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Research Paper

A systematic review and meta-analysis of discharged COVID-19 patients retesting positive for RT-PCR

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ABSTRACT

Background: With the increased number of patients discharged after having COVID-19, more and more studies have reported cases whose retesting was positive (RP) during the convalescent period, which brings a new public health challenge to the world.

Methods: We searched PubMed, Web of Science, The Cochrane Library, CNKI, WanFang and VIP from December 1, 2019 to December 31, 2020. The included studies were assessed using JBI critical appraisal tools and Newcastle-Ottawa Scale. The RP rate of discharge patients was analyzed by a meta-analysis. We adhered to PRISMA reporting guideline.

Findings: We have included 117 studies with 2669 RP participants after discharge. The methodological quality of 66 case reports were low to high, 42 case series and 3 cohort study were moderate to high, 3 case-control studies were moderate and 3 cross-sectional studies were low to moderate. The clinical manifestations of most RP patients were mild or asymptomatic, and CT imaging and laboratory examinations were usually normal. The existing risk factors suggest that more attention should be paid to sever patients, elderly patients, and patients with co-morbidities. The summary RP rate was 12.2% (95% CI 10.6–13.7) with high heterogeneity ($I^2 = 85\%$).

Interpretation: To date, the causes and risk factors of RP result in discharged patients are not fully understood. High-quality etiological and clinical studies are needed to investigate these issues to further help us to make strategies to control and prevent its occurrence.

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1. Introduction

Since the outbreak of COVID-19 in December 2019, the pandemic has spread to 235 countries, areas or territories of the world [1]. The International Committee on Taxonomy of Viruses (ICTV) has named

the organism SARS-COV-2 [2], and the World Health Organization (WHO) has named the disease Coronavirus Pneumonia 2019 (COVID-19). As of December 31, 2020, there has been a total of 80,733,033 confirmed cases worldwide, including 1,783,619 deaths [1].

There are various detection methods for coronavirus, and RT-PCR (real-time reverse transcriptases-polymerase chain reaction) test is the one most used [3,4]. As more and more patients have been cured and discharged from hospitals, the RT-PCR results of some patients have been reported as turning positive again during the convalescent period. The Lan et al. paper [5] was the first to report four cases of discharged patients retesting positive (RP) by RT-PCR test during

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Research in context

Evidence before this study

We searched PubMed, Web of Science, The Cochrane Library, CNKI, WanFang and VIP from December 1, 2019 to December 31, 2020. Among the 3818 references, 117 articles met our pre-planned study selection criteria. We also found six systematic reviews and/or meta-analyses. The existing systematic reviews reported on the characteristics, potential reasons, infectivity, treatment and outcome of discharged patients RP for RT-PCR. However, none of them were comprehensive in terms of literature search. The three meta-analysis papers, including 17, 14 and 9 cases respectively, reported estimates of 12%, 32.9% and 15%, respectively for the RP rate of discharged patients.

Added value of this study

Through a rigorous and comprehensive systematic review, we not only reported the characteristics of RP patients (such as clinical manifestations, serological tests and virology), pooled the RP rate, performed the subgroup analysis of gender, but also summarized and analyzed the risk factors of RP patients, and the possible causes of RP results.

Implications of all the available evidence

We hope that the results of the current systematic review and meta-analysis will promote the implementation of appropriate discharge standards and management measures, so as to improve people's understanding, diagnosis and proper management of RP patients. We suggested that discharged patients should still use personal protection to reduce the possibility of re-infection or transmission.

December 31, 2020, by using six databases: PubMed, Web of Science, The Cochrane Library, CNKI, WanFang and VIP. We applied no restrictions for language of publications. Studies were selected for further consideration through screening of titles, abstracts, and methods for relevance based on the selection criteria after excluding duplications. Three independent researchers (Xiangying Ren, Xiangge Ren and Jiaao Lou) screened retrieved articles and two of them reviewed each article. The same investigators independently assessed full texts of records deemed eligible for inclusion. Any discrepancies were resolved by discussion with other co-authors.

Studies were selected based on the following inclusion criteria: (1) Studies about discharged patients with confirmed SARS-CoV-2 infection whose RT-PCR test results were re-positive at any time after discharge; (2) Reported outcomes of interest included description of clinical symptoms, relevant examination results of the RP patients such as, sample types of nucleic acid test, IgG/IgM antibodies, CT imaging, contact tracing, infection ability, treatment, psychological status, prognosis, virology, risk factors of RP; (3) Original research with any type of study designs. Exclusion criteria were: (1) Patients with other serotypes of severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus infection; (2) The full texts of studies were not available.

2.2. Data extraction and quality assessment

Two independent reviewers (Xiangying Ren, Xiangge Ren) extracted data from each eligible study and then proceeded to cross check the results. Disagreements between reviewers regarding extracted data were resolved through discussion and consensus of the third reviewer (Jiaao Lou). The following information was extracted: first author name, date of publication, country, type of study (case report, case series, cohort study, cross-sectional study, case control study), age and sex of the RP patients, the proportion of RP patients in discharged patients, sample type of RT-PCR test, time from discharge to first RP by RT-PCR, serological tests and the CT imaging results of the RP patients. Included articles were independently assessed for quality by three reviewers (Yuqing Deng, Xiaoyan Li and Yuexian Shi) using criteria based on the standard principles of quality assessment. The methodological quality of the included case reports, case series, cross-sectional and case control studies was assessed based on JBI critical appraisal tools [10]. The quality of each checklist item was graded as Yes, No, Unclear or Not applicable. The methodological quality for the cohort studies were assessed based on Newcastle-Ottawa Scale [11]. The three reviewers then shared the quality assessment checklist results and obtained consensus through discussion.

2.3. Data synthesis and analysis

If no clinical heterogeneity was considered, we performed a meta-analysis using a random-effects model for the RP rate of discharged patients among studies where the sample size of discharged patients exceeded 30 based on the Central Limit Theorem [12]. I^2 statistic was used to estimate the statistical heterogeneity among the pooled studies [13]. We conducted a cumulative meta-analysis to analyze whether the results tended to be stable with the increase of sample size. We also did sensitivity analyses and then carried out effect-size combination [14], so as to test the reliability of the results. Finally, we explored the risk of publication bias using the Egger tests [14]. Statistical analyses were executed with the statistical package RStudio.

We assumed that different gender, age, disease severity and comorbidities might have an impact on patients who were RP. Therefore, the subgroup analyses were performed by these four factors. Gender (female or male) and age (< 60 years or \geq 60 years) were divided in two groups, respectively. The severity of disease was divided into four types: (1) Mild Type, defined as that the clinical

convalescence, which has aroused worldwide attention. More studies since have reported similar incidents. One of the largest case series of RP patients for COVID-19 is from Italy, which reported 976 RP patients out of 7127 discharged patients, with a RP rate of 13.7% [6].

The presence of the RP patient has raised public questions regarding current discharge standards. Are discharge standards too lax? Why do some COVID-19 patients test positive again after they leave the hospital? Is it due to re-infection or relapse? Are the RP patients contagious? All of these issues may exacerbate public panic about COVID-19: it may affect community management of the discharged populations, and pose new potential risks to social and public health. Other reviews on a similar topic have mainly reported on the clinical manifestations of RP patients, sample types of nucleic acid test, and the potential causes of RP [7,8]. Knowledge about the RP patients is still inadequate and limited.

Thus, the purposes of this systematic review and meta-analysis are to comprehensively analyze the COVID-19 patients with RP RT-PCR result after discharged through the inclusion of extensive relevant studies; focus on the clinical characteristics, the possible causes and risk factors.

2. Methods

This review was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [9].

2.1. Search strategy and selection criteria

An extensive search strategy (appendix p 2) was designed to retrieve all relevant articles published from December 1, 2019 to

symptoms were mild with no pneumonia manifestations found in imaging. (2) Moderate Type, patients had symptoms such as fever and respiratory tract symptoms with pneumonia manifestations seen in imaging. (3) Severe Type, patients who met any of the following criteria: respiratory rate ≥ 30 breaths/min; oxygen saturations $\leq 93\%$ in resting state; arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg. Patients with $> 50\%$ lesion progression within 24 to 48 h in lung imaging should be treated as severe cases. (4) Critical Type, meeting any of the following criteria: occurrence of respiratory failure requiring mechanical ventilation; presence of shock; other organ failure that requires monitoring and treatment in the ICU [15]. And co-morbidities were classified into "yes" or "no" categories.

2.4. Role of the funding source

The funder of the study had no role in data collection, data analysis, or data interpretation. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Search results

A total of 3818 records were identified in the initial literature search. After removing 916 duplicates, 2902 articles were screened by titles and abstracts, and 2742 articles were excluded. One hundred and sixty studies were reviewed from the full texts and finally 117 articles met the inclusion criteria and were analyzed in the systematic review and meta-analysis (Fig. 1). Excluded studies and the reason are shown in appendix pp 107–110. Of the 117 eligible studies, there were 66 case reports [5,16–80], 42 case series [6,81–121], 3 cohort studies [122–124], 3 cross-sectional studies [125–127] and 3

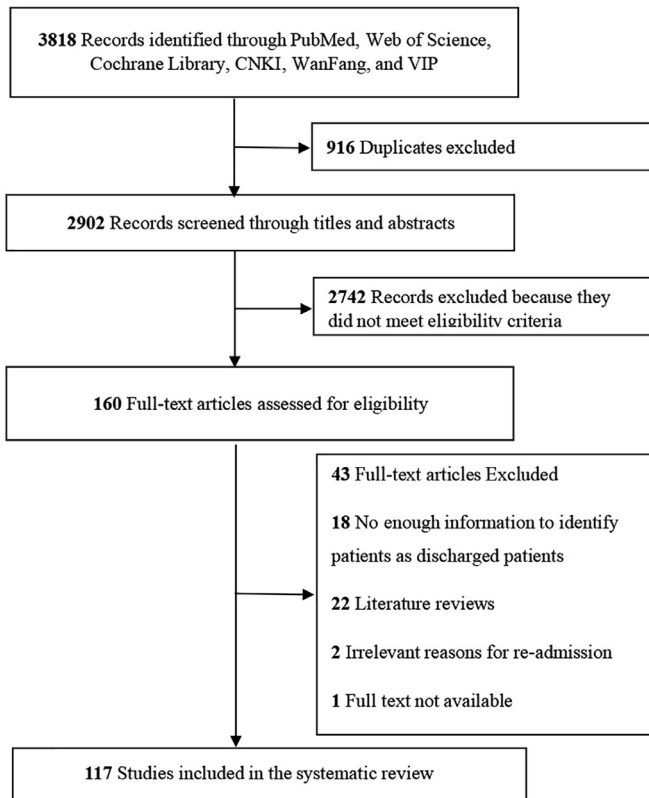


Fig. 1. Study selection.

case-control studies [128–130]. One hundred studies were from China, 7 from Italy, 3 from Korea, 2 from France, 5 each from Iran, Brunei Darussalam, Switzerland, America and Portugal. Characteristics of included studies are presented in Table 1.

3.2. Study quality assessment

Overall, the methodological quality of 66 case reports (appendix pp 3–51) were low to high, 42 case series (appendix pp 51–88) were moderate to high and 3 case-control studies (appendix pp 91–93) were moderate. Most studies reported the demographic information and clinical symptoms of patients in detail, and all studies utilized WHO endorsed diagnostic methods. Most studies were conducted in only one hospital and usually restricted to limited geographic areas, and their representativeness was very limited. The methodological quality of three cross-sectional studies were low to moderate (appendix pp 88–91). In the cross-sectional study, 2 of 3 studies did not have clear exposure factors. The methodological quality of two of the three cohort studies were moderate, while the other was high (appendix pp 94–96). Neither cohort study mentioned whether they controlled for confounding factors.

3.3. Characteristics of RP patients

In the included studies, the total sample size was 19,795 and 2669 RP patients were reported. Most RP patients' clinical manifestations, laboratory tests and CT imaging showed only mild abnormalities or were normal, and they had no or mild symptoms, such as cough, fever, and fatigue, but a few RP patients died because of co-morbidities.

3.3.1. Symptoms of RP patients

Nineteen studies ($n = 101$) [16,18,22–25,32,35,36,49–51,59,73,76,97,104,107,115] showed that discharged patients had no symptoms when the nucleic acid test was positive. Among 55 studies, 1054 RP patients had symptoms, cough (19.82%) [20,26,29–31,34,38,42,44,49,52,60,62,63,66,67,69,71,74,78,81,83–85,88,89,91,94,95,98,101,103,106,108,110,119,121,125,127,130] and fever (14.99%) [20,28,29,41,44,46,49,52,67,78,82–85,95,102,103,106,119,130] were the main symptoms, followed by fatigue (6.26%) [30,31,49,61,64,66,81,82,84,85,88,95,103,106,110,130], dyspnea (3.60%) [30,40,44,66,82,85,89,95,108,110,119], chest pain and stuffiness (3.51%) [20,34,40,42,57,61,80,83,85,89,91,95,103,106,109,121,130], myalgia (2.94%) [67,78,83,85,88,110,119,130], sore throat (2.37%) [42,49,80,81,84,85,113,119,121,130], headache (1.68%) [20,26,84,85,113,119,130], diarrhea (1.42%) [20,30,40,42,81,84,85,106,110,119,130], sputum production (1.21%) [81,84,127] and only a few patients had inappetence (0.75%) [52,66,81], shortness of breath (0.75%) [20,81,84,130], nasal congestion (0.28%) [85,130], chill (0.27%) [63,119], nausea (0.18%) [88,130], confusion (0.18%) [44,85], itchy throat (0.18%) [41,42], weakness (0.18%) [60,71], arthralgia (0.09%) [26], vomiting (0.09%) [119] and expectoration (0.09%) [119].

3.3.2. Sample types of nucleic acid test

Almost all of the patients underwent nasopharyngeal swabs during the convalescent period, and according to regional and hospital's requirements, a combination of nasopharyngeal swabs, fecal and sputum testing was used in 7 studies ($n = 101$) [27,34,35,45,74,81,84]. In these samples, as long as one sample was positive, regardless of whether the patient had clinical symptoms or CT imaging, the patients were defined as RP patients and were re-admitted to hospital.

3.3.3. Results of IgG/IgM antibodies

There were 34 studies [16,22–24,27,28,32,37,38,40,43,46,47,51,59,60,66,67,69–71,75,77,83,85,95,96,98,100,103,106,108,109,117] reported that viral RNA could still be detected in patients with SARS-CoV-2 specific IgM and IgG antibodies present, including

Table 1
Characteristics of included studies.

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
Female	male											
Zhang et al. [54]	China	Case report	–	3	9, 6, 8	3/-	10 d	–	positive	–	–	Neither clinical symptoms nor pathological changes in lung imaging were found in any cases. Urine and stool normal. No abnormality was found either in electrocardiogram and echocardiography, or in liver, gallbladder, and kidney ultrasound
Gao et al. [24]	China	Case report	–	1	70	1/-	14 d	positive	–	–	positive	Clinical features were all normal, with acute exudative lesions on chest CT scanning images substantially improved
Dou et al. [18]	China	Case report	–	1	34	1/-	14 d	positive	–	–	–	Patient showed no obvious clinical symptoms and chest CT showed that the bilateral lesions were completely absorbed
Sun et al. [45]	China	Case report	4	–	3–45	4/-	14 d	negative	positive	negative	–	Clinical manifestations, laboratory characteristics and chest CT findings showed obvious improvement in all patients
Ye et al. [51]	China	Case report	1	–	72	1/-	9 d	positive	–	–	positive	Chest CT revealed new ground-glass shadows in the patient
Xing et al. [48]	China	Case report	1	1	40, 20	2/62	1–4 d	positive	–	–	–	All patients were asymptomatic and chest CT showed no deterioration
Yoo et al. [52]	Korea	Case report	–	1	8	1/-	14 d	positive	–	positive	–	Reoccurrence and deterioration of cough. Laboratory and imaging studies showed no remarkable abnormalities
Zhou et al. [58]	China	Case report	–	1	40	1/-	–	–	–	–	–	Recurrent pneumonia after hospital discharge, with progression of lesions on CT scan, fever, elevated levels of ferritin and IL2R and reappearance of lymphocytopenia
Qin et al. [43]	China	Case report	–	3	68, 56, 37	3/-	2–6 d	positive	–	–	3 IgG positive 1 IgM positive	Routine blood reexamination, C-reactive protein, blood biochemistry and chest CT showed no obvious abnormalities and no obvious clinical symptoms
Teng et al. [25]	China	Case report	–	1	24	1/-	8 d	positive	–	positive	negative	No obvious cough, sputum production, fever, chest tightness, fatigue, abnormalities on chest CT or changes on imaging, and no obvious abnormalities were found in routine blood tests or related indicators
Chen et al. [17]	China	Case report	2	2	29, 12, 49, 34	4/17	3 d	3 positive	1 positive	–	–	The symptoms and CT manifestations of one patient were not exacerbated. Other patients reported no clinical manifestations
Wang et al. [46]	China	Case report	–	1	8	1/-	15 d	positive	–	–	positive	Reoccurrence of fever which was quickly controlled after hospital admission. No abnormalities were found in CT images
He et al. [26]	China	Case report	1	–	39	1/-	8 d	positive	–	–	–	On the 8th day of home isolation symptoms of dry cough, arthralgia, and headache reappeared without fever. Chest CT showing a small GGO shadow in the lower lobe of the right lung, but the lesion in the left lung had almost completely resolved
Cao et al. [16]	China	Case report	5	3	26–72	8/108	6–28 d	positive	–	–	8 IgG positive 2 IgM positive	No chest symptoms shown on the second admission, CT was almost normal with no signs of viral infection. Laboratory tests of the readmitted patients showed all had normal white blood cell count, neutrophil count, lymphocyte count, hemoglobin, blood platelet count, albumin, total bilirubin, urea nitrogen, creatinine, and D dimer

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Table 1 (Continued)

Study	Country	Study type	Sex		Age (years, mean ± SD, interquartile interval, range)	RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean ± SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Female	male				Upper respiratory tract specimen	Faeces specimen	sputum specimen		
Zheng et al. [56]	China	Case report	–	–	23–57	3/20	7 d	2 positive	positive	–	–	All three cases had improved with no fever, and showed improvement in WBC, lymphocyte counts, and CT scans
Li et al. [35]	China	Case report	2	2	71, 72, 37, 73	4/13	5–14 d	positive	2 positive	positive	–	No clinical symptoms of the 4 RP patients and no disease progression found in lung CT scans
Qiao et al. [42]	China	Case report	1	–	30	1/15	14 d	positive	–	–	–	Patient presented with itchy throat, occasional discomfort in the right chest and occasional coughing with expectoration, while remaining afebrile. Laboratory tests were almost normal. CT scan showed a light density shadow in the right lower lobe of the lung
Li et al. [31]	China	Case report	1	1	35, 36	2/-	14,17 d	positive	–	–	–	Case 1: Chest CT showed small airway lesions or uneven distribution of pulmonary blood vessels, while laboratory tests showed no obvious abnormalities Case 2: Chest CT showed cord shadow in the middle lobe of right lung, and no obvious abnormality was found in other laboratory examinations
Yao et al. [50]	China	Case report	1	3	30, 28, 30, 7-month	4/35	12–20 d	positive	–	–	–	All patients had no clinical symptoms
Feng et al. [22]	China	Case report	4	1	19–60	5/-	5–9 d	positive	–	–	3 IgG positive 2 IgM positive	After re-admission, all the patients had no fever, cough or other discomfort, and CT examination showed that the lesions were further absorbed since discharge from hospital
Du et al. [21]	China	Case report	1	–	63	1/-	9 d	–	–	positive	–	Chest CT showed absorption of bilateral lower lung lesions, obvious fibrous lesions, and increased GGO shadow in upper lobe of both lungs
Li et al. [33]	China	Case report	–	1	25	1/-	15 d	positive	–	–	–	No obvious abnormalities were found in chest CT
Li et al. [36]	China	Case report	1	2	71, 37, 73	3/7	5–7 d	–	–	positive	–	Routine blood examination, C-reactive protein, blood biochemistry and chest CT showed no obvious abnormalities and no obvious clinical symptoms
Yang et al. [49]	China	Case report	1	5	32–71	6/14	3–14 d	3 positive	2 positive	–	–	No new clinical symptoms and original symptoms were not aggravated. The results of blood routine reexamination, C-reactive protein, blood biochemistry and chest CT plain scan showed no obvious abnormalities
Zhao et al. [55]	China	Case report	1	7	33	8/109	4 d (2 cases) 7 d (6 cases)	3 positive	5 positive	–	–	12.50% patients had cough, and the rest were asymptomatic. They did not cause any secondary transmission. Five patients were local cluster cases
Lan et al. [5]	China	Case report	2	2	30–36	4/-	5–13 d	positive	–	–	–	Patients remained asymptomatic on clinician examination and chest CT findings showed no change from previous images. No reported contact with any person with respiratory symptoms. No family member was infected
Du et al. [20]	China	Case report	2	1	71	3/126	11–20 d	positive	–	–	–	All RP patients were asymptomatic. Two RP patients had increased serum LDH and CRP levels. RP patients did not report contact with any person who had a fever and respiratory symptoms after discharge. No family member infection was reported
Lafaie et al. [29]	France	Case report	3	–	84, 90, 84	3/-	–	–	–	–	–	All three patients died from co-morbidities
Liu et al. [39]	China	Case report	2	2	8–46	4/-	4–12 d	3 positive	positive	–	–	The positive respiratory tract results in patients were observed prior to the digestive tract symptoms
Liu et al. [37]	China	Case report	–	1	35	1/-	10 d	positive	negative	–	IgG positive	Clinical symptoms had disappeared but re-emerged, but just presented with slight cough

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Table 1 (Continued)

Study	Country	Study type	RP patients		RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results	
			Sex Female male	Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen			
Li et al. [34]	China	Case report	–	1	41	1/-	17 d	positive	positive	positive	–	The chest CT image shows scattered plaques and GGOs in both lungs
Huang et al. [28]	China	Case report	–	1	40	1/-	5 d	positive	–	–	positive	The follow-up CT showed some consolidation enlarged in left lower lobe and right upper lobe, while other linear consolidation remained
Zhang et al. [53]	China	Case report	1	6	10 month-35	7/-	11–23 d	1 positive	6 positive	–	–	All cases were asymptomatic and chest CT images showed no change from the pre-discharge scans. No reports of contact with any suspected or confirmed persons
Loconsole et al. [40]	Italy	Case report	–	1	48	1/-	30 d	positive	–	–	positive	New symptoms developed: dyspnea and chest pain. Imaging showed segmental and sub-segmental signs of arterial micro-embolism with some parcel areas of GGOs
Fu et al. [23]	China	Case report	2	1	36, 74, 34	3/-	7–12 d	positive	–	–	IgG positive	All chest CT scans showed multiple patchy GGO shadows in lungs. Patient's remained afebrile with no special symptoms during readmission
Ravioli et al. [44]	Switzerland	Case report	2	–	81, 77	2/-	13,23 d	positive	–	–	–	Case 1: RP patient re-admitted with dyspnea, fever and confusion. Chest CT revealed infiltrates in the right upper lobe as well as bilateral pleural effusion. The patient died 4 days post admission Case 2: Chest CT exhibited ubiquitous GGOs predominantly in the right upper lobe
Wang et al. [47]	China	Case report	–	1	33	1/-	14 d	positive	–	–	positive	No reported clinical manifestations
Landi et al. [30]	Italy	Case report	3	3	57.5	6/29	22 d	positive	–	–	–	Patients remained asymptomatic or with mild symptoms during the convalescent period
Hu et al. [27]	China	Case report	1	–	36	1/-	16 d	positive	negative	positive	IgM positive	Sixteen days post-discharge, the patient retested positive with a kit (Daan) different from that (Genuo) used during hospitalization
Dou et al. [19]	China	Case report	1	1	21,56	2/-	17 d	positive	positive	–	–	Compared with the hospitalization CT examination, the density and area of lesion in both cases showed significant decrease in the first follow-up examination after discharge
Peng et al. [41]	China	Case report	3	4	67,38,29,21 (others unknown)	7/-	8,11,7,14,4,9,9 d	6 positive	1 positive	–	–	Four of the seven RP patients (patient 1–4) were from one family, including one child, and the remaining three were young to middle-aged. All 7 RP patients had shorter hospital stays, lower medical costs, and milder symptoms in their second hospital visit than in their first hospitalization. Nonorganic insomnia and increased anxiety were observed in 2 RP patients
Li et al. [32]	China	Case report	–	1	50	1/-	–	positive	–	–	positive	Patient was asymptomatic, chest CT scans showed improvement of original lesions, with only a few GGOs
Zhou et al. [57]	China	Case report	1	–	40	1/-	10 d	positive	–	–	–	Patient presented with chest pain and cough with sputum production. Chest CT scan showed absorption of lung disease
Liu et al. [38]	China	Case report	–	1	35	1/-	15 d	positive	negative	–	IgG positive	Chest CT imaging showed new lesions in the upper left lung. This patient did not contact any other persons with respiratory symptoms, and no person who contacted her was infected
Goldman et al. [60]	American	Case report	–	–	60–69 (specific age unknown)	1/-	140 d	–	–	–	positive	The patient was less severely ill by physiologic, laboratory and radiographic parameters, with higher Ct values. The results of viral sequencing showed re-infection with a different strain

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Table 1 (Continued)

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
Female	male											
Wei et al. [59]	China	Case report	1	–	68	1/-	18 d	–	–	positive	positive	This patient had persistent viral RNA positivity for more than 4 months after initial illness in the presence of low neutralizing antibodies, but without prolonged clinical symptoms. Multiple anti-viral drug treatments had no impact and there was no evidence of re-infection. No infection occurred to the three family members living with her
Zanardi et al. [76]	Italy	Case report	2	–	33,27	2/-	–	positive	–	–	–	Two asymptomatic pregnant women recovered from SARS-CoV-2 infection who retested positive. Both of them gave birth to healthy babies
Zhou et al. [79]	China	Case report	–	6	15–20 5–10 60–70 40–50 20–30 30–40 (specific age unknown)	6/-	–	–	positive	–	–	The anal swab positivity rate for SARS-CoV-2 RNA in discharged patients was 14.3% (6/42). In the positive group, 40% of the patients (2/5) had a positive stool occult blood test (OBT), but none had diarrhea. The median duration of fever and major symptoms (except fever) in the positive patients was shorter than that of the negative patients. The incidence of asymptomatic cases in the positive group (33.3%) was also higher than that of the negative group (5.6%)
Wu et al. [70]	China	Case report	1	1	8,46	2/-	14 d,7 d	–	positive	–	positive	All indicators of two patients' re-examination were normal, and they were released from isolation after recovery. They were cured without additional treatment, with the appearance of antibodies and the recovery of immune functions
Wu et al. [71]	China	Case report	1	5	50.83 \pm 23.83	6/-	3–15 d	4 positive	2 positive	–	IgG positive	The main symptoms included fatigue, dry cough and pharyngeal or chest discomfort, which were generally milder in the re-positive period. Laboratory indexes and the pulmonary lesions were significantly improved. All close contacts were SARS-CoV-2 RNA-negative
Hu et al. [61]	China	Case report	7	1	46.25 \pm 17.70	8/117	12.5(11.8–16.3) d	positive	–	–	–	Most of them (7/8) were asymptomatic and CT showed no obvious change with the previous manifestation. Only one 57-year-old female patient demonstrated mild fatigue and chest distress, CT showed small areas of ground-glass opacities in the left lung and small nodules in the right lung. No close contacts or family members were infected. The first time positive Ct value upon hospitalization and second time positive Ct value after discharge, showed no significant difference
Zhang et al. [77]	China	Case report	3	1	36,54,50,55	4/-	15 d,25 d,6 d,15 d	positive	–	–	4 IgG positive 3 IgM positive	All presented with no symptoms, and the chest CT scan of three cases was normal
Song et al. [69]	Korea	Case report	3	1	73,33,31,18 month	4/-	4 d,9 d,9 d,9 d	positive	–	–	positive	In 4 RP patients, the highest levels of IgG and IgM antibodies were reached after about a month of the onset of the initial symptoms. Then, the IgG titers plateaued, and the IgM titers decreased, regardless of RT-PCR results. The IgG and IgM levels did not increase after the post-negative positive RT-PCR results in any of the patients

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Table 1 (Continued)

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
			Female	male								
Lee et al. [63]	Korea	Case report	4	2	29.5(17–72)	6/-	–	positive	–	–	–	A complete genome sequence from one of the 6 patients: a 21-year-old woman was acquired. phylogenetic analysis of the viral RNA of positive retest was clustered into a subgroup distinct from that of the initial infection, suggesting that this was a re-infection of SARS-CoV-2 with a different subtype from that of the primary strain
Luciani et al. [65]	Italy	Case report	1	–	69	1/-	41 d	positive	–	–	–	After three months of hospitalization symptoms resolved, and two consecutive NPST were negative
Xie et al. [72]	China	Case report	1	3	9,6,4,9	4/-	–	–	positive	–	–	Positive viral RNA in the stool specimens persisted for a long time in all 4 children after pharyngeal swabs turned negative during follow-up, especially in 3 asymptomatic children
Patrocínio de Jesus et al. [67]	Portugal	Case Report	–	1	41	1/-	10 d	positive	–	–	IgG positive	The patient clinically improved on methylprednisolone 80 mg/day (for 7 days followed by tapering), piperacillin/tazobactam, and remdesivir and was extubated after 7 days. His-family (mother, father, and wife) also developed respiratory symptoms and all tested positive for SARS-CoV-2. Importantly, they were shielding and reported no other risk contact besides the one with the patient
Yang et al. [73]	China	Case report	1	–	32	1/-	20 d	positive	–	–	–	No discomfort, fever, cough or expectoration. Blood routine and CT were not abnormal
Li et al. [64]	China	Case report	1	1	32,7 month	2/-	14 d	1 positive	1 positive	–	–	One patient occur occasional fatigue, both of cases have normal temperature and no other symptoms
Qin et al. [68]	China	Case report	–	3	68,56, 37	3/-	2–3 d	positive	–	–	–	The viral load of the specimens was very low and showed weak positive results. Treatment with Lianhua Qingwen antiviral drug
Zhu et al. [80]	China	Case report	1	–	50	1/-	11 d	positive	–	–	–	There were two consecutive re-positive results, the first about 11 d, presented with fever of 37.4 °C, dry pharynx, and slight chest tightness but no other symptoms
Yin et al. [74]	China	Case report	–	1	31	1/-	7 d	negative	positive	negative	–	No fever, mild cough, no obvious sputum, no abdominal pain, diarrhea, CT normal
Zhi et al. [78]	China	Case report	2	3	11,29,51,49,39	5/-	1–13 d	positive	positive	–	–	One asymptomatic patient and 4 with mild symptoms
Ma et al. [66]	China	Case report	1	–	54	1/3	16 d	positive	–	–	positive	Wheezing and chest discomfort after activity which improved, after taking Chinese medicine
Kong et al. [62]	China	Case report	1	1	40/28	2/-	11,14 d	positive	–	–	–	Asymptomatic after discharge. The viral nucleic acid repeatedly positive for more than 60d
Yu et al. [75]	China	Case report	–	1	38	1/-	33 d	positive	–	–	IgG positive	The chest CT image shows increased lung texture, no ground glass shadow, no cable fiber foci lung
Li et al. [89]	China	Case series	11	4	23–68	15/105	9–30 d	positive	–	–	–	All patients' physical conditions were stable with no obvious decreased immunity, and there was no deterioration seen in the CT images. Only one patient (6.7%) had consolidation
Yuan et al. [101]	China	Case series	17	8	28	25/172	7.32 \pm 3.86 d	11 positive	14 positive	–	–	CT scan results indicated that 12 showed improvement of original lesions compared with images prior to first hospital discharge, while another 8 patients showed no worsening compared to previous results. Lymphocyte counts for all 25 patients pre hospital discharge were significantly positively correlated ($r = 0.52, p = 0.008$) with the time interval for virus reappearance

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Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
			Female	male								
Tian et al. [97]	China	Case series	8	12	37.2	20/147	17-25 d	positive	–	–	–	All patients remained asymptomatic, with no reduction in leukocytes or lymphocytes. Compared with chest CT images at the first discharge, no progressive lesions were observed
Li et al. [90]	China	Case series	24	35	38	59/330	–	positive	–	–	–	The longest time from the first discharge to the last nucleic acid test was 57 days. Clinical manifestations of these patients were not reported
Liang et al. [92]	China	Case series	–	–	–	12/40	–	positive	–	–	–	Clinical manifestations of these patients were not reported
Zhou et al. [105]	China	Case series	4	7	58.55 \pm 19.35	11/-	–	positive	–	1 positive	–	Eight patients (72.8%) developed clinical symptoms post-discharge. 11 patients were discharged after the results of the C-reactive protein level was higher than pre-discharge, the difference was statistically significant, and there were no statistical differences in pre and post-discharge results of the leukocyte count, lymphocyte count, neutrophil count, platelet count, D-dimer, albumin, erythrocyte sedimentation rate, calcitonin original level and scope of chest HRCT lung lesions at checkup
Shi et al. [96]	China	Case series	–	–	–	17/108	3–7 d	–	5 positive	2 positive	15 IgG positive 2 IgM negative	Clinical manifestations of these patients were not reported
Ai et al. [81]	China	Case series	15	15	44.77 \pm 18.9	30/281	1–31 d	13 positive	16 positive	1 positive	–	The readmitted patients showed significantly reduced symptoms, were afebrile and most were asymptomatic
Zhuo et al. [107]	China	Case series	3	3	43.833 \pm 18.766	6/33	7 d	positive	–	–	–	Nucleic acid reactivation was associated with the degree of fever on admission and whether imaging at admission indicated pneumonia
Deng et al. [84]	China	Case series	36	25	54.79	61/576	–	36 positive	17 positive	8 positive	–	These RP patients were characterized by older age, chronic co-morbidities and mild conditions. They had no contact with any person presenting respiratory symptoms, and no family member infection was found
Zhu et al. [106]	China	Case series	12	5	54	17/98	4 d	–	–	–	6 IgG positive IgM positive 10 IgG positive IgM negative	The levels of CD3-CD56 + NK cells during hospitalization and 2-weeks post discharge were higher in the RP group than in the NRP group
Zheng et al. [103]	China	Case series	15	12	44	27/285	7 d	positive	–	–	–	RP events occurring in nearly 10% of COVID-19 patients shortly after the negative tests were not associated with worsening symptoms and were unlikely to reflect re-infection. Patients' lack of efficiency in virus clearance was a risk factor for RP result. Older RP patients (\geq 60 years old) were more susceptible to clinical symptoms at readmission
Chen et al. [83]	China	Case series	51	30	62	81/1087	9 d	positive	–	–	72 IgG positive 68 IgM positive	Multivariable regression analysis identified elevated serum IL-6, increased lymphocyte counts and CT imaging features of lung consolidation during hospitalization as the independent risk factors of recurrence
Yuan et al. [100]	China	Case series	13	7	41.5	20/182	7 d (13 cases) 14 d (7 cases)	14 positive	6 positive	–	14 IgG positive 10 IgM positive	There were no significant differences between the RP group and the NRP group in age, sex, co-morbidities, epidemiological information, initial symptoms, and the level of antibodies. Patients aged under 18 years and those mild and moderately affected showed a higher re-positive rate. The RP group experienced longer hospital stay

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Table 1 (Continued)

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
			Female	male								
Zou et al. [108]	China	Case series	30	23	62-19	53/257	4-6 d	positive	–	–	34 IgG positive 19 IgM positive	The frequency of recurrently positive RT-PCR results was significantly lower in those with 3 consecutive negative results (5.4%) than in those with only 2 consecutive negative results (20.6%)
Liu et al. [94]	China	Case series	4	11	48	15/92	–	positive	–	–	–	The increase in serum SARS-CoV-2 specific IgM and IgG levels correlated with the positive conversion of RT-PCR retests. The RP group had higher levels of IgM at the time of discharge and higher levels of IgM and IgG at the time of retest
Zhao et al. [102]	China	Case series	4	3	5-7	7/14	14 d	positive	–	–	–	Children who experience reactivation had higher neutrophil percentage and neutrophil-to-lymphocyte ratio (NLR) but a lower leukocyte count and lymphocyte percentage, underwent fewer nucleic acid tests, were older but none of these differences were significant
Ye et al. [99]	China	Case series	6	6	52.3 \pm 14.4	12/117	7–14 d	–	4 positive	8 positive	–	Multivariable regression showed increasing odds of positive SARS-CoV-2 retest after discharge associated with longer hospital stay, and lymphocytopenia on admission
Li et al. [91]	China	Case series	7	12	48	19/71	4-4 d	positive	–	–	–	Sixteen of the 19 RP patients were in group A (discharged earlier), and 3 were in group B (discharged later). A lower proportion of patients in Group B tested positive after discharge, and Group B required 3 consecutive negative RT-PCR test results before discharge
Liu et al. [93]	China	Case series	–	–	–	9/51	7–14 d	positive	–	–	–	Three cases complained of dry cough, 1 case complained of cough with sputum, and the other 6 showed no clinical symptoms. Compared with the pre-discharge CT features, the lesions were significantly reduced, and the lesion density had decreased. Lung damage was fully absorbed in 55.6% discharged RP patients. There were no instances of them infecting others
Bongiovanni et al. [82]	Italy	Case series	64	61	26–95	125/1146	3–43 d	positive	–	–	–	Twenty-nine patients (23.2%) developed clinical symptoms: fever ($n = 16$), malaise/fatigue ($n = 9$) and respiratory failure ($n = 4$)
Hu et al. [87]	China	Case series	4	7	4–58	11/69	9–17 d	positive	–	–	–	All patients were asymptomatic
Gousseff et al. [85]	France	Case series	5	6	55	11/-	4–27 d	positive	–	–	positive	All 11 patients showed CT scan signs of acute COVID-19 during the second episode. Two patients died of ARDS recurrence and another from worsening of chronic right heart failure
Habibzadeh et al. [86]	Iran	Case series	4	5	–	9/13	–	positive	–	–	–	All patients were asymptomatic
Zheng et al. [104]	China	Case series	15	12	19–79	27/285	–	positive	–	–	20 IgG positive 16 IgM positive	Most patients showed near-complete resolution of pulmonary CT abnormalities on re-admission, with no pulmonary re-infection
Cento et al. [6]	Italy	Case series	–	–	–	976/7127	14 d	positive	–	–	–	None of the patients monitored after discharge have ever shown a resurgence of symptoms, regardless of RT-PCR results
Jiang et al. [88]	China	Case series	6	–	45-2	6/35	8,14,7,7,8,8 d	positive	–	–	–	Of the 6 positive cases, one experienced significant symptom during the convalescent period, one had occasional cough, and four cases were asymptomatic. No significant difference between recurrent and control cases in leukocyte, lymphocyte, neutrophil, platelet, and albumin counts

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Table 1 (Continued)

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean ± SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean ± SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
			Female	male								
Mei et al. [95]	China	Case series	12	11	27–89	23/651	4–38 d	positive	–	–	7 IgG positive 5 IgG positive negative	Fifteen patients (65%) were asymptomatic at the time of the retest whereas eight (35%) had at least one symptom associated with active COVID-19. Specifically, six patients (26%) presented with fever, two (9%) with cough, one (4%) with fatigue, one (4%) dyspnea, and one (4%) chest tightness
Wong et al. [98]	Brunei Darussalam	Case series	9	12	47	21/106	11–18 d	positive	–	–	14 positive	The RP risk is more than six times higher in persons aged 60 years and above. The average Ct value of RP patients was lower pre-discharge compared to their readmission Ct value. Out of 111 close contacts tested, none were found to be positive as a result of exposure to a RP patient
Zheng et al. [120]	China	Case series	2	7	51,25, 56,75, 11,49, 52,38,33	9/41	3–14 d	1 positive	8 positive	–	–	The clinical manifestation of patients were 1 asymptomatic, 1 mild, 6 moderate and 1 critical
Hu et al. [113]	China	Case series	17	13	57.5(27–84)	30/188	–	positive	–	–	–	There was no significant difference in age, sex and severity of disease between the non-re-positive group and the re-positive group ($P>0.05$)
Chen et al. [110]	China	Case series	86	103	34(24–49)	189/1282	8(IQR 5–13)	–	–	–	–	Patients in the group that tested positive again were younger with a higher proportion of moderate symptoms in the first hospitalization than in the negative group. During the second hospitalization, no RP patients showed any new symptoms, 78.31% showed further improved on chest CT scan compared with the first discharge. None of the close contacts developed COVID-19
Peng et al. [117]	China	Case series	9	5	7.2 ± 4.8	14/38	–	positive	positive	–	positive	Family cluster infection, higher WBC count, and longer plasma prothrombin time (PT) are the early risk factors for RP in recovered COVID-19 children
Landi et al. [115]	Italy	Case series	10	12	56.4 ± 15.7	22/131	14 d	positive	–	–	–	Persistent sore throat (prevalence ratio=6.50, 95% CI 1.38, 30.6) and symptoms of rhinitis (prevalence ratio=3.72, 95% CI 1.10, 12.5) were risk factors for retesting positive for SARS-CoV-2
Zhou et al. [121]	China	Case series	16	7	51.0(42–58)	23/368	14 d	positive	–	–	–	Using multivariate Cox regression analysis, risk factors associated with RP included a higher ratio of lymphocyte/white blood cell on admission, lower peak temperature during hospitalization, and the presence of comorbidities, particularly hypertension or chronic respiratory system diseases. Antivirus treatment with arbidol was associated with a lower likelihood of RP
Huang et al. [114]	China	Case series	41	28	–	69/417	14 d	positive	–	–	–	16.7% recovered patients with PCR positive recurring one to three times, despite being in strict quarantine. Younger patients with mild pulmonary respiratory syndrome had higher risk of PCR positivity recurrence
He et al. [112]	China	Case series	13	17	66 (42–71)	30/267	14 d	positive	–	–	–	Mild and moderate clinical characteristics were not able to identify risk of patients retesting positive. However, severe and critical cases classified high according APACHE II and CURB-65 scores, were more likely to become re-positive after discharge

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Table 1 (Continued)

Study	Country	Study type	RP patients			RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean \pm SD, interquartile range, range)	Type of specimen collection			Serological tests IgG/IgM	Results
			Sex		Age (years, mean \pm SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen		
			Female	male								
Wang et al. [119]	China	Case series	7	5	55.5 \pm 13.7	12/193	14 d	positive	–	–	–	The incidence of re-positive virus detection in patients who recovered from COVID-19 during quarantine was 6.2%
Liao et al. [116]	China	Case series	–	–	–	10/28	2–15 d	positive	–	–	–	A total of 10 patients tested SARS-CoV-2 positive at least once and 9 had more than two SARS-CoV-2 positive tests within 30 days after being discharged from the hospital
An et al. [109]	China	Case series	22	16	–	38/262	14 d	positive	positive	–	positive	These RP patients were characterized as young and displayed mild and moderate conditions, fewer symptoms but similar plasma antibody levels during their hospitalization compared to NRP patients. Upon hospital readmission, these RP patients showed no obvious symptoms or disease progression. All close contacts of RP patients tested negative and showed no suspicious symptoms
Tang et al. [118]	China	Case series	14	8	28 (IQR 20–38)	22/209	–	9 positive	13 positive	–	–	Re-positive test was significantly associated with older age (OR=0.95, 95%CI 0.93–0.98) and diarrhea during hospital stage (OR=10.44, 95%CI 1.60–68.16)
Hao et al. [111]	China	Case series	12	11	–	23/369	–	positive	positive	–	–	Results indicated that albumin/globulin ratio may potentially have a predictive effect in “re-positive” discharged COVID-19 patients
Wang et al. [124]	China	Cohort study	4	4	46.5	8/131	7–14 d	positive	–	–	–	(RP for RT-PCR is not the measurement outcome of this cohort study.) All 8 RP patients were asymptomatic at the time of discharge. Most had no obvious symptoms after discharge. At the endpoint of this study, seven showed negative SARS-CoV-2 nucleic acid tests. None had contacted infection after discharge during the convalescent period
Chang et al. [122]	China	Cohort Study	–	–	–	4/67	7,28,15,33d	positive	–	–	–	(RP for RT-PCR is not the measurement outcome of this cohort study.) There were 4 RP patients on the follow-up tests, and none had viral presence for more than 22 days. Their samples were sent to a viral culture facility where virus culture could not be established
He et al. [123]	China	Cohort study	–	–	56 median	24/420	–	–	–	–	–	A total of 325 subjects were exposed to comprehensive intervention, including Baduanjin exercise, Foot baths, Moxibustion with acupoint application, Tongzhi Granule and Wuhan Kangyi Decoction. 95 controls had no intervention. The recurrence rate of positive RT-PCR test results with comprehensive intervention was 2.8% (9/325), and that with no intervention was 15.8% (15/95)
Wang et al. [126]	China	Cross-sectional study	–	–	–	16/67	< 14 d	–	positive	–	–	Clinical manifestation of these patients was not reported
Lu et al. [125]	China	Cross-sectional study	42	45	28	87/619	7 d	69 positive	68 positive	–	–	All 87 RP cases had mild or moderate symptoms at initial diagnosis and were younger on average. RP cases ($n = 59$) exhibited similar neutralization antibodies (NAbs) titre distributions to other COVID-19 cases ($n = 218$) tested. No infectious strain could be obtained by culture and no full-length viral genomes could be sequenced from RP cases
Wu et al. [127]	China	Cross-sectional study	–	–	46.5	10/60	3–24 d	5 positive	6 positive	–	–	None of the RP patients had clinical symptoms of COVID-19 after hospital readmission, except for occasional cough in patients 1 and 2, both of whom were older than 70 years with multiple co-

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Table 1 (Continued)

Study	Country	Study type	RP patients		RP patients/ discharged patients	Time from discharge to first RP for RT-PCR (days, mean ± SD, interquartile range)	Type of specimen collection			Serological tests IgG/IgM	Results	
			Sex	Age (years, mean ± SD, interquartile interval, range)			Upper respiratory tract specimen	Faeces specimen	sputum specimen			
Chen et al. [128]	China	Case control study	27	17	44/-	14 d	-	-	-	-	-	morbidities. 9 medical staff exposed to one of the RP patients had negative RT-PCR results and had no symptoms in the following 2 months All the 44 relapse cases were classified as mild to moderate on readmission. In comparison to 32 cases retesting negative after 14 days isolation post-discharge, relapse cases had markedly elevated concentrations of ALT ($P = 0.020$) and AST ($P = 0.007$). Moreover, subgroup analysis showed mild to moderate abnormal concentrations of ALT and AST in relapse cases
Wang et al. [130]	China	Case-control study	14	12	26/144	-	38.3 ± 22.6	positive	-	-	-	All patients were asymptomatic
Hu et al. [129]	China	Case-control study	25	26	51/153	13.49 ± 4.24 d	45 median	positive	-	positive	-	All patients were asymptomatic

234 patients who were IgG positive and 164 who were IgM positive. Fifteen studies reported that both IgG and IgM were positive in RP patients [24,28,32,40,46,47,51,59,60,66,69,70,85,109,117]. However, one RP patients was reported as testing negative for antibodies in one study [25].

3.3.4. Findings of CT imaging

In most patients, CT imaging had improved compared with the first admission, and pulmonary lesions were fully absorbed in some patients. However, among 656 RP patients having abnormalities in CT imaging, there were bilateral pulmonary infiltration (15.2%) [20,28,29,83,84,116,117], consolidation of lung tissue (7.8%) [77,79,83,86,117], ground-glass opacity (GGO) (7.7%) [20,44,67,78,84,86,89,104,119], pulmonary plaques (3.5%) [34,80,84], fibrinous exudation on the surface of the lung (2.7%) [34,104,117], pneumonia (1.4%) [20,29,104,116], the light density shadow of the lung (0.6%) [51,77,84], interstitial abnormalities (0.4%) [84], bilateral proximal lobar pulmonary embolism (0.4%) [29,40], segmental and sub-segmental signs of arterial micro-embolism (0.3%) [40], and pleural effusion (0.15%) [65].

3.3.5. Contact tracing and infection ability of RP patients

Fourteen studies reported that RP patients had contacted with others before they were RP for RT-PCR [5,18,20,30,37,42,47,52,59,67,84,93,98,110]. In these studies, only one study reported one RP patient whose family members developed respiratory symptoms and tested positive for SARS-COV-2 nucleic acid [67]. Other studies reported that these contact persons were neither diagnosed with COVID-19 nor had any respiratory symptoms.

3.3.6. Treatment from discharge to RP result

Most of the reports did not mention whether the discharged patients continued to take antiviral drugs during the convalescent period. Two studies mentioned that the discharged patients did not take any drugs during the convalescent period [47,101]. Fu et al. reported that three RP patients had received traditional Chinese medicine treatment during isolation after discharge [23]. Patrocínio de Jesus et al. described a patient who received prednisolone after discharge [67]. He et al. reported that the patients received various interventions during convalescent period, including Baduanjin exercise, Tongzhi Granule, Moxibustion with acupoint application [123].

3.3.7. Treatment of RP patients after re-admission

Most of the studies did not mention the treatment management for the patients who were readmitted. In the ones that reported treatment strategies, most RP patients took chloroquine phosphate, Lopinavir, Arbidol Hydrochloride or Interferon-2B [21,25,37,51,97]. Some patients were also treated with immune-related drugs such as thymic pentapeptide [97] or immunoglobulin [51]. Traditional Chinese medicines were also used for treatment during the second hospitalization [53,77,109,116,124].

3.3.8. Psychological status of RP patients

Only two studies reported the psychological status of patients after re-hospitalization. Mei et al. reported an 80-years-old RP patient with suicidal tendency during re-hospitalization [95]. Peng et al. found nonorganic insomnia and increased anxiety in two RP patients [41].

3.3.9. Prognosis of RP patients

Eight studies reported prognosis of RP patients, and four of which reported that the RP patients ($n = 4$) were in good physical condition [25,26,40,59]. Raviol et al. reported that an 81-year-old patient who had been readmitted to hospital with dyspnea, fever, and unconsciousness, suffered progressive symptoms leading to death [44]. Gousseff et al. reported the deaths of three elderly patients with co-

morbidities, two of whom died from acute respiratory distress syndrome and one from chronic right heart failure [85]. Bongiovanni et al. reported 11 patients with an average age of 86.4 years who died during follow-up [82]. Lafaie et al. reported three elderly female patients with multiple co-morbidities who died after relapse [29].

3.4. Virology

3.4.1. Viral load

Five studies with total 16 RP patients reported that their Ct (Cycle threshold) values was higher than those at their first hospitalization, suggesting a decrease in viral load [43,47,60,63,98]. Liu et al. reported that 3 of 4 RP patient's viral load decreased with the length of discharge time, but one patient had risen [39]. Song et al. reported that the Ct values fluctuated in all the four patients [69]. Gao et al. reported that the patient who tested repeatedly positive after discharge had higher viral loads at the first and third admission than during the middle term of the disease [24]. Hu et al. found no difference in viral load in eight RP patients between the first positive and repeated positive tests [61].

3.4.2. Viral gene sequencing

Lu et al. reported that they obtained zero full-length SARS-CoV-2 genomes by sequencing 94 samples from 54 patients and the corresponding sequencing coverage ranged from 0.00% to 75.48% [125]. Goldman et al. reported sequenced viruses from two distinct episodes of symptomatic COVID-19 separated by 140 days in a single patient, and found the patient was re-infected with a new strain [60]. Lee et al. reported that they obtained the complete genetic sequence of the virus from one female patient among 6 RP patients, suggesting that there was a re-infection of SARS-CoV-2 with a subtype that was different from that of the primary strain [63].

3.4.3. Virus cultivation

Three studies reported virus culture from 40 nasopharyngeal or fecal swab samples from RP patients. Two studies failed to produce live virus [122,125] and only the third study, Gousseff et al., reported that one of two patients had a positive virus culture and this was accompanied by typical SARS-CoV-2 cytopathic disease [85].

3.5. Re-infection

Two studies found through viral gene sequencing that the positive nucleic acid tests were due to re-infection in 2 patients [60,63].

3.6. Risk factors for RP patients

Based on the results of included studies [83,98,99,107,110,112,115,117,118,121,129], we found that patients classified with a severe first episode [112], aged 60 years and above [98], and co-morbidities were more likely to be RP after discharge [99,121], especially those having hypertension or chronic respiratory diseases [121].

When compared with the patients without RP results, the RP patients had a higher level of fever [107,129], a higher proportion with symptoms like diarrhea [118], sore throat, and rhinitis [115], and a higher level of some laboratory indices such as serum IL-6 [83], ALT, AST [110], erythrocyte sedimentation rate, D-dimer [129], lymphocyte ratio [121] than those at the first hospitalization. However, neutrophil counts were comparatively lower [107]. According to the results of CT scans, the proportion of patients with lung consolidation or bilateral pulmonary infiltration were higher in the RP patients [83]. Moreover, they may have had a longer hospital stay [99,129], and higher proportion receiving antibiotics and/or glucocorticoid treatment that those when they were first infected [99].

In addition to the above results, Deng et al. reported that in pediatric patients infected with SARS-CoV-2, family cluster infection,

higher white blood cell counts, and longer plasma prothrombin time are the early risk factors of RP [117].

3.7. The results of meta-analysis

3.7.1. The RP rate of discharged patients

Forty-three studies with a sample size of more than 30 and with a total of 17,774 discharged patients were included in the meta-analysis according to our pre-planned rule. Among them, 39 studies were conducted in China, 3 in Italy, and 1 in Brunei Darussalam. The range of discharged patients for every study was from 34 to 7127, the RP rates ranged from 2.38% [20] to 36.8% [117]. The pooled RP rate was 12.2% (95% CI 10.6–13.7) with high heterogeneity ($I^2 = 85\%$) (Fig. 2). Cumulative meta-analysis showed that the point estimation value was gradually stable with the increase of sample size, and the confidence interval was gradually narrowed, indicating that the accuracy of results improved with larger samples (appendix p 97).

After removing one study from the analysis each time, the results of 42 sensitivity analyses showed good consistency with the range of RP rate from 12.0% to 12.6% (appendix p 98). Meanwhile, Egger's test showed there was publication bias among the studies ($P = 0.0027$).

3.7.2. The results of subgroup analysis

Twelve studies [20,83,87,90,91,99,100,103,104,106–108] also reported RP rates for males and females, respectively. The results showed that RP rate of females was 12.3% (95% CI 8.9–16.2) and males was 12.1% (95% CI 8.1–16.8) with high heterogeneity ($I^2 = 75\%$) (appendix p 99).

There are no available data for us to calculate the results of subgroup analyses for age, disease severity and co-morbidities.

4. Discussion

In this systematic review and meta-analysis, the clinical manifestations of the RP patients were usually normal or mild, and the CT imaging and laboratory examination were mostly normal. However, the RP patients accounted for approximately 12% of the discharge patients, which is enough to arouse our concern. Are they not cured or have they been re-infected? Are the RP patients infectious or not, and what are the risk factors causing them to retest positive? All these problems need to be explored in depth at this time.

The chief reasons for patient becoming RP are potentially as follows:

1. The results of RT-PCR may be a false negative at discharge. RT-PCR results are often used as an indicator of patients' diagnosis, discharge and isolation, but the sensitivity of RT-PCR detection is affected by many factors, such as sample type, sample collection, sample transportation and instability of test kits or variance of technicians in different labs. At present, nasopharyngeal swab samples are commonly used for RT-PCR test. The operation of collecting samples is highly dependent on the operator's experience and it is possible that the location of the samples is not accurate. Even if the operation is correct, the target virus might not be collected [16], which might lead to the possibility of false negative test results at discharge.
2. The emergence of RP results may due to incomplete elimination of the virus. The clearance of novel coronavirus from the body may take a long time [131–133], even after a respiratory specimen had tested negative for a coronavirus, stool samples have tested positive for the virus for up to five weeks [132]. Two studies reported that patients still shed the virus during the convalescent period which was confirmed by samples collected in the isolation room [134,135]. One study reported that patients discharged from hospital might present with SARS-CoV-2 reactivation [136].

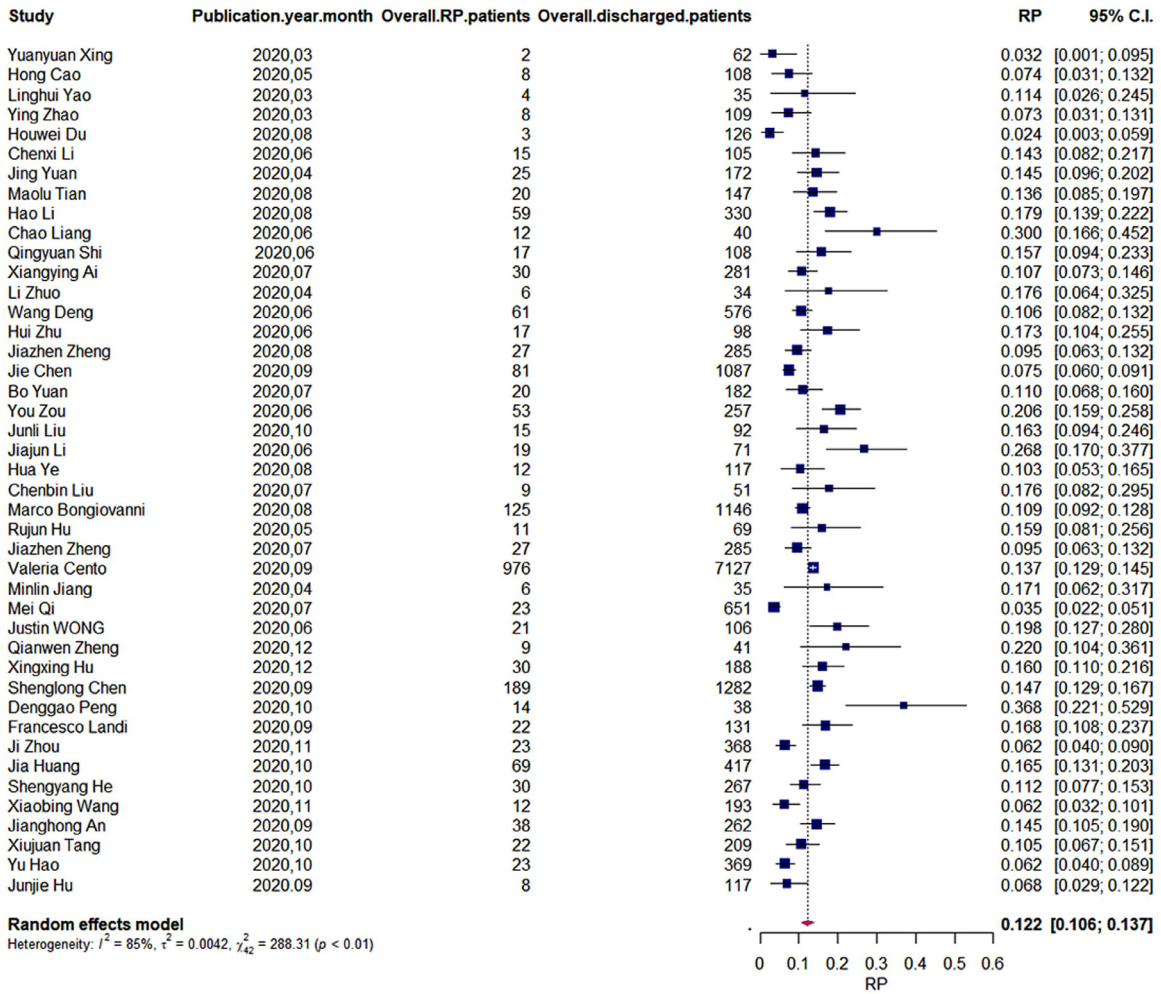


Fig. 2. Forest plot of RP rate of discharged patients.

Short duration of immunity that could explain the reactivation of the virus after a period of negative viral testing.

We have not been able to confirm the exact correlation between the factors such as use of the glucocorticoids, older age, co-morbidities and the RP events at present, but our results show that patients with these characteristics have a relatively high likelihood of RP results. Glucocorticoids are still used in the treatment of COVID-19, although their clinical application has been controversial [137]. Some studies have shown that although glucocorticoids can inhibit lung inflammation, they can also damage the activity of B and T lymphocytes, and may inhibit pathogen clearance and immune response of the body [138,139]. Immunosenescence in older patients also impairs innate and adaptive immune responses [140,141]. There seems to be a common denominator among these factors: they all have some degree of influence on the body's immune response. Immune response is the body's response to viral infection. Macrophages, neutrophils and dendritic cells produce a nonspecific innate response that slows the virus' progress and may even prevent the virus from causing symptoms [142]. After this non-specific response, the body will generate an adaptive immune response that specifically binds to the virus, and the adaptive response of this combination may clear the virus from the body [141]. Therefore, we can infer that if the patient's immune response has been suppressed, the process of viral clearance may also be prolonged, and the ability to inhibit virus replication will be relatively weakened. Therefore, the nucleic acid test results may become positive again after discharge.

Although nearly 12% of patients still test positive after discharge based on the available evidence, most of these patients were asymptomatic or with mild symptoms, the viral load was low, the virus culture showed no activity, and there were only one report of infection in close contacts, suggesting that the possibility of further virus transmission was low [143]. We should not be panic about RP patients.

But recently, some studies have reported that discharged patients may become re-infected with different strains of the virus [144-149], which reminds us that re-infection appears to be a possibility in convalescent patients. When confirming the diagnosis of re-infection, it is necessary to identify two different phylogenetic strains [150]. To et al. reported the first case of reinfection with COVID-19, whose result of whole genome analysis showed that different virus strains were identified in each infection event [147]. These rare phenomena suggested that previous exposure to COVID-19 might not guarantee total immunity [148].

Above all, it is still necessary for discharged patients to use personal protection to reduce the possibility of re-infection or transmission. In addition, some RP patients experienced high psychological pressure, leading to organic insomnia and anxiety aggravation, which in turn may lead to the change of their conditions [41]. It is necessary to give sufficient mental health care for these RP patients.

Although six systematic reviews and/or meta-analyses have been already published [142,151-155], none of them were comprehensive in terms of literature search. For example, one systematic review did not report the results of a systematic search, the number of included studies was uncertain [151]. Another one systematic review only

described the number of days from discharge to relapse and the symptoms of PR patients, which provided less information [142]. Three meta-analysis included small numbers of cases, including 17 [155], 14 [154] and 9 [153] cases, respectively. And five of them did not assess the quality assessment [151–155]. We have summarized and analyzed the clinical characteristics of these RP cases, pooled the RP rate, performed the subgroup analysis of gender, focused on the possible causes of RP results, and provided some suggestions for management.

However, there are some limitations in this current review. First, most available studies were from China, and were single-center observational studies. Additionally, some study types were unclear. Second, the quality of most articles was not high. Many of studies have design faults, and some problems may exist in the statistical methods. For example, the potential confounding factors were not controlled, which might lead to uncertain estimation. Third, in the meta-analysis section, we did not conduct subgroup analyses for age, disease severity and co-morbidities, because the data of the relevant subgroups could not be completely extracted and merged.

In conclusion, most of the RP patients had normal clinical manifestations or only mild symptoms, and laboratory and CT imaging showed improvement compared with those at their first discharge. In the future, more high-quality studies with appropriate sample size calculation are urgently needed to help us understand the etiology and pathological mechanism of being RP, and further help us to make strategies to control and prevent its occurrence.

Declaration of Competing Interest

All authors reported grants from Emergency Special Project for COVID-19 of Wuhan Municipal Health Commission, during the conduct of the study. Jin et al. [15,156] conducted clinical practice guidelines on COVID-19. Jin, Yao, Zeng, Huang, Luo, and Wang reported grants from Entrusted Project of National Center for Medical Service Administration, National Health and Family Planning Commission China, Special Project for Emergency of the Ministry of Science and Technology, First Level Funding of the Second Medical Leading Talent Project in Hubei Province, National Key Research and Development Program of China, and Special Project for Emergency of Hubei Province, outside the submitted work [15,156]. Ren and Shi reported grants from First Level Funding of the Second Medical Leading Talent Project in Hubei Province, National Key Research and Development Program of China, and Special Project for Emergency of Hubei Province, outside the submitted work [15]. Jin, Zeng and Yao are the first author and corresponding authors, respectively and are members of the steering group, Ren, Huang, Luo, Wang and Shi are authors and are members of the systematic review group in *Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: An evidence-based clinical practice guideline (updated version)* [15]. Jin, Zeng are first author and corresponding author, respectively and are members of the steering group, Yao, Huang, Luo and Wang are authors and members of the systematic review group in *A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)* [156]. Zeng and Jin reported research projects involving infection of healthcare workers during this epidemic, which was supported by Special Project for Emergency of Hubei Province (2020FCA008).

Contributors

Yinghui Jin, Xiaomei Yao and Xiantao Zeng conceived and designed the study. Xiangying Ren, Xiangge Ren and Jiaao Lou were involved in the search process, study selection and data extraction, and wrote the manuscript. Qiao Huang, Yongbo Wang, Siyu Yan, Yunyun Wang, Lisha Luo and Liye Lu were involved in data analysis, study selection and data handling, and commented on drafts of the

manuscript. Yuqing Deng, Xiaoyan Li and Yuexian Shi were involved in the quality assessment and commented on the manuscript. Yinghui Jin, Xiaomei Yao and Xiantao Zeng revised the manuscript. All authors reviewed the study findings and approved the final version before submission.

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Data sharing statement

The data used in this study were gathered from publicly available studies and available from the corresponding authors upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100839.

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