Annals of Global Health

Characteristics of COVID-19 Recurrence: A Systematic Review and Meta-Analysis

ORIGINAL RESEARCH

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ABSTRACT

Background: Previous studies reported the recurrence of coronavirus disease 2019 (COVID-19) among discharge patients. This study aimed to examine the characteristic of COVID-19 recurrence cases by performing a systematic review and meta-analysis.

Methods: A systematic search was performed in PubMed and Embase and gray literature up to September 19, 2020. A random-effects model was applied to obtain the pooled prevalence of disease recurrence among recovered patients and the prevalence of subjects underlying comorbidity among recurrence cases. The other characteristics were calculated based on the summary data of individual studies.

Results: A total of 41 studies were included in the final analysis, we have described the epidemiological characteristics of COVID-19 recurrence cases. Of 3,644 patients recovering from COVID-19 and being discharged, an estimate of 15% (95% CI, 12% to 19%) patients was re-positive with SARS-CoV-2 during the follow-up. This proportion was 14% (95% CI, 11% to 17%) for China and 31% (95% CI, 26% to 37%) for Korea. Among recurrence cases, it was estimated 39% (95% CI, 31% to 48%) subjects underlying at least one comorbidity. The estimates for times from disease onset to admission, from admission to discharge, and from discharge to RNA positive conversion were 4.8, 16.4, and 10.4 days, respectively.

Conclusion: This study summarized up-to-date evidence from case reports, case series, and observational studies for the characteristic of COVID-19 recurrence cases after discharge. It is recommended to pay attention to follow-up patients after discharge, even if they have been in discharge quarantine.

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TO CITE THIS ARTICLE:
Hoang T. Characteristics of COVID-19 Recurrence: A Systematic Review and Meta-Analysis. *Annals of Global Health*. 2021; 87(1): 28, 1–11. DOI: *https://doi.org/10.5334/aogh.3163*

DOI: 10.5334/aogh.3163

INTRODUCTION

Since December 2019, the world has been experiencing a public health crisis due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of September 01, 2020, about 26 million confirmed cases and 0.8 million deaths were reported from 213 countries and territories [1]. Several nationwide studies retrospectively investigated clinical features and the epidemiological characteristics of patients infected with SARS-CoV-2 [2–4]. Particularly, aging and underlying chronic diseases were reported to much contribute to the severity of coronavirus disease 2019 (COVID-19) [5–6]. However, patients with COVID-19 were generally less severe than SARS and Middle East respiratory syndrome (MERS), with the fatality rate of 9.6%, 34.3%, and 6.6% for SARS, MERS, and COVID-19, respectively [7]. Recently, it has been reported that SARS-CoV-2 RNA shedding duration could prolong up to 83 days [8–9]. In addition, the recurrence of SARS-CoV-2 after two consecutive negative detection of SARS-CoV-2 (sample collection interval of at least 1 day) has been observed among patients who had been discharged from health care units and received regular follow-up [8]. In general, recurrent cases can be defined as the relapse disease from a similar or same strain causing the primary infection and/or the reinfection disease from the distinct strain from the one causing the original infection [10–11]. Therefore, this systematic review and meta-analysis was conducted to examine the prevalence of either underlying conditions or comorbidities among recurrent COVID-19 cases, in addition to times from disease onset to hospital admission, from admission to hospital discharge, and from discharge to positive RNA conversion.

METHODS

An electronic search of PubMed and Embase was conducted for English language studies published from the inception until September 19, 2020. The keywords for searching were as follows: "(COVID-19 OR SARS-CoV-2) AND (recurrence OR recurrences OR reinfection OR re-infection OR re-positive)". Additionally, hand searching for related reports of the Centers for Disease Controls and bibliography of relevant studies was performed to obtain relevant information. For each study, the following information was extracted: first author's name, country, study type, number of recurrence cases and discharged patients, the sample used for reverse transcription polymerase chain reaction (RT-PCR), mean or median age (years), number of males, females, and cases underlying any chronic diseases (including chronic obstructive pulmonary disease, cardiovascular disease, hypertension, diabetes, liver or kidney disease, and cancer), times from disease onset to admission, from admission to discharge, and from discharge to positive conversion (days).

In this study, heterogeneity was quantified by the I^2 statistics, in which $I^2 > 50\%$ was defined as potential heterogeneity [12]. Given data are from different populations of various characteristics, a random-effects model was used to calculate the pooled effect size and its 95% confidence interval (CI) when the evidence from at least two individual studies was available [13]. All the statistical analyses were performed using STATA 14.0 software.

RESULTS

The study selection process is presented in ***Figure 1***. Initial 550 records were retrieved through PubMed (N = 239) and Embase (N = 311) and additional one gray literature through hand searching was identified. Among records after removing duplicates and non-English publications (N = 128), 423 studies were potentially relevant through reviewing titles and abstracts. After reviewing full-text articles, 15 studies were excluded because they reported overlapping cases (N = 6) or irrelevant population (N = 3), there was no information for outcomes of interest (N = 4), and they were studies of mechanisms or modeling (N = 2). The remaining 41 studies were therefore eligible for the final analysis [14–54].

A detailed description of extracted data of included studies is shown in ***Table 1***. Thirty-eight studies reported 466 recurrence cases from China (N = 33, 435 cases), Korea (N = 1, 83 cases), Iran (N = 1, 1 case), Brunei (N = 1, 21 cases), Italy (N = 2, 3 cases), France (N = 1, 11 cases), Brazil (N = 1, 1

DOI: 10.5334/aogh.3163

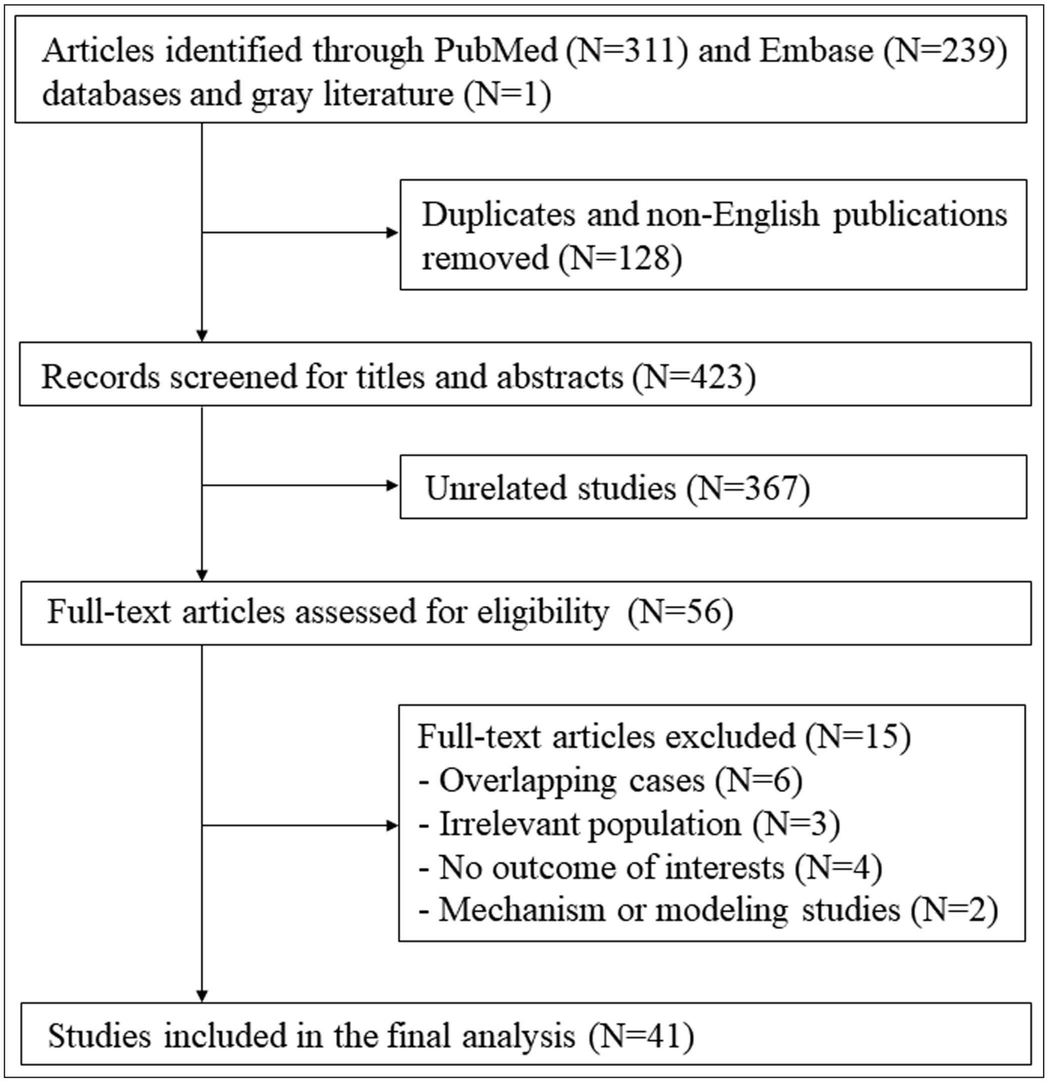

Figure 1 Flowchart of study selection.

case), and US (N = 1, 1 case). The study design included case reports (N = 14), case series (N = 6), and observational studies (N = 21).

The calculation of the epidemiological characteristics of COVID-19 recurrence cases is presented in ***Table 2***. Data for age were provided from 34 studies for 379 recurrence cases, with a mean age of 41.7 years. Among 542 recurrence cases from 39 studies, 233 cases were males, which accounted for 43%. Times from disease onset to admission, from admission to discharge, and from discharge to RNA positive conversion were available for 52, 276, 464 cases from 13, 22, and 31 studies, respectively. The estimates for times from disease onset to admission, from admission to discharge, and from discharge to RNA positive conversion were 4.8, 16.4, and 10.4 days, respectively.

The prevalence of COVID-19 recurrence cases after discharge was calculated from data of 21 observational studies (***Figure 2***). Among 3,644 discharged patients, the RT-PCR test turned to be positive in 406 Chinese, 83 Korean, and 21 Bruneian subjects. Overall, the prevalence of recurrence cases was 15% (95% CI, 12% to 19%). Substantial heterogeneity among studies was observed, with I^2 of 86.32%. In the subgroup analysis by population, the prevalence was reported to be 14% (95% CI, 11% to 17%) for China, 31% (95% CI, 26% to 37%) for Korea, and 20% (95% CI, 13% to 28%) for Brunei.

Furthermore, it was reported 106 subjects underlying comorbidity among a total of 271 recurrence cases, which accounted for 39% (95% CI, 31% to 48%) (***Figure 3***). There was no evidence of heterogeneity (I^2 = 42.08%). Subgroup analysis showed the proportion of 64% (95% CI, 35% to 85%) for France cases and 38% (30% to 45%) for Chinese cases.

Table 1 Summary of studies reporting recurrence of COVID-19 cases after discharge.

STUDY	COUNTRY	STUDY TYPE	NO. OF RECURRENCE CASES	NO. OF DISCHARGED PATIENTS	SAMPLE FOR TESTING	AGE (YEARS)	MALE/ FEMALE	NO. OF CASES UNDERLYING COMORBIDITY	TIMES FROM ONSET TO ADMISSION (DAYS)	TIMES FROM ADMISSION TO DISCHARGE (DAYS)	TIMES FROM DISCHARGE TO POSITIVE CONVERSION (DAYS)
Alonso FOM	Brazil	Case report	1		Respiratory swab	26	1/0				34
An J	China	Observational	38	242	Nasal and anal swab	32.8	16/22				
Batisse D	France	Case series	11		Naso-pharyngeal swabs	55	6/5	7			
Bongiovanni M	Italy	Case series	2		Nasopharyngeal swab		0/2	2			
Cao H	China	Observational	8	108	Deep nasal cavity or throat swab	54.4	3/5	0			16.3
Chen D	China	Case report	1		Oropharyngeal swab	46	1/0		8		
Chen J	China	Observational	81	1087	Throat swab	62	30/51	29		12	9
Chen Y	China	Observational	4	17	Oropharyngeal, nasopharyngeal, and anal swab	32	2/2			18.25	11.25
Duggan NM	US	Case report	1			82	1/0	1	7	39	10
Fu W	China	Case series	3		Nasopharyngeal swab	48	1/2			12	9.3
Gao G	China	Case report	1			70	1/0	1	5	15	12
Geling T	China	Case report	1		Pharyngeal swab	24	1/0	0		10	8
He F	China	Case report	1		Throat swab	39	0/1		10	13	8
Hu R	China	Observational	11	69	Nasopharyngeal swab	27	7/4	3		10	14
Huang J	China	Observational	69	414	Nasopharyngeal and anal swab		28/41	22	3	20	11
KCDC	Korea	Observational	83	269			28/41				14.3
Li J	China	Case report	1		Nasopharyngeal and oropharyngeal samples	71	0/1		14		
Li XJ	China	Case report	1			41	1/0		19	9	19
Li Y	China	Observational	6	13	Oral swabs, nasal swabs, sputum, blood, faeces, urine, vaginal secretions, and milk	51.3	3/3	3			10.2
Liang C	China	Observational	11	22	Throat swab						
Liu T	China	Observational	11	150	Throat swab	49	6/5				

(Contd.)

STUDY	COUNTRY	STUDY TYPE	NO. OF RECURRENCE CASES	NO. OF DISCHARGED PATIENTS	SAMPLE FOR TESTING	AGE (YEARS)	MALE/ FEMALE	NO. OF CASES UNDERLYING COMORBIDITY	TIMES FROM ONSET TO ADMISSION (DAYS)	TIMES FROM ADMISSION TO DISCHARGE (DAYS)	TIMES FROM DISCHARGE TO POSITIVE CONVERSION (DAYS)
Loconsole D	Italy	Case report	1		Nasopharyngeal swab	48	1/0	0		15	30
Luo A	China	Case report	1		Throat swab	58	0/1		7	15	22
Mardani M	Iran	Case report	1		Nasopharyngeal swab	64	0/1				
Peng J	China	Case series	7		Throat swab		4/3			16.7	10.1
Qiao XM	China	Observational	1	15	Nasopharyngeal and throat swab	30	0/1			14	15
Qu YM	China	Case report	1		Throat swab and sputum	49	1/0		4		
Tian M	China	Observational	20	147	Pharyngeal swabs	37.15	11/9	7	2.5	18.65	17.25
Wang P	China	Case report	1		Throat swab	33	1/0		8	21	15
Wang X	China	Observational	8	131		48.75	4/4	0			11.375
Wong J	Brunei	Observational	21	106	Nasopharyngeal swab	43.1	12/9			17	13
Xiao AT	China	Observational	15	70	Throat swab, deep nasal cavity swab	64	9/6				
Xing Y	China	Case series	2		Throat swab and stool tests		1/1		6	15.5	6.5
Ye G	China	Observational	5	55	Throat swab	32.4	2/3	0			10.6
Yuan B	China	Observational	20	182	Nasopharyngeal swab or anal swab	39.9	7/13	6	5.1	20.8	9.45
Yuan J	China	Observational	25	172	Cloacal swab and nasopharyngeal swab	28	8/17			15.36	5.23
Zhang B	China	Case series	7		Throat and rectal swab	22.4	6/1			15.4	9.7
Zheng KI	China	Observational	3	20	Salivary and fecal						7
Zhou X	China	Case report	1		Oropharyngeal swab	40	1/0		6	16	7
Zhu H	China	Observational	17	98	Sputum and pharyngeal swab	54	5/12				4
Zou Y	China	Observational	53	257	Throat swabs	62.19	23/30	29			4.6

DOI: 10.5334/aogh.3163

CHARACTERISTIC	NO. STUDIES	NO. OF RECURRENCE CASES	RESULT
Age (years)	34	379	41.7
Male (no., %)	39	233	542 (43%)
Times from onset to admission (days)	13	52	4.8
Times from admission to discharge (days)	22	276	16.4
Times from discharge to positive conversion (days)	31	464	10.4

Table 2 Epidemiological characteristics of COVID-19 recurrence cases.

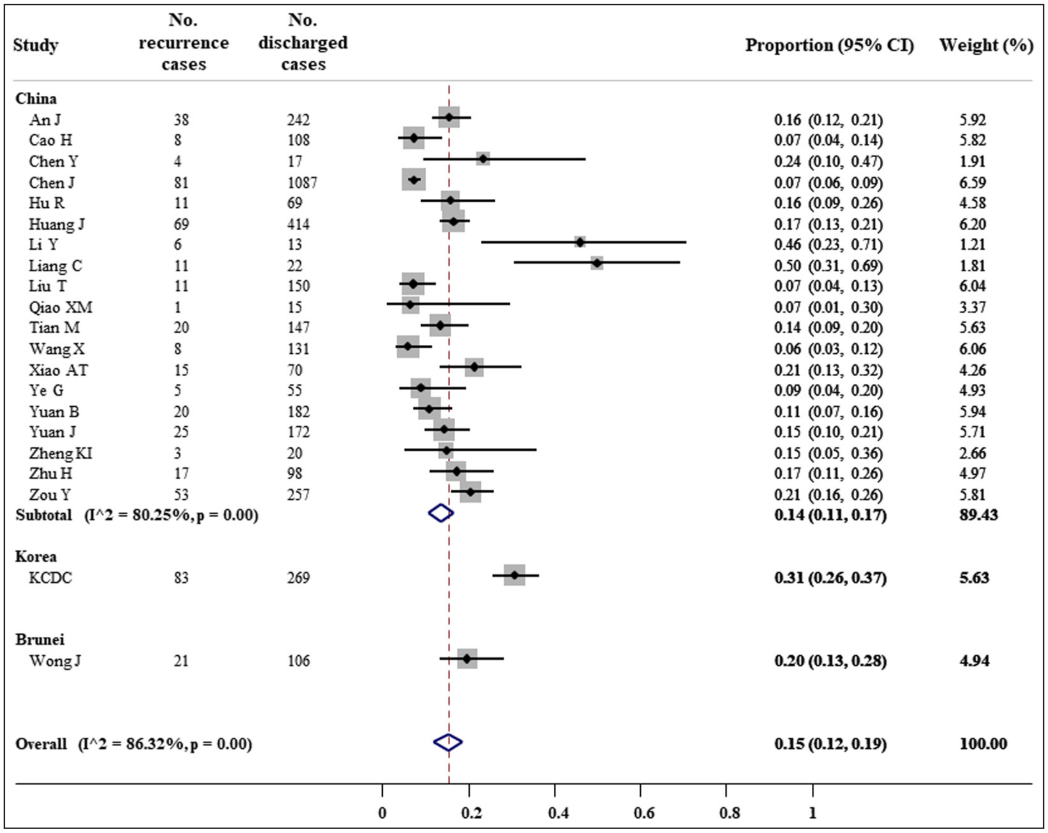

Figure 2 Forest plot for meta-analysis of COVID-19 recurrence prevalence.

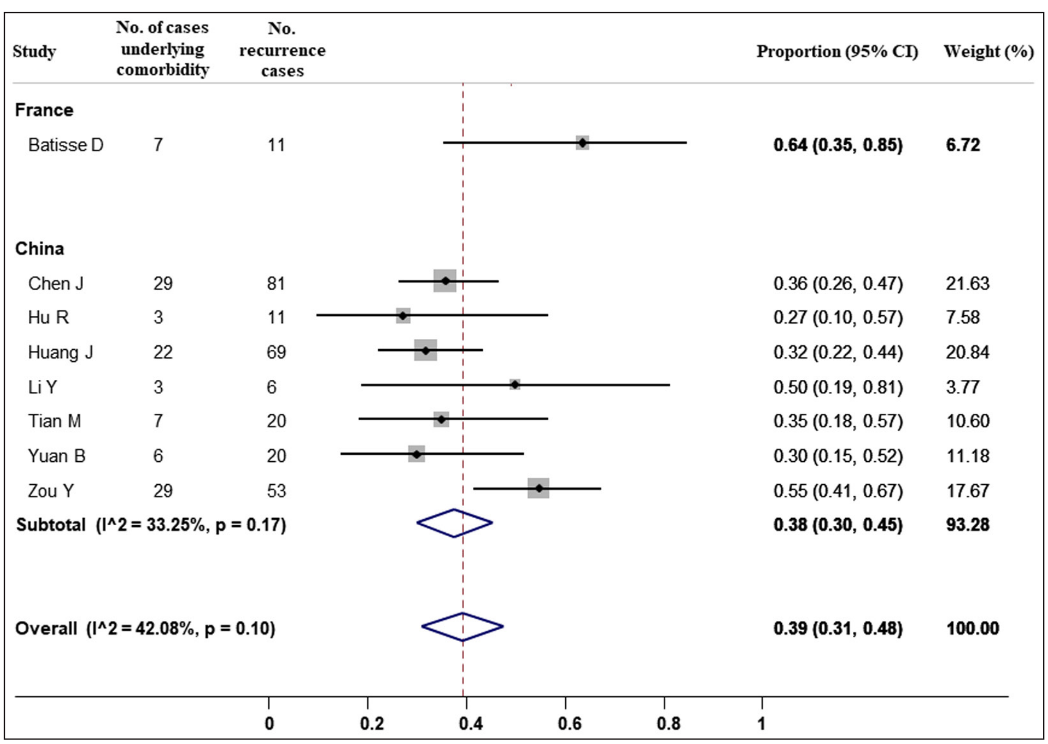

Figure 3 Forest plot for meta-analysis of comorbidity among COVID-19 recurrence cases.

DISCUSSION

Previous studies have reported the persistent detection of viral RNA by in a nasopharyngeal or oropharyngeal swab, however, most of the cases were asymptomatic, the possibility of viral reinfection has been therefore proposed and investigated by many researchers [55]. In this systematic review and meta-analysis of 41 studies, we have described the epidemiological characteristics of COVID-19 recurrence cases. Of 3,644 patients recovering from COVID-19 and being discharged, an estimate of 15% (95% CI, 12% to 19%) of patients re-infected with SARS-CoV-2 during the follow-up. This proportion was 14% (95% CI, 11% to 17%) for China, 31% (95% CI, 26% to 37%) for Korea, and 20% (95% CI, 13% to 28%) for Brunei. Among recurrence cases, it was estimated 39% (95% CI, 31% to 48%) subjects underlying at least one comorbidity.

According to the guidelines of the World Health Organization, a patient can be discharged from the hospital after two consecutive negative results in a clinically recovered patient at least 24 hours apart [56]. However, the discharge criteria for confirmed COVID-19 cases are additionally required according to different countries [57]. The determination of recurrence cases can be caused by false negatives, which ranged from 2% to 29% according to a meta-analysis of 957 hospitalized patients [58]. The reason for false negatives can be due to the source of specimens, sampling procedure, and the sensitivity and specificity of the test kit [8]. In a preprint study of 213 Chinese patients, a total of 205 throat swabs, 490 nasal swabs, and 142 sputum samples were collected, and the false-negative rates were reported of 40%, 27%, and 11% for the throat, nasal, and sputum samples, respectively [59]. Due to the lack of individual data, we were not able to examine the prevalence of recurrence cases in the subgroup analysis by types of specimens.

Furthermore, it may require considering prolonged SARS-CoV-2 shedding in asymptomatic or mild cases and recurrence of viral shedding [60], which related to the intensity of inflammation and immune response [61]. Data from 68 patients revealed a significantly longer duration of viral shedding from sputum specimens (34 days) than nasopharyngeal swabs (19 days) [62]. Consistent findings were reported in an asymptomatic case with viral detection positive in stool but negative in nasopharyngeal swab lasts for 42 days [63]. Similarly, the positive rate of the SARS-CoV-2 RNA test was shown to be highest for the sputum sample (100%), followed by nasal swab (75%), oral swab (40%), and stool specimen (38%) [64]. Nevertheless, although the RT-PCT results of discharge patients were possible to turn positive, it is necessary to distinguish between reactivation and reinfection cases [8].

Regarding the protective immunity, Alonso, et al. hypothesized the first mild viral infection might not strong enough to establish a detectable humoral response [65]. It was also possible for the absence of IgM and IgG antibodies, which were capable of connecting to the virus and preventing it from entering the host cell [66], in the acute and convalescent serum of the reinfected patients [67]. Although neutralizing antibodies and memory B and T cells again some common human coronaviruses (HCoV) such as HCoV-229E and HCoV-OC43 were also suggested to confer cross-immunity against SARS-CoV-2 [68], a report based on data on 150 patients showed that the presence of serum IgM and IgG was not significantly associated with a lower rate of disease recurrence (OR = 0.92, 95% CI = 0.27–3.16) [69].

Factors related to the recurrence of COVID-19 remain unclear because of inconsistent findings. Although disease severity may be associated with the worse immune response, An J, et al. reported the lower recurrence rate among subjects with severe or moderate disease at baseline than those with mild disease (odds ratio [OR] = 0.23, 95% CI = 0.10–0.53) [15]. However, the proportion in subjects with severe disease did not differ in those with moderate or mild disease (OR = 1.06, 95% CI = 0.57–1.96) [20]. Also, while subjects underlying diseases such as hypertension and diabetes are more likely to be susceptible with disease infection and severity [70], the recurrence proportion was not significantly different between those with and without any chronic diseases, in Chen, et al.'s study (OR = 0.71, 95% = 0.42–1.20 for hypertension and OR = 0.85, 95% CI = 0.42–1.75 for diabetes)and Huang et al.'s study (OR = 0.98, 95% = 0.52–1.87 for hypertension and OR = 0.46, 95% CI = 0.14–1.55 for diabetes) [20, 28].

This study summarized up-to-date evidence from case reports, case series, and observational studies for the characteristic of COVID-19 recurrence cases after discharge. However, several limitations need to be mentioned. First, 80% of the included studies (33/41) with 78% recurrence cases (435/556) come from the Chinese population, which may reduce the availability to generalize the pooled estimates into other populations. Second, heterogeneity for the prevalence of recurrence cases was substantially presented among studies. The different characteristics, discharge criteria, and the test samples used among study populations included in this meta-analysis may have contributed to the heterogeneity. Third, all the estimates in the current study are based on aggregate data from published articles. Failure to obtain individual patient data may lead to bias due to the lack of full exploration and adjustment for patient characteristics [71]. Last, due to the lack of data, we were unable to assess the characteristic of recurrence individuals due to false negative or prolonged shedding.

In summary, an estimate of 15% of COVID-19 patients tested SARS-CoV2 positive after discharge. Among them, 39% of subjects were underlying comorbidity. It is recommended to pay attention to follow-up patients after discharge by closely monitoring their clinical characteristics such as illness severity, confusion, urea, respiratory rate, and blood pressure after two negative RT-PCR results of the discharge [72], even if they have been in the discharge quarantine for 14 days [73–74]. Further studies are needed to determine factors associated with positive RT-PCR in COVID-19 patients after discharge.

DATA ACCESIBILITY STATEMENT

Data for all the analyses are available in ***Table 1***.

COMPETING INTERESTS

The author has no competing interests to declare.

PUBLISHER'S NOTE

This paper underwent peer review using the *Cross-Publisher COVID-19 Rapid Review Initiative*.

AUTHOR CONTRIBUTION

TH designed the outline of the work, analyzed the data, and wrote the manuscript.

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TO CITE THIS ARTICLE:
Hoang T. Characteristics of COVID-19 Recurrence: A Systematic Review and Meta-Analysis. *Annals of Global Health*. 2021; 87(1): 28, 1–11. DOI: *https://doi.org/10.5334/aogh.3163*

Published: 24 March 2021