SYSTEMATIC REVIEW

Clinical and epidemiological features of patients with COVID-19 reinfection: a systematic review

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Abstract

Recurrent positivity in a patient with COVID-19 may be due to various reasons, not necessarily reinfection. There is concern about the occurrence frequency of reinfection. Five databases and a preprint/preprint repository were searched. All case reports, case series, and observational studies were included. Bias was assessed for each study with the Newcastle-Ottawa Scale tool and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA-2020). After eligibility, 77 studies were included for qualitative synthesis (52 case reports, 21 case series, and four case-controls; 1131 patients included). Of these, 16 studies described a second contact with the SARS-CoV-2 positive case, five studies described healthcare profession-related infection, ten studies described that the source of reinfection was likely to be from the community, one study described travel-related infection, nine studies described vulnerability-related infection due to comorbidity. The mean number of days from discharge or negative test to reinfection ranged from 23.3 to 57.6 days across the different included studies. The risk of bias for all case report/series studies was moderate/high. For observational studies, the risk of bias was low. Reinfection of patients with COVID-19 occurs between the first and second month after the first infection, but beyond, and 90 days have been proposed as a point to begin to consider it. The main factor for reinfection is contact with COVID-19 positive cases.
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Introduction

Approximately 18 months ago, the world witnessed the beginning of one of the worst pandemics that contemporary humanity has experienced; it is the Coronavirus Disease 2019 (COVID-19), which began as an outbreak of atypical pneumonia at the end of December 2019 in the city of Wuhan, China [1]. After a few days, it was confirmed to be a new coronavirus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

A few weeks after the outbreak, cases were reported outside China's borders, which is why the World Health Organization (WHO) declared this new respiratory disease a global health emergency [3]. On March 11, 2020, it officially declared a pandemic [4]. After this declaration, various strategies were implemented in the different countries of the world to stop the spread of the disease, such as closing borders, quarantining regions or entire countries, closing companies, schools, and universities; however, despite all this, cases increased, and mortality was on the rise.

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Several countries expected to obtain herd immunity due to the increase in cases; however, this was not achieved [5]. In the meantime, different institutions and companies around the world began a race in the development of vaccines as another measure to stop the spread of COVID-19; some were able to successfully pass phase 3 with efficacies above 50% as the cut-off point established by the CDC, and commercialization began [6]. Many countries have started vaccinations, protecting first their health professionals, following with vulnerable populations such as the elderly or people with chronic comorbidities; although in most countries, this is very slow due to accessibility issues.

Regarding the possibility of reinfection with SARS-CoV-2 and developing COVID-19 disease again, there are worrying reports of cases of reinfection, i.e., people who have tested positive again in molecular or antigenic tests for the virus up to seven months after discharge, ranging from mild to severe cases [7]. It should be noted that reinfection or relapse of COVID-19 disease is not a common entity and should be studied in greater depth [8]; these reinfected patients should be followed up for a more extended period, and the clinical, epidemiological profile should be studied, as well as genetic sequencing of the virus to determine the presence of any variant [9,10]. The objective of this systematic review was to evaluate the clinical and epidemiological characteristics in patients with COVID-19 reinfection.

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020, *Supplement table*) [11]. The PROSPERO registry is CRD42021231573. The study evaluated the clinical and epidemiological features in patients with reinfection of COVID-19.

Data sources

We searched PubMed, Scopus, Web of Science, Ovid-Medline, Embase, and a preprints/preproofs repository ("https://www.medrxiv.org"). Some studies were also identified through a manual Google search. We performed a search strategy that can be found in the Supplementary table. No restriction was applied to the language. Searches only included documents published from inception to May 19, 2022. Primary search terms were "reinfection", "reinfection drug", "COVID-19".

Eligibility criteria

We included all the case report, case series, and observational studies. Systematic reviews, narrative reviews, conference proceedings, editorials, and letters to the editor without original data were excluded. The population will be patients with mild, moderate or severe COVID-19, independently of the associated comorbidities before the first infection. The main risk factor identified among the studies is reinfection by COVID-19, or recurrence regardless of the time after the first infection.

Outcomes

The outcomes were the severity of the second infection of COVID-19 (reinfection) or recurrence and the number of days until reinfection by COVID-19.

Study selection

According to the inclusion and exclusion criteria, two authors (FE, LP) independently screened search results by title and abstract using the web program rayyan (rayyan-qcri.org). Relevant studies were selected and searched by full text for the next phase of assessment. Discrepancies were consulted with another author (JB), and a consensus was reached. The selection of articles in each stage of the review process was made using Microsoft Excel®.

Data extraction

Two authors (CJ, MH) independently extracted the data using pre-piloted Excel spreadsheets. Again, discrepancies were consulted with another author (JB). The data extracted from each study were: author, year, country, type of research, number of patients, age, gender, type of patients (pre-infection and post-infection comorbidities), risk factors (exposure), the severity of first infection o symptoms during reinfection.

Risk of bias assessment

Two authors evaluated the risk of bias independently. Cohorts and case-control were assessed with the Newcastle–Ottawa scale. We used the modified Newcastle–Ottawa scale (NOS) tool [12]. For case report/series, the studies were evaluated with methodological quality assessment tools and synthesis of case series and case reports [13]. Again, discrepancies were consulted with another author (JB).

Ethical considerations

This is a systematic review of published and available information in which no human subjects participated. Thus, no ethics committee approval was required.

Results

Selection of studies

The search yielded 1400 results. After duplicates were excluded, 869 titles and abstracts were reviewed, of which 730

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were excluded, and 139 scientific papers were evaluated in detail. Finally, 77 studies were included for the qualitative synthesis [14–50, 51–91] (Fig. 1).

Characteristics of the studies included

Of the included studies in this systematic review, 52 studies were case report, 21 studies were case series, and four studies were case-control studies. The studies were grouped by risk factor or reason for infection. Of these, 16 studies that described a second contact with SARS-CoV-2 positive case reported a total of 165 reinfected patients with COVID-19 and five patients with recurrence of COVID-19. The mean of days after discharge or test-negative until reinfection was 56.1 (SD 53.5). These studies reported asymptomatic and mild to moderate severity of COVID-19 reinfection. Likewise, five studies that described infection related to the health profession reported a total of 11 reinfected patients with COVID-19 and two with recurrence of COVID-19. The mean of days after discharge or test negative until reinfection was 57.6 (SD 58.7). These studies reported mild to moderate severity of COVID-19 reinfection.

On the other hand, ten studies described that the source of reinfection was likely from the community and reported 107 reinfected patients with COVID-19 and 103 with recurrence of COVID-19. The mean of days after discharge or test negative until reinfection was 28.7 (SD 27.1). These studies reported mild to severe cases of COVID-19 reinfection.

Likewise, one study described travel-related infection and reported only one reinfected patient with COVID-19. The mean of days after discharge or test negative until reinfection was 102 days.

Finally, nine studies described infection related to the vulnerability due to comorbidity and reported 17 reinfected patients with COVID-19 and 423 with recurrence of COVID-19. The mean of days after discharge or test negative until reinfection was 23.3 (SD 45.8). These studies reported mild to severe cases of COVID-19 reinfection.

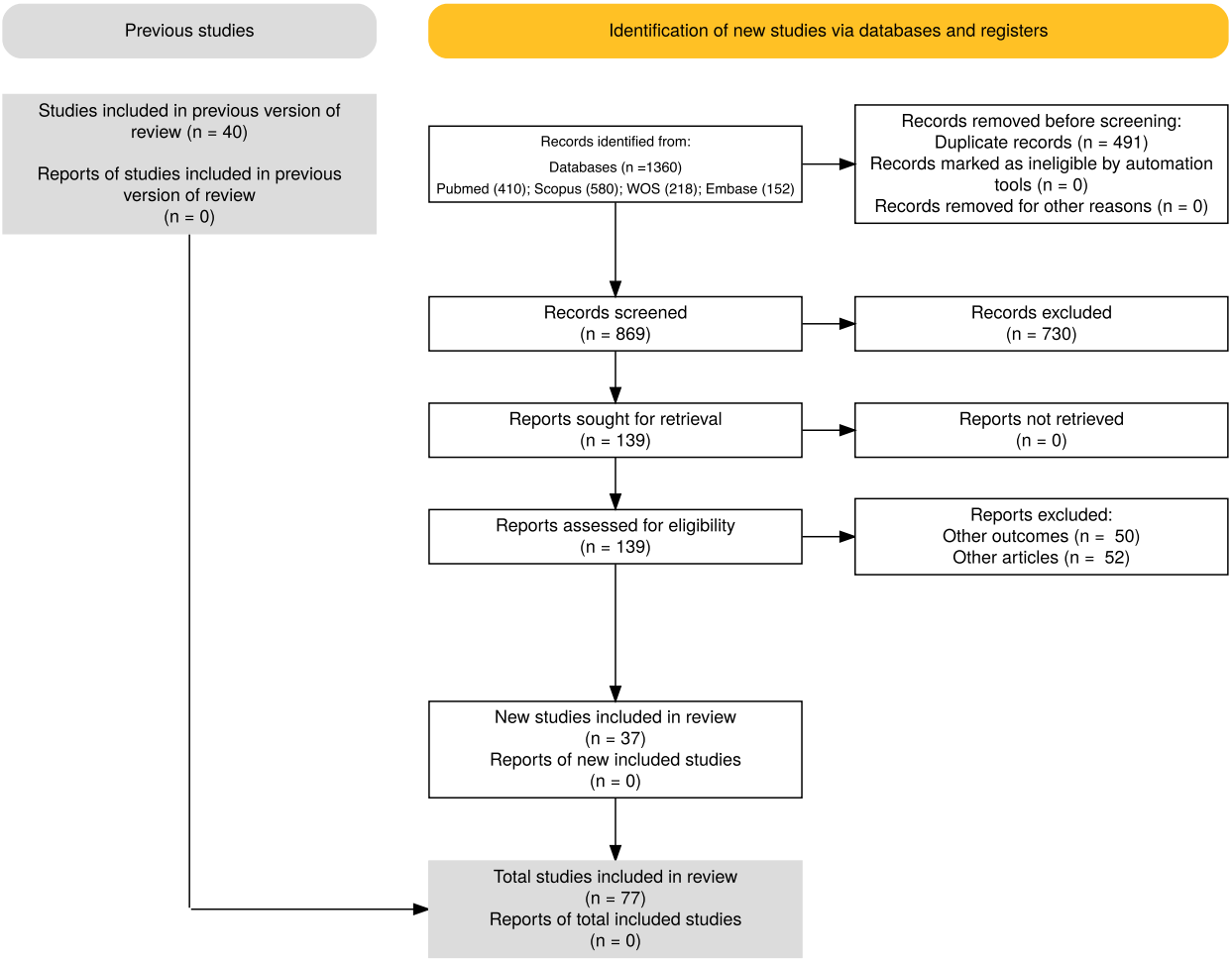


FIG. 1. Flow-chart of the study selection process.

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Finally, 36 studies did not report the risk factor or reason for reinfection and reported 87 reinfected patients with COVID-19 and 598 with recurrence of COVID-19. The mean of days after discharge or test negative until reinfection was 39.8 (SD 63.4). These studies reported asymptomatic, mild to severe cases of COVID-19 reinfection.

Assessment of risk of bias

All the case-control design studies had a low risk of bias with the Newcastle Ottawa Scale assessment. Case report and case series studies were not assessed with the risk of the bias assessment tool.

Discussion

Main findings

Our study found that patients with COVID-19 reinfection were in many risk groups, as a second contact with SARS-Cov-2, related to health profession, reinfection likely from the community, travel-related infection, and vulnerability due to comorbidity.

Reinfection and recurrence of disease by COVID-19

The human body has innate and adaptive immunity. When any viral infection occurs, IgM antibodies usually appear within one to two weeks [92]. These antibodies are then mobilized against the virus and then slowly begin to disappear. A few weeks after the infection has disappeared, IgG antibodies appear. SARS-CoV-2 positive patients begin to have detectable antibodies 10 to 14 days after the onset of symptoms, although antibody levels in patients with mild disease may be low or undetectable [93].

Protective, sustainable, and long-lasting immunity following COVID-19 infection is uncertain, and the possible associated mechanisms are not yet fully understood [94]. The immune response to COVID-19 may be variable and patient-specific regarding antibody development and persistence of antibodies in serum over time [95]. To consider the net protective effect of antibodies against reinfection, the evidence is still inadequate, and further research is warranted to clarify the interplay between the roles of adaptive and innate immunity. Immunosuppressive factors, such as drugs or pathological conditions, may hinder viral clearance and be associated with SARS-CoV-2 reactivation [96].

Inadequate immune response coupled with an inflammatory process could explain the recurrence of clinical symptoms. However, in some patients, viral RNA has been detected during the second episode, which allows us to understand the theory of reinfection or rebound virus replication [97]. Recurrences of COVID-19 must be differentiated from the persistence of viral RNA remnants that can be detected in respiratory samples up to 6 weeks after symptom onset in clinically cured patients [58].

The SARS-CoV-2 reinfection was first confirmed in August 2020 in Hong Kong by genetic sequencing of two samples collected by nasal swab from the same patient with a time difference of 142 days [92]. It was evident that the viral genomes belong to different lineages, one of which was more incident between March and April 2020, while the other is close to the strains found today [17]. Several causes have now been described for SARS-CoV-2 testing in COVID-19 patients to become positive again during the recovery period, including false RT-PCR results, intermittent viral shedding, viral reactivation or reinfection with another strain of SARS-CoV-2, or exposure to a contaminated environmental surface after discharge [98]. However, there is some possibility of false-negative RT-PCR results before patients are discharged.

In the recurrence of SARS-CoV-2, the transmission capacity depends on the cause of the re-positivity test. In addition, the replication capacity of the virus decreases when the amount of viral genetic material in the epithelial cell is low. Theoretically, if the patient is reinfected or if the virus reactivates, these patients are a potential source of transmission [49]. However, results of re-positivity testing among discharged patients have only been performed by PCR on different specimens. The RT-PCR test cannot distinguish between live and dead virus. To date, no cases of infection have been reported among persons who were in contact with repositive patients.

It is currently unclear whether the reappearance of SARS-CoV-2 RNA among COVID-19 patients after discharge could be contagious. Genetic traces of the virus detected by RT-PCR do not correlate with the transmission. However, if repositive patients are indeed carriers of live virus, they could become a potential new source of infection for others. Therefore, it is necessary to monitor the patient after discharge to prevent the spread of the pandemic. Since no treatment against SARS-CoV-2 has yet been approved and no specific vaccine is available, quarantine and prevention of infection in the community are crucial to controlling its spread [99].

Risk factors to reinfection and recurrence of disease by COVID-19

Regarding the second contact with SARS-CoV-2, the risk, in general, has been estimated to be of low risk. Likewise, related to the health profession, currently under high coverage for vaccination will be of low risk. Nevertheless, in the past, and among the first case reports, healthcare workers presented reinfection (e.g. India). In the same way, reinfection likely

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occurs from community transmission. Another risk factor is the travel-related infection, which currently, with regional variants circulation may pose a different risky exposure. Finally, related to the vulnerability due to comorbidities, some studies show that uncomplete vaccine schedules at those patients may pose a risk for infection but is less clear for reinfection.

Regarding to the time between reinfection, the study of Sootodeh et al. [100], referred that there are two times for epidemiological and clinical assessment of suspected reinfection cases [1]: persons with at least one detection of SARS- Cov-2 RNA test, more than 90 days after the first detection of SARS- Cov-2 RNA, whether or not symptoms were present, and [2] persons with COVID-19-like symptoms and detection of SARS-Cov-2 RNA between 45 and 89 days since first SARS-Cov-2 infection, with evidence of close-contacts with a confirmed case and without evidence of another cause of infections. This systematic review included only 25 studies and only 15 studies found reinfection.

Limitations

Still, the number of observational studies is limited. Most of the reports of reinfection consist of case series and case reports, then is still challenging to meta-analyze the prevalence of reinfection from observational studies.

Conclusions

Reinfection of patients with COVID-19 occurs between the first and second month after the first infection. The main factor for reinfection is contact with COVID-19 positive cases. However, some guidelines have provided a point of 90 days and beyond to suspect reinfection, whilst before as possible persistent infection. Further studies are required.

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Conflicts of interest disclosure

No author has a conflict of interest.

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Disclosure statement

Authors declare that they have no conflict of interest.

Patient consent

No patient consent was required for the conduct of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2022.101021.

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