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SARS-CoV-2 Reinfection Rate: A Systematic Review and Meta-analysis

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ABSTRACT

Backgrounds: Reinfection among COVID-19 patients is still a challenging issue in the medical literature. Therefore, the current meta-analysis was conducted to estimate the pooled incidence rate of reinfection among COVID-19 patients.

Materials & Methods: A comprehensive search was conducted in PubMed, Web of Science, and Scopus databases from July 1 to October 1, 2021. Original studies which estimated the incidence rate of COVID-19 reinfection were included. CASP (Critical Appraisal skills program) was used to assess the quality of studies. Data were analyzed by STATA statistical software Version 15 (StataCorp, College Station, TX, USA).

Findings: A total of 3803 articles were found, of which 16 articles remained after title, abstract, and full text screening. The minimum and maximum incidence rates of reinfection were 0.001 and 0.73%, respectively. The pooled estimated incidence rate of COVID-19 reinfection was 0.11% (95% confidence interval: 0.02-0.20, $p< .001$, $I^2 = 100.0$). The highest pooled estimated incidence rate of reinfection was observed in people <50 years old (0.14%) (95% CI: 0.001-0.34, $p<.001$, $I^2 = 100$). Regarding the time elapsed after the first infection, the highest reinfection rate occurred four months after the first infection (0.12%) (95% CI: 0.001-0.27, $p< .001$, $I^2 = 100$).

Conclusion: The incidence rate of reinfection among COVID-19 patients is expected to be high. However, it seems that the influence of factors including the age of patients and the time elapsed after the first infection must be considered.

Keywords: COVID-19, Reinfection, Treatment failure, Meta-analysis.

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Introduction

As a global public health threat [1], the SARS-COV-2 virus has affected health systems in many countries [2]. Most patients with this disease experience symptom including fever, cough, headache, diarrhea, sore throat, and fatigue, and some also experience loss of smell and taste, myalgia, or arthralgia [3]. The transmission rate of the disease could be reduced by increasing the information about the characteristics of the virus and the epidemiological characteristics of the disease. Avoiding being in crowded and unventilated places, observing hand hygiene, and using a face mask could prevent the disease transmission [4-6]. An important question that is raised here is whether infected people could get this disease again or not [7]. Reinfection means that the infected person recovers but then becomes infected again [8]. Immune responses against SARS-COV-2 have been discussed in some studies [9, 10]. The results of these studies indicate that people are protected against SARS-COV-2 after being infected by the virus [10]. Also, mutations in the virus genome may make it resistant to treatment and vaccination [11]. On the other hand, studies have showed that some patients may be still infected with the SARS-COV-2 virus without any obvious clinical symptoms after being discharged from the hospital [12]. The incidence rate of reinfection varies from less than 0.5% to more than 5% [13]. However, the cost of treating reinfection and rehospitalization is significant [14].

Objectives: Therefore, the current meta-analysis was

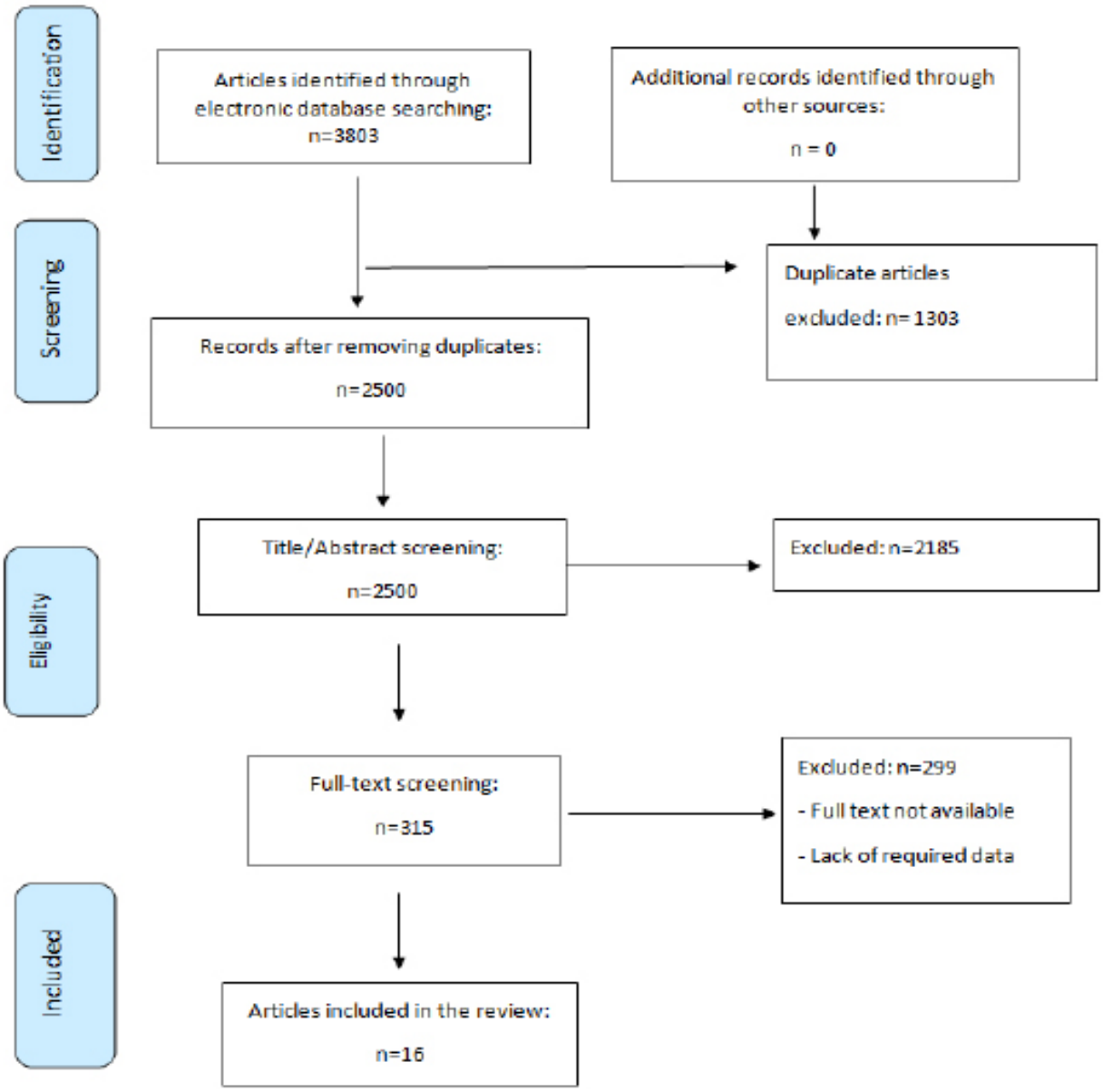

Figure 1) PRISMA 2009 flow diagram of the studies included in the current systematic review

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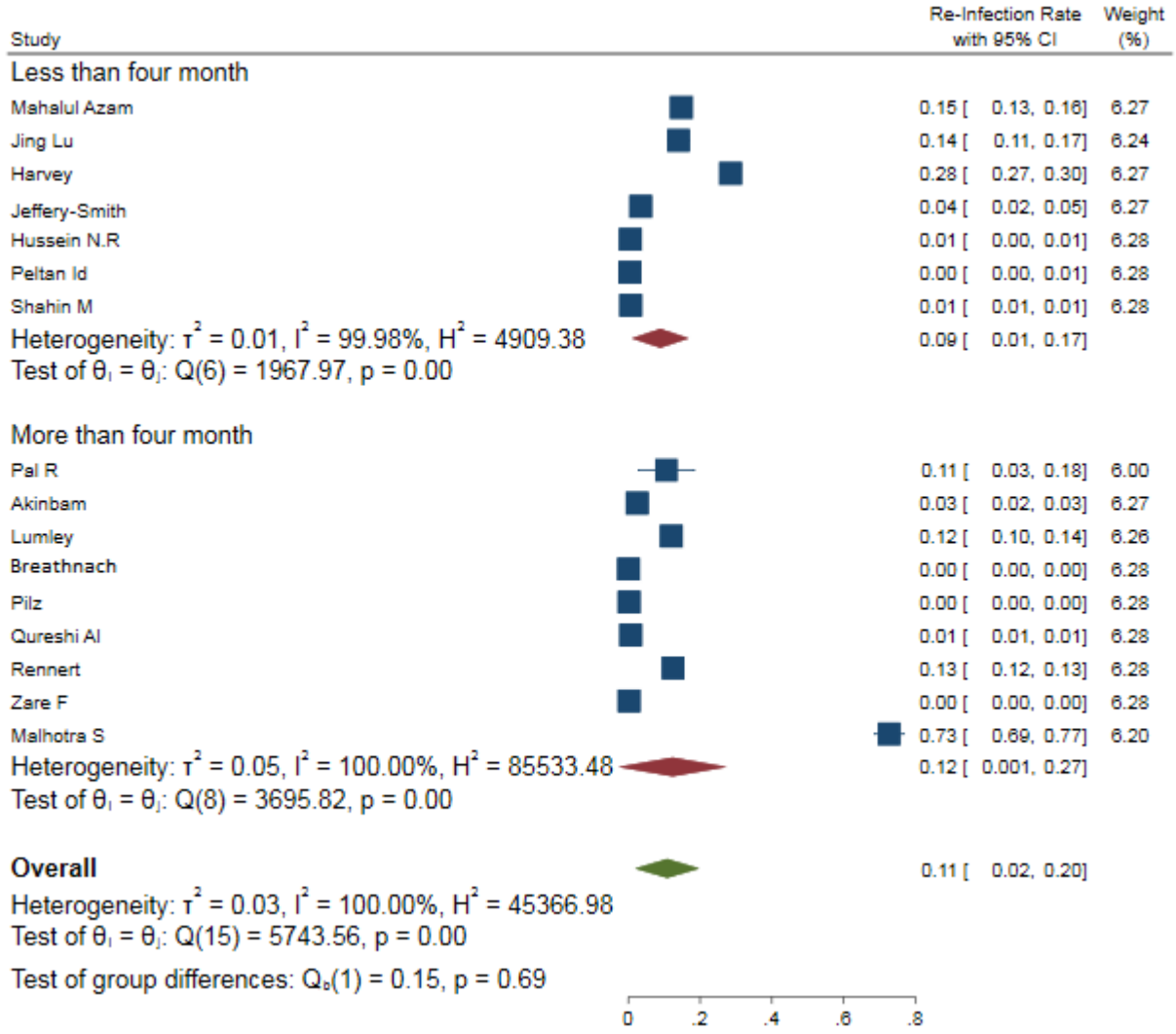

Figure 2) Forest plot for the pooled estimation of COVID-19 reinfection rate by the time elapsed after the first infection

conducted to estimate the pooled incidence rate of reinfection among COVID-19 patients.

Materials and Methods

Search strategy: This systematic review and meta-analyses was conducted to examine the available English-language literature on the incidence rate of COVID-19 reinfection according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines (2009).

The incidence rate of COVID-19 reinfection was determined through a comprehensive search (July 1 to October 1, 2021) in PubMed, Web of Science, and Scopus databases. The following search terms were used in this review: "reinfect*", "recurr*", "relaps*", "recurrence" [Mesh], "reactivation", "recrudescenc*", "flare" & "up", "protective immunity", "postinfection immunity", "herd immunity", OR "postinfection" AND "coronavirus" [Mesh], "ncov", "covid19", "sars-cov*", "sarscov2", "2019-nCoV", "SARS-CoV", "2019 coronavirus", "2019 corona virus", "novel corona virus", "new corona virus", "2019 corona virus", "novel coronavirus", "new coronavirus", OR "2019 coronavirus".

Study selection and data extraction: All original papers published on the incidence rate of COVID-19 reinfection were included. Also, non-original papers (including case reports, case series, reviews, and letters to the editor) were excluded. Studies were entered into Endnote software for the screening process. After removing duplicate articles, the titles of the remaining studies were checked, and unrelated studies were excluded. In the second step, the abstracts of all studies were screened, and those that met the inclusion criteria entered the full-text review step. Two authors independently screened the final full texts, and in cases of disagreement, a third author was consulted. The extracted data included: the first author's last name, study year, country, sample size, gender, and reinfection rate.

Risk of bias assessment: The CASP (Critical

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Appraisal skills program) checklist was used to assess the risk of bias. Two authors performed quality assessments independently. The third author was involved in cases of disagreement.

Statistical analysis: Cochran's Q test with a significance level of $p< .1$ and I^2 statistic with values >75% were assessed to check the heterogeneity between different studies. To fix high heterogeneity (I^2 =99.7% and $p< .001$), the random-effects meta-analysis model was used to estimate pooled reinfection incidence rate. Data were analyzed by STATA statistical software Version 15 (StataCorp, College Station, TX, USA).

Findings

A total of 3803 records were retrieved through searching the electronic databases PubMed, Scopus, and Web of Science; potentially relevant articles were identified after removing 1303 duplicate articles. In the second step, 2185 articles were excluded after screening their titles and abstracts for inclusion and exclusion criteria. Of the remaining 315 records, 299 were excluded due to lack of relevant data or because they were not original articles. Finally, 16 papers that reported the incidence rate of COVID-19 reinfection were included in the final analysis (Figure 1).

The overall pooled estimated incidence rate of COVID-19 reinfection was 0.11% (95% confidence interval: 0.02-0.20, $p< .001$, I^2= 100.0). The minimum and maximum incidence rates of reinfection were reported as 0.001 and 0.73%, respectively (Table 1). Regarding the time elapsed after the first infection, the highest reinfection rate occurred four months after the first infection (0.12%) (95% CI: 0.001-0.27, $p< .001$, I^2= 100) (Fig. 2). The highest pooled estimated incidence rate of COVID-19 reinfection was observed in people <50 years old (0.14%) (95% CI: 0.001-0.34, $p< .001$, I^2= 100) (Fig. 3).

Meta-regression: To recognize the effect of factors on heterogeneity, the sample size and the mean age of participants were entered into a meta-regression

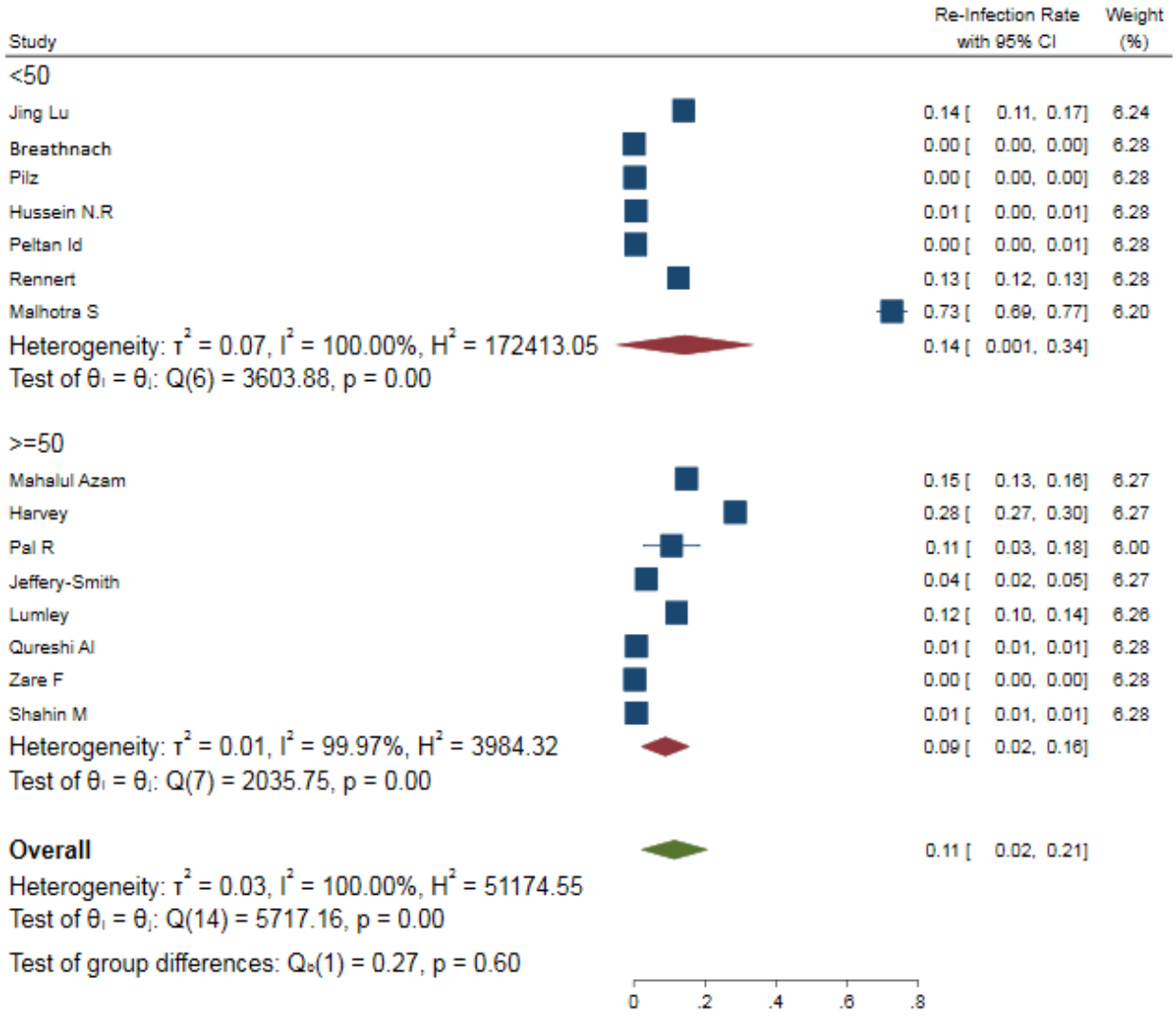

Figure 3) Forest plot for the pooled estimation of COVID-19 reinfection rate by age groups

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Table 1) Included studies in the current meta-analysis

First Author	Year	Country	Sample Size	Gender	Recurrence Rate(%)
Azam M. [15]	2020	China	2568	Both	0.148
Lu J. [16]	2020	China	619	Both	0.14
Harvey RA. [17]	2020	United States	3786	Both	0.285
Pal R. [18]	2020	India	61	Both	0.106
Akinbami LJ. [19]	2020	USA	1418	Both	0.025
Jeffery-Smith A. [20]	2021	United Kingdom	656	Both	0.035
Lumley S. [21]	2021	United Kingdom	1177	Both	0.12
Breathnach AS. [22]	2021	UK	10727	Both	0.0007
Pilz S. [23]	2021	Austria	14840	Both	0.0025
Hussein NR. [24]	2021	Duhok(Kurdistan)	5609	Both	0.006
Peltan ID. [25]	2021	USA	23176	Both	0.0049
Qureshi Al [26]	2021	USA	9119	Both	0.007
Rennert L. [27]	2021	USA	16101	Both	0.125
Zare F. [28]	2021	Iran	4039	Both	0.0025
Sheehan MM. [29]	2021	Turkey	8845	Both	0.007
Malhotra S. [30]	2022	India	472	Both	0.726

model assessed. The effect of the mentioned factors on heterogeneity between studies was not statistically significant (age: p= 0.26, and sample size: p= .06). **Publication bias**: According to Begg's and Egger's tests, there was a significant publication bias (p= .002).

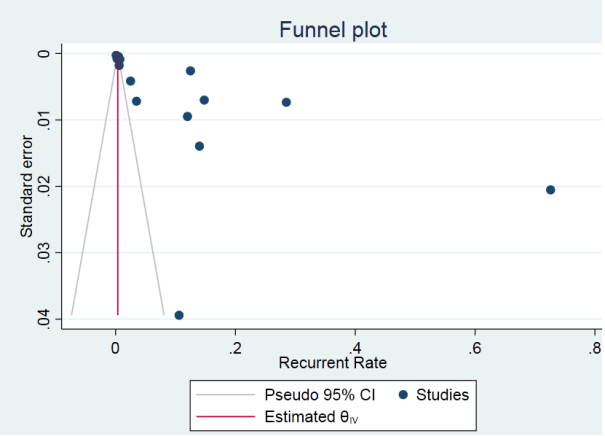

Figure 4) Funnel plot of COVID-19 reinfection rate

Discussion

The COVID-19 pandemic has spread around the world, and more and more people are getting the disease every day. Also, the rate of recovery from this disease is high [31]. Awareness of individuals about the potential risk of reinfection is important to prevent the transmission of SARS-CoV-2 and ultimately control the epidemic [32]. In the current systematic review and meta-analysis, the incidence rate of COVID-19 reinfection was estimated before the emergence of O-micron variant (November 24, 2021) [33]. SARS-CoV-2 could reduce T cells [34] and also increase IL-6 levels significantly [35]. Decreased cellular immune response may lead to reinfection. Reinfection with the SARS-CoV-2 virus may have two main reasons: 1) reinfection with the same virus strain due to the decline in immunity over time or the failure of acquired immunity [36] and 2) viral mutations [37]. Some factors may affect the reinfection rate. For example, patients who were initially infected by the ancestral SARS-CoV-2 were not tested for antibodies and were not hospitalized [38]. Thus, the accurate identification of reinfected cases may not be achieved simply. Furthermore, the incidence rate of reinfection is expected to be overestimated due to false-positive results [38]. Thus, the incidence rate of reinfection in some of the included studies might have been overestimated.

The present study results indicated a relatively low incidence rate of COVID-19 reinfection in the general population (0.11%) (95% CI: 0.02-0.20). In a study by Sotoodeh et al. (2022), the incidence rate of reinfection in COVID-19 patients was 3 per thousand pa-

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tients [4]. A meta-analysis of 30,000 previous studies found no reports of clinical reinfection after a 70-day period from the initial infection [39]. In another study by Ren et al. (2021), a 12% repositivity rate was reported [40]. Chivese et al. (2022) showed that the prevalence of reinfection was 0.2% [41]. Piri et al. (2021) reported a reinfection rate of 4.21% [42]. Murillo et al. (2021) reported a risk of 0.26% for reinfection in Mexico [43]. In a study by Rasine et al. (2022), the estimated incidence rate of reinfection was 3.3 per 100 people per year [44]. Gallais et al. (2021) reported a reinfection rate of 0.4 per 100 people per year [45]. The incidence rate of reinfection in a study by Lumley et al. (2021) was reported as 0.47 per 100 people per year [21]. Abu-Raddad et al. (2021) in Qatar reported a reinfection rate of 0.36 per 10 000 person-weeks [46]. Hansen et al. (2021) reported a recurrence rate of 2 per 100 people per year [47]. The incidence rate of reinfection observed in the current meta-analysis was low compared to those reported in previous studies. This discrepancy in the incidence rate of reinfection could be explained by the difference in follow-up time in these studies.

There was a lack of agreement in the definition of reinfection, and different definitions were presented in the included studies for COVID-19 reinfection. For example, reinfection was described in some studies as continual viral shedding and in others as re-positivity of COVID-19 PCR test 27 days after a negative test [48]. The highest estimated incidence rate of COVID-19 reinfection was observed in people <50 years old. It has been reported that patients who experience relapse after hospital discharge are mostly elderly patients with comorbidities. Factors such as age, diminished immune function, structural lung disease, and pulmonary fibrosis may affect the risk of reinfection [49].

Some limitations must be considered. First, there was a possibility of overestimating the incidence rate of reinfection due to the lack of a gold standard for confirmation in the included studies. Second, detailed clinical information was not available in most of the included studies, specifically immunity features. Finally, subgroup analyses based on disease severity, vaccination status, definition of reinfection, comorbidities, and gender could not be done due to the lack of required data.

Conclusion

Based on this study results, the possibility of reinfection after recovery is not unexpected. The current study showed that there is a possibility of COVID-19 reinfection. Therefore, public health measures, including vaccination, must be emphasized to contain the pandemic. Factors that are related to the risk of reinfection have not yet been well recognized; therefore, more studies are needed to understand the factors influencing the incidence of COVID-19 reinfection by considering different factors such as vaccination status, disease severity, definition of reinfection, comorbidities, and gender.

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Authors' contributions: YA and MS formulated the research questions, designed the study, developed the preliminary search strategy, conducted the quality assessment, methodology, and formal analysis, prepared drafts of the manuscript, and reviewed and edited the manuscript. KB and KA refined the search strategy by conducting iterative database queries and incorporating new search terms, searched and collected the articles, and reviewed the manuscript content. All authors reviewed and approved the final version of the manuscript.

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