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Review

Assessment and management of asymptomatic COVID-19 infection: A systematic review



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ABSTRACT

Background: COVID-19 can be asymptomatic in a substantial proportion of patients. The assessment and management of these patients constitute a key element to stop dissemination.

Aim: To describe the assessment and treatment of asymptomatic infection in patients with a confirmed diagnosis of COVID-19.

Methods: We searched five databases and search engines for preprints/preproofs, up to August 22, 2020. We included cohort, cross-sectional, and case series studies, reporting the assessment and management of asymptomatic individuals. We extracted data on total discharges with negative PCR, length of hospitalization, treatment, and number of patients who remained asymptomatic. A random-effects model with inverse variance method was used to calculate the pooled prevalence.

Results: 41 studies (nine cross-sectional studies, five retrospective studies and 27 reports/case series; 647 asymptomatic individuals), were included, of which 47% were male (233/501). The age of patients was between 1 month and 73 years. In patients who became symptomatic, length of hospitalization mean was 13.6 days (SD 6.4). Studies used lopinavir/ritonavir, hydroxychloroquine plus ritonavir/lopinavir, hydroxychloroquine with and without azithromycin, ribavirin plus interferon and interferon alfa. The proportion of individuals who remained asymptomatic was 91% (463/588 patients; 95%CI: 78.3%–98.7%); and asymptomatic individuals discharged with negative PCR was 86% (102/124 individuals; 95%CI: 58.4%–100%).

Conclusions: There is no standard treatment for asymptomatic COVID-19 individuals. There are no studies of adequate design to make this decision. It has been shown that most asymptomatic individuals who were followed have recovered, but this cannot be attributed to standard treatment.

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1. Introduction

The novel coronavirus disease (COVID-19 or SARS-CoV-2 infection) pandemic is currently of great global concern [1,2]. The spectrum of presentations of those infected with SARS-CoV-2 can range from asymptomatic to mild upper respiratory tract infections to severe acute respiratory syndrome and death in humans. The coronavirus group includes the coronavirus that causes Middle East Respiratory Syndrome and the virus that causes Severe Acute Respiratory Syndrome (SARS-CoV) [3,4]. The expansion of the pandemic was rapid and uncontrolled since transmission events have been occurring between susceptible and infectious individuals. The intensive global spread of the infection led the World Health Organization (WHO) to declare SARS-CoV-2 infection as a pandemic [5,6].

The clinical features vary, but the most common early symptoms, in those who are symptomatic, are fever (98%), cough (76%), and myalgia or fatigue (44%) [2]. Less common symptoms are sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3–6%) [7,8]. Dyspnea does not appear in all patients, some patients may have lymphopenia, and others may have abnormal changes on chest computed tomography (CT) scan. However, some patients do not present symptoms previous to the diagnosis, being described as asymptomatic individuals [9,10].

Recent studies of SARS-CoV-2 include individuals who did not have symptoms but were screened for infection because they had family members, close contact, or had been in countries with confirmed cases [11,12]. In many cases, the test had to be done more than once for confirmation [13]. Despite being asymptomatic, medical isolation is recommended due to their high capability of transmission [1].

The evaluation of asymptomatic carriers is difficult and data are limited, but of utmost importance because of their potential to spread the virus in the general population [12]. Currently, there is no synthesis of information on the assessment and management of asymptomatic SARS-CoV-2 infection. Such an evidence synthesis could improve evidence-based decisions. Therefore, our aim was to conduct a systematic review to describe the assessment and treatment of asymptomatic infection in individuals with a confirmed diagnosis of COVID-19.

2. Methods

2.1. Protocol

A systematic review of the literature was performed following the PRISMA recommendations (Preferred Reporting Items for Systematic reviews and Meta-Analyses, 2009) [14]. The complete protocol was registered in PROSPERO (CRD42020176244). Asymptomatic individuals were defined as subjects without any symptoms at the time of diagnosis.

2.2. Data sources

The search was performed in the following databases: PubMed, Scopus, Web of Science, Ovid-Medline, Embase, and search engines for preprints/preproofs ("Other sources", <https://www.medrxiv.org>). We included case-control studies, cohorts, cross-sectional, reports, and case series studies, as published articles or in their preprints/preproofs versions. There were no language restrictions. We searched records up to August 22, 2020. We included studies that assessed and treated asymptomatic infection in individuals with a confirmed diagnosis of SARS-CoV-2 by RT-PCR and described at least one of the outcomes of interest. Experimental studies, systematic reviews, narrative reviews, conference proceedings, editorials, and letters to the editor without original data were excluded.

2.3. Outcomes

The primary outcome was total discharges with negative RT-PCR at the end of the follow-up. Additional outcomes of interest were length of hospitalization, treatment in asymptomatic infection individuals, and number of individuals who remained asymptomatic.

2.4. Study selection

After the search, two authors (CDA and CSR) independently conducted the review by title and abstract according to the inclusion and exclusion criteria. Relevant studies were selected and searched by full text for the next phase of assessment. Discrepancies were consulted with another author (JBM), and a consensus was reached. The selection of articles in each phase of the review process was made in the Endnote X9 program.

2.5. Data extraction

Two authors (FOGS and CAAR) extracted the data using elaborate excel formats. Again, discrepancies were discussed and resolved with another author (JBM). The data extracted from each study were: study information (first author, year of publication, type of study and country), number of cases or participants, type of treatment, type of risk contact, length of asymptomatic period and outcomes follow-up. The individual definitions of each study were not considered.

2.6. Risk of bias assessment

Cohorts and case control studies were assessed with Newcastle–Ottawa scale [15]. For the cross-sectional studies, we used the modified Newcastle–Ottawa scale (NOS) tool [16]. For case reports and cases series, the studies were evaluated with a tool based methodological quality and synthesis of case series and case reports.

2.7. Statistical analysis

A random-effects model with inverse variance method and Freeman-Tukey double arcsine transformation was used to calculate the pooled prevalence rates as well as their 95% confidence intervals (CIs). DerSimonian-Laird estimator for τ^2 was used. Heterogeneity between the studies was evaluated by I^2 statistics, and $I^2 > 50\%$ or $P < 0.05$ indicated significant heterogeneity. The analysis was performed in R 3.5.2, using *meta* package.

2.8. Ethical considerations

This is a systematic review of published and open access information so no ethics committee approval was required.

3. Results

3.1. Selection of studies

The search yielded 1683 results. After duplicates were excluded, 1415 titles and abstracts were reviewed, 1359 of these were excluded, and 56 scientific papers were evaluated in detail. Finally, 41 studies were included for the qualitative synthesis [9,17–56], and 38 studies were included for the quantitative synthesis (Fig. 1).

3.2. Characteristics of the studies included

All studies were published in 2020. Twenty-eight studies were performed out in China, four studies were performed in Italy, four studies were developed in USA, one study was performed in Iran, one study in Malaysia, one study was performed in France, one study in Republic of

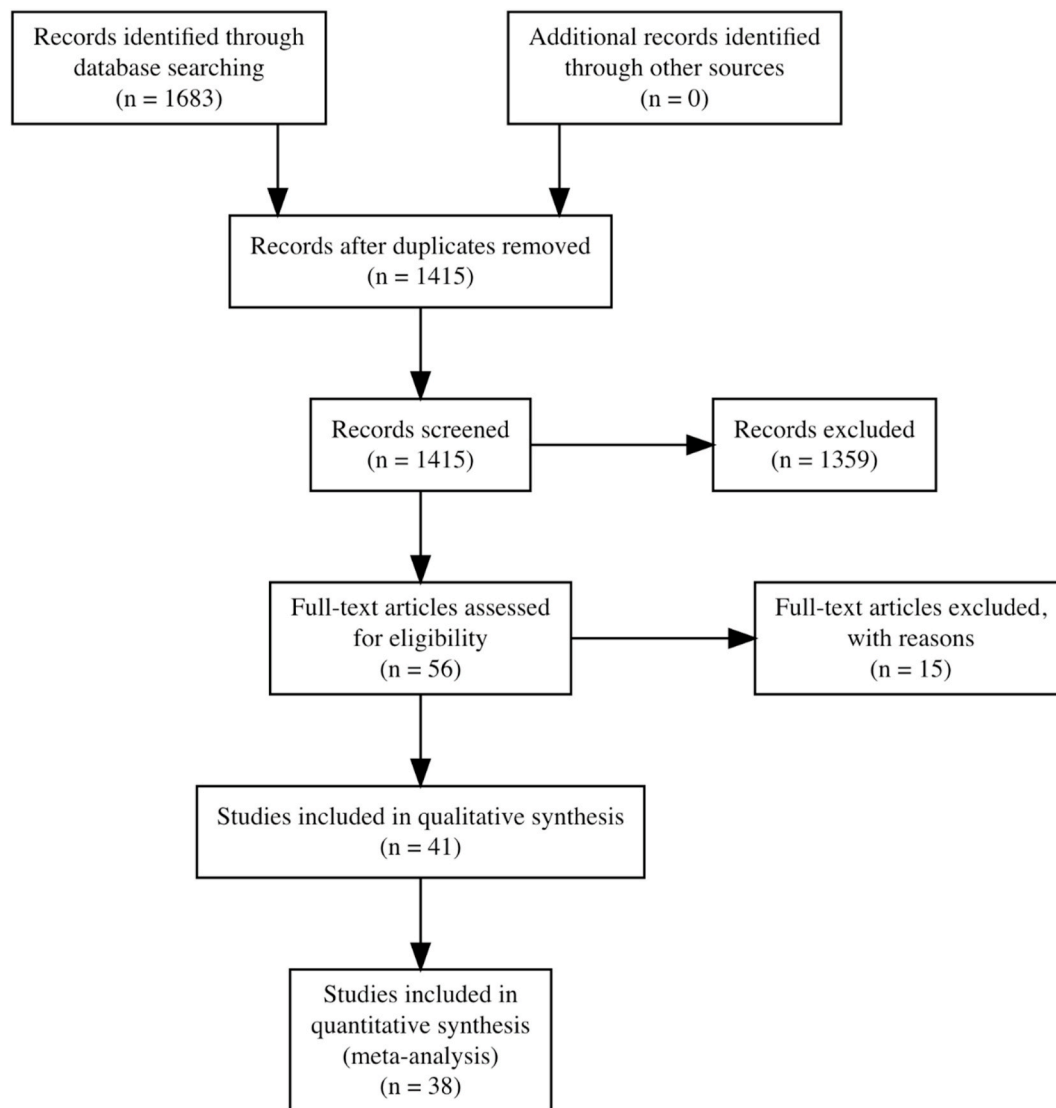


Fig. 1. Flowchart of study selection.

Korea and one study was performed in South Korea. Nine cross-sectional studies, five retrospective studies, and twenty-seven reports/case series were included. Overall, studies included 647 individuals who were asymptomatic on admission to healthcare centres; 47% (233/501) were male. Individuals were aged from 1 month to 73 years. Individuals included had a confirmed diagnosis of SARS-CoV-2 by RT-PCR (Table 1). All individuals in included studies informed that they had contact with confirmed COVID-19 cases, for example, contact with an infected person or Wuhan citizen, contact with an infected family member, or health staff.

3.3. Assessment of risk of bias

Regarding the selection domain, all studies had complete fulfillment criteria in each question. Regarding the comparability domain, only two studies [48,57] performed descriptive analyses by controlling for relevant factors (i.e., age groups and familial clusters). Regarding the outcome domain, most of the studies had complete stars in each question, except one study [50], which did not perform a statistical test. The number of stars ranged from seven to eight (Appendix Table 1).

3.4. Primary outcomes of asymptomatic individuals with COVID-19

The mean length of hospitalization was 13.6 (SD 6.4) days [24,32,37,48,55,56,58,59]. Regarding the length of asymptomatic period, twenty-one studies reported that all assessed individuals remained asymptomatic [9,19,21–24,30,32–35,38,39,41,42,45,47,49,52,53,55], nineteen studies reported that some individuals developed symptoms during hospitalization or follow-up, and one study did not report any follow-up. One study describes that the only asymptomatic individual throughout the study, was asymptomatic except for slight shortness of breath during activity [31]; one study did not report the length of time its individual remains asymptomatic [48]. In general, it was not possible to quantify the average time individuals remained asymptomatic from diagnosis and during hospitalization.

Twenty-one studies reported drug management. Eleven studies used lopinavir/ritonavir and another antivirals [9,17,22,24,29,31,34,35,37,45,49]; three studies used hydroxychloroquine plus ritonavir/lopinavir [17,22,43]; another study used ribavirin plus interferon [9], or interferon alfa only [42]. One study reported the use of antibiotics and antifungal therapy [26].

At the end of follow-up, no study reported death as an outcome of an asymptomatic infection. In one cross sectional-study, 29% had a positive test (nucleic acid) after previous negative results [26]. The rest of the

Table 1
Characteristics of included studies in systematic review.

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Hu et al.	2020	Cross-sectional	China	24	8 (33.3)	32.5 (IQR 5–95)	All were close contacts of COVID-19 patients in Nanjing	5 patients (20.8%) developed symptoms during follow-up. Median length of asymptomatic period: 1 day (2 patients with 0 day, 2 patients with 1 day, and 1 patient with 2 days)	Clinical: All the five cases developed fever without chills, with body temperatures ranges 36.5 °C–38.0 °C, but none presented high fever (>39 °C). One case also had cough, fatigue and nasal congestion. Another case presented cough, fatigue, dizziness and arthralgia. Images: Twelve (50.0%) cases showed ground-glass or patchy shadows in lungs in their chest CT images. Five (20.8%) cases showed stripe shadows in lungs, an atypical image finding.	21 cases (87.5%) received antiviral therapy. One case also received antibiotics therapy, antifungal therapy plus immunoglobulin therapy. Immunoglobulin therapy was also given to 2 cases. All these cases were treated with interferon atomization. None of the cases developed severe pneumonia, requiring systemic corticosteroids treatment, mechanical ventilation, or admission to ICU.	18 cases (75.0%) had the virus cleared (2 continuous negatives of nucleic acid tests), among whom 9 cases were discharged from the hospital while the rest 9 were kept in hospital for further observation. Six cases had nucleic acid tests reversed to positive after one negative result. Of particular concern, one case showed positive again even after the continuous negative of nucleic acid tests.
Tuo Ji et al.	2020	Cross-sectional	China	41	Not reported	Not reported	They had epidemiological clues for COVID-19 contact	Not mentioned	Not mentioned	Not mentioned	After quarantined for at least 14 days, all the persons had no signs of illness Not mentioned
Kimball et al.	2020	Cross-sectional	USA	13	Not reported	Not reported	They had history of exposure to epidemic areas or close contact with an infected individual.	3 cases stay asymptomatic during the follow-up 1 week. The rest 10 cases developed symptoms and the mean interval from testing to symptom onset in the presymptomatic residents was 3 days	Clinical: fever (eight residents), malaise (six), and cough (five).	Not mentioned	
Wang Xiaobing et al.	2020	Cross-sectional	China	30	Not reported	Not reported	They had history of exposure to epidemic areas or close contact with an infected individual.	14 cases stay asymptomatic during the follow-up 24 days	Clinical: 16 cases developed symptoms, Fever occurred in 6 of 30 ones (20%), with cough in 8 of 30 (26.7%), myalgia in 3 of 30 (10%), dyspnea in 2 of 30 (6.7%), runny nose in 1 of 30(3.3%),	Not mentioned	2(2.0%) patients with aggravation of illness during follow up(n = 100)

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Wang Y. et al.	2020	Cross-sectional	China	55	22 (40%)	49 (IQR 2–69)	Close contact with family member diagnosed with SARS-CoV-2 infection	70.9% developed symptoms during follow-up. 1–7 days	nasal congestion in 1 of 30 (3.3%) and abdominal pain in 3.3%. Images: Not mentioned Clinical: Seven cases had mild cough and seven cases had low fever 3–5 days later (two cases presenting both cough and fever, which later complicated with hypoxia (SpO ₂ = 90%) and restlessness). Images: 16 (29.1%; 16/55) patients showed normal first chest CT. 37 cases showed pneumonia in first chest CT	Lopinavir/Ritonavir was given to all cases as initial therapy for 7 days. Two cases with hypoxia received intravenous immunoglobulin 10 g/day and methylprednisolone (1–2 mg/kg/day) therapy for 3 days. Heated humidified high-flow nasal cannula (HHHFNC) was used for 5 days. Eventually, the two patients recovered without complication	None of the cases were admitted to ICU. All the cases recovered and were discharged home
⁵ Meng et al.	2020	Cross-sectional	China	58	26(44.8%)	42.6 (16.6)	Epidemiological history (100%)	3.71 ± 2.86 days	Clinical: eight patients developed fever; nine patients developed cough; eight patients developed fatigue; two patients developed shortness of breath; and one patient developed diarrhea. Images: frequent findings in CT were multiple lesions (62.1%), bilateral lesions (41.4%), peripheral distribution (75.9%) and ground glass opacities (51.7%)	Not mentioned	All patients were discharged after treatment.
Breslin et al.	2020	Cross-sectional	USA	14	0 (0)	Not reported	Not mentioned	6 patients developed symptoms within the first seven days after positive swab result. 4 stays asymptomatic.	Clinical: 8 patients developed fever intra or post-partum. 6 patients developed cough, myalgias, chest pain, anosmia, and/or dysgeusia. 2 patients were admitted to ICU due to obstetrical	Patients with intra or postpartum fever received antibiotics for suspected intraamniotic infection or endometritis	13 patients (including 1 ICU-admitted patient) were discharged. The other remaining patient stays in ICU with renal Insufficiency without mechanical

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Kong et al.	2020	Cross-sectional	China	100	55 (55.0%)	37.7 ± 19.0	History of recent travel or residence in the outbreak area or Contact history with COVID-19 patients.	17 (27.4%) developed relevant symptoms days (median: 7 days, range: 1–13 days) after diagnosis	complications including respiratory distress. Images: Not mentioned Cough, Pharyngalgia or Runny nose, Fever, Chills or fatigue, Muscle aches or headaches. Among the 60 asymptomatic cases who demonstrated positive CT findings, 37 cases showed typical multiple peripheral patchy ground glass opacities, some of who showed parenchymal consolidation, interlobular septal thickening, bronchial wall thickening and halo signs or reverse-halo signs. Eighteen cases showed single or several scattered ground glass opacities. 5 cases showed nodular ground glass opacities.	antiviral therapy if the CT imaging showed positive findings for pneumonia.	ventilation nor dialysis There were no deaths in the asymptomatic group. All other patients were discharged from the hospital
Lu Y et al.	2020	Cross-sectional	China	29	17 (58.6%)	7 (interquartile range 6–11)	Not mentioned	Stay asymptomatic	Non symptoms. 9 (32%) has pneumonia in chest radiological study	All patients were administered antiviral therapy, of which interferon-α nebulization was the most frequently used. None of the patients required oxygen therapy.	All patients discharge after 10 days
Ma et al.	2020	Retrospective cohort study	China	11	6(54.5)	23(range 1–60)	3 were residents of Wuhan,1 Wuhan visitor, 7 close contact with confirmed case	Stay asymptomatic	7 have patchy shadows or ground glass opacity on CT	All patients received antiviral treatment, including lopinavir/ritonavir tablets, arbidol, and inhalation of recombinant human interferon	9(81.8) of them discharge at the end of the follow-up, and 2 remain hospitalized because they still positive
	2020		China	63	34(54%)	39.30 ± 16.45		Stay asymptomatic			

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Wang Y et al.		Retrospective cohort study					17(27%) Exposure history in Hubei and 18 (28.6%) family cluster		Non symptoms.29 had anormal chest CT findings	Antiviral treatment with α -Interferon inhalation and Lopinavir/Ritonavir oral with Thymosin injection	All patients were discharged
Xu et al.	2020	Retrospective cohort study	China	15	10 (66.7)	27.0 (17.0, 36.0)	Contact with suspected or confirmed patients	Stay asymptomatic	Non symptoms. Ground-glass opacity (40%) and pneumonia(52%)	interferon α -2b, arbidol, lopinavir/ritonavir	All patients were discharged
London et al.	2020	Retrospective cohort study	USA	22	0(0%)	30.5 (interquartile range 24.5–34.8)	Testing for COVID-19 became universal for all antepartum and labor and delivery admissions	Stay asymptomatic	Non symptoms. Images nor mentioned	No treatment	All discharge after 10 days
Qiu et al.	2020	Retrospective cohort study	China	10	Not reported	Not reported	They had history of exposure to epidemic areas or close contact with an infected individual.	Stay asymptomatic	Non symptoms. Images: No abnormal radiographic	Interferon alfa treatment	In one case: 10 days to become SARS-CoV-2 PCR-negative. All patients were cured.
Albano et al.	2020	Case series	Italy	6	2 (33.3)	62.2 (8.7)	Not mentioned	2 patients developed symptoms	Clinical: Case 4: several days later of the diagnosis, fever and dyspnoea appeared Case 7: Fever and cough appeared one day after the scan. Images: No reported	Hydroxychloroquine plus Ritonavir/ Lopinavir (3 cases)	Not mentioned
Dong et al.	2020	Case series	China	1	1(100%)	26	Nurse, contact with an infected person	Stay asymptomatic	Non symptoms. Chest CT with no sign of pneumonia	Treated with antiviral drugs including Arbidol and Prezcoibix (Darunavir and Cobicistat tablets)	Discharged 4 days later after testing negative in two consecutive RT-PCR assays
Lin et al.	2020	Case report	China	1	1(100%)	61	Close contact with a novel coronavirus pneumonia patient more than 10 days prior admission	Since admission, the patient has remained with only mild shortness of breath after activity on the 11th day of admission	Clinical: Mild shortness of breath after activity on the 11th day of admission. Images: Day 1: CT showed multiple ground glass opacities in the right lung. Day 3, CT revealed an enlarged lesion with small areas of consolidation in the center. Day 6, CT	During hospitalization the main treatment has been oral antiviral drugs (Lopinavir and Ritonavir tablets), interferon and methylprednisolone	Day 23: Patient remains hospitalized because his nucleic acid test is still positive

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Ling et al.	2020	Case report	China	4	Not reported	Not reported	The majority patients had a history of exposure in Wuhan or to infected patients	Stay asymptomatic	showed a further increase of lesions. Day 9, CT showed the lesions progressed further and involved both lungs, with thickened interlobular septa around the lesion in the upper lobe of the right lung; in addition, there were small bilateral pleural effusions. Day 23, CT showed that pleural effusions had resolved, and bilateral pulmonary lesions improved. Non symptoms. Images: Chest CT images showed no significant abnormalities	Not mentioned	2 of 4 patients subsequently presented two consecutive negative nucleic acid detection at least 24 h apart and finally recovered
Nicastri et al.	2020	Case report	Italy	1	1(100%)	Not reported	Contact with Wuhan person	The patients developed signs during follow-up	Clinical: Day 2: Mild conjunctivitis. Day 10–11: Tonsillar exudate. Images: Chest CT were normal	Lopinavir/ritonavir	The isolation regimen was stopped, and the patient discharged at the end of 14-day quarantine after obtaining two SARS-CoV-2 negative samples 24 h apart near
Polverari et al.	2020	Case report	Italy	1	1(100%)	73	Patient declared no suspected expositions to infected people	3 days	Images: PET/CT revealed the presence of bilateral, diffuse and peripheral predominant ground-glass opacities in the lower lobes	Not mentioned	Patient with non-small cells lung cancer, 3 days after the diagnosis intensive care unit was necessary for rapid disease progression and severe respiratory distress syndrome. Not mentioned
Poli et al.	2020	Case report	Italy	1	1(100%)	1 month	Close contact with the grandfather who was later hospitalized for COVID-19	Stay asymptomatic	Non symptoms. Images not reported	Not mentioned	Not mentioned

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
Bai et al.	2020	A case report of familial cluster	China	1	0	20	lives in Wuhan	Stay asymptomatic	Non symptoms. Images: Chest CT images showed no significant abnormalities	Not mentioned	Not mentioned
Chan et al.	2020	A case report of familial cluster	China	1	1(100%)	10	close contacts of COVID-19 patient	Stay asymptomatic	Non symptoms. Images: ground-glass lung opacities	Not mentioned	Admitted to hospital under isolation, supportive care, and remained stable at 9th day
Le et al.	2020	A case report of familial cluster	China	1	1(100%)	55	Contact with Wuhan person	Stay asymptomatic	Non symptoms. Images not mentioned	Not mentioned	Patient was discharged after 2 consecutive negative PCR results
Lu S. et al.	2020	A case report of familial cluster	China	2	0	Not reported	Relatives (elder sister and son) of a coronavirus confirmed patients	Both patients stay asymptomatic	Non symptoms. Images: Patient B: Chest CT showed multiple patchy and ground glass shadows in both lungs. Patient C: No signs in chest CT	Both patients were given ribavirin plus interferon antiviral and symptomatic treatment	Not mentioned
Pan et al.	2020	A case report of familial cluster	China	2	1(50%)	Not reported	Contact with Wuhan person	Stay asymptomatic	Non symptoms. Images: Normal CT chest	Not mentioned	Not mentioned
Qian et al.	2020	A case report of familial cluster	China	2	1(100%)	Not reported	Husband and one grandchildren of an index case	Both patients stay asymptomatic	Non symptoms. Images nor mentioned	Not mentioned	Not mentioned
Tong et al.	2020	A case report of familial cluster	China	3	1(33.3%)	28(IQR 12–42)	Wife of an index case. Son and wife of another index case	Patients stay asymptomatic	Non symptoms. Images nor mentioned	Not mentioned	Not mentioned
Ye et al.	2020	A case report of familial cluster	China	3	3(100%)	28(IQR 23–50)	Contact with Wuhan person	One case stay asymptomatic, the rest developed symptoms 1 and 2 days later. during follow-up 4 weeks	Clinical: 2 patients developed fever and cough. Images: Chest CT images showed Ground-glass changes (Case 3 and 5). No abnormalities of Case 2	Not mentioned	In case 2: 10 days to become PCR-negative. The rest still hospitalized and PCR-positive
Zhang et al.	2020	A case report of familial cluster	China	1	1(100%)	10	Contact with an infected person	Stay asymptomatic	Non symptoms. Images: chest radiograph demonstrated ground glass opacities	Not mentioned	22 days later the patient was discharged.
Sutton et al.	2020	Case series	USA	29	0 (0)	Not reported	Lives in New York	26 patients stay asymptomatic and three patients developed fever before postpartum discharge (median	Clinical: Fever developed in 3 patients before postpartum discharge	Two febrile patients received antibiotics for presumed endomyometritis (although 1 patient did not have	Not mentioned

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
								length of stay, 2 days)		localizing symptoms), and one patient received supportive care	
Du et al.	2020	Case series	China	8	5 (62.5%)	Not reported	Familial cluster	5.43 ± 6.33 days.	Clinical: three patients developed mild symptoms, and five patients developed conventional symptoms. Images: frequent findings were lung injury (five patients) and bilateral lesions (three patients).	Treated according to the plan of the National Health Commission (trial version 5)	Not mentioned
Samsami et al.	2020	Case series	Iran	8	5 (62%)	49.7(13.1)	5 patients had history of close contact with a suspected COVID-19 case	Two patients experienced mild symptoms during hospitalization. Six patients remained asymptomatic	Clinical: Two patients developed fever, cough, and myalgia. Images: Chest CT showed findings compatible with pneumonia in all patients	All patients received hydroxychloroquine with or without azithromycin	All patients were discharged from hospital. None of the patients required ICU
Zhou et al.	2020	Case series	China	13	Not reported	Not reported	Close contact of confirmed cases	10 patients remained asymptomatic and three patients developed symptoms at the second day of hospitalization	Images: 12 patients showed multiple ground-glass opacities and four of these showed radiographic progression during hospitalization, but all showed improvement before discharge. One patient had no evidence of radiographic abnormalities consistent with COVID-19. Clinical: Three patients developed symptoms at the second day of hospitalization (sore throat, non-productive cough, chest distress, and diarrhea).	Not mentioned	All patients tested SARS-CoV-2-RT-PCR-negative at a median time of 13 days (range 3–19 days).
See et al.	2020	Case series	Malaysia	4	3 (75%)	6.4 (4.3)					

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Table 1 (continued)

Author	Year	Type of study	Country	Total of asymptomatic individuals	Male (n, %)	Age (mean, SD)	Type of risk contact	Length of asymptomatic period	Clinical and imaging features	Treatment	Outcomes of patients at the end of study
							Contact with an infected person in china	Only one patient remained asymptomatic	Clinical: case 1 had fever and diarrhea, case 2 has fever and upper respiratory tract symptoms, and case 3 had mild cough and wheeze. Images: chest X-ray showed opacities in two patients. No information on the rest.	Paracetamol in two patients, penicillin V in one patient	All patients recovered
An et al.	2020	Case series	China	25	Not reported	Not reported	22 were family members in care of confirmed patients with COVID-19. 3 patients were cleaning of medical waste and hospital-transportation staff	16 stars asymptomatic. Nine patients developed symptoms.	Clinical: 9 patients developed mild cough and/or other symptoms. Images: 24 patients had abnormal CT findings in the lung. Approximately two-thirds had an involvement of a single lobe, and two-thirds had only a ground-glass density shadow.	The 9 symptomatic patients received chloroquine 500 mg twice daily for seven days and Arbidol 200 mg three times a day for no more than ten days.	All patients recovered. 16 recovered without any symptoms during the follow-up, and 9 recovered with resolved symptoms.
Danis et al.	2020	Case series	France	1	Not reported	Not reported	Contact with an infected person	Stay asymptomatic	Non symptoms. Images nor mentioned	No anti-viral treatment	The symptoms of all cases resolved rapidly, without anti-viral treatment
Chang M. et al.	2020	Case series	Republic of Korea	10	6(60%)	65 ± 12.8 years	Contact history with COVID-19 patients	Stay asymptomatic	Non symptoms. All patients (100%) had ground glass opacity (GGO) on chest CT predominantly distributed peripherally and posteriorly	hydroxychloroquine sulfate and lopinavir/ritonavir	All patients were discharged from hospital. None of the patients required ICU
Kim et al.	2020	Case series	Korea of South	10	4(40%)	31 years (interquartile range 17.8–55.8 years).	Contact with confirmed COVID-19 case	7 patients stay asymptomatic and 3 patients developed symptoms 1 or 2 days later the diagnosis	Three patients who were asymptomatic on admission developed myalgia, fever, and a cough.	No anti-viral treatment	It was found that RT-PCR was indeterminate or negative 14 days after diagnosis in entirely asymptomatic individuals
Song et al.	2020	Case series	China	8	5(62.5%)	10.1 ± 4.3	Family members confirmed with COVID-19 prior to children	Stay asymptomatic	Non symptoms, patchy, GGOs	Azithromycin, Oseltamivir, Arbidol, Traditional Chinese medicine	All patients were discharged
Yang et al.	2020	Case series	China	23	11(33.3%)	37 (26–45)	Not mentioned	Stay asymptomatic	Non symptoms. Images nor mentioned	No mentioned	No deaths reported

SD= Standard deviation; IQR: interquartile range.

cases were discharged or remained hospitalized for further observation after having the virus cleared; however, one patient remained hospitalized due to a positive test even on the 23rd day [31].

Random-effects meta-analyses were carried out using the number of individuals who remained asymptomatic until the end of study, patients discharged with negative PCR, and a total of asymptomatic individuals. The proportion of individuals who remained asymptomatic was 91% (463/588 individuals; 95%CI: 78.3%–98.7%). The meta-analysis indicated that between-study variability was high (τ^2 0.09; heterogeneity $I^2 = 85.7\%$ [81.2%–89%] p-value of <0.0001) (Fig. 2). The prevalence of asymptomatic individuals discharged with negative PCR were 86% (102/124 individuals; 95%CI: 58.4%–100%). The meta-analysis indicated that between-study variability was high (τ^2 0.1; heterogeneity $I^2 = 80.5\%$ [66.9%–88.5%] p-value of <0.0001) (Fig. 3).

4. Discussion

4.1. Main findings

Our study clinically described hospitalized individuals who had contact with persons who had COVID-19 confirmed or suspected

infection, such as health care workers or Wuhan citizens. The included studies report that most individuals remained asymptomatic until discharge. Regarding the imaging characteristics, most patients showed ground-glass or patchy shadows in lungs, and consolidation patterns in first chest CT. In this systematic review, the most prescribed treatment was an antiviral drug combination, most notably lopinavir/ritonavir although, other studies used immunoglobulin therapy. 86% of asymptomatic individuals recovered (or tested negative after first positive test) and were discharged home.

4.2. What is known in the literature about our research?

COVID-19 has respiratory and systemic implications. The clinical and epidemiological characteristics are comparable with SARS [60]. Diagnosis is not only based on the symptoms but also on the history of exposure to the virus. Thus, effective tests are required to recognize patients regardless of the presence of symptoms.

RT-PCR and other laboratory tests can detect asymptomatic cases, and confirm asymptomatic infection [61], but they have the limitation that their sensitivity with one test is not optimal and two tests are ideally needed to optimize detection capacity [62]. Then, only knowing this

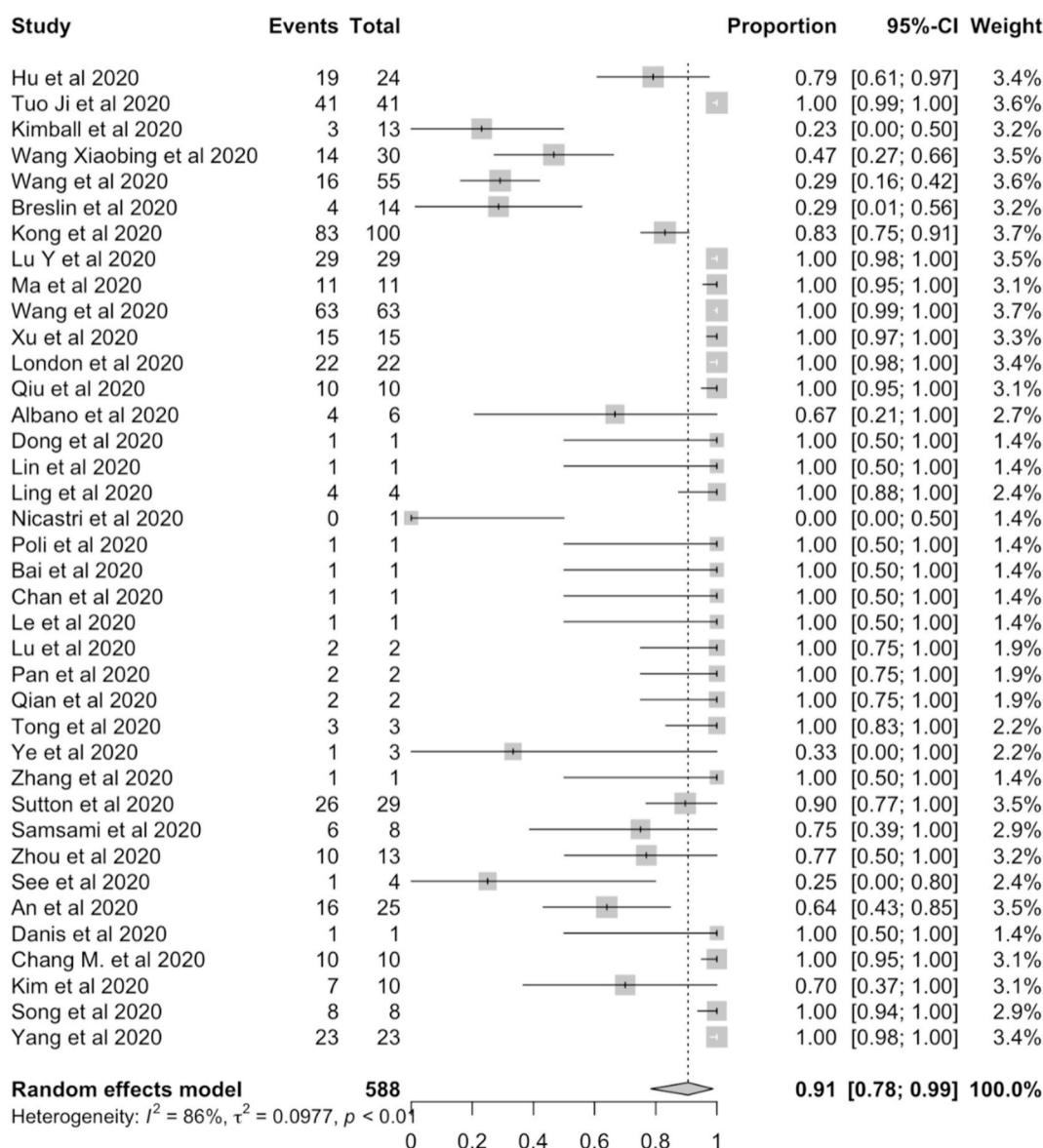


Fig. 2. Prevalence meta-analysis of patients who remained asymptomatic (events) and asymptomatic individuals (total).

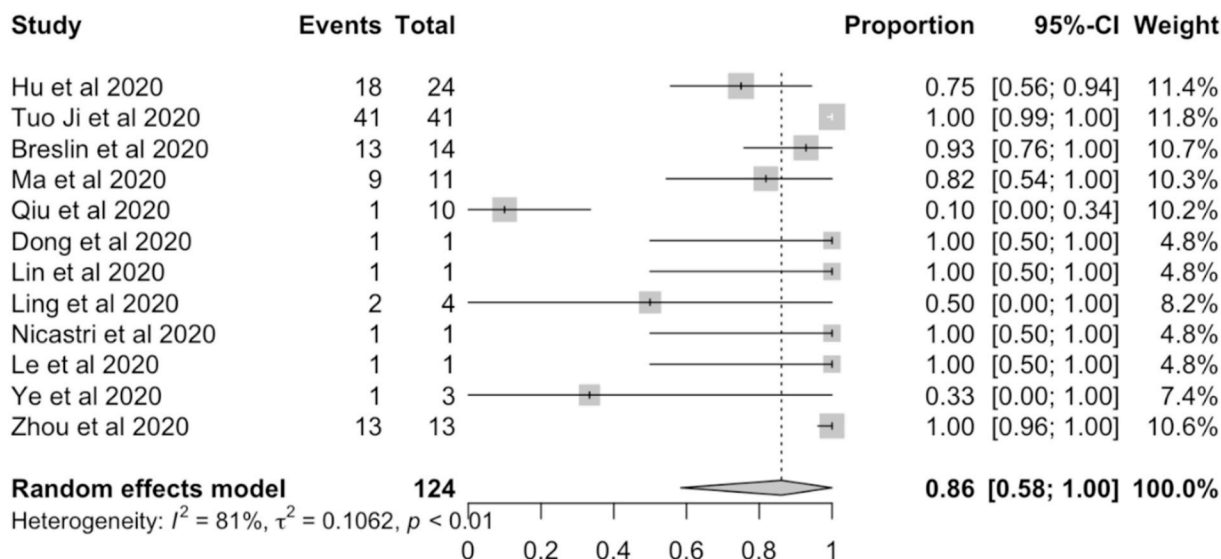


Fig. 3. Prevalence meta-analysis of discharged patients (events) and asymptomatic individuals (total).

dissemination capacity will allow us to understand the rapid spread and propose measures to stop and control the pandemic. In this way, the transmission of COVID-19 and the spectrum of disease can be understood, and the spread of the pandemic controlled by using these diagnostic tools [63].

The mechanisms by which asymptomatic carriers transmit the SARS-CoV-2 and the extent of such transmission are still unclear. There are several reports in the medical literature such as one from Bai et al. [19], who report a positive case who remained asymptomatic for more than 20 days. An individual becomes an asymptomatic carrier when their antiviral defense is strong. In this sense, the immune response limits the infection but cannot completely block the replication of SARS-CoV-2 [64]. So, the spread of the infection from asymptomatic persons may occur. However, the low viral load indicates a relatively low risk of transmission to other individuals. However, if the immune response against SARS-CoV-2 is dissociated from viral replication, the viral load is higher, so the risk of community transmission is significantly higher too [64].

4.3. Identification of asymptomatic people to control the spread of the disease

Asymptomatic individuals generate uncertainty for identification, diagnosis, and treatment, which compromises infection control and the spread of the disease [65]. Also, individuals with mild, nonspecific, and asymptomatic symptoms are difficult to identify and quarantine [66]. Based on the evidence obtained, we observed that the viral load is usually low. If this is also the case for SARS-CoV-2, the risk should remain low. Studies on the natural history of SARS-CoV-2 infection in humans are urgently needed [67].

The monitoring of viral loads, clinical presentations, and antibody titers over time in such asymptomatic persons is necessary to provide important information. Information is needed on how many of the asymptomatic individuals will develop symptoms in a later phase, whether virus shedding from the subjects is indeed less robust, and how often they may transmit SARS-CoV-2 to others [3].

Symptoms of COVID-19 are non-specific and the disease presentation can range from asymptomatic to severe pneumonia and death [12]. Some studies suggest that pre-symptomatic or asymptomatic carriers may cause COVID-19 transmission. It cannot be established whether the greatest proportion of contagion resides in asymptomatic individuals or in those who have already developed symptoms before the diagnosis is established [61,68,69]. So, a standardized definition of asymptomatic

cases is important for assessing the true severity of disease and for optimizing public health control [70].

Based on the included reports, the following definitions can be proposed: 1) The pre-symptomatic case includes an infected individual (confirmed with RT-PCR test) in their incubation period that currently is without symptoms, but, he/she develops symptoms in the future. This is a retrospective definition [28]. 2) The paucisymptomatic case includes a confirmed RT-PCR test infected patient with mild upper respiratory infection symptoms, such as cough, mild conjunctivitis, or mild tonsillar exudate [37]. Finally, 3) an asymptomatic case is a confirmed RT-PCR test infected individual without any respiratory or other symptom during all the period of infection until the discharge of the patient with two sequential RT-PCR negative tests. This is also a retrospective definition.

During the current pandemic situation, where daily surveillance is necessary, we can consider a "potential asymptomatic individual" to be one with confirmed RT-PCR test without any respiratory or other symptom in the last two weeks till the diagnosis date. If the patient develops any sign or symptom related to the infection, it automatically is cataloged as a pre-symptomatic or paucisymptomatic patient. Additionally, we must consider dermatological [71], neurological [72], and gastrointestinal [73] signs and symptoms as atypical presentations of COVID-19 presentation.

Currently, most national and international infectious diseases societies recommend SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to the virus. Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19. Additionally, it is important to remember that an asymptomatic individual, depending on timing of exposure, may be a presymptomatic individual that may develop symptoms later, and then should be followed up [23,26,74-77].

4.4. How should asymptomatic individuals with COVID-19 be treated?

Asymptomatic individuals may remain in that state and may not develop moderate-severe symptoms (viral pneumonia and hypoxia) so hospitalization is not essential, and home isolation with monitoring is the first measure of care [78]. This home isolation should be monitored remotely and to date, there are few protocols in place on this topic. In depth surveillance is needed for individuals who have risk factors for severe disease despite their asymptomatic condition, because of the risk of progression to symptomatic disease with severe outcome in the second week after the onset of any symptoms [79]. Overall, management of patients who warrant hospitalization consists of ensuring appropriate

infection control and supportive care (including oxygenation and potentially ventilatory support for acute respiratory distress syndrome) [80].

In our study we did not find strong evidence for the use of treatment schemes (with or without drugs), so it is not possible to provide therapeutic guidelines for the treatment of asymptomatic infections [81].

4.5. What does our study add to the literature?

In relation to the identification of the SARS-CoV-2, the included studies used molecular techniques, which are the first line to confirm suspected cases. The RT-PCR has proven to be a sensitive and specific method for the detection of the agent in respiratory samples even for asymptomatic persons. Following these techniques, the studies reported a prevalence of asymptomatic infection ranging from 4% to 80% [82], defining an asymptomatic case as a laboratory-confirmed case that does not develop symptoms. These individuals can continue spreading from person to person in the community and at health facilities. Additionally, our study adds a proposal for the standardization concept for pre-symptomatic, paucisymptomatic, and asymptomatic individuals.

On the other hand, we found no guidelines or evidence-based consensus that strongly recommend treatment for asymptomatic individuals. Several investigators have proposed specific treatment regimens ranging from drugs to treat symptoms to the use of anti-viral combinations such as lopinavir/ritonavir, although the effectiveness of such regimens is still in question. It is not known whether lowering viral load in asymptomatic individuals will have any impact on reducing transmission. Despite that, most of the asymptomatic individuals have good overall clinical outcomes without complications.

4.6. Limitations

Our study has some limitations. First, we included observational studies that do not have a comparison group. Second, the published reports and case series do not provide enough level of evidence for decision making, so this systematic review is oriented to the description and explanation of the findings, and not to validate or refute based on the evidence. Third, although the evaluation and clinical evolution in most of the studies included in this review have a common factor, we cannot conclude that the treatments adopted in each case are effective in considering them as standards in other disease contexts. The scientific production the numbers of papers on COVID-19 are increasing day by day [83] with new evidence on the identification, management of role in community transmission of asymptomatic individuals so it is possible that our findings will be quickly outdated. Finally, another limitation is that most of the included studies are from China [84], some from the USA and Korea, very few from central Europe, one study from Iran and one from Malaysia, but none from Oceania, and from Latin America, as these regions came later to research on COVID-19, compared to China and USA.

5. Conclusions

Early recognition of individuals at risk of COVID-19 infection is the most effective prevention measure to avoid the spread of the disease. Individuals at risk of infection are those who are in direct contact with positive patients whether or not they have developed symptoms. The diagnosis of all asymptomatic individuals follows the same protocol as patients with symptoms. There is no standard treatment for asymptomatic COVID-19 individuals. There are no studies of adequate design to make this decision. Most infected asymptomatic cases, seven out of ten, remain asymptomatic. All individuals at risk require immediate diagnostic evaluation to avoid spreading the disease. Most of the asymptomatic individuals have overall good clinical outcomes without complications. Protocols and guidelines are needed to remotely monitor and guide care for asymptomatic cases.

Declaration of competing interest

None for all authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tmaid.2021.102058>.

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