it is important and necessary to include new studies for systematic review on this topic. Accordingly, our study aimed to comprehensively review the reported literatures, perform a meta-analysis, and assess the incidence and outcomes of COVID-19 in rheumatoid arthritis patients to clarify this important clinical issue.

Materials and methods

The review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30, 31] and employed a Population, Exposure, Control, Outcome, and Study Design (PECOS) framework to guide study inclusion. Two authors independently conducted comprehensive searches across multiple databases, extracted data, and assessed methodological quality. Discrepancies were resolved through consensus or consultation with a third author.

Criteria for considering the studies for this review

Participants

Only adult patients diagnosed with rheumatoid arthritis were considered.

Exposure

Studies focusing on individuals diagnosed with rheumatoid arthritis were included.

Control

Cohort studies included participants without rheumatoid arthritis, while case–control studies included non-COVID-19 patients.

Outcomes

Primary outcomes included incidence, risk, severe COVID-19(Severe COVID was defined as a condition where symptoms were worse than normal COVID but did not require hospitalization), hospitalization rates, admission to the ICU, and COVID-19 mortality. Studies lacking specific outcomes for rheumatoid arthritis patients were excluded.

Study design

Quantitative observational studies such as cohort, cross-sectional (descriptive and analytical), and case–control studies were considered, with descriptive cross-sectional studies reporting only prevalence grouped separately. Only studies published in full text in English were eligible.

Search Strategy and Study Selection

A systematic review of PubMed, EMBASE, Scopus, and the Cochrane Library was conducted from inception to March 17, 2024, using Boolean operators and truncation symbols to combine search terms. The detailed search strategy is provided in Supplementary Information S1. Additional studies were identified by screening reference lists and contacting authors for supplementary data as needed.

Study selection involved initial screening by two authors, who evaluated titles and abstracts followed by full-text reviews to determine final inclusion.

Data extraction and management

Data extraction was independently performed by two authors using a structured spreadsheet (available on request). The extracted information included the study characteristics (authors, publication year, design, settings, participants), outcomes, and event and sample

sizes. When necessary, clarification was sought from the original study authors.

Quality of evidence

The risk of bias among the included studies was assessed using the Newcastle–Ottawa Scale (NOS) [32], with studies scoring six or more stars considered high quality. Methodological quality and bias risk were evaluated independently by two authors using the NOS and the Joanna Briggs Institute critical appraisal checklist [33]. Funnel plots and statistical tests (Begg's and Egger's) were employed to assess publication bias, with sensitivity analysis conducted to gauge bias impact.

Statistical analysis

Data synthesis and statistical analyses were performed using STATA14 software. Prevalence rates were calculated with 95% CIs, and ORs/RRs were computed for risk outcomes. Statistical heterogeneity was assessed using Cochran's Q statistic and Higgins and Thompson's I^2, with the fixed-effect model used for meta-analysis when $p \geq 0.10$ and $I^2 \leq 50\%$. Substantial heterogeneity prompted subgroup and sensitivity analyses. A p value < 0.05 indicated statistical significance.

Results

Results of literature search

A total of 17,490 relevant citations were initially identified through electronic databases and other search sources (PubMed 1195, EMBASE 3289, Cochrane Library 115, Scopus 12891 and other search sources 0), with 2286 duplicates removed. Ultimately, 62 studies [25–27, 34–92] were included in the qualitative synthesis after all ineligible articles were excluded, and all studies were included in the meta-analysis. All studies were published in English, and the details of the study selection process are illustrated in the flowchart (Fig. 1).

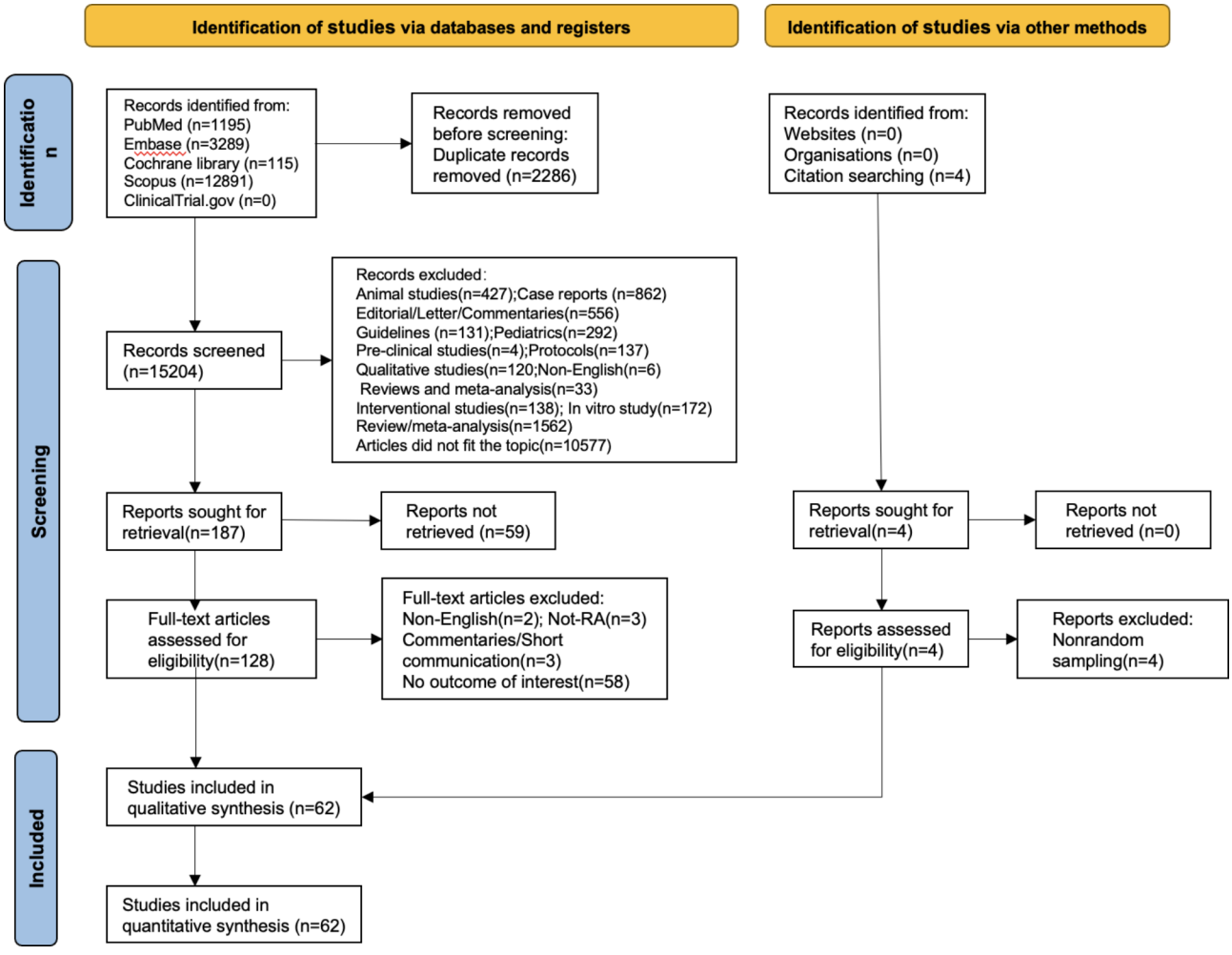


Fig. 1 Flowchart

Characteristics of the included studies

There were 3 case–control studies, 31 cohort studies (retrospective or prospective cohort studies, population-based cohort studies), 15 cross-sectional studies (direct or web-based cross-sectional studies), and 13 prevalence studies. The studies spanned various years, with publications ranging from 2020 to 2024. Predominantly, studies originated from the USA ($n=8$), followed by Italy ($n=6$), Spain ($n=6$), India ($n=5$), and several other countries. The total sample included 690,191 patients with rheumatoid arthritis. The detailed characteristics of the studies are presented in Table 1.

Quality Assessment of the included studies

All studies underwent rigorous quality and bias assessment using the Joanna Briggs Institute guidelines. Supplementary Information S2 provides detailed results. In prevalence studies, some studies failed to report on the methods used to identify the disease and their reliability. In cross-sectional studies and cohort studies, the risk of bias was attributed to factors such as the identification and handling of confounders. For case–control studies, cross-sectional studies, and cohort studies, we also used the Newcastle–Ottawa Scale (NOS) for scoring, and all studies scored above six stars, indicating good overall quality with acceptable bias risk (Supplementary Information S3). Overall, most studies were observed to be of good quality with an acceptable risk of bias.

Results of the Meta-analysis

Prevalence of COVID-19 and Risk of COVID-19

Thirty-six studies reported on the incidence of COVID-19 among rheumatoid arthritis patients. According to a random-effects model, due to significant heterogeneity (I^2 = 99.96%, $p=0.00$), the pooled prevalence was 11% (95% CI 6–17%) (Fig. 2a).

Twelve studies assessed the association between rheumatoid arthritis and COVID-19 risk. Moderate heterogeneity (I^2 = 63.3%, $p=0.002$) warranted a random-effects model, revealing a pooled OR of 1.045 (95% CI 0.969, 1.122) (z=2.76, $p=0.006$) (Fig. 2b).

Severe COVID-19 in patients with rheumatoid arthritis

Eleven studies examined severe COVID-19 among rheumatoid arthritis patients with COVID-19. The significant heterogeneity (I^2 = 97.79%, $p=0.00$) led to the use of a random-effects model, which estimated a pooled prevalence of 18% (95% CI 11–26%) (Fig. 3a).

Eight studies investigated the association between rheumatoid arthritis and severe COVID-19. Significant heterogeneity (I^2 = 98.3%, $p=0.000$) was observed, with a pooled OR of 1.354 (95% CI 1.002, 1.706) (z=1.49, $p=0.135$) (Fig. 3b).

COVID-19-related hospitalization and ICU admission

Fourteen studies reported on COVID-19-related hospitalization in rheumatoid arthritis patients. The significant heterogeneity (I^2 = 99.61%, $p=0.00$) led to the use of a random-effects model, which estimated a pooled prevalence of 29% (95% CI 20–39%) (Fig. 4a). Thirteen studies assessed this association, revealing a pooled OR of 1.319 (95% CI 1.055, 1.584) (z=2.74, $p=0.006$) (Fig. 4b).

Seven studies reported COVID-19-related ICU admissions in rheumatoid arthritis patients. The significant heterogeneity (I^2 = 99.23%, $p=0.00$) necessitated a random-effects model, which estimated a pooled prevalence of 10% (95% CI 5–16%) (Fig. 5a). The pooled OR was 1.498 (95% CI 1.145, 1.850) (z=3.06, $p=0.002$) across the five studies (Fig. 5b).

Mortality in COVID-19 rheumatoid arthritis patients

Sixteen studies reported COVID-19-related mortality among rheumatoid arthritis patients. Significant heterogeneity (I^2 = 97.48%, $p=0.00$) was detected with a random-effects model, which estimated an overall mortality rate of 8% (95% CI 5–11%) (Fig. 6a). For the association between rheumatoid arthritis and COVID-19 mortality, the pooled OR from thirteen studies was 1.377 (95% CI 1.168, 1.587) (z=3.31, $p=0.001$) (Fig. 6b).

All the results of the above meta-analysis are shown in Table 2.

Sensitivity analysis and publication bias

Sensitivity analysis using STATA 14 confirmed the stability of the meta-analysis results, with no significant deviations noted upon removal of influential studies. Publication bias assessments revealed potential bias in COVID-19 and severe COVID-19 incidence studies by examining funnel plots (Supplementary File S4a, c), supported by Begg's and Egger's tests ($p=0.001$ and $p=0.016$, respectively) (Table 3). Other outcomes showed no significant publication bias (Supplementary File S4b, d, e, f, g, h, i, j), reinforcing the robustness of the findings. All the results of Begg's and Egger's tests are shown in Table 3.

Discussion

Summary of the main results

This meta-analysis aimed to comprehensively assess COVID-19 outcomes in patients with rheumatoid arthritis, addressing gaps left by previous reviews with limited study inclusion [29]. Most studies were from the USA, Italy, and Spain, highlighting potential underreporting in other regions due to resource constraints.

Our findings indicated a greater prevalence of COVID-19 among rheumatoid arthritis patients (12%) than among the global average (approximately 8%) (based on

Table 1 Characteristics of the included studies and patients

Study ID, year, county	Study design; Study settings; Study duration	Number of participants in the study	Age of RA cohort	Female/male in RA cohort	COVID-19 outcomes reported
Ferri C et al., 2021; Italy	Observational multicenter study; Telephone survey; NS	1641 ASD patients with 695 RA patients	(63 ± 13) [a]	518/177	Prevalence of COVID-19
Freites N et al., 2020; Spain	Prospective observational study; Single tertiary Hospital; 1 March 2020 to 24 April 2020	123 AIRD–COVID patients with 50 RA patients	NS	NS	Risk of hospitalization
Mena V et al., 2020; Spain	Cross-sectional observational study; HRUM Emergencies; March 13 to April 12, 2020	1537 IAD patients with 13 RA patients	NS	NS	Death
Soldevila-D et al., 2020; Spain	Cross-sectional study; Hospital del Mar; September 2019 to March 2020	2544 IMID patients with 538 RA patients	NS	424/114	Prevalence of COVID-19
Alzahrani et al., 2020; Saudi Arabia	Retrospective study; Single tertiary care center; March 2020 to November 2020	47 RD patients with 25 RA patients	NS	NS	Severe COVID-19
Annamalai et al., 2020; India	Multi-center retrospective observational study; Six tertiary care centers; April 01, 2020 to October 15, 2020	85 RD- COVID patients with 44 RA patients	NS	NS	Hospitalization
Attauabi M et al., 2021; Denmark	Population-based cohort study; The Danish COVID-IMID cohort; January 28, 2020 to September 15, 2020	71,733 IMID patients with 13,015 RA patients	NS	NS	Prevalence of COVID-19
Bachiller-Corral et al., 2021; Spain	Retrospective single-center observational study; Ramóny Cajal Hospital; March 1, 2020 to April 30, 2020	4592 IRD patients with 1708 RA patients	NS	NS	Hospitalization; Risk of hospitalization
Belleudi et al., 2021; Italy	Retrospective cohort Study; Regional administrative healthcare databases; NS	65,230 IMID patients with 20,299 RA patients	64 (52–75) [b]	15,184/5115	Prevalence of COVID-19; Risk of COVID-19; Risk of hospitalization; Risk of death
Bower et al., 2021; Sweden	Cohort study; Swedish nationwide multiregister linkages; March–September 2020	110,567 IJD patients with 53,455 RA patients	69 (57–77) [b]	39,022/14,433	Risk of hospitalization; risk of ICU; Risk of death
Cordtz et al., 2021; Denmark	Cohort study; the linkage of several Danish nationwide registers; March 1 to August 12, 2020	29,440 RA patients	67.3 (56.7–75.7) [b]	20,990 /10,101	Death; Risk of hospitalization; Risk of severe COVID-19
Fernandez-G et al., 2021; Spain	Observational longitudinal study; Single tertiary hospital in Madrid; March 1 to April 15,2020	3951 IRD patients with 1486 RA patients	NS	NS	Risk of hospitalization
Florence et al., 2021; France	Cohort study; Lille University Hospital; February 24 to April 17, 2020	694 IRMD patients with 213 RA-COVID-19 patients	NS	NS	Prevalence of COVID-19; Severe COVID-19; Death
Gamboa-C et al., 2021; Peru	Cohort follow-up; Hospital Nacional Guillermo Almenara Irigoyen-EsSalud; March to November 2020	1148 ARDs patients with 169 RA patients; 75 RA-COVID patients	NS	NS	Prevalence of COVID-19
Guillaume et al., 2021; France	Observational monocentric cohort study; Adolphe de Rothschild Foundation Hospital; Apr 17 to Nov 2, 2020	459 IMID patients with 149 RA patients	NS	NS	Risk of COVID-19
Jung et al., 2021; Korea	Cross-sectional study; Nationwide COVID-19 cohort database by the Korea National Health Insurance Corporation; NS	35 RA-COVID patients,121 controls	NS	NS	Severity of COVID-19; Admission to ICU; Death; Risk of COVID-19; Risk of death
Naderi et al., 2021; Iran	Multicenter cohort-based observational study; Rheumatology clinics of academic hospitals of Isfahan; April and July 2020	954 RD patients with 215 RA patients;9 RA-COVID patients	51.09 (52 [43–60]) [c]	175/40	Prevalence of COVID-19; Hospitalization; Death; Admission to ICU
Pileggi et al., 2021; Brazil	Cross-sectional analysis; Web-based platform using telephone calls; March 29 to May 17, 2020	5166 RD patients with 402 RA patients;16 RA-COVID patients	NS	NS	Prevalence of COVID-19

Table 1 (continued)

Study ID, year, county	Study design; Study settings; Study duration	Number of participants in the study	Age of RA cohort	Female/male in RA cohort	COVID-19 outcomes reported
Raike et al., 2021; USA	Retrospective cohort study; US multicenter research network (TriNetX); NS	9730 RA patients	(61.1 ± 15.3) a	7280/2450	Hospitalization; Admission to ICU; Death; Severe COVID-19; Risk of hospitalization; Risk of severe COVID-19; Risk of admission to ICU; Risk of death
Saadoun et al., 2021; France, Germany, Italy, Portugal, Spain, and the UK	Multicenter cross-sectional study; Six tertiary referral centers in France, Germany, Italy, Portugal, Spain, and the UK; June 7 to Dec 8, 2020	3136 IMID patients with 891 RA patients;39 RA-COVID patients	NS	NS	Prevalence of COVID-19
Sarzi-P et al., 2021; Italy	Multicenter retrospective study; Italian regions of Lombardy and Marche; March 15 to April 23,2020	10,260 RD patients with 5373 RA patients;23 RA-COVID patients	NS	NS	Prevalence of COVID-19
Shobha et al., 2021; India	Prospective multicenter noninterventional longitudinal ongoing study; 14 specialist rheumatology centers across Karnataka; March 2020 to August 10, 2020	3807 RD patients with 1964RA patients;12 RA-COVID patients	NS	NS	Prevalence of COVID-19
Hasseli et al., 2021; Germany	Prevalence study; German COVID-19 registry for IRD patients;30th March to 16th November 2020	104 RA-COVID-19 patients	NS	NS	Hospitalization; Death
Batıbay et al., 2021; Turkey	Prevalence study; Gazi University Hospital; July to December 2020	320 IRD patients with 109 RA patients;6 RA-COVID patients	NS	NS	Prevalence of COVID-19; Death
Alsaed et al., 2022; Qatar	Single-center retrospective matched cohort study; A medical center; March 2020 to March 2021	141 ARD patients with 57 RA patients	NS	NS	Severe COVID-19; Risk of severe COVID-19
Assar et al., 2022; Iran	Prevalence study; Emam Reza and Golestan Hospitals; Feb 18 and Aug 22, 2020	1000 RD patients with 371RA patients; 78 RA-COVID patients	NS	NS	Prevalence of COVID-19; Risk of COVID-19
Becetti et al., 2022; Qatar	Cross-sectional study; Telephonic survey; April 1 to July 31, 2020	700 ARD patients with 260 RA patients; 34 RA-COVID patients	NS	NS	Prevalence of COVID-19
Curtis et al., 2022; USA	Retrospective cohort study; The Optum COVID-19 EHR dataset; February 1 to December 9, 2020	2306 RA-COVID patients	61 (19–89) [b]	1795/511	Hospitalization; Admission to ICU; Death; Risk of hospitalization; Risk of admission to ICU; Risk of death
Eder et al., 2022; Canada	Population-based, matched cohort study; The health administrative data; January 1 to July 31, 2020	134,964 RA patients	NS	NS	Risk of hospitalization
Figueroa-P et al., 2022; USA	Retrospective, comparative, multicenter cohort study; Mayo Clinic and Mass General Brigham in the USA; March 1, 2020 to June 6, 2021	582 RA patients	62 (14) [a]	421/161	Hospitalization; Death; Severe COVID-19; Risk of hospitalization; Risk of severe C OVID-19; Risk of death
Gomides et al., 2022; Brazil	Cross-sectional analysis; ReumaCoV- Brazil Registry; May 24, 2020, to January 31, 2021	489 RA patients	(53 ± 12) [a]	443/46	Prevalence of COVID-19; Hospitalization
Gracia et al., 2022; Spain	Cross-sectional survey; Google form platform; April to October 2020	1526 AD patients with 46 RA patients;2 RA-COVID patients	NS	NS	Prevalence of COVID-19
Marozoff et al., 2022; Canada	Population-based matched cohort study; British Columbia; February 6, 2020 to August 15,2021	6279 ARD patients with 2067 RA patients;	60.1 (18.3) [a]	1445/622	Risk of admission to ICU

Table 1 (continued)

Study ID, year, county	Study design; Study settings; Study duration	Number of participants in the study	Age of RA cohort	Female/male in RA cohort	COVID-19 outcomes reported
Oztas et al., 2022; Turkey	Cohort study; Rheumatology outpatient clinics of Istanbul University-Cerrahpasa and Istanbul University; June 1 to September 1, 2020	89 RA patients; 4 RA-COVID patients	(53.9 ± 10.3) [a]	73/16	Prevalence of COVID-19; Risk of COVID-19; Hospitalization
Patil et al., 2022; India	Cohort study; 14 specialist rheumatology centers across Karnataka and one center in Kerala; April-December 2020	9212 AIRD patients with 4558 RA patients; 120 RA-COVID patients	NS	NS	Prevalence of COVID-19; Risk of death
Rorat et al., 2022; Poland	Retrospective real-world study; The SARS Ter national database; 1 March 2020 and 31 January 2022	136 RA patients	NS	NS	Death
Sonaglia et al., 2022; Italy	Observational study; The province of Udine, Italy; September 2019 to November 2020	936 RA patients; 16 RA-COVID patients	NS	NS	Prevalence of COVID-19
Valladales-R et al., 2022; Colombia	Observational study; A health care institution; 1 April 2020 to 31 May 2021	2566 RA patients; 130 RA-COVID patients	61.9 (53.3–69.4) [b]	2080/486	Prevalence of COVID-19; Hospitalization; Admission to ICU; Death
Wang et al., 2022; China	Cohort Study; The Health Improvement Network; February 2020 to September 2020	17,268 RA patients; 42 RA-COVID patients	(64.9 ± 13.5) [a]	12,295/4973	Prevalence of COVID-19; Risk of COVID-19
Yue et al., 2022; USA	Retrospective analysis; Optum EHR database; February 1, 2020 to March 3,2021	6108 RA patients	(61.5 ± 14.8) [a]	4714/1394	Risk of severe COVID-19
Li et al., 2022; UK	Cohort study; UK primary care database; December 8, 2020 to October 31, 2021	15,901 RA patients	(64.8 ± 13.7) [a]	11,258/4643	Prevalence of COVID-19; Hospitalization; Death; Risk of COVID-19; Risk of hospitalization; Risk of death
Eder et al., 2023; Canada	Population-based, matched cohort study; Adult residents from Ontario, Canada; January 2020 to December 2020	493,499 IMIDs patients with 134,964 RA patients; 1349 RA-COVID patients	NS	NS	Prevalence of COVID-19; Risk of COVID-19
Geng et al., 2023; China	Prevalence study; A tertiary hospital in Beijing; December 8, 2022 to January13, 2023	2005 AIIRDs patients with 290 RA patients;228 RA-COVID patients	NS	NS	Prevalence of COVID-19; Risk of COVID-19
Jain et al., 2023; India	Prospective, non-interventional longitudinal cohort study; 15 referral rheumatology centers; Apr-Dec,2021	2969 AIRD patients with 129 RA patients	NS	NS	Risk of COVID-19; Risk of death
Khalaf et al., 2023; USA	Retrospective cohort study; The National Inpatient Sample (NIS) database; 2020	21,175 RA patients;	68[d]	15,458/5717	Risk of death
Rizzi et al., 2023; Italy	Prospective cohort; NS; October to December 2021	17 RA patients; 2 RA-COVID patients	NS	NS	Prevalence of COVID-19; Risk of COVID-19
Sarı et al., 2023; Türkiye	Prevalence study; İstanbul Fatih Sultan Mehmet Training and Research Hospital; July 2020 and January 2021	71 RA patients; 14 RA-COVID patients	NS	NS	Prevalence of COVID-19; Severe COVID-19
Scirocco et al., 2023; Italy	Retrospective, observational design; The national CONTROL-19 Database; March 26, 2020 to March 1, 2021	524 RA patients; 131RA-COVID patients	60.6 (13.1) [a]	389/135	Prevalence of COVID-19
Singh et al., 2023; USA	Cohort study; Database; January 1,2020 and September 16,2021	69,549 RA patients; 22,956 RA-COVID patients	61.00 (51.0, 71.0) [b]	17,492/5464	Prevalence of COVID-19; Hospitalization; Admission to ICU; Death
Svensson et al., 2023; Denmark	Cohort study; Danish national registers; March 2020 to January 2023	30,919 RA patients; 13,011RA-COVID patients	52.1(40.3–63.8) [b]	21,895/9024	Prevalence of COVID-19; Risk of COVID-19; Risk of hospitalization; Risk of death; Risk of Severe COVID-19

Table 1 (continued)

Study ID, year, county	Study design; Study settings; Study duration	Number of participants in the study	Age of RA cohort	Female/male in RA cohort	COVID-19 outcomes reported
Tsai et al., 2023; Taiwan	Retrospective cohort study; the US Collaborative Network in TriNetX; January 1, 2018 and December 31, 2022	7284 RA patients; 753 RA-COVID patients	NS	5908/1376	Prevalence of COVID-19; Hospitalization; Death; Severe COVID-19
Zamora-A et al., 2023; Philippines	Prevalence study; The Global Rheumatology Alliance registry; March 2020 to August 2021	164 IRDs patients with 25 RA	NS	NS	Risk of hospitalization; Risk of death
Bagheri-H et al., 2023; Iran	Retrospective cross-sectional study; Ali-Ibn-Abi-Talib Hospital, Rafsanjan University of Medical Sciences; NS	200 RA patients;34 RA-COVID patients	NS	140/60	Prevalence of COVID-19
Abdulnaby et al., 2023; Egypt	Multicenter case-control study; Cairo University Hospitals; September 2020 and February 2021	66 RD patients with 32 RA patients;	NS	NS	Severe COVID-19
Armağan et al., 2023; Turkey	Single-center retrospective study; Ankara City Hospital Rheumatology Clinic; May to December 2021	98 ARD patients with 62 RA patients;14 RA-COVID patients	NS	NS	Prevalence of COVID-19
Nair et al., 2023; India	Prevalence study; A tertiary care center from South India; October 2019 to May 2021	76 RA patients;4 RA-COVID patients	NS	NS	Prevalence of COVID-19
Anand et al., 2023; USA	Cohort study; Veterans Health Administration electronic health records; January 1, 2020 to September 30, 2022	1355 RA-COVID patients	NS	280/1075	Severe COVID-19; Risk of severe COVID-19
Davis et al., 2024; USA	Retrospective case-control; The National Inpatient Sample database; January 1 to December 31, 2020	21,545 RA-COVID patients	68.75 (0.20) [a]	15,711/5834	Risk of death
Embaby et al., 2024; Egypt	Prevalence study; Cairo University hospitals and private rheumatology centers; The start of pandemic in 2019 till 30 June 2022	300 RA-COVID patients	(48.92 ± 12.1) [a]	187/13	Severe COVID-19; Death
Cordtz R et al., 2022; Denmark	Cohort study; Several Danish nationwide registers; January 1 to October 5, 2021	81,818RA patients;1942 RA-COVID patients	NS	58,233/23,585	Prevalence of COVID-19; Hospitalization
Le M et al., 2023; Belgium	Longitudinal prospective monocentric study; Hospital Erasme (Brussels, Belgium); April 2021 and February 2022	79 RA patients;7 RA-COVID patients	61.0 (52.5–68.0) [b]	63/16	Prevalence of COVID-19
Mahdavi et al., 2021; Iran	Cross-sectional study; Tabriz University of Medical Sciences; 14 December 2020 to 14 March 2021	128 RA-COVID patients	(52.3 ± 13.9) [a]	107/21	Hospitalization; Admission to ICU; Death

ASD inflammatory autoimmune systemic diseases, AIRD autoimmune inflammatory rheumatic diseases, IMIDs immune-mediated inflammatory diseases, IAD inflammatory articular diseases, RD rheumatic diseases, IRDs inflammatory rheumatic diseases, IJDs inflammatory joint diseases, IRMD inflammatory rheumatic and musculoskeletal diseases, ARDs autoimmune rheumatic diseases, UK United Kingdome, USA United States of America. NS not specified.

[a]Mean with standard deviation; [b]Median with IQR; [c]mean (median [IQR]); [d]Mean

data provided on the WHO website(https://data.who.int/dashboards/covid19/cases?n=c)).

In addition, a statistically significant association between rheumatoid arthritis and COVID-19 was found in the risk estimate, which suggested that patients with rheumatoid arthritis were more susceptible to COVID-19 than the general population. This was consistent with the results of prior studies highlighting rheumatoid arthritis patients' elevated infection risk [93]. Factors such as immunosuppression, chronic inflammatory states, and comorbidities might also be causes [94]. Notably, certain rheumatoid arthritis treatments, such as DMARDs, glucocorticoids and etanercept, are associated with increased COVID-19 risk. For example, Assar et al. reported that patients treated with >20 mg/d prednisolone were at increased risk of getting COVID-19 [56]. *Gracia* et al. reported that anti-TNF-alpha treatment was associated with a more than 3-fold increased risk of contracting COVID-19 [62]. A study conducted by Valladales et al. suggested that the incidence of COVID-19 was greater among patients with rheumatoid arthritis who received DMARDs and glucocorticoids simultaneously than among patients with rheumatoid arthritis who did not receive these drug combinations [68]. Bagheri et al. provided evidence that etanercept therapy might increase the risk of developing COVID-19 in patients with rheumatoid arthritis [83]. Apparently, the mechanism might stem from the suppression of a protective immune state in rheumatoid arthritis patients.

Our meta-analysis revealed that the incidence of severe COVID-19 among rheumatoid arthritis patients was 18%. For the risk of severe COVID-19, some studies have

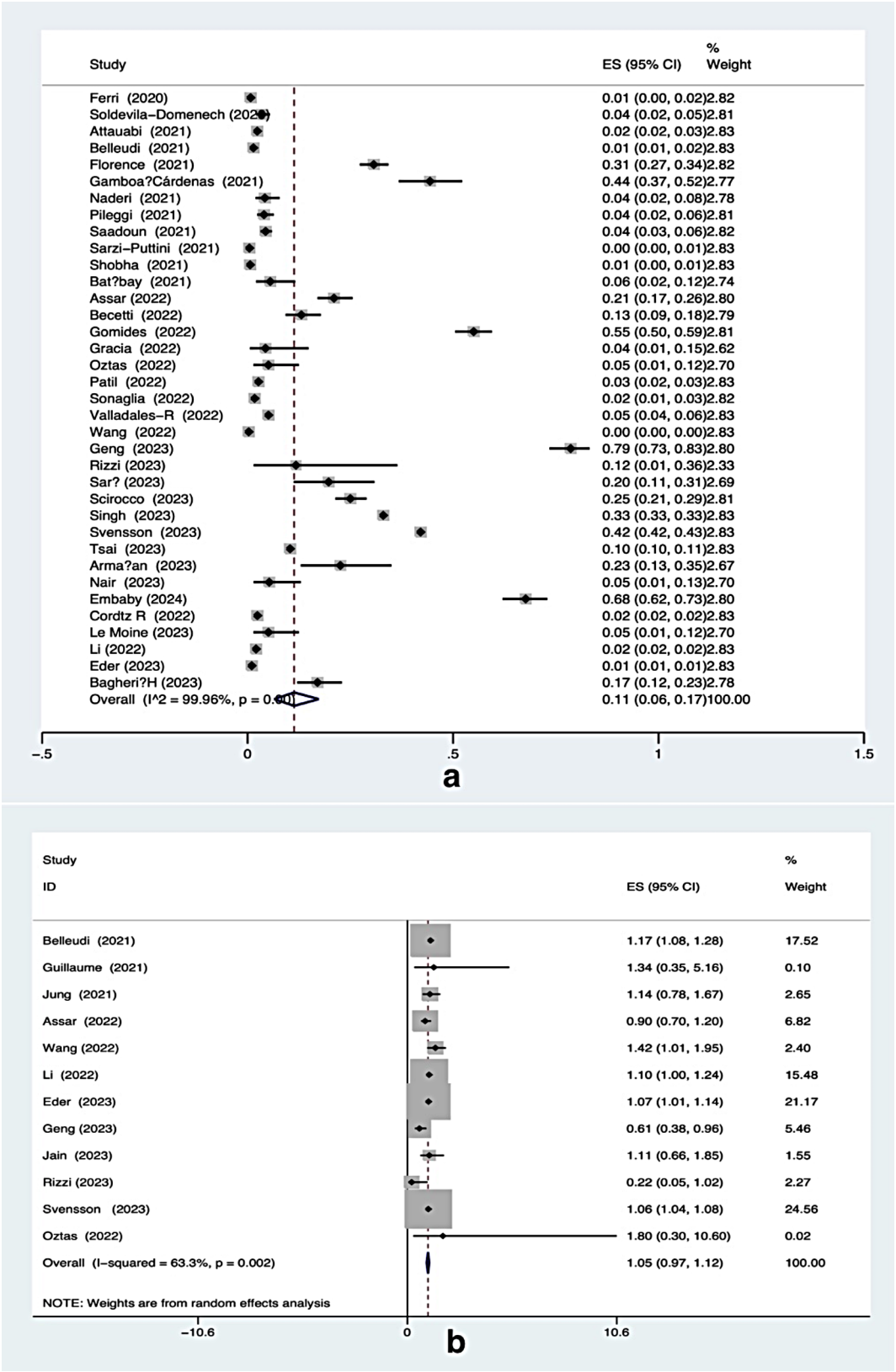
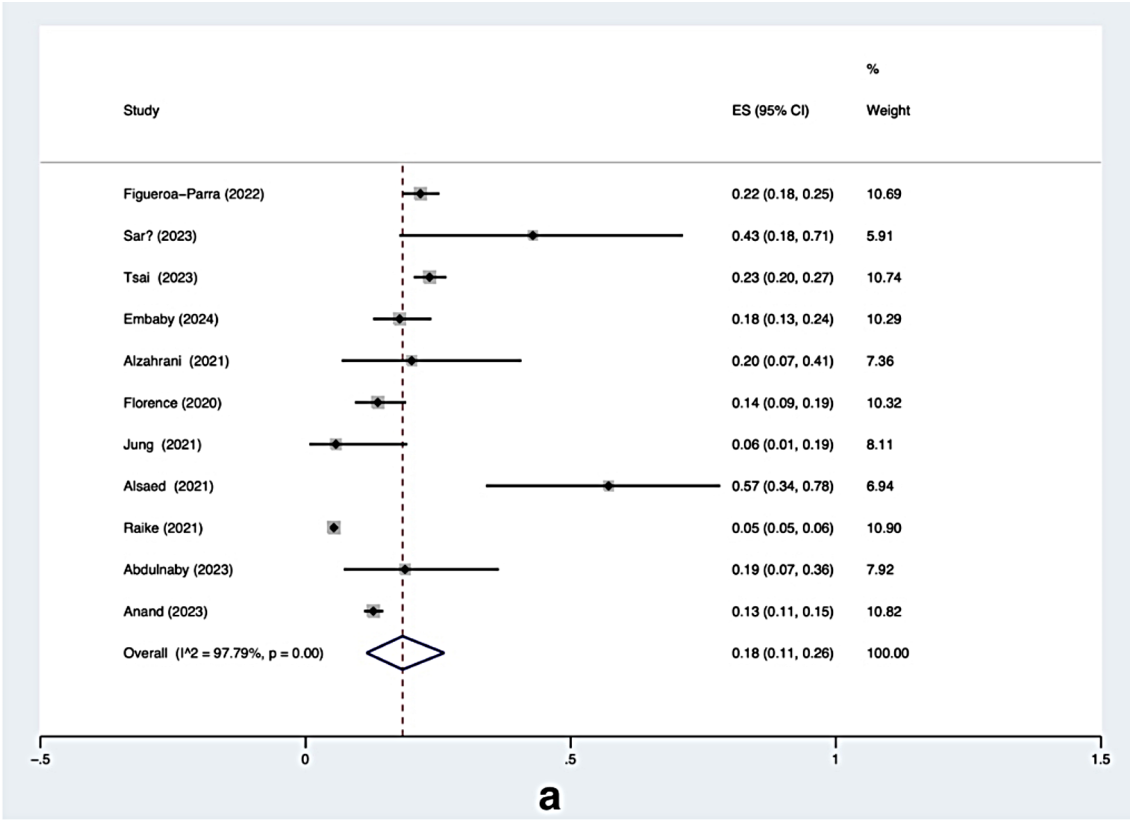


Fig. 2 (**a**)Prevalence of COVID-19 in RA patients; (**b**) Risk of COVID-19 among RA patients



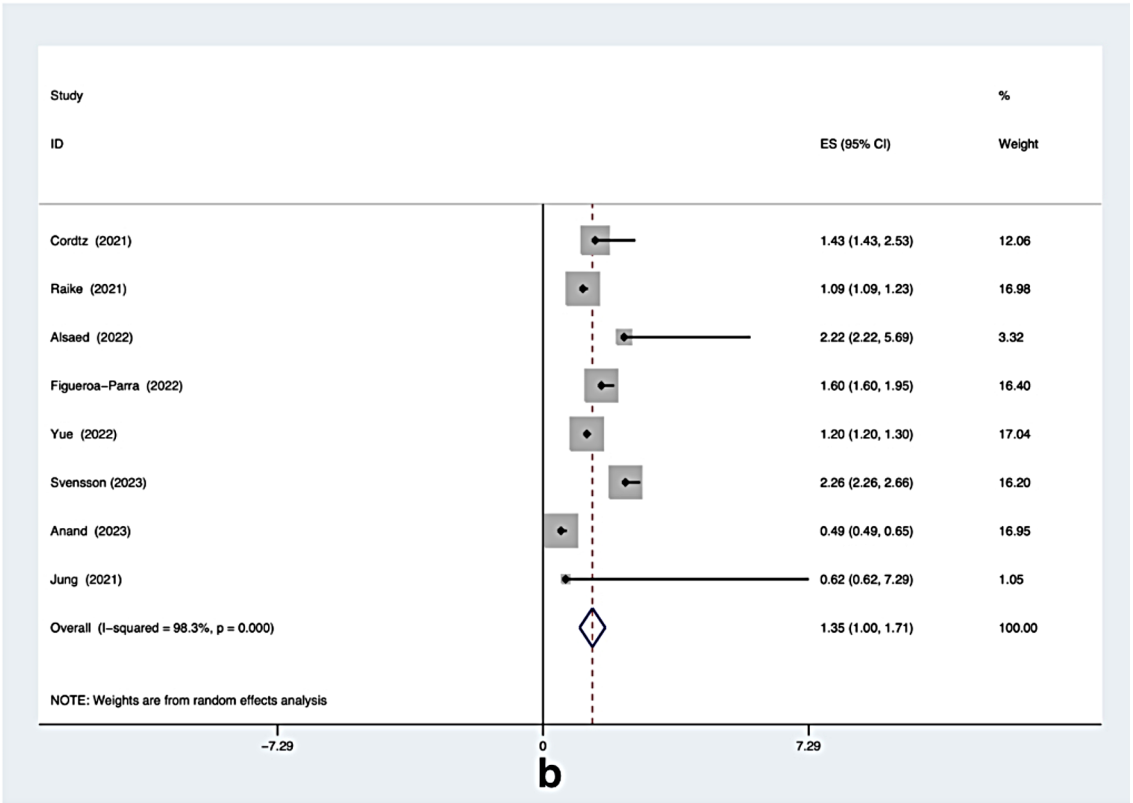
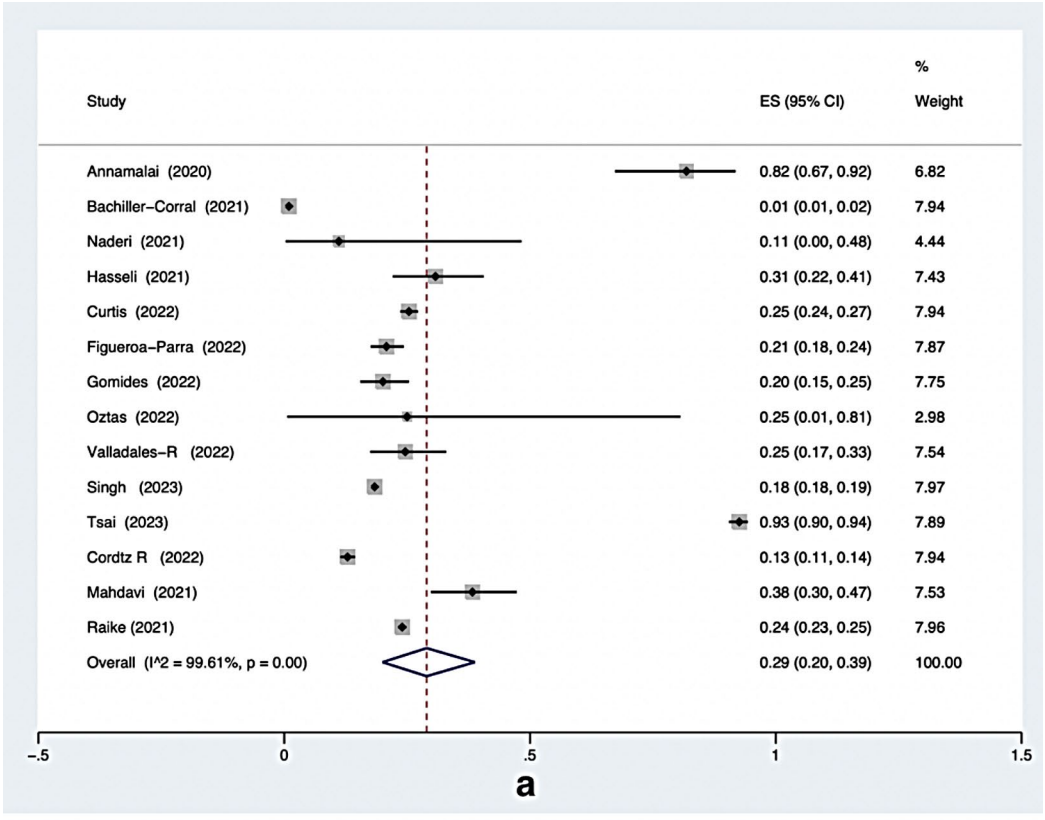


Fig. 3 (**a**) Severe COVID-19 among RA patients; (**b**) Risk of severe COVID-19 among RA patients



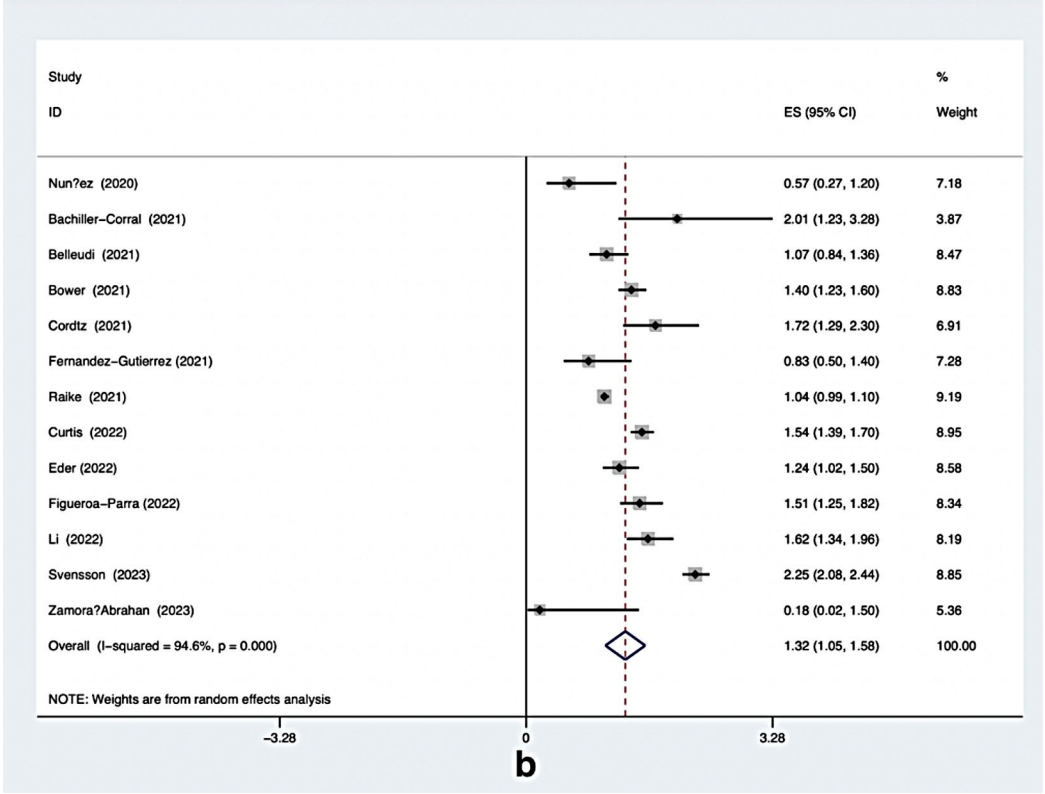


Fig. 4 (**a**) COVID-19 hospitalization among RA patients; (**b**) Risk of COVID-19 hospitalization among RA patients

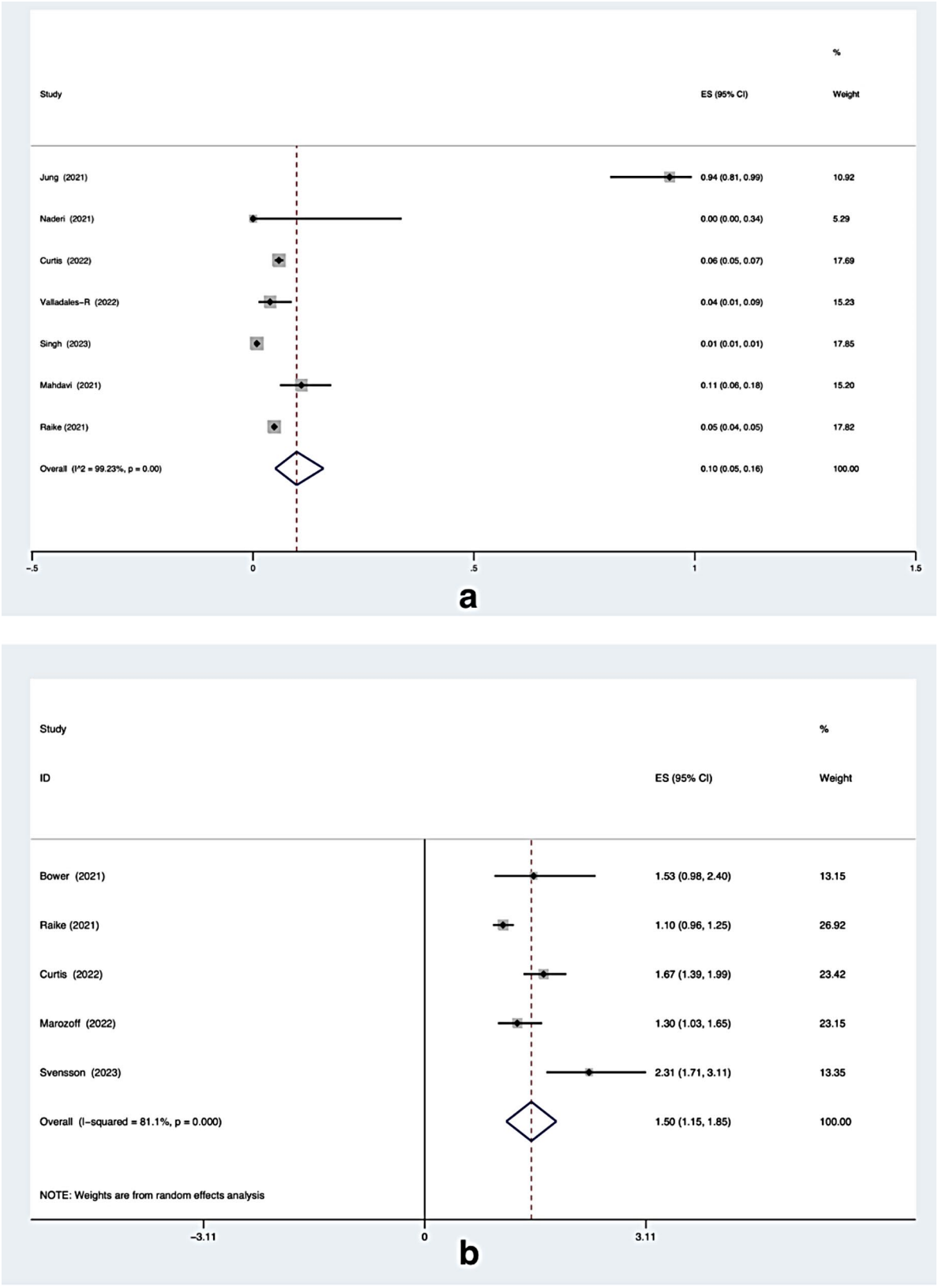
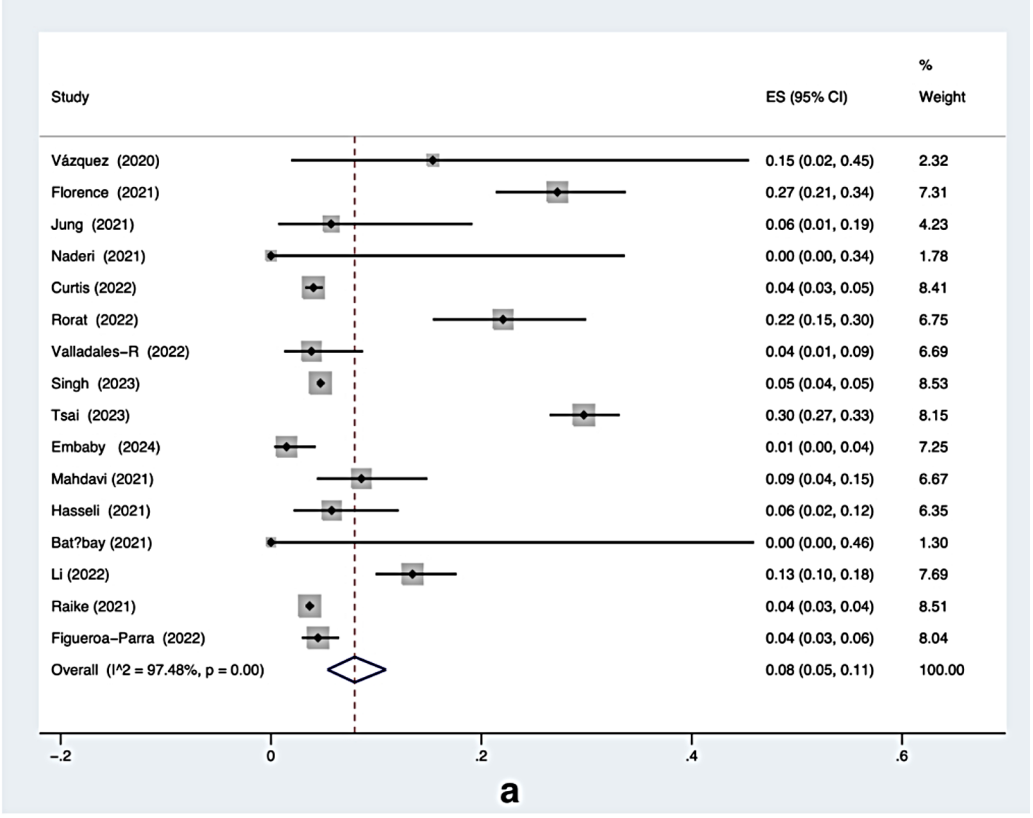


Fig. 5 (**a**) ICU admission due to COVID-19 among RA patients; (**b**) Risk of ICU admission due to COVID-19 among RA patients



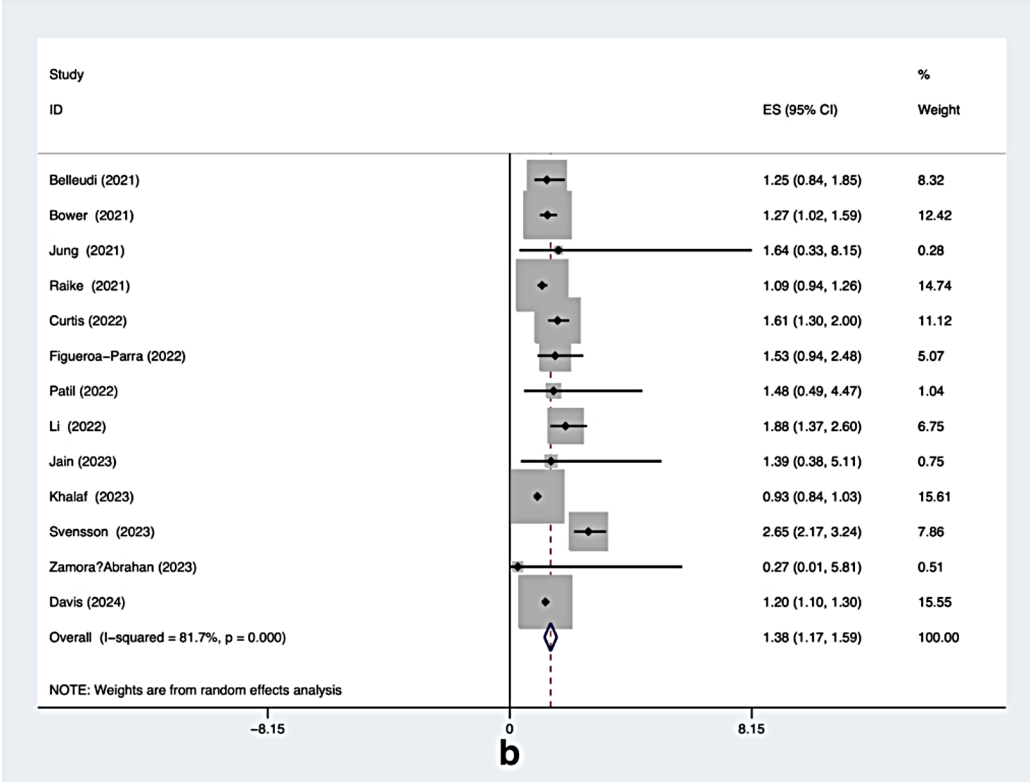


Fig. 6 (**a**)Morality rate in COVID-19 RA patients; (**b**) Risk of dying from COVID-19 in RA patients

Table 2 The results of the meta-analysis. Note: $^{**}p < 0.01$, $^{\triangle}p > 0.05$.ICU: intensive care unit

	NO. of included studies	Heterogeneity		Model	Results of meta-analysis		
		I^2(%)	*p*-value		Pooled rate or OR(95%CI)	*p*-value	Z
Prevalence of COVID-19 in RA patients	36	99.96	0.00	random	0.11 (0.06–0.17)	0.00**	7.12
The risk of COVID-19 in RA patients	12	63.3	0.002	random	1.045 (0.969, 1.122)	0.006**	2.76
Severe COVID-19 in RA patients	11	97.79	0.00	random	0.18(0.11–0.26)	0.00**	8.02
The risk of severe COVID-19 in RA patients	8	98.3	0.000	random	1.354 (1.002, 1.706)	0.135$^{\triangle}$	1.49
COVID-19-related hospitalization in RA patients	14	99.61	0.00	random	0.29(0.20–0.39)	0.00**	9.52
The risk of COVID-19-related hospitalization in RA patients	13	94.6	0.000	random	1.319 (1.055, 1.584)	0.006**	2.74
COVID-19-related admission to ICU in RA patients	7	99.23	0.00	random	0.10(0.05–0.16)	0.00**	5.83
The risk of COVID-19-related admission to ICU in RA patients	5	81.1	0.000	random	1.498 (1.145, 1.850)	0.002**	3.06
COVID-19 mortality in RA patients	16	97.48	0.00	random	0.08(0.05–0.11)	0.00**	9.20
The risk of dying from COVID-19 in RA patients	13	81.7	0.00	random	1.377 (1.168, 1.587)	0.001**	3.31

Table 3 Results of Begg's test and Egger's test. Note: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{\triangle}p > 0.05$. ICU: intensive care unit

	NO. of included studies	Begg's test		Egger's test		
		z	*p*	t	*p*	
Prevalence of COVID-19 in RA patients	36	3.43	0.001**	0.38	0.705$^{\triangle}$	
The risk of COVID-19 in RA patients	12	0.21	0.837$^{\triangle}$	-0.05	0.962$^{\triangle}$	
Severe COVID-19 in RA patients	11	0.31	0.755$^{\triangle}$	2.97	0.016*	
The risk of severe COVID-19 in RA patients		8	-0.12	1.000$^{\triangle}$	0.02	0.985$^{\triangle}$
COVID-19-related hospitalization in RA patients	14	0.44	0.661$^{\triangle}$	0.97	0.353$^{\triangle}$	
The risk of COVID-19-related hospitalization in RA patients	13	1.40	0.161$^{\triangle}$	0.24	0.818$^{\triangle}$	
COVID-19-related admission to ICU in RA patients	7	0.00	1.000$^{\triangle}$	1.76	0.139$^{\triangle}$	
The risk of COVID-19-related admission to ICU in RA patients	5	0.73	0.462$^{\triangle}$	1.39	0.258$^{\triangle}$	
COVID-19 mortality in RA patients	16	0.77	0.444$^{\triangle}$	1.63	0.125$^{\triangle}$	
The risk of dying from COVID-19 in RA patients	13	-0.06	1.000$^{\triangle}$	1.12	0.288$^{\triangle}$	

reported that patients with rheumatoid arthritis have an increased risk of severe COVID-19 [44, 60, 70, 80]. In contrast, other studies have suggested that COVID-19 severity is not associated with rheumatoid arthritis [25, 51, 55]. Overall, the pooled results indicated that rheumatoid arthritis was not a risk factor for severe COVID-19. This discrepancy underscores the need for standardized severity definitions and more data to clarify these findings.

The hospitalization and ICU admission rates for COVID-19 in rheumatoid arthritis patients were notably high, at 29% and 13%, respectively. Similarly, the pooled mortality rate of 9% among rheumatoid arthritis patients due to COVID-19 starkly contrasted with the global mortality rate of approximately 1% (roughly calculated according to data provided on the WHO website)[1]. In addition, rheumatoid arthritis patients might be more likely to be hospitalized due to COVID-19, and a similar trend was observed in terms of the risk of ICU admission for COVID-19. Moreover, compared with control patients, rheumatoid arthritis patients had a greater risk of dying from COVID-19. These outcomes suggest that compared with the general population, rheumatoid arthritis patients are more likely to experience severe COVID-19 and have worse clinical outcomes.

Figueroa et al. reported that rheumatoid arthritis with interstitial lung disease might be a substantial contributor to severe COVID-19 in patients with rheumatoid arthritis [60]. A study conducted by Gomides et al. demonstrated that heart disease and the use of glucocorticoids were associated with a greater number of hospital admissions for COVID-19 in patients with rheumatoid arthritis [61]. Singh et al. reported that rituximab was associated with hospitalization and ICU admission for COVID-19 in patients with rheumatoid arthritis [79]. Similarly, Tsai et al. reported that patients with rheumatoid arthritis caused by the use of Janus-associated kinase inhibitors (JAKis) had a significant risk for hospitalization, mortality or composite adverse outcomes, especially mortality, among those without COVID-19 vaccination [81]. In addition, advanced age, comorbid conditions (such as hypertension and diabetes), and a history of previous serious infections might be associated with a more severe COVID-19 disease course [73, 79, 84, 85, 89]. Some treatment options for rheumatoid arthritis might contribute to severe COVID-19 outcomes in patients with rheumatoid arthritis. However, compared with the comparator cohort, patients with rheumatoid arthritis were at a greater risk of severe or critical COVID-19, while non-TNFi biologics and systemic therapies did not further increase the risk [58]. These results might guide

the development or modification of treatment plans for rheumatoid arthritis patients infected with SARS-CoV-2 or other similar viruses [83].

Potential biases in the review process

There was a significant level of heterogeneity observed in the pooled analysis of all outcomes, such as the prevalence of COVID-19, the risk of severe COVID-19, the prevalence and the risk of COVID-19-related hospitalization, the prevalence of admission to the ICU due to COVID-19 and the risk of admission to the ICU due to COVID-19, and the mortality and the risk of death from COVID-19, except for the risk of COVID-19 and the prevalence of severe COVID-19. Heterogeneity might stem from varying follow-up durations, disparate pandemic control measures, and regional differences in healthcare protocols. Subgroup analyses were not conducted due to insufficient data granularity. In addition, different treatments for rheumatoid arthritis and disease activity might also result in heterogeneity. However, publication bias was minimal, suggesting that the included studies were generally of high quality. Sensitivity analysis confirmed the robustness of our findings.

Limitations

Limitations include potential underreporting of data, especially from regions with limited resources. Variability in outbreak severity and control measures between countries also introduced inevitable heterogeneity. And due to the lack of relevant details, it was difficult to analyze some important points such as drug combination and disease activity in patients with RA. Additionally, the inclusion of single-center and small-scale studies might have influenced the overall results.

Conclusion

In conclusion, our meta-analysis revealed that compared with non- rheumatoid arthritis patients, rheumatoid arthritis patients are at greater risk of COVID-19 infection, hospitalization, ICU admission, and mortality. However, no significant association was found between rheumatoid arthritis and severe COVID-19. Future research should focus on standardizing severity definitions and assessing the impact of specific rheumatoid arthritis treatments on COVID-19 outcomes to optimize patient management strategies.

Abbreviations

COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	The Newcastle–Ottawa Scale
JAKis	Janus-associated kinase inhibitors

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

V.K.W.W and WY designed the study. JL, GJP, LXW, and LY collected the data. JL and GJP drafted the manuscript. V.K.W.W, and WY contributed to revise the manuscript. All authors reviewed the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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