International Journal of
Immunopathology
& Pharmacology

Original Research Article

International Journal of
Immunopathology and Pharmacology
Volume 35: 1–7

DOI: 10.1177/20587384211027679
journals.sagepub.com/home/iji
SAGE

Clinical features and corresponding immune function status of recurrent viral polymerase chain reaction positivity in patients with COVID-19 : A meta- analysis and systematic review

Xingxiang Ren*, Xiankun Wang*, Ziruo Ge, Shuping Cui and Zhihai Chen

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) was declared a global pandemic in March 2020. Since then, several studies have found COVID-19 patients with recurrent viral polymerase chain reaction (PCR) positivity.

Methods: On May 6, 2021, an exhaustive literature search of the Web of Science, PubMed, Cochrane Library, Chinese National Knowledge Infrastructure databases, Embase, Wan Fang Data, VIP database, Sinomed database, BioRxiv, MedRxiv, and Research Square was conducted to find describing the laboratory indicators of recurrent and non-recurrent viral PCR positivity in patients with COVID-19. The data were statistically analyzed using STATA version 15.0.

Results: In total, 22 studies—comprising 5154 laboratory-confirmed COVID-19 cases—were included in the analyses. Patients with less severe COVID-19 illness (i.e. those clinically classified as mild or common-type) seemed to exhibit recurrent PCR positivity more commonly than patients with more severe illness (i.e. those classified as severe or critical). There were also significant differences between the two groups in terms of the rates of headaches and dizziness, in addition to the levels of aspartate aminotransferase, C reactive protein, interleukin-6, and lactate dehydrogenase. Further, there were variations in the ratio of CD4+ T cells/CD8+ T cells on admission to the hospital.

Conclusion: In comparison to COVID-19 patients with non-recurrent viral PCR positivity, patients with recurrent virus PCR positivity seem to experience more severe immune function suppression upon hospital admission.

Keywords

clinical features, COVID-19, immune function status, meta-analysis, recurrent viral positivity

Date received: 19 January 2021; accepted: 27 May 2021

Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic in March 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the β-coronavirus genus.[1] Currently, in China, COVID-19 patients are discharged from the hospital for observation when they meet the following criteria: (1) normal body temperature for more than three days; (2) significant relief from respiratory symptoms; (3) lung imaging showing significant improvement in prior acute exudative lesions; and (4) two consecutive respiratory tract samples testing negative for virus nucleic acid

Center of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China

*These authors equally contributed to this work.

Corresponding author:
Zhihai Chen, Center of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, 8 Jingshun East Street, Chaoyang District, Beijing 100015, China.
Email: chenzhihai0001@126.com

(sampled at least 24 h apart).[2] In China, patients undergo regular retesting for virus nucleic acid after they are discharged from the hospital. As a result, several studies have found COVID-19 patients with recurrent viral polymerase chain reaction (PCR) positivity.[3] Gidari et al.[4] reported a series of COVID-19 patients with recurrent virus PCR positivity in Italy. The emergence of COVID-19 patients with recurrent virus PCR positivity poses a challenge to the prevention and control of the pandemic. Therefore, it is imperative to investigate the clinical features and corresponding immune function status of COVID-19 patients with recurrent virus PCR positivity.

Although there have been several studies on the clinical manifestations and laboratory test expressions of patients with recurrent virus PCR positivity, there is a lack of meta-analyses summarizing relevant data on patient immune function status. To this end, this study examines immune function status-related manifestations and laboratory indicators of COVID-19 patients with recurrent virus PCR positivity.

Methods

Search strategy and selection criteria

On May 6, 2021, a comprehensive literature search was conducted; the search included English databases such as Embase, Pubmed, Web of Science, and Cochrane Library; Chinese databases such as Wanfang Data, China National Knowledge Infrastructure Database, Traditional Chinese Medicine Database, and VIP Database; and preprinted platforms such as BioRxiv, MedRxiv, and Research Square. The keywords included "2019-nCoV infection," "2019 novel coronavirus disease," "COVID-19," "COVID-19 pandemic," "COVID-19 virus disease," "coronavirus disease 2019," "2019 novel coronavirus infection," "2019-nCoV disease," "coronavirus disease-19," "COVID-19 virus infection," "SARS-CoV-2 infection," "reactivation," "recurrent," and "relapse." A flow-chart of the literature review process is shown in Figure 1. The protocol for this research was registered on the PROSPERO platform (CRD42020206385).

Study selection and data extraction

The inclusion criteria for this meta-analysis were as follows: 1. the studied patients must meet one or more of the following diagnostic criteria: (1) COVID-19 RNA detected in the patients' specimens by PCR or (2) virus isolated from the patients' blood samples; (2) the study must be prospective or retrospective; (3) the study must be related to recurrent PCR positivity in COVID-19 patients; (4) laboratory data must be available for the recurrent and non-recurrent groups separately upon hospital admission. The exclusion criteria were as follows: (1) non-Chinese or non-English studies; (2) reviews; (3) studies with ambiguous definitions of COVID-19; (4) duplicate publications.

Two independent reviewers (Ren and Wang) reviewed the titles and abstracts of each retrieved study. If these studies satisfied the inclusion criteria, the two reviewers separately and independently read the entire text. The inclusion or exclusion of each study was determined through a discussion and consensus between the two reviewers; disagreements were resolved by a third investigator.

The following data were extracted from each article that met the inclusion criteria: sample size; general information on the patients, including sex, age, smoking history, epidemiological history, and complications; and clinical data, including initial symptoms, treatment time, vital signs, therapeutic drugs, and dosage.

Quality assessment

The quality of each included study was determined by referring to the Newcastle-Ottawa Scale (NOS).

Meta-analysis

The meta-analysis was performed using STATA version 15.0. I^2 analysis and the Q tests were used to evaluate the heterogeneity among the included studies. When $I^2 < 50\%$ and $p > 0.1$, it can be concluded that there is no statistical heterogeneity among the included studies, and a fixed-effect model can be used; if heterogeneity is present, a random-effect model should be used.

Results

Literature search, basic information, and quality assessments

The literature search revealed a total of 4833 related articles. After removal of duplicates and application of the inclusion and exclusion criteria, 22 articles[5–26] remained. The detailed process of study screening is shown in Figure 1. Basic information on all included

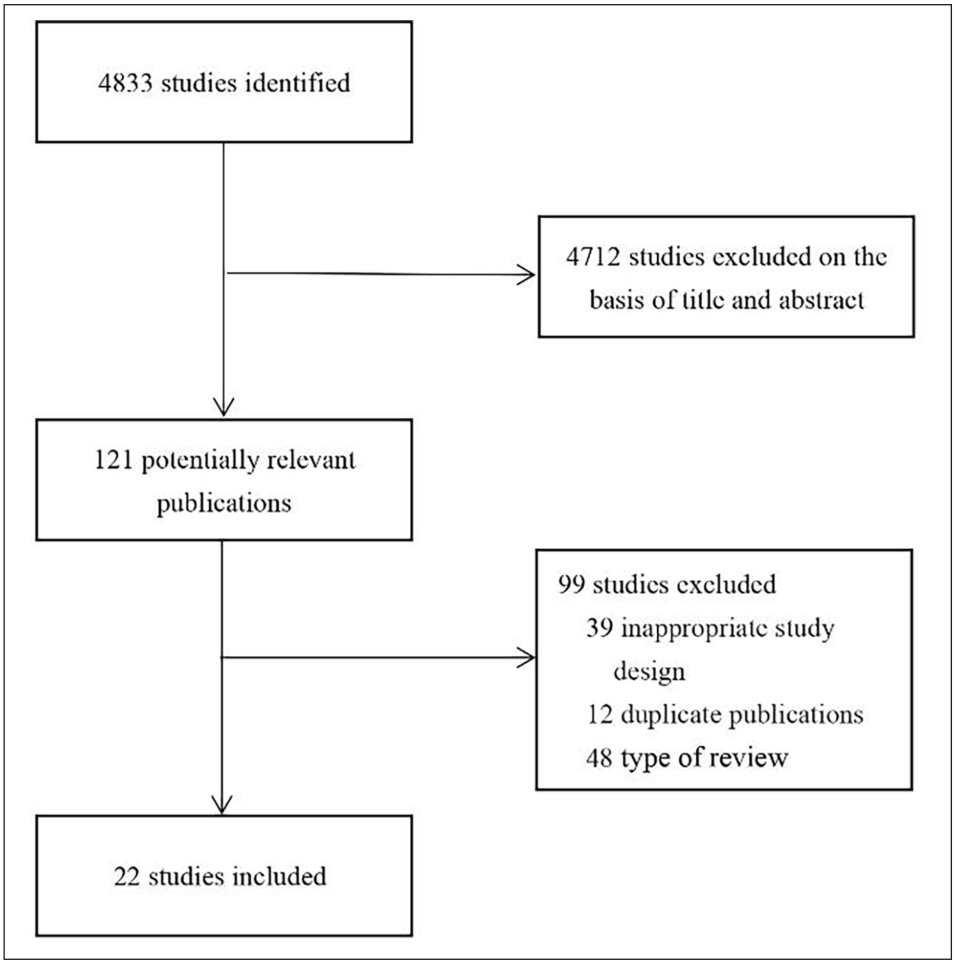

Figure 1. Flow diagram of the review process.

studies is provided in Table 1. Each study was rated according to the NOS scale, each of which scored over six stars. The star rating of each study, according to the NOS scale, is provided in Table 1.

Gender

A total of 22 studies were included to analyze the role of gender. The meta-analysis returned an odds ratio (OR) of 0.89 (95% CI: 0.74 to 1.07; $P = 0.228$), indicating no statistical difference in the distribution of gender between the recurrent or non-recurrent group (Supplemental Figure 1a). A funnel plot was then drawn, which was found to be fairly symmetrical (Supplemental Figure 1b).

Severity of illness

A total of six studies were included to analyze the role of the severity of the illness. The results revealed that the occurrence of recurrent PCR positivity in milder patients (clinically classified as mild or common-type illness) was 2.90 times higher than that of severe patients (clinically classified as severe or critical illness) (OR = 2.90, 95% CI: 1.54–5.46, $P = 0.001$) (Supplemental Figure 2).

Headache and dizziness symptoms

A total of five studies were included for the analysis of headache symptoms and two for the analysis of dizziness symptoms. The occurrence of headache symptoms in patients with recurrent PCR positivity was 2.52 times higher than that of patients with non-recurrent PCR positivity (OR = 2.52, 95% CI: 0.95–6.69; $P = 0.064$) (Supplemental Figure 3a). The occurrence of dizziness symptoms in patients with recurrent PCR positivity was 5.33 times higher than that of patients with non-recurrent PCR positivity (OR = 5.33, 95% CI: 1.46–19.55; $P = 0.009$) (Supplemental Figure 3b).

Table 1. Basic information and quality evaluation of previous research.

Author	Year	Type	Recurrent group	Non-recurrent group	NOS			
					Selection	Comparability	Outcome	Scores
Chen	2020	Case-control study	986	81	☆☆☆	☆☆	☆☆☆	8☆
Hui	2020	Case-control study	81	17	☆☆☆	☆☆	☆☆☆	8☆
Xiao	2020	Case-control study	40	29	☆☆☆	☆☆	☆☆	7☆
Zheng	2020	Cohort study	27	258	☆☆☆	☆☆	☆☆☆	8☆
Du	2020	Case-control study	3	123	☆☆☆	☆☆	☆☆☆	8☆
Yuan	2020	Cohort study	20	162	☆☆☆	☆☆	☆☆☆	8☆
Hu	2020	Case-control study	11	58	☆☆☆	☆☆	☆☆☆	8☆
Tong	2020	Case-control study	42	58	☆☆☆	☆☆	☆☆	7☆
Zhou	2020	Case-control study	6	27	☆☆☆	☆☆	☆☆☆	8☆
Zhao	2020	Case-control study	7	7	☆☆	☆☆	☆☆	6☆
Li	2020	Case-control study	11	9	☆☆☆	☆☆	☆☆	7☆
An	2020	Case-control study	38	204	☆☆☆	☆☆	☆☆	7☆
Huang	2020	Case-control study	69	345	☆☆☆	☆☆	☆☆☆	8☆
Chen	2021	Cohort study	29	80	☆☆☆	☆☆	☆☆☆	8☆
Ao	2021	Cohort study	25	26	☆☆	☆☆	☆☆	6☆
Zhao	2021	Case-control study	241	170	☆☆	☆☆	☆☆☆	7☆
Adrielle	2021	Case-control study	33	62	☆☆☆	☆☆	☆☆	7☆
Hu	2020	Case-control study	30	158	☆☆	☆☆	☆☆	6☆
Chen	2020	Cohort study	189	1093	☆☆☆	☆☆	☆☆☆	8☆
Jiang	2021	Case-control study	15	28	☆☆	☆☆	☆☆	6☆
Liu	2020	Case-control study	11	139	☆☆☆	☆	☆☆☆	7☆
Wong	2020	Case-control study	21	85	☆☆	☆☆	☆☆	6☆

Aspartate aminotransferase (AST), C reactive protein (CRP), interleukin-6 (IL-6), and lactate dehydrogenase (LDH)

A total of six studies were included for the analysis of CRP level, four for AST level, four for LDH level, and two for IL-6 level. We found the proportion of patients with levated AST levels in the recurrent group was lower than that in the recurrent group (OR = 0.18, 95% CI: 0.06–0.60; $P = 0.005$) (Supplemental Figure 4a). The proportion of patients with elevated CRP levels in the recurrent group was lower than that in the non-recurrent group (OR = 0.68, 95% CI: 0.45–1.03; $P = 0.07$) (Supplemental Figure 4b). The proportion of patients with elevated IL-6 levels in the recurrent group was higher than that in the non-recurrent group (OR = 2.28, 95% CI: 1. 18–0.85; $P = 0.014$) (Supplemental Figure 4c). The proportion of patients with elevated LDH levels in the recurrent group was lower than that in the non-recurrent group (OR = 0.58, 95% CI: 0.31–1.09, $P = 0.091$) (Supplemental Figure 4d).

T cell subsets

Two studies were included to investigate the T cell subsets. There were no statistically significant differences in CD3+ T cell count (WMD = −18.57, 95% CI: −166.60 to 129.45, $P = 0.681$) (Supplemental Figure 5a), CD8 + T cell count (WMD = −116.70, 95% CI: −163.85 to −69.54, $P = 0.851$) (Supplemental Figure 5b), and CD4+ T cell count (WMD = −58.27, 95% CI: −105.94 to −10.59, $P = 0.155$) (Supplemental Figure 5c) between the two groups. The ratio of CD4+ T cells/CD8+ T cells in the non-recurrent group was higher than that in the recurrent group (WMD = −0.22, 95% CI: −0.35 to −0.09, $P = 0.002$) (Supplemental Figure 5d).

IgM titer

Two studies were included to analyze the IgM titer. The I2 = 0.0% and $P > 0.1$, revealing no heterogeneity among the included studies. The WMD = −0.22 (95% CI: −0.35 to −0.09, $P = 0.001$), indicating that the IgM titer in the recurrent group was lower than that in the non-recurrent group (Supplemental Figure 6).

Discussion

The statistical results showed that patients with mild to moderate illness more commonly exhibited recurrent PCR positivity in comparison to severe and critical patients. The results revealed two possible reasons for this. The first is that previous studies have shown that patients with higher immunoglobulin levels are more likely to experience severe illness,[27] and it can be speculated that high levels of immunoglobulins are more conducive to virus clearance. Second, we argue that severe cases receive more aggressive treatment (such as antiviral treatments and longer hospitalization time), which tends to lead to virus elimination. Additionally, the results revealed that the recurrent group was more likely to develop neurological symptoms (headaches and dizziness) than the non-recurrent group. Previous studies have confirmed that β-coronavirus is generally neuro-invasive in animals and humans.[28–33] It is difficult to prevent the virus from entering the central nervous system due to the influence of the blood-brain barrier and craniocerebral structure. This could explain why patients with nervous system-related symptoms have a higher recurrent positivity rate.

The results for the laboratory indicators indicated that the proportion of patients with elevated AST, IL-6, LDH and CRP levels in the recurrent group was lower than those in the non-recurrent group. IL-6 is an important cytokine in the human body, which has a variety of physiological functions, including the regulation of immune cell proliferation and differentiation.[34] Dysregulation of IL-6 signaling is associated with lymphoproliferative and inflammatory diseases, including Castleman disease and rheumatoid arthritis.[34] High IL-6 levels are regarded to be independent risk factors for COVID-19 progression and severity.[35] Herold et al.[36] analyzed 89 COVID-19 patients and found that high CRP levels were a good predictor for the need for mechanical ventilation. Jin et al.[37] studied 651 COVID-19 patients and found that elevated LDH was an independent risk factor for the severity of COVID-19. Non-recurrent group patients have a higher AST level, indicating that non-recurrent group patients are more likely to have liver damage. This may be related to the higher proportion of severe and critically ill patients in the non-recurrent group. Previous studies by Wu et al.[38,39] have also shown that abnormal liver biochemical indicators increase the risk of poor prognosis for COVID-19 patients, which is consistent with our conclusion. These results indicate that COVID-19 patients with recurrent PCR positivity experienced milder illness at the time of hospital admission compared to non-recurrent patients. This is consistent with the aforementioned conclusion regarding the severity of disease ratings.

The analysis of the immune status of patients upon admission revealed that the ratio of CD4+ T cells/CD8+ T cells and the IgM titer in recurrent patients were lower than those in non-recurrent patients. The ratio of CD4+ T cells/CD8+ T cells was decreased, which reflects typical dysfunction of cellular immunity.[40] The decreased IgM titer in patients indicates that humoral immunity dysfunction was more obvious in recurrent patients. Cellular and humoral immunity dysfunction could contribute to a decrease in the patient's immune response to SARS-CoV-2. Current research suggests that the organ and tissue damage observed in patients with COVID-19 is not completely and directly caused by SARS-CoV-2, but more due to an excessive secondary immune-inflammatory response.[41] The findings regarding the aforementioned immune characteristics could explain why the laboratory indicators in recurrent patients that reflect damage to tissues and organs were lower than those of non-recurrent patients. Furthermore, weakened immune function is not conducive to the elimination of the virus,[42] which could explain the emergence of recurrent patients.

Although the included studies clearly stated that the COVID-19 recurrent patients were confirmed by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR), only a few studies reported the Ct value, which is a limitation of this meta-analysis. In addition, owing to the small number of valid studies, comparisons of the laboratory indicators between the recurrent and non-recurrent PCR positivity patients may be unreliable. With the publication of more relevant studies over the coming year, additional meta-analyses can be conducted to verify these conclusions. Furthermore, most of the studies included in the literature review focus on China. This could lead to issues when attempting to apply the results to other regions.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (82072295). The funders had no role in the study design, data collection and analysis, decision to publish the work, or preparation of the manuscript.

ORCID iDs

Shuping Cui https://orcid.org/0000-0002-8997-9352
Zhihai Chen https://orcid.org/0000-0002-5140-1256

Supplemental material

Supplemental material for this article is available online.

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