Review Article

A systematic review on the readmission of COVID-19 Patient: frequency and individual factors

ABSTRACT

Background and Objectives: The COVID-19 pandemic has severely damaged the world economy. Due to the COVID-19 infection, hospitalization is in high demand. Numerous COVID-19 patients are treated medically, released from the hospital, and then relapse and need to undergo treatment because they test positive. This places a strain on the health services, and the number of relapses is rarely reported in the literature**.** The purpose of the study is to assess individual and frequency-based factors that influence readmission of COVID-19 patients**.**. **Method**s: This study uses a systematic review of the literature, using the PICO strategy for the construction of the research question, the bibliographic search and the best available scientific information in the systematization. **Results:** The traits of the chosen studies are compiled in Table 3. In the period from March 30, 2020, to February 23, 2021, 28 studies were published. The majority of studies were carried out in China, with Wuhan reporting the highest number. There were also some studies conducted outside of China, including one from South Korea, six from the United States specifically, one from Spain, and one from Turkey. Age 65 was a risk factor for readmission or re-positive rates, which ranged from 3.6% to 67.1%. **Conclusion**: The hospital strictly controls Covid-19 patients before they are allowed to leave the hospital to prevent recurrence as a result of relapse in Covid-19 patients during the pandemic.

Keywords: The readmission of COVID-19 Patient, A systematic review, Frequency and individual factors, Relaps (re-infection)

1. INTRODUCTION

Covid-19 is designated as a pandemic disease that spread to all countries around the world. WHO announced covid 19 as an international pandemic on March 11, 2020. As of October 21, 2021, there were 241,886,635 confirmed cases, with the death reaching 4,919,755. (1) Coronavirus disease (COVID-19) is a communicable disease that infected from mild to severe respiratory illness. Adults with comorbid diseases such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer have a greater exposure of establishing severe COVID-19 infections. Drops of sputum or take from the nose when coughing or sneezing is a mechanism for the spread of the COVID-19 virus. (2)

Epidemiological research has been carried out on the mechanisms of transmission and prevention, including vaccinations that have been carried out in many countries around the world. Several studies have reported the incidence of readmission/reinfection/recurrence of Covid 19. Readmission affects the continuity of health services, especially when hospitals are facing a significant increase in the number of new cases. This becomes a double burden for health services. Currently, there is still limited literature on the level of COVID-19 readmission. (3)(4) Understanding the epidemiology of readmission will provide an overview of re-evaluating current criteria for hospital

discharge, improving patient outcomes during a pandemic, and establishing evidence-based policies for the handling of COVID-19. This systematic review focus on identifying the characteristics, frequency, and clinical features of readmission patients.

2. MATERIALS AND METHOD

Review Methods

A systematic review is a review based on empirical evidence determined according to certain criteria to answer research questions that have been formulated previously. To reduce bias, explicit and systematic methods are used to make conclusions more reliable. (5) A systematic review can be carried out on prevalence and incidence data. This review is useful for policymakers to provide information related to various health care problems, especially those that are the current and future burden of disease. (6)

The prevalence or incidence review aims to measure the burden of disease (either at the local, national, or global level). Prevalence shows the distribution of the population anguish a specific disease. Incidence indicates the frequency of occurrence of the disease. (7) The Joanna Briggs Institute has established a prevalence and incidence review. (6)

Assessment of prevalence and incidence data in this review used the mnemonic CoCoPop (condition, context, and population). Condition refers to health conditions, diseases, symptoms of readmission. Context refers to environmental factors that have an impact on prevalence or incidence. The population is defined as individual factors that indicate the characteristics of respondents. (6) Table 1 illustrates the CoCoPop structure of this study.

Tabel 1. CoCoPop structure

Condition	Readmission, recurrence, relapse, reinfection, rehospitalized of COVID-19
Context	The country that occurs, the period
Population	Frequency and individual factors

Research Question

Research questions (RQ) were determined to focus the whole process of systematic review methodology. The research questions for this literature review can be constructed, as displayed in table 2.

Tabel 2. Research questions (RQ)

ID	RQ	Motivation
RQ 1	In which country did the readmission occur?	identify in which countries the most readmissions are reviewed
RQ 2	What is the rate of readmission cases?	Identify the magnitude of the problem of readmission events
RQ 3	What is the median number of days of readmission since the patient discharge?	Identify when readmission occurs
RQ 4	What are the individual factors in readmission patients?	Identify individual risk factors for readmission.

RQ 1 to RQ 2 aims to summarize the prevalence or incidence in a particular jurisdiction. (6) RQ 3 to RQ 4 describes variables such as symptoms and risk factors. (6) The subsection of research questions for this literature review is displayed in Figure 1.

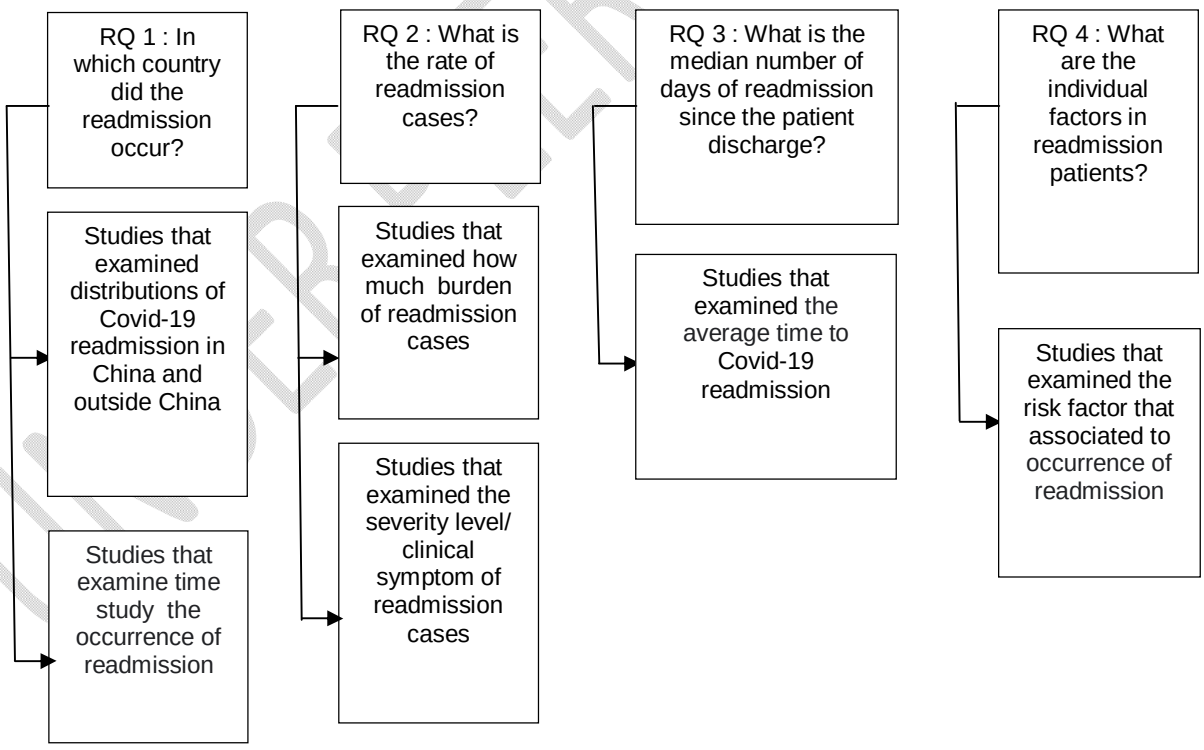

Figure 1 The subsection of research questions

Search strategy

We conducted a systematic search until 23 February 2021. A search of research articles relevant to this research topic was conducted using keywords : (Readmission OR Recurrence OR Relapse OR Reinfection OR Rehospitalized) AND (Covid 19 OR COVID-19) AND (Patient). PubMed and Science direct were the primary databases of research.

The literature search development were compiled using Mendeley. After screening for duplication, article titles and summaries sourced from the database are removed to the Mendeley citation manager. Articles that did not fit the inclusion criteria were rejected from the review.

Inclusion and exclusion criteria

Inclusion criteria are as follows:

1. Research that reports recurrent COVID-19 symptoms
2. Readmission occurred after being discharged from the hospital
3. Research paper

Exclusion criteria are as follows:

1. Studies not published in English
2. Editorial/ Commentary letter
3. Review articles
4. Case report

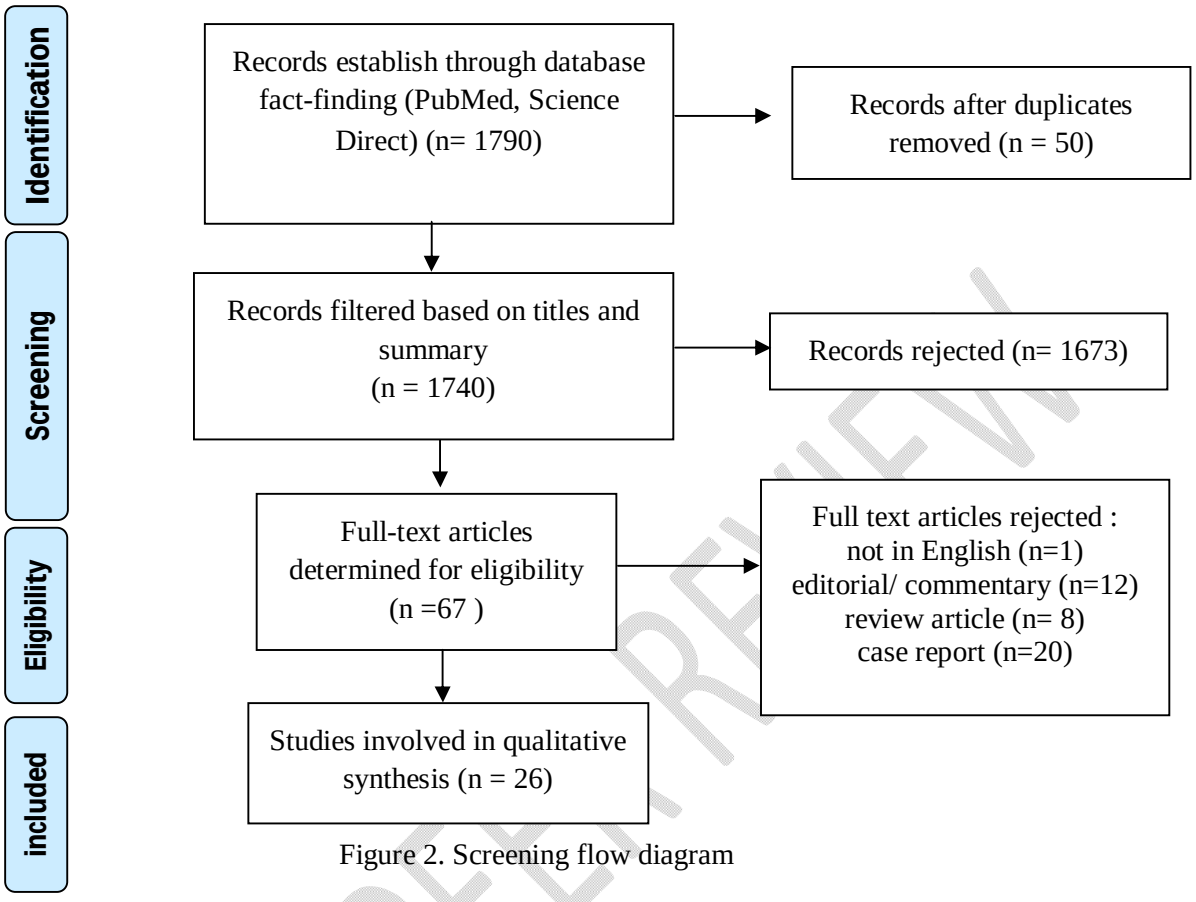

Figure 2. Screening flow diagram

Data screening and eligibility

In this study, we identified 1790 articles via a literature search and 50 duplicates were removed. After reviewing the title and summary, 1740 articles were rejected and 67 articles full-text articles were determined for eligibility. A total of 1740 articles were rejected because did not contain any information on the readmission, recurrent, relapse, rehospitalization, or reinfection of COVID-19. Applying the selection criteria, only 26 articles met the inclusion criteria and were involved in the final review (Figure 2).

Data collection and analysis

Data were collected in the following categories when available: Author, Study date, Study country, Study design; Rate of readmissions, Median days, Individual factors of readmission.

3. RESULT

The country did the readmission occurs

Table 1 compiles the characteristics of the selected studies. These studies were 28 reported between March 30, 2020, and February 23, 2021. The majority of studies were

conducted in China (17/26) where the highest number was reported in Wuhan (4/17) and some studies were conducted outside China: there was one study from South Korea (8), six from the USA (9)(10)(3)(11)(12)(13), one from Spain (14), and one from Turkey (15).

All of the studies report the study dates in 2020, the majority of studies were studied until May 2020 (15/26) and the other studied until March (11/26). The majority of studies were retrospective studies (10/26), cohort studies (8/26), observational studies (3/26), two case-control studies, two case series studies, and one descriptive study. All of the articles' study the case of Covid 19 in 2020 based on the electronic medical record.

Rate of readmission cases

The readmission rate or re-positive ranged from 3.6% to 67.1%. The positive result is confirmed by PCR or nasopharyngeal swab. Somani et al. found the minimum incidence (3.6%, N= 2864), and Lee et al. found the maximum incidence (67.1%, N= 73). (12)(10)

Median days of readmission

Median days represent the average duration of viral shedding, symptoms, and outcome. When a positive case is found, quarantine must be carried out until a negative result is obtained. This shows that prolonged viral shedding affects a longer quarantine period. (16)

The individual factors in readmission

Eleven studies report clinical severity. There were only 2 studies that state the guidelines for determining clinical severity, namely admit to the guidelines of the National Health Commission (NHC) and the Chinese Guidelines for Diagnosis and Treatment for Novel Coronavirus Pneumonia. (17)(18)

The average length of stay readmission range from 3 to 30 days. The highest report by Gao et al, and the lowest report by UyaroĞlu et al. (19)(4) The median range period from disease onset to readmission ranged from 2.6 days to 29 days. (20)(21) Risk factor of readmission or re-positive of covid 19 describe in table 2.

4. DISCUSSION

Coronavirus disease (COVID-19) has caused havoc in the world. COVID-19 infection has led to high demand for hospital admissions. Many COVID-19 patients were clinically cured and discharged from the hospital but were readmission again because they showed positive test results. This becomes a burden for the health service. To date, published data on relapse are very limited.

Understanding readmission epidemiology will provide an overview of re-evaluating current criteria for hospital discharge, improving patient outcomes during the pandemic, and establishing evidence-based action for COVID-19 prevention and medication. This review found that the incidence of readmission in hospitals in China was higher (17/26) than those outside China (9/26). That's because the coronavirus disease (COVID-19) pandemic was initiated in Wuhan, China, in December 2019. The highest cases were found in Hubei Province (75%). The cause of exposure was Wuhan residents or people who visited Wuhan or had close contact with Wuhan residents (86%). The highest cases were classified as non-pneumonia and mild pneumonia (81%). (22)

The results of this study indicate that research in China was carried out before March 2021, while outside China began at the end of February 2020. On January 30, 2020, WHO global alert public health emergency of international interest. The cases in China there are 7736 confirmed cases, 170 deaths, and outside China are 82 confirmed cases. On Feb 11, 2020, China announce an epidemic of acute respiratory symptoms in Guangdong to the WHO. (22) This is following the WHO's determination of the status of Covid-19 as a Pandemic on March 11, 2020.

The higher readmission rate has occurred in Shenzhen, China. Patients with positive NP swab RT-PCR test results after an average of 21 days recurring intervals showed that 19.4% had a second experienced and 3.2% had a third recurrence after a mean interval of 9 and 8 days, commonly. After discharge, the average length of viral shedding at 1st was 7 days, 2nd was 5 days and 3rd was 7 days. (23) When compared with the first admission, patients who were re-detectable as positive had moderate clinical symptoms, decreased viral loads, less length of stay, and enhanced lung status upon readmission. Lack of efficiency in virus approval is an exposure factor for detectable as positive. Older re-detectable as a positive case ($\geq$ 60 years) were more sensitive to clinical symptoms at readmission. (24)

In this study, the readmission rate range from 3.6% to 67.1%. According to research Wang et al., there were three confirmed SARS-CoV-2 cases with constant gastrointestinal symptoms and the presence of SARS-CoV-2 RNA in samples during readmission after previously being declared cured. The cause is a persistent infection in the intestines. (25) The cause of readmission is because the virus is very damaging to the patient's immune function, especially in patients with comorbidities, so the virus is not completely cleared. (17)

Readmission also occurs when there is respiratory suffering followed by mental health disease and thrombotic episodes. In the study of Atalla et al, readmission occurred in the first 12 days after the patient was discharged. This is related to the development and complications of COVID-19. At the time of readmission, a longer treatment is needed so that it requires the utilization of more health care resources. (3)

In the study by Somani et al, 103 (3.6%) returned to the hospital 14 days later, of which 56 (54.4%) get readmission and 47 (45.6%) get emergency services (ED). Generally caused by respiratory problems (50%). (12)

Several studies report the severity level of illness. Tian et all reported all severity illnesses to include mild 15%, moderate 60%, severe 15%, and critically ill 10%. (17) The majority of the cases were moderate. The moderate category indicates that based on clinical or imaging assessments, the individual has a lower respiratory disease and an oxygen saturation (SpO2) of 94%. (26) Lu et all reported that all re-positive patients only had moderate, with the average age of the sufferer being lower than the general COVID-19 case. (27)

The average length of hospital stay ranged from 3 to 30 days. A less length of stay at first admission is correlated with larger readmission incidence. (8) Insufficient length of stay is one of the reasons for the positive result of the SARS-CoV-2 RNA test after discharge. (28) Patients are allowed to leave the hospital if they meet the criteria: 1) Normal body condition for more than three days; 2) Respiratory manifestation improved 3) Pulmonary imaging present absorption of infection, 4) Nucleic acid test was negative for two continuous tests of respiratory tract case (sputum and nasopharyngeal swab). (26) The COVID-19 Discharge Care Program consisting of

moderate discharge criteria and post-discharge control by telephone was correlated with low readmission rates and increased patient satisfaction. (11) The length of stay for those who were re-positive was significantly shorter than that of those who were not. This means that the length of stay in the hospital is important. (29) Research conducted by Hua Ye et al showed that cases with a longer length of stay and having lymphopenia were potential risk factors for a positive retest for SARS-CoV-2 after discharge from the hospital. (30)

The median days from discharge to readmission range from 2.6 days to 29 days. Readmission risk factors after 30 days of hospital discharge are a complicated situation of comorbidities, disease severity affecting index hospitalization, the changeover to outpatient care, and patient improvement. Early readmission is correlated with poorer outcomes and harms the patient's quality of life. (13) Regardless of the cohort study, based on 8 studies, the detection of recurrence of SARS-CoV-2 followed by readmission had been reported within the range 3-29 days after meeting criteria for discharge.

Several studies report risk factors of readmission. Attala et all reported that readmission patients had consequently higher rates of hypertension, diabetes, chronic lung disease, liver disease, cancer, and substance abuse than those who did not. (3) The most common cause of readmission is respiratory distress. (12) Older age and female are risk factors for repeated positive results. (31) Readmission risk factors were age 65 years, the existence of certain chronic circumstances, medication in the 3 months before the first COVID-19 admission, and health care skills at home. (9) Chen et all reported that elevated serum IL-6 increased lymphocyte counts and CT imaging appearance of lung consolidation during hospitalization as the independent risk factors of recurrence. (32) The readmission rates of men, older age, the Charlson Comorbidity Index score, and patients with medical benefits showed a high risk of readmission. There was a higher risk of readmission for the patients with chest radiographs, computed tomography scans taken and lopinavir/ritonavir at the time of their first admission. The readmission rate of patients with underlying diseases was two times higher than those without an underlying disease. (8) Patients who are immunocompromised and have a fever for 48 hours before discharge have a greater risk of readmission. (11) Fatigue, number of initial symptoms, and creatine kinase levels were also associated with repeated positive RT-PCR results. (33)

5. CONCLUSION

This systematic review contributes evidence of readmission among COVID-19 patients. This review also contributes to median days from discharge to admission. Patients with older age, have a comorbidity of hypertension and diabetes, and immunocompromised patients were at increased risk for readmission. Therefore, physicians and policymakers should consider this high rate when making discharge decisions, distribute patients with a high risk of readmission, and organize patients before and after discharge, and patients monitoring after discharge and tight self of isolation for recovered patients should be well applied.

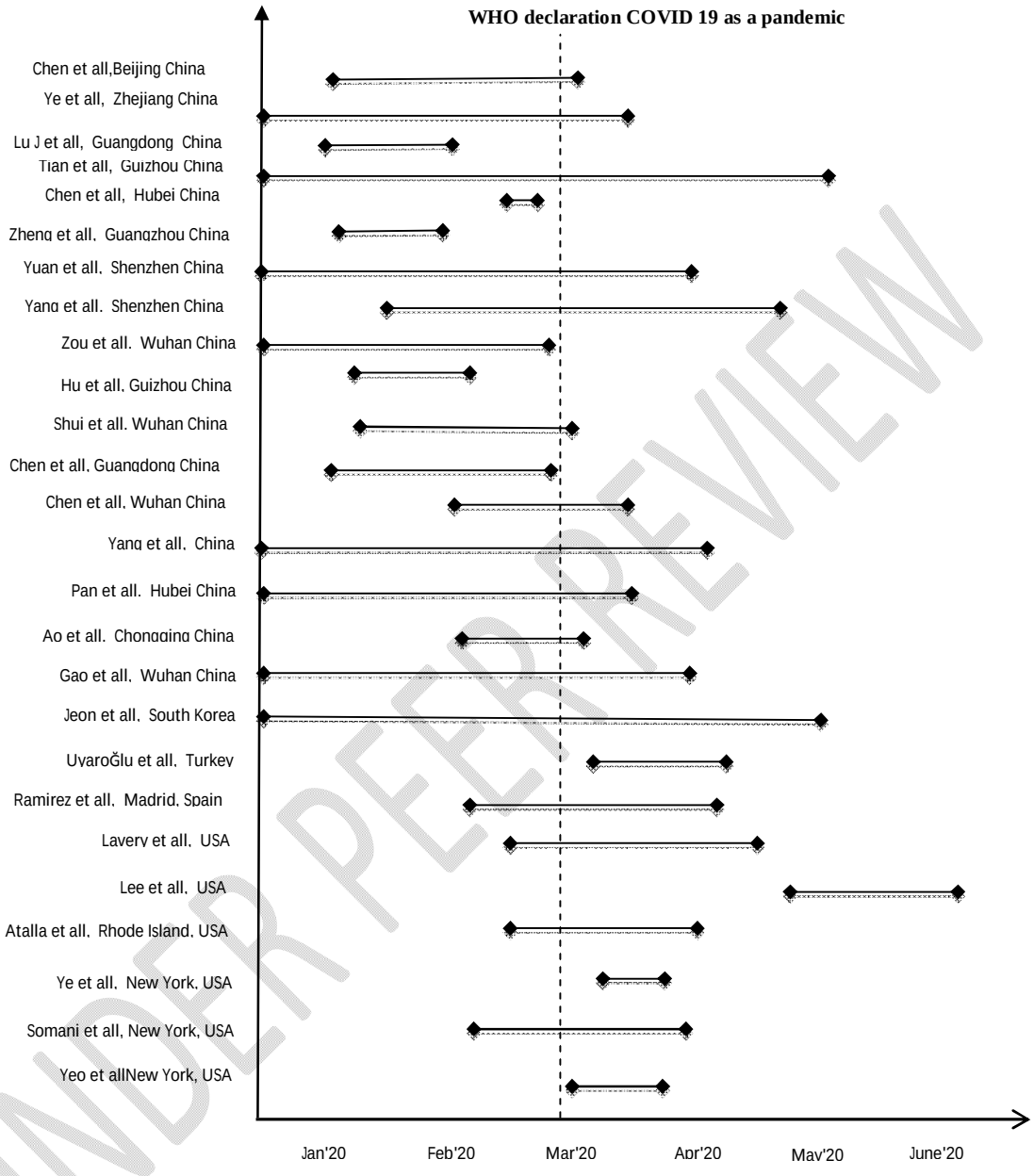

Figure 3. Study date and country

Table 3. Clinical manifestation and individual factors

No	First Author	Study design	Sample size (patients)	Rate of readmissions/ Redetectable positive SARS-CoV-2 RNA	Clinical severity/ clinical symptoms	Median days viral RNA positive/ readmission post-discharge	Av LOS readmission/ median hospitalization	Individual factors of readmission
1	Zhihai Chen	retrospective cohort study	109	27% (29)	N/A	29 days (IQR 27–42)	21 days (IQR 17–36)	Risk factors for SARS-CoV-2 reactivation or convalescent individuals who have difficulty with practicing social distancing should undergo active surveillance to detect disease reactivation.
2	Hua Ye	retrospective cohort study	117	10.3% (12)	N/A	15 days (IQR 12-18)	19 days (IQR 14.3-27)	Longer hospital stay and lymphopenia could be potential risk factors for positive SARS-CoV-2 retest in COVID-19 patients after hospital discharge.
3	Lu J	retrospective study	619	14% (87)	Mild 52.9% (46), moderate 47.1% (41)	7 days (range 2-19)	14 days	All re-positive cases only mild or moderate symptoms in the initial diagnosis, with the median age being significantly lower than of the general COVID-19 cases.
4	Tian et al.	observational study	147	13.61% (20)	Mild 15% (3), moderate 60% (12), severe 15% (3), Critically ill 10% (2)	17.25 days (range 7-47)	16.1 days	N/A
5	Chen M	retrospective study	11	36.4% (4)	N/A	16.00 ± 7.14 days (range 6 - 27)	(7.00 ± 2.56) days	Compared with the first hospitalization, there were significant decreases in gastrointestinal symptoms (5 vs. 0, P=0.035), elevated levels of both white blood cell count（P=0.036） and lymphocyte count (P=0.002), remarkedly decreases in CRP and SAA (P<0.05) in the second hospitalization.
6	Zheng et all.	prospective cohort study	285	9.5% (27)	Mild 11.1% (3), moderate 88.9% (24)	7 days	18 days	Compared to the first admission, RP patients generally had milder clinical symptoms, lower viral load, shorter length of stay, and improved pulmonary conditions at readmission. Patients' lack of efficiency in virus clearance was a risk factor for RP results. It is noteworthy that elder RP

								patients (≥ 60 years old) were more susceptible to clinical symptoms at readmission.
7	Yuan B	a cohort study on the follow-up	182	10.99% (20)	N/A	N/A	20.8 ± 7.1 days	The time from admission to discharge of the repositives was significantly shorter than for the non-re-positives, indicating that the length of hospital stay might be important.
8	Lavery et all	cohort	106,543	9% (9,504)	N/A	8 days (IQR 3–20).	8 days (IQR 4–15)	Risk factors for readmission included age ≥65 years, presence of certain chronic conditions, hospitalization within the 3 months preceding the first COVID-19 hospitalization, and discharge to a skilled nursing facility or with home health care.
9	Yang C	observational study	479	19% (93)	Asymptomatic 8% (7), mild 14% (13), moderate 74% (69), severe 3% (3), critical 1% (1)	8 days (range 7–14)	20 days (range 17–24)	An intermittent, non-stable excretion of low-level viral RNA may result in recurrent-positive occurrence, rather than re-infection. Recurrent-positive patients pose a low transmission risk.
10	Zou Y	retrospective cohort study	257	20.6% (53)	General type 67.9% (36), severe 28,3% (15), critical 3.8% (2)	3 days (range 1-12)	N/A	Hypertension, diabetes, and coronary heart disease were the most common underlying diseases, followed by other respiratory diseases, cerebrovascular disease, and malignant tumors.
11	Hu R	case series study	69	15,9% (11)	Mild 9.1% (1), moderate 81.8% (9),critical 9.1% (1)	14 days (range 9-17)	10 days (range 7-24)	Fatigue, number of initial symptoms, and creatine kinase level could be associated with recurrent positive RT-PCR results, but further verification is required because of the limited number of patients.
12	Jeon et al.	case-control	7590	4.3% (328)	N/A	N/A	9 days (range 1–18)	The readmission rates of men, older age, the Charlson Comorbidity Index score, and patients with medical benefits showed a high risk of readmission. There was a higher risk of readmission for the patients with chest radiographs, computed tomography scans taken and lopinavir/ritonavir at the time of their first admission. The readmission rate of patients with underlying diseases was two times higher than those without an

								underlying disease.
13	Shui TJ	retrospective study	758	7.78% (59)	Mild 27.12% (16), moderate 67.80% (40) , severe 5.08% (3)	8 days (IQR 4–11)	N/A	No risk factors
14	Chen SL	retrospective study	1282	14.74% (189)	N/A	8 days (IQR 5–13)	10 days (IQR 6–17)	The short-term recurrence of positive SARS-CoV-2 RNA in discharged patients is not a relapse of COVID-19, and the risk of onward transmission is very low.
15	Chen et al.	retrospective study	1087	7.6% (81)	Mild 84.0% (68), severe 14.8% (12), critical 1.2% (1)	9 days (range 3-18, IQR 7-10)	12 days (range 4-27, IQR 7-17)	Elevated serum IL-6, increased lymphocyte counts, and CT imaging features of lung consolidation during hospitalization as the independent risk factors of recurrence.
16	Yang Z	consecutive cohort	79	7.9% (7)	Mild 14.3% (1), moderate 85.7% (6)	N/A	18.3±5.35 days	Significant CT imaging and clinical feature differences were found between atypical and typical COVID-19 patients for all three atypical presentation categories investigated
17	Lee JT	descriptive statistics	73	67.1% (49)	N/A	14 days (IQR 10.3-19)	N/A	N/A
18	Pan L	retrospective study	1350	14 patients	N/A	2.6 days	8 days	Several endpoints including prothrombin time, activated partial thromboplastin time, aspartate aminotransferase, and creatinine were significantly lower on the second admission than on the first admission.
19	Ao Z	retrospective study	51	49% (25)	N/A	N/A	14 days (IQR 12–19)	No significant difference

20	Gao C	retrospective study	599	35.9% (215)	Moderate 95.0% (569), severe 5.0% (30)	10 days (IQR 7-14)	30 days (range 23-40)	Older age and being female were risk factors for recurrent positive results.
21	UyaroĞlu OA	an observational, single-center study	154	7.1% (11)	Mild 18.1% (2), moderate 81.9% (9)	8.1 days (IQR=5.2)	3 days (IQR=3)	N/A
22	Ramírez et all	nested case-control	1368	4.4% (61)		6 days (IQR 3–10)	6 days (range 4–14)	Immunocompromised patients and those presenting with fever during the 48 hours before discharge were at greater risk of readmission to the hospital.
23	Atalla E	retrospective review	279	6.8% (19)	N/A N/A	5 days (IQR 3.00-13.00)	6 days (range 3-12)	There was a significantly higher rate of hypertension, diabetes, chronic pulmonary disease, liver disease, cancer, and substance abuse among the readmitted compared with non-readmitted patients.
24	Ye S	Retrospective case series	409	7.6% (31)	N/A	4 days (IQR 3, 7, range 0–14)	5.0 ± 3.9 days	No significant differences
25	Somani et al.	Retrospective cohort study	2864	3,6% (103)	N/A	4,5 days	4.7 days (IQR 2.9-9.1)	The most common cause for return to hospital was respiratory distress. Returning patients were more likely to have a history of COPD and hypertension and have had a shorter length of stay and a lower frequency of therapeutic anticoagulation use during their index hospitalization.
26	Yeo I	retrospective observational study	1062	4.5% (48)	N/A	5 days	6 days (range 2–10)	A peak serum creatinine level measured during the index hospitalization was linearly associated with the risk of 30-day readmission

DATA AVAILABILITY

Supporting information papers and files contain all necessary information. This study will assist researchers in identifying critical areas of reinfection in readmission of COVID-19 patients, including frequency and individual factors in hospital.

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