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The incidence of the novel coronavirus SARS-CoV-2 among asymptomatic patients: A systematic review



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ABSTRACT

Background: The recent outbreak of the coronavirus disease 2019 (COVID-19) has quickly spread globally since its discovery in Wuhan, China, in December 2019. A comprehensive strategy – including surveillance, diagnostics, research, and clinical treatment – is urgently needed to win the battle against COVID-19. Recently, numerous studies have reported the incidence of SARS-CoV-2 in asymptomatic patients. Yet, the incidence and viral transmission from the asymptomatic cases are not yet apparent. **Aim:** To estimate the incidence of COVID-19 among asymptomatic cases and describe its epidemiological and clinical significance this review systematically examined the published literature on SARS-CoV-2 in asymptomatic patients.

Methods: The literature was searched through four scientific databases: PubMed, Web of Science, Scopus, and Science Direct.

Results: Sixty-three studies satisfied the inclusion criteria. The majority of the reported studies were from China. However, there was a lack of SARS-CoV-2 epidemiological studies, from several countries worldwide, tracing the actual incidence of COVID-19, especially in asymptomatic patients. Studies with a large sample size (>1000) estimated that the percentage of people contracting SARS-CoV-2 and likely to be asymptomatic ranged from 1.2–12.9%. However, other studies with a smaller sample size reported a much higher incidence and indicated that up to 87.9% of COVID-19 infected individuals could be asymptomatic. Most of these studies indicated that asymptomatics are a potential source of infection to the community.

Conclusion: This review highlighted the need for more robust and well-designed studies to better estimate COVID-19 incidence among asymptomatic patients worldwide. Early identification of asymptomatic cases, as well as monitoring and tracing close contacts, could help in mitigating the spread of COVID-19.

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Introduction

Infectious diseases impose a major global health threat, leading to 15 million deaths annually (Fauci et al., 2005). Although the percentage of mortality due to infectious diseases has declined, numerous new infectious diseases have recently been identified and reported. The novel coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, was firstly identified in Wuhan, China, in late December 2019 as an outbreak of unusual viral pneumonia (Mousavizadeh and Ghasemi, 2020). Later, the World Health

Organisation (WHO) declared a global public health emergency. The total number of infected cases reached 4.4 million by May 2020 (WHO, 2020). Consequently, educational institutions, business centres, public transport, and other social interactions were locked down to prevent the spread of COVID-19 and ease the burden on health facilities. SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus with six open reading frames that codes for structural proteins, including surface (S), envelope (E), membrane (M), and nucleocapsid N proteins (Khailany et al., 2020). Based on the genomic structures and phylogenetic analysis of SARS-CoV-2, the virus belongs to genera *Betacoronavirus*, which includes SARS-CoV and MERS-CoV. Yet, SARS-CoV-2 has differences in its genomic makeup that can influence its pathogenesis.

The most effective approach in preventing and mitigating the adverse consequences of this viral pandemic requires the

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development of effective surveillance programmes, incorporated with laboratory preparedness. Diagnostic laboratory tests play a significant role in the rapid and accurate detection of new viruses (Song et al., 2019; Parreira, 2018). Currently, real-time reverse-transcription polymerase chain reaction (RT-PCR) testing is the main technique used for the diagnosis of COVID-19. However, false-negative RT-PCR results occur in up to 30% of COVID-19 patients (Wikramaratna et al., 2020; Breslin et al., 2020; Qin et al., 2020). This could be due to the collection of inappropriate or insufficient sample, inaccurate conditions of sample transportation and storage, as well as collecting the sample too late in the disease process.

On the other hand, serology testing could cover this gap, since detecting SARS-CoV-2 IgG antibodies could indicate recovery or immunity from COVID-19 infection. Besides, IgM could be detected in the acute phase of infections. Although manual enzyme-linked immunoassay (ELISA) kits could be subjected to non-specific binding and cross-reactivity with other coronaviruses such as MERS-CoV and SARS-CoV-1, the most commercially available antibodies use lateral flow assays (Al Kahlout et al., 2019). However, ELISA and automated-based assays were also recently

introduced. The diagnostic performance, including sensitivity and specificity, of these assays was better than lateral flow assays (Amanat et al., 2020). It worth mentioning that there is a high percentage of COVID-19 asymptomatic patients who could transmit the infection to all communities. For instance, the asymptomatic ratio of COVID-19 was estimated to be 41.6% of Japanese individuals who were evacuated from China (He et al., 2020). Similarly, 72% of people infected with COVID-19 on board the Diamond Princess cruise ship were asymptomatic (LSHTM, 2020). However, the extent of viral transmission from the asymptomatic cases is not yet clear. Positive RT-PCR results only imply potential infectivity. A prospective study was published on 28 March 2020, in which the viral load and clinical manifestations of 2147 close contacts of symptomatic and asymptomatic COVID-19 cases were followed up (Chen et al., 2020). The study concluded that the virus infection rate of close contacts with asymptomatic patients was 4.11%.

Since the transmission ability of asymptomatic individuals should not be ignored, it was interesting to conduct this systemic review to paint a picture of the current status and incidence of SARS-CoV-2 in asymptomatic patients. Therefore, this review

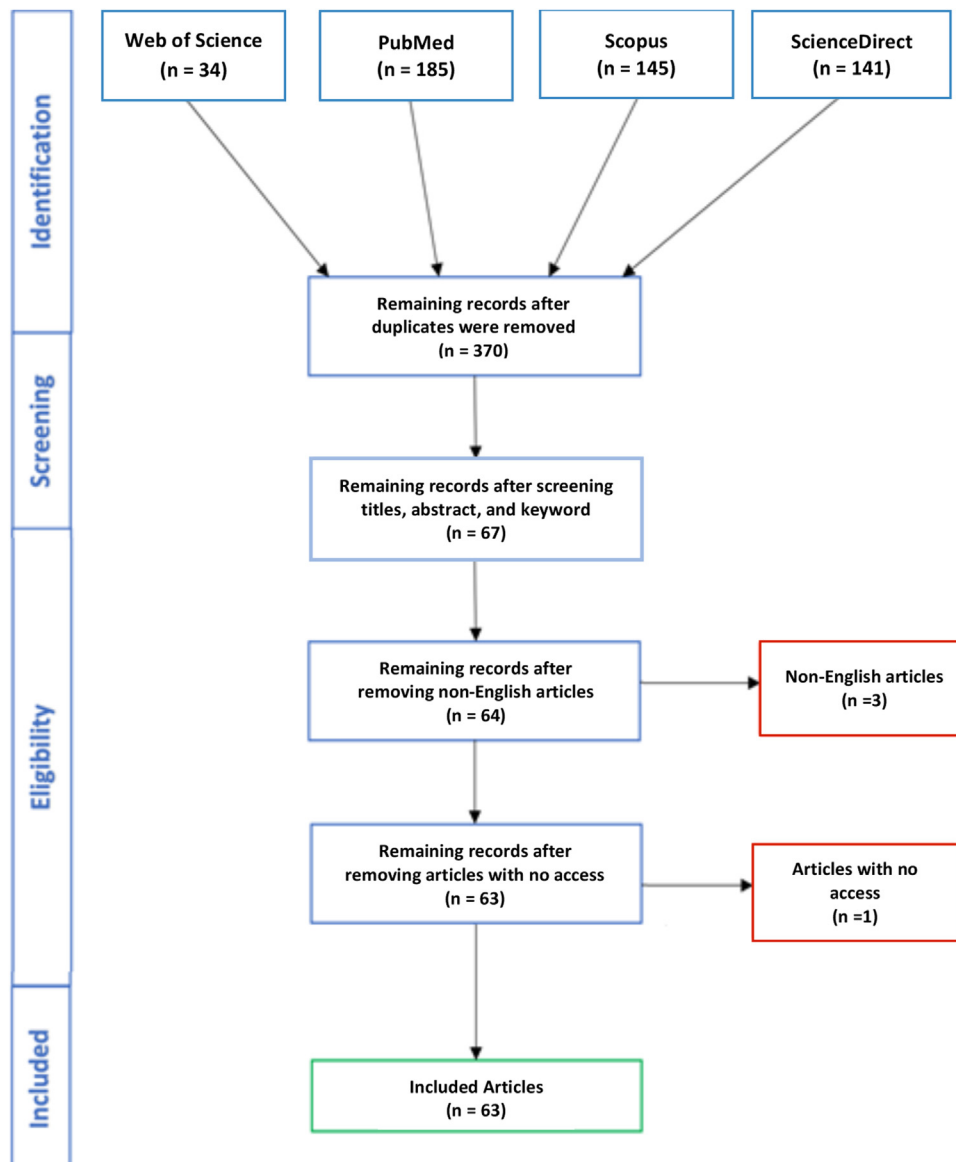


Figure 1. Flow diagram of the search strategy and article selection.

Table 1
Characteristics and summary data of the included studies.

Country	Type of study	Total case number	Number of asymptomatic patients	Age/mean age	Gender	Clinical features	Chest CT findings	Reference
China (Guangzhou)	Correspondence	295	45 (15.2%)	–	–	RT-PCR positive for SARS-CoV-2. Thirty patients started to show a few clinical symptoms after 3–14 days	Persistent negative CT findings. Fifteen were CT scan positive (after 3–6 days) for COVID-19 pneumonia	Ling et al. (2020)
China (Guangzhou)	Correspondence	5	2 (40%)	3-year-old male 33-year-old female	1 male 1 female	Normal lymphocyte counts. Positive qRT-PCR results	Normal chest CT images	Pan et al. (2020a)
China (Guangzhou)	Research letter	–	7	Age range: 21–56 years	4 males 3 females	Positive for SARS-CoV-2 by RT-PCR	A 56-year-old showed multiple ground-glass-like high-density shadows on both lungs	Li et al. (2020)
China (Guangdong)	Research article (familial cluster)	5	1 (20%)	10-year-old	Male	RT-PCR positive for SARS-CoV-2. Lymphopenia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels	Ground-glass lung opacities	Chan et al. (2020)
China (Wuhan)	Research article	–	58	The average age of patients was 42.60 ± 16.56 years old	26 males and 32 females	After a short-term follow-up, 16 patients (27.6%) presented symptoms with lower lymphocyte count and higher CRP, mainly including fever, cough and fatigue	Ground-glass opacity in 55 (94.8%) with peripheral in 44 (75.9%). Distribution unilateral in 34 (58.6%) and mostly involving one or two lobes in 38 (65.5%)	Meng et al. (2020)
China (Wuhan)	Research letter (familial cluster)	–	5	37-year-old wife 7-year-old fraternal twins 62-year-old grandfather 64-year-old grandmother	2 females 1 male Twins gender not determined	Throat swab specimens tested for SARS-CoV-2 were positive by PCR, except for one patient who tested negative on four consecutive throat swab specimen tests for SARS-CoV-2 but whose stool specimen was positive for SARS-CoV-2	Abnormal chest CT scans showing features consistent with SARS-CoV-2 infection in one of the twins	Luo et al. (2020a)
China (Wuhan)	Case report	–	1 (diagnosed as advanced lung adenocarcinoma)	56-years	Male	RT-PCR of SARS-CoV-2 and IgM were negative, while his serological IgG antibody to SARS-CoV-2 was positive	CT scan was negative	Ouyang et al. (2020)
China (Wuhan)	Case report	–	1	8-year-old	Female	No clinical symptoms or decreased lymphocyte count. Positive for SARS-CoV-2 IgG	Normal chest CT image	Jiang et al. (2020a)
China (Wuhan)	Research article	1012	30 (3%)	The median age was 50 years (range: 6–89)	–	Positive RT-PCR for SARS-CoV-2. During follow-up from admission to the end, fever occurred in 6, with cough in 8, myalgia in 3, dyspnoea in 2, nasal congestion in 1, and abdominal pain in 1. Fourteen of 1012 patients (1.4%) remained asymptomatic during the whole follow-up	Small patchy opacities (38.7%) and ground-glass opacities (55.4%)	Wang et al. (2020a)
China (Wuhan)	Research article	155	51 (33%)	–	–	Positive RT-PCR for SARS-CoV-2	CT showed no signs of viral pneumonia	Wang et al. (2020b)
China (Hubei)	Letter to the Editor	–	25	Average age 42.2 years (range: 28–73)	17 males 8 females	16 of the patients recovered without any symptoms. Nine developed a mild cough and/or other symptoms	Two-thirds of the patients had involvement of a single lobe, and two-thirds had a ground-glass density shadow. The least common CT finding was interlobular septal thickening	An et al. (2020)
China (Hubei)	Case report	–	1	3 months	Male	No nasal congestion, cough, shortness of breath, cyanosis, nausea, vomiting, and diarrhoea. Good mental response and crying sound. All blood, liver and kidney tests were normal. RT-PCR positive for SARS-CoV-2	Chest X-ray showed a slightly thicker texture of the right lung	Zhang et al. (2020)

Table 1 (Continued)

Country	Type of study	Total case number	Number of asymptomatic patients	Age/mean age	Gender	Clinical features	Chest CT findings	Reference
China (Shanghai)	Letter to the Editor	328	13 (3.9%)	Mean age was 51.8 years (range: 25–80)	6 males 7 females	Leucocytes were below the normal range in two patients (15.4%). Ten patients (76.9%) had differing degrees of elevation of the ESR. Liver, renal and coagulation function were within the normal range. No fever. Positive RT-PCR for SARS-CoV-2	A patient developed signs such as pneumonia on chest CT	Zhou et al. (2020a)
China (Nanjing)	Research article	–	24 screened due to close contact with COVID-19 patients	Cases with symptoms after diagnosis (n = 5) 53.0 (range: 23.0–65.0) Cases without symptoms after diagnosis (n = 19) 32.0 (15.0–57.0) 36-year-old 19-year-old	8 males and 16 females	Five cases (20.8%) developed symptoms (fever, cough, fatigue, etc.) during hospitalisation. Five (20.8%) presented stripe shadowing in the lungs. The remaining seven had no symptoms during hospitalisation. Four had C-reactive protein levels ≥ 10 mg/L	Twelve (50.0%) cases showed typical CT images of the ground-glass chest	Hu et al. (2020)
China (Hunan)	Research article	78	2 (2.5%)	36-year-old 19-year-old	Males	Positive RT-PCR for SARS-CoV-2. Patient 1: laboratory evaluation showed an elevated myoglobin, ALT, and uric acid level. Patient 2: laboratory tests including blood routine test, erythrocyte sedimentation rate, C-reactive protein and three items of myocardial enzyme spectrum were all negative	Chest CT scan was negative for both	Mao et al. (2020)
China (Guangdong)	Short communication	–	3	–	Patient 1: not determined Patient 2: female Patient 3: male	No fever, cough and expectoration during hospitalisation	Patient 1: multiple patchy and ground-glass shadows with uneven density and fuzzy edges in the outer zone of both lungs	Lu et al. (2020a)
China (Anhui)	Short communication	–	1	22-year-old pregnant woman	Female	No cough, dyspnoea or diarrhoea was noted	CT re-examination showed a small amount of pleural effusion on both sides	Lu et al. (2020b)
China (Zhejiang)	Research article (observational cohort study)	36	10 (28%)	Age range: 0–16 years; mean 8.3 years	–	Decreased lymphocytes, high levels of procalcitonin, D-dimer, and creatine kinase MB	–	Qiu et al. (2020)
China (Hefei)	Prospective contact-tracing study	–	1	22-year-old	Male	–	Lung infiltrates	Huang et al. (2020)
China (Jinan)	Research article	47	11 (23.4%)	Median age: 23 years (range: 1–60)	6 males 7 females	Pharyngeal swab COVID-19 nucleic acid was positive. The blood cell test results showed that 27.3% (3/11) had decreased white blood cell and 36.4% (4/11). The patients had increased lymphocyte count as well as high D-dimer levels, C-reactive protein and ESR were also reported	4 (36.4%) showed bilateral involvement and 3 (27.3%) showed unilateral involvement	Ma et al. (2020)
China	Research article	2143	94 (12.9%)	Median age 7 years (range: 2–13)	–	No clinical symptoms and signs, while the 2019-nCoV nucleic acid test was positive	The chest imaging was normal	Dong et al. (2020)
China	Clinical observations	83	1 (1.2%)	50-year old	Female	Persistent positivity of the virus nucleic acid in her throat swabs and anal swabs for at least 17 days, suggesting that she was very likely a healthy carrier	–	Luo et al. (2020b)

Table 1 (Continued)

Country	Type of study	Total case number	Number of asymptomatic patients	Age/mean age	Gender	Clinical features	Chest CT findings	Reference
China	Research article (familial cluster)	5	2 (40%)	28-year-old 23-year-old	Males	Patients were afebrile without any clinical signs. On days 3–5 of hospitalisation, the 23-year-old man developed fever and cough symptoms. Other laboratory examinations showed increasing C-reactive protein	Chest CT images showed no abnormalities On days 3–5 of hospitalisation, the 23-year-old man's chest CT scans showed ground-glass opacities in the lungs	Ye et al. (2020)
China	News journal article	166	130 (78%)	–	–	–	–	Day (2020a)
China	Research article	21	5 (20.8%)	25 (10–61) years	3 males 3 females	RT-PCR positive for SARS-CoV-2. One case generated SARS-CoV-2 specific antibody responses	–	Yongchen et al. (2020)
China	Research article	72,314	889 (1.2%)	Most were aged 30–79 years median age: 29.5 years	–	Positive viral nucleic acid test results but without any COVID19 symptoms	–	Surveillances (2020)
China	Research article (hospitalised patients)	–	26	–	16 males 10 females	RT-PCR positive for SARS-CoV-2. C-reactive protein and lymphocytes count were normal in all patients. Three patients had reduced albumin and two patients with slightly elevated creatinine levels	Nine patients with normal CT scans, 10 patients with typical manifestations (patch-like, ground-glass opacities distributed in the extrapulmonary zone), seven patients with changes in a unilateral lung, and three patients with changes in bilateral lungs	Pan et al. (2020b)
China	Familial cluster study	8	3 (37.5%)	35-year-old 53-year-old 3-month-old infant	Female	RT-PCR positive for SARS-CoV-2. No clinical symptoms	Ground-glass opacities except in the infant	Jiang et al. (2020b)
China	Research letter	6	1 (16.6%)	20-year-old	Female	RT-PCR positive for SARS-CoV-2. No elevated temperature measured or self-reported fever and no gastrointestinal or respiratory symptoms, including cough and sore throat, reported or observed by the physicians	Normal chest CT image	Bai et al. (2020)
Japan (Cruise Ship)	Rapid communication	634	328 (51.7%)	Female age range: 0–59 years. Males: not determined	313 female 321 male	SARS-CoV-2 positive by PCR	–	Mizumoto et al. (2020)
Japan	Research article	112	38 (33.9%)	Age range: 61.5–73.75 years	22 females 16 males	RT-PCR positive for SARS-CoV-2. IgM was detected in 27.8% of the collected specimens and IgG was detected in 3.3%	Chest CT showed abnormal lung findings consistent with the radiographic features of COVID-19 in 22 (57.9%)	Imai et al. (2020)
USA (Texas)	Case report	–	1	63-year-old	Female	SARS-Cov2 nasopharyngeal swab RT-PCR positive. No respiratory symptoms, normal body temperature, no recent travel	CT-simulation scan revealed interval development of new multifocal ground-glass opacities of the lungs	McCinnis et al. (2020)
USA (Washington)	Research article	48	27 (56%)	Mean age: 75.9 years	14 females 13 males	Real-time RT-PCR to test all samples. 15 reported no symptoms and 12 reported stable chronic symptoms. Fifteen (56%) residents who were asymptomatic at the time of testing had documented cognitive impairment	–	Arons et al. (2020)
USA (Washington)	Synopsis	23	13 (57%)	Mean age: 80.7 years	–	The RT-PCR testing cycle threshold (Ct) values indicated large quantities of viral RNA	–	Kimball et al. (2020)
USA (Washington)	Editorial	48	27 (56%)	–	–	RT-PCR positive for SARS-CoV-2	–	Gandhi et al. (2020)

Table 1 (Continued)

Country	Type of study	Total case number	Number of asymptomatic patients	Age/mean age	Gender	Clinical features	Chest CT findings	Reference
USA (New York)	News journal article	33	29 (87.9%)	–	Pregnant females	RT-PCR positive for SARS-CoV-2	–	Mayor (2020)
USA (New York)	Case series	43	14 (32.6%)	Maternal age ranged 20–39 years with a mean age of 26.9 years	Pregnant females	PCR-confirmed SARS-CoV-2. Eight patients developed fever ranging from 37.9–39.2 °C during hospital admission	–	Breslin et al. (2020)
Italy (Brescia)	Report (Incidental Findings)	Patients with different types of cancer	7	Median age 64.6 years old (Range: 55–79) years	2 males 5 females	RT-PCR positive for SARS-CoV-2	Patient 3: chest CT showed a suspicious retrosternal lymph node but no lung pathology. Patient 5: Thoracic CT displayed several ground-glass opacities in the right lung. Patient 7: CT showed diffuse interstitial pneumonia with peripheral ground-glass opacities	Albano et al. (2020)
Italy	Case report	–	1	1 month	Male	Real-time PCR confirmed infection The infant is a cystic fibrosis patient. He never developed a fever or any signs of infection.	–	Poli et al. (2020)
Italy	News journal article	3300	90 (2.7%)	–	–	RT-PCR positive for SARS-CoV-2	–	Day (2020b)
Germany	Correspondence	–	4	Patient 1: 33-year-old 44-year-old	Patient 1: male Male	RT-PCR positive for SARS-CoV-2	–	Rothe et al. (2020)
Iran (Tehran)	Case report	–	1	–	–	RT-PCR positive for SARS-CoV-2	Patchy ground-glass opacity in the upper lobe of the right lung	Asadollahi-Amin et al. (2020)
Iran	Case report	multiple trauma patients admitted to hospital	8	49.71 ± 13.13 (range: 34–67) years	62.5% male	None of the patients had COVID-19 symptoms at the time of admission to the hospital. RT-PCR positive for SARS-CoV-2. Laboratory results showed 4 (50%) patients with slight increase in C-reactive protein	Pneumonia in chest CT scan	Samsami et al. (2020)

Abbreviations: RT-PCR, reverse transcription–polymerase chain reaction; CT, computed tomography.

provided significant insights into COVID-19 infection and could help health authorities to determine the need for social distancing close contact restrictions in specific areas or populations.

Methods

Search strategy

A systematic review of all literature published on COVID-19 in asymptomatic patients was performed using four databases: PubMed, Web of Science, Scopus, and ScienceDirect. The search covered all literature within the databases up to April 2020. The four databases were searched without filters with the keywords: “COVID-19”, “SARS-CoV-2”, “seroprevalence”, and “asymptomatic” to ensure complete coverage of all literature. Therefore, results that were letters and commentaries were also included. All retrieved citations were imported into Clarivate Analytics, Philadelphia, Pennsylvania, United States, and duplicates were removed using the Clarivate Analytics, Philadelphia, Pennsylvania, United States built-in ‘Find Duplicates’ feature. Finally, the titles and abstracts of the remaining citations were screened to remove any irrelevant articles.

Study selection

The following inclusion criteria were used in study selection: (i) published in a peer-reviewed journal, letters, case reports, and commentaries; (ii) articles studying the COVID-19 infection in asymptomatic patients; and (iii) articles published in English or at least with an abstract in English. A schematic of the search strategy and study selection process is shown in [Figure 1](#). Studies that reported the coinfection of COVID-19 with other viruses as well as comorbidities, such as cancer and cystic fibrosis, were also included in this study. No exclusion criteria were followed unless the studies did not report the incidence of SARS-CoV-2 in asymptomatic patients, were published in a non-English language, or did not have full-text access.

Data extraction and analysis

The studies included in this systematic review were analysed twice by the same individual to ensure accurate capture of the information. The analysed data included the incidence of SARS-CoV-2 in asymptomatic COVID-19 patients, incidence of COVID-19

infection, routes of transmission, laboratory diagnostic tests, laboratory results, as well as CT scan findings.

Results

Search findings

The search yielded 505 studies, of which 370 citations remained after removing duplicates (Figure 1). After screening the titles, abstracts and keywords, 312 citations were excluded. The removed citations included irrelevant studies. The remaining 67 citations were screened against the eligibility criteria. Of these, one study was removed due to the unavailability of full-text access. Furthermore, three studies were removed: two for being published in languages other than English with no English abstract. The remaining 63 studies were included in this study for further analysis, and they consisted of letters to the editor, commentaries, case reports, and research studies.

Epidemiological findings

The reviewed studies covered SARS-CoV-2 incidence worldwide. Country-wise, the majority of the studies were from China ($n=44$) and included different provinces such as Wuhan, Shenzhen, Guangzhou, Beijing, Shanghai, Hunan, Nanjing, Guangdong, Anhui, Hubei, Zhejiang, Jinan, and Hefei (Table 1). The remaining studies were published in Japan ($n=2$), Italy ($n=3$), Germany ($n=1$), Iran ($n=2$), and USA ($n=6$), which included studies from Texas, Washington and New York. However, there was a lack of SARS-CoV-2 epidemiological studies tracing the actual incidence of COVID-19, especially in asymptomatic patients from several countries worldwide.

Looking at all the included studies with a large sample size (>1000 cases), these studies (Table 1, highlighted with bold text) estimated that the percentage of people who contracted SARS-CoV-2 and likely to be asymptomatic ranged from 1.2–12.9%. However, the other studies with a smaller sample size (<1000) reported a much higher incidence and indicated that up to 87.9% of COVID-19 infected individuals could be asymptomatic (Table 1). Most of these estimates were based on RT-PCR results. On the other hand, the estimated seroprevalence of antibodies to SARS-CoV-2 was reported to be higher. For instance, a study that was performed on 2857 blood donors from Rio de Janeiro showed 23.7% IgM positive cases, 11.4% IgG positive cases, while both IgM and IgG were detected in 64.9% (Amorim Filho et al., 2020). This could be due to the limitation of nasal swabs, since a PCR diagnosis could be negative even though antibody detection is positive. In fact, this finding was reported in a study where four of 317 asymptomatic participants had a negative PCR diagnosis, while antibody testing was positive (Korth et al., 2020). Therefore, solely relying on molecular testing could significantly underestimate the seroprevalence of SARS-CoV-2, especially in asymptomatic individuals.

Discussion

The spread of COVID-19 is an emerging condition with pandemic potential that threatens all countries. More than three million cases of COVID-19 have been confirmed worldwide over the last 4 months. Numerous epidemiologic investigations have identified an association with respiratory droplet transmission. Yet, understanding of the transmission risk is incomplete. It is worth mentioning that COVID-19 asymptomatic individuals may pose a significant public health threat. The majority of these patients might be unaware of their disease and therefore not isolate themselves or seek treatment, consequently unknowingly transmit the virus to others. It is believed that this is the first

systematic review study that has investigated the incidence of SARS-CoV-2 in asymptomatic patients.

A total of 63 of 505 screened studies reporting COVID-19 asymptomatic patients were included in this review. Epidemiological data, clinical laboratory results, CT image findings, and medical and contact history of the patients are critical knowledge that should be carefully studied when a new infectious disease emerges (Rodriguez-Morales et al., 2020). Although asymptomatic patients with SARS-CoV-2 were uncommon, studies have shown that the prevalence of SARS-CoV-2 in asymptomatic patients is underestimated and might increase. For instance, a review paper showed that the rate of asymptomatic individuals with Middle East Respiratory Syndrome coronavirus (MERS-CoV) ranged from 0–28.6% (Al-Tawfiq and Gautret, 2019). It was also reported that 75% of COVID-19 infected individuals could be asymptomatic (Day, 2020b).

COVID-19 infection ranges from asymptomatic to severe respiratory distress. Clinically it shows a milder infection in children, and many studies have reported children with asymptomatic COVID-19 infection. For instance, a study in China (Guangzhou) reported an asymptomatic 3-year-old male who tested positive for SARS-CoV-2, yet had normal lymphocyte counts and chest CT images (Pan et al., 2020a). Similarly, a study reported in China (Wuhan) showed a 3-year-old male asymptomatic patient with positive RT-PCR for SARS-CoV-2 and normal lymphocyte counts and chest CT images (Li et al., 2020). The reason for having a benign clinical course and low incidence of COVID-19 in children compared with adults is still unknown. A proposed hypothesis suggested that it might be due to the low expression of ACE2 receptors, high plasticity of their immune system, or to the exposure of other coronaviruses, which are generally more common in children (Cruz and Zeichner, 2020; Jia et al., 2005). Children may play a major role in community-based viral transmission. For instance, it was reported that viral shedding in a stool sample could persist for several weeks after diagnosis (Cai et al., 2020; Xiao et al., 2020). This poses a threat of viral transmission through the faecal-oral route, particularly for infants and children who are not toilet trained. Most of the reported COVID-19 cases in children were due to close contact with family members with SARS-CoV-2 infection (Table 1). Many experts believe that undetermined asymptomatic cases of COVID-19 infection could be an important source of contagion (Day, 2020a). Therefore, early identification of asymptomatic cases, as well as monitoring and tracing close contacts, could help in mitigating the spread of COVID-19 infection.

Another factor that increases the asymptomatic rate of COVID-19 is the inaccuracy of diagnostic testing. A recent article highlighted key important steps to be considered when designing seroprevalence studies, as well as experts' opinion on the recent studies. A major concern raised about the recently published results was the type of antibody test used, since most of them were inaccurate in supporting the conclusions (Offord, 2020). It was reported that the manual ELISA kits are subject to cross-reaction with other coronaviruses such as SARS-CoV-1 and MERS-CoV (Al Kahlout et al., 2019). This depends on the type of antibody or antigen used to coat the plates. For instance, a recent study used a previously developed ELISA method based on bat SARS-CoV Rp3N protein, since it does not cross-react with other human coronaviruses except SARS-CoV (Zhou et al., 2020b). This method successfully detected IgM and IgG antibodies against SARS-CoV-2 in early cases of COVID-19. Yet, various studies, such as the studies included in this review, used Chinese-manufactured test kits that are not approved by Chinese authorities or the US Food and Drug Administration (FDA). A seroprevalence population-based study was carried in Santa Clara County, USA, and suggested that $>30\%$ of positive cases are missed by the PCR test and result in

an underestimation of the incidence (Bendavid et al., 2020). The most significant implication of their findings is that the true infection rate is much higher than the reported number of cases. For instance, the study showed that the infection was 50–85-fold higher than confirmed positive cases by PCR (Bendavid et al., 2020). Although most of the included articles in this study used RT-PCR to confirm asymptomatic cases, no serological or other tests were performed to accurately estimate the incidence of SARS-CoV-2 in asymptomatic patients. In other words: PCR is considered the gold standard for diagnosis; however, if the sample was collected ≥ 14 weeks after infection, the viral genome/antigen might not be detected. Therefore, it could underestimate the prevalence of the infection.

Some of the included studies reported that the patients were positive for SARS-CoV-2 IgG, which suggests that the patients were asymptomatic SARS-CoV-2 carriers. The differential use of serology for confirming acute infection is not appropriate without additional collaboration of results. Therefore, combining both molecular and serological testing would be the best approach to accurately estimate the prevalence of COVID-19 infection, especially if the patient is at later stages of the infection and does not show symptoms (Younes et al., 2020).

Although governments in many countries are planning to conduct large-scale seroprevalence surveys, many laboratories try to rely on well-established and validated tests rather than rapid tests. The latter is based on blood collected from finger pricks to detect SARS-CoV-2 antibodies; however, the test performance and efficacy are not up to the required level, and many false results have been detected. Both specificity and sensitivity are essential in detecting SARS-CoV-2 to prevent false positive and negative results. It is unreliable to examine the test performance and efficacy of rapid tests based on finger-prick blood compared with the ELISA test, which uses venous blood. Consequently, this prevents underestimation of the asymptomatic COVID-19 infection rate.

Such positive cases may contribute to the silent spread of the virus. One of the significant limitations of many studies reporting asymptomatic cases is the difficulty in differentiating between asymptomatic or pre-symptomatic people, who are asymptomatic at the time of testing and develop symptoms later on. Citing data from China, WHO officials said on 01 April, “some cases of asymptomatic carriers have been confirmed by finding and testing people who were in close contact with COVID-19 patients. For those who tested positive without symptoms, follow-up exams confirmed that about 25% continued to show no signs”. For instance, a clinical study with a small sample size from China, performed in March 2020, followed up 24 asymptomatic positive PCR patients; 60% of them were pre-symptomatic and showed COVID-19 symptoms after 1–3 weeks (Hu et al., 2020). More follow-up studies should be performed to determine whether these cases continue to be asymptomatic or eventually develop symptoms. The question remains to be answered with further follow-up studies: can these asymptomatic or pre-symptomatic individuals spread the infection?

Conclusion

COVID-19 is a new infectious disease that has infected more than three million people in many countries all over the world. The severity and clinical manifestation of COVID-19 varies, and some individuals have been reported as asymptomatic. Based on the results of this study, many of the COVID-19 infected cases show no symptoms, and the infection could be transmitted during the incubation period. Consequently, asymptomatic patients are considered carriers and a potential source of infection to the community. Therefore, additional research studies on the

epidemiological significance of COVID-19 asymptomatic cases are required.

Conflicts of interest

The authors declare no conflict of interest.

Contributions

Conceptualization, GKN; data curation, DWA and GKN; writing – original draft preparation, DWA; writing – review and editing, DWA and GKN; supervision, GKN; project administration, GKN; funding acquisition, GKN. All authors have read and agreed to the published version of the manuscript.

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Ethical approval

The work presented in this manuscript does not involve work with animals or with human subjects, and therefore does not require ethics clearance.

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