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

Duaa W. Al-Sadeq, Gheyath K. Nasrallah

PII: S1201-9712(20)30533-6

DOI: https://doi.org/10.1016/j.ijid.2020.06.098

Reference: IJID 4403

To appear in: International Journal of Infectious Diseases

Received Date: 15 May 2020
Revised Date: 27 June 2020
Accepted Date: 29 June 2020

Please cite this article as: { doi: https://doi.org/

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.



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

Duaa W. Al-Sadeq^{1,2}, Gheyath K. Nasrallah^{1,3*}

*Correspondence: Gheyath K. Nasrallah, Ph.D., Department of Biomedical Science, College of Health Sciences, Qatar University, Doha, Qatar, P.O. Box 2713, Doha, Qatar. Phone: +974-4403-4817, Fax: +974-4403-1351, email: gheyath.nasrallah@qu.edu.qa

Highlights

- The true incidence of SARS-COV-2 is much higher than the reported number of cases.
- Large sample size studies showed 1.2-12.9% incidence of SARS-COV-2 among asymptomatics.
- Studies with a small sample size showed up to 87.9% incidence among asymptomatics.
- Asymptomatic individuals could be a potential source of infection to the community.

¹Biomedical Research Center, Qatar University, QU health, Doha, Qatar.

²College of Medicine, Member of QU Health, Qatar University, P.O. Box 2713, Doha, Qatar

³ Department of Biomedical Science, College of Health Sciences, Qatar University, QU health, Doha, Qatar.

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 reported the incidence of SARS-CoV-2 in asymptomatic patients. Yet, the incidence and viral transmission from the asymptomatic cases are not apparent yet. Aim: this study aims to systematically review the published literature on SARS-CoV-2 in the asymptomatic patients to estimate the incidence of COVID-19 among asymptomatic cases, as well as describe its epidemiological and clinical significance. Method: the literature was searched through four scientific databases: PubMed, Web of Science, Scopus, and Science Direct. **Results:** a total of 63 studies satisfied the inclusion criteria where 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 (n>1000) estimated that percentage of people contracting SARS-CoV-2 and are likely to be asymptomatic ranges from 1.2-12.9%. However, the 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 asymptopatics 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. The early identification of the asymptomatic cases, as well as monitoring and tracing close contact, could help in mitigating the spread of COVID-19.

Keywords: COVID-19, SARS-CoV-2, Asymptomatic carrier, Viruses, Incidence

1. Introduction

Infectious diseases impose a major health threat globally, leading to 15 million deaths annually [1]. Although the percentage of mortality due to infectious diseases has declined, numerous new infectious diseases have been identified and reported recently. 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 [2]. Later, the World Health Organization (WHO) declared a public health emergency worldwide, and the total number of infected cases reached 4.4 million by May 2020 [3]. Consequently, educational institutions, business centers, public transport, and other social interaction were locked down points 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 (ORFs) that codes for structural proteins, including surface (S), envelope (E), membrane (M), and nucleocapsid N proteins [4]. 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 that can influence its pathogenesis.

The most effective approach to prevent and mitigate the adverse consequences of this viral pandemic requires the development of effective surveillance programs, incorporated with laboratory preparedness. Diagnostic laboratory tests play a significant role in the rapid and accurate detection of new viruses [5, 6]. 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 [7-9]. 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, most commercially available antibodies utilize lateral flow assays (LFA) [10]. However, recently ELISA and automated-based assays were also introduced. The diagnostic performance, including sensitivity and specificity, of these assays, were better than the LFA [11]. It worth mentioning that there is a high percent 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 [12]. Similarly, 72% of people infected with COVID-19 on board the Diamond Princess cruise ship were asymptomatic [13]. However, the extent of viral transmission from the asymptomatic cases is not clear yet. The positive RT-PCR results only imply the potential infectivity. A prospective study was published on March 28 in which the viral load and clinical manifestations of 2,147 close contacts of symptomatic and asymptomatic COVID-19 cases were followed up [15]. 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 of interest to conduct a systemic review to paint a picture of the current status and incidence of SARS-CoV-2 in asymptomatic patients. Therefore, this study would give significant insights into COVID-19 infection and help health authorities to determine the need for social distancing close contact restrictions in specific areas or populations.

2. Methods

2.1. Search Strategy

We conducted a systematic review of all literature published on COVID-19 in the asymptomatic patients using four databases: PubMed, Web of Science, Scopus, and ScienceDirect. The search covered all literature within the databases up to April 2020. The databases were queried with the keywords: "COVID-19", "SARS-CoV-2", "seroprevalence", and "asymptomatic" to ensure complete coverage of all literature. The four databases were searched without filters. Therefore, results that were letters and commentaries were also included. All retrieved citations were imported into EndNote X8, and duplicates were removed using the EndNote X8 built-in "Find Duplicates" feature. Finally, the titles and abstracts of the remaining citations were screened to remove any irrelevant articles.

2.2. Study Selection

The following inclusion criteria were used in study selection: (i) published in a peerreviewed 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.
Besides, 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, published in a non-English language, or do not have full-text access.

2.3. Data Extraction and Analysis

The studies included in this systematic review were analyzed two times by the same individual to ensure accurate capture of the information. The analyzed data included the incidence

of SARS-Cov-2 in the asymptomatic COVID-19 patients, incidence of COVID-19 infection, routes of transmission, laboratory diagnostic tests, laboratory results, as well as CT scan findings.

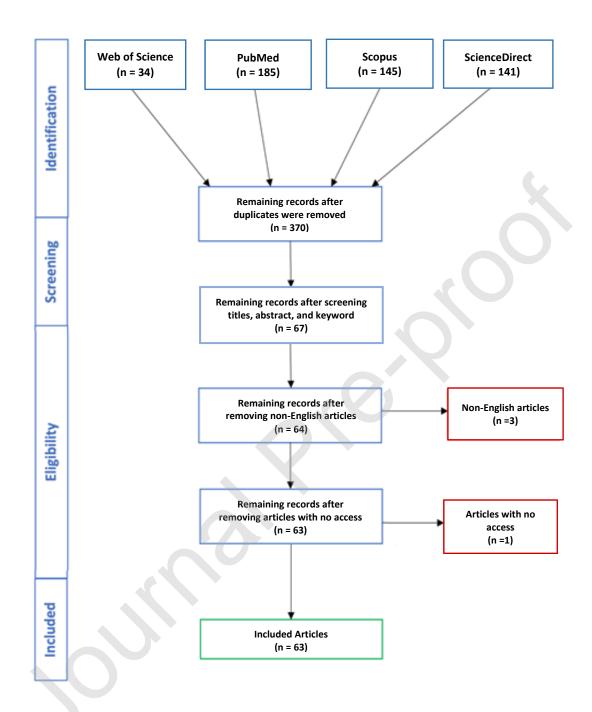


Figure 1. Flow diagram of the search strategy and article selection.

3. Results

3.1 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 as well as research studies.

3.2 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 from several countries worldwide, tracing the actual incidence of COVID-19, especially in asymptomatic patients.

Looking at all the included studies with a large sample size (n>1000 cases), these studies (Table 1, highlighted with bold text) estimated that percentage of people contracting SARS-CoV-2 and are likely to be asymptomatic range from (1.2-12.9%). However, the other studies with a smaller sample size (n<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 2,857 blood donors from Rio de Janeiro showed 23.7% of IgM positive cases, 11.4% of IgG positive cases,

while both IgM and IgG was detected in 64.9% [16]. This is could due to the limitation of the nasal swab since the PCR diagnostic could be negative though antibody detection is positive. In fact, this finding was reported in a study where four subjects out of 317 asymptomatic participants had negative PCR diagnostic, while antibody testing was positive [17]. Therefore, relying only on molecular testing could significantly underestimate the seroprevalence SARS-CoV-2, especially in asymptomatic individuals.

4. Discussion

The spread of COVID-19 is an emerging condition with pandemic potential that threatens all countries. Over the last four months, more than three million cases of COVID-19 have been confirmed worldwide. Numerous epidemiologic investigations identified an association with respiratory droplet transmission. Yet, understanding of the transmission risk is incomplete. It worth mention 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. To the best of our knowledge, this is the first systematic review study that investigated the incidence of SARS-CoV-2 in asymptomatic patients.

A total of 63 out of 505 screened studies reporting COVID-19 asymptomatic patients were included in this review. Epidemiological data, clinical laboratory results, CT image findings, as well as the medical and contact history of the patient are critical knowledge that should be carefully studied when a new infectious disease emerged [59]. Although asymptomatic patients with SARS-CoV-2 were uncommon, studies showed that the prevalence of SARS-CoV-2 in asymptomatic patients is underestimated and might increase. For instance, a review paper showed the rate of asymptomatic individuals with the Middle East Respiratory Syndrome coronavirus (MERS-CoV) ranged from 0% to 28.6% [60]. Besides, it was reported that 75% of COVID-19 infected individuals could be asymptomatic [55].

COVID-19 infection ranges from asymptomatic to severe respiratory distress. Yet, clinically is shows a milder infection in children, and many studies reported children patients with asymptomatic COVID-19 infection. For instance, a study in China (Guangzhou) reported an asymptomatic 3-years old male who tested positive for SARS-CoV-2, yet, had normal lymphocyte

counts and chest CT images [19]. Similarly, a study reported in China (Wuhan) showed a 3-years old male asymptomatic patient with positive RT-PCR for SARS-CoV-2 and normal lymphocyte counts and chest CT images [20]. It is unknown yet the reason of having a benign clinical course and low incidence of COVID-19 in children compared to adults. 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 common in kids [61, 62]. Besides, children may play a major role in community-based viral transmission. For instance, it was reported that viral shedding in the stool sample could persist for several weeks after diagnosis [63, 64]. Consequently, it poses a threat of viral transmission through the fecal-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 [41]. Therefore, the early identification of the asymptomatic cases, as well as monitoring and tracing close contact, 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. For instance, 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 inaccurate to support the conclusions [65]. It was reported that the manual ELISA kits are subject to cross-reaction with other coronaviruses such as SARS-CoV-1 and MERS-CoV [10]. This depends on the type of antibody or antigen used to coat the plates. For instance, a recent study used previously developed ELISA method based on bat SARS-CoV Rp3 N protein since it does

not cross-react with other human coronaviruses except SARS-CoV [66]. The 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 tests kit that are not approved by Chinese authorities or the US Food and Drug Administration (FDA). Besides, until to date, a seroprevalence population-based study was carried in Santa Clara County, USA and suggested that over 30% of positive cases are missed by the PCR test and results in an underestimation of the incidence. 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 to 85-fold higher than confirmed positive cases by PCR [67]. Besides, 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. Yet, if the sample was collected after 14 weeks or more after infection, the viral genome/antigen might not be detected. Therefore, it could underestimate the prevalence of the infection.

Besides, some of the included studies reported that the patients were positive for SARS-CoV-2 IgG, which suggested that the patient was an asymptomatic SARS-CoV-2 carrier. The differential use of serology for confirming acute infection is not appropriate without the 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 [68].

Although governments in many countries are planning to conduct largescale seroprevalence surveys, many laboratories try to rely on well-established and validated lab tests, rather than rapid tests. The latter is based on blood collected from finger pricks to detect SARS-

CoV-2 antibodies. Yet, the test performance and efficacy are not up to the required level, and many false results were detected. Both specificity and sensitivity are essential in detecting SARS-CoV-2 to prevent false positive and negative results. It is not reliable to examine the test performance and efficacy of rapid tests based on finger-prick blood compared to the ELISA test, which utilizes collect venous blood. Consequently, preventing the underestimation of asymptomatic COVID-19 infection rate.

Such positive cases may contribute to the silent spread of the virus. Yet, one of the significant limitations of many studies reporting asymptomatic cases is the difficulty of differentiating between asymptomatic or pre-symptomatic, who are asymptomatic at the time of testing and later on they developed symptoms. Citing data from China WHO officials said on April 1 "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, done 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 [31]. More follow-up studies should be done to determine whether these cases continue to be asymptomatic or eventually develop symptoms. Whether these asymptomatic or pre-symptomatic individuals can spread the infection, a question remained to be answered with further follow-up studies.

5. Conclusion

COVID-19 is a new infectious disease that 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 were reported as asymptomatic. Based on the results of this study, many of the COVID-

19 infected cases show no symptoms, and that 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.

Contributions: Conceptualization, G.K.N.; data curation, D.W.A. and G.K.N.; writing—original

draft preparation, D.W.A.; writing—review and editing, D.W.A. and G.K.N.; supervision,

G.K.N..; project administration, G.K.N.; funding acquisition, G.K.N. All authors have read and

agreed to the published version of the manuscript.

Funding: This work is supported by QNRF grant no. RRC-032 grant was given to G.K.N. We

would like also to thank Oatar National Library (a member of Oatar Foundation) for sponsoring

the publication fees of this article.

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.

Conflicts of Interest: The authors declare no conflict of interest.

14

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment: We would like to thank Nadin Younes for reviewing this article.

References

- 1. Fauci, A.S., N.A. Touchette, and G.K. Folkers, *Emerging infectious diseases: a 10-year perspective from the National Institute of Allergy and Infectious Diseases*. Emerging infectious diseases, 2005. **11**(4): p. 519-525.
- 2. Mousavizadeh, L. and S. Ghasemi, *Genotype and phenotype of COVID-19: Their roles in pathogenesis*. Journal of Microbiology, Immunology and Infection, 2020.
- 3. WHO, Coronavirus disease (COVID-19) Pandemic. 2020.
- 4. Khailany, R.A., M. Safdar, and M. Ozaslan, *Genomic characterization of a novel SARS-CoV-2.* Gene Reports, 2020: p. 100682.
- 5. Song, Z., et al., From SARS to MERS, Thrusting Coronaviruses into the Spotlight. Viruses, 2019. **11**(1).
- 6. Parreira, R., *Laboratory Methods in Molecular Epidemiology: Viral Infections.* Microbiol Spectr, 2018. **6**(6).
- 7. Wikramaratna, P., et al., *Estimating false-negative detection rate of SARS-CoV-2 by RT-PCR.* medRxiv, 2020.
- 8. Breslin, N., et al., *COVID-19 infection among asymptomatic and symptomatic pregnant women:*Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM, 2020: p. 100118.
- 9. Qin, C., et al., 18 F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. European Journal of Nuclear Medicine and Molecular Imaging, 2020: p. 1-6.
- 10. Al Kahlout, R.A., et al., *Comparative serological study for the prevalence of anti-MERS coronavirus antibodies in high-and low-risk groups in Qatar.* Journal of immunology research, 2019. **2019**.
- 11. Amanat, F., et al., *A serological assay to detect SARS-CoV-2 seroconversion in humans.* Nature medicine, 2020: p. 1-4.
- 12. He, D., et al., *The relative transmissibility of asymptomatic COVID-19 infections among close contacts.* International Journal of Infectious Diseases, 2020. **94**: p. 145-147.
- 13. London School of Hygiene and Tropical Medicine. *Almost 75% of people on board Diamond Princess with COVID-19 may have been asymptomatic.* 2020 16/6/2020]; Available from: https://www.lshtm.ac.uk/newsevents/news/2020/almost-75-people-board-diamond-princess-covid-19-may-have-been-asymptomatic.
- 14. Mizumoto, K., et al., *Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020.* Eurosurveillance, 2020. **25**(10).
- 15. Chen, Y., et al., *The epidemiological characteristics of infection in close contacts of COVID-19 in Ningbo city*. Chinese Journal of Epidemiology, 2020. **41**(0): p. 0-0.
- 16. Amorim Filho, L., et al., Seroprevalence of IgG and IgM anti-SARS-CoV-2 among voluntary blood donors in Rio de Janeiro, Brazil.
- 17. Korth, J., et al., SARS-CoV-2-specific antibody detection in healthcare workers in Germany with direct contact to COVID-19 patients. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology, 2020. **128**: p. 104437-104437.
- 18. Ling, Z., et al., Asymptomatic SARS-CoV-2 infected patients with persistent negative CT findings. European Journal of Radiology, 2020. **126**.
- 19. Pan, X., et al., Asymptomatic cases in a family cluster with SARS-CoV-2 infection. The Lancet Infectious Diseases, 2020. **20**(4): p. 410-411.
- 20. Li, C., et al., Asymptomatic and Human-to-Human Transmission of SARS-CoV-2 in a 2-Family Cluster, Xuzhou, China. Emerging infectious diseases, 2020. **26**(7).

- 21. Chan, J.F.-W., et al., A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet, 2020. **395**(10223): p. 514-523.
- 22. Meng, H., et al., *CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China*. Journal of Infection, 2020.
- 23. Luo, Y., et al., Asymptomatic SARS-CoV-2 Infection in Household Contacts of a Healthcare Provider, Wuhan, China. Emerg Infect Dis, 2020. **26**(8).
- 24. Ouyang, W., et al., Alert to Potential Contagiousness: A Case of Lung Cancer with Asymptomatic SARS-CoV-2 Infection. J Thorac Oncol, 2020.
- 25. Jiang, X., et al., Asymptomatic SARS-CoV-2 infected case with viral detection positive in stool but negative in nasopharyngeal samples lasts for 42 days. J Med Virol, 2020.
- Wang, X., et al., Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. Clin Microbiol Infect, 2020.
- 27. Wang, Z., et al., Household transmission of SARS-CoV-2. Journal of Infection, 2020.
- 28. An, P., et al., Asymptomatic Patients with Novel Coronavirus Disease (COVID-19). Balkan medical journal, 2020.
- 29. Zhang, Y.H., et al., [2019 novel coronavirus infection in a three-month-old baby]. Zhonghua Er Ke Za Zhi, 2020. **58**(3): p. 182-184.
- 30. Zhou, X., et al., *Follow-up of asymptomatic patients with SARS-CoV-2 infection*. Clinical Microbiology and Infection, 2020.
- 31. Hu, Z., et al., *Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China*. Science China Life Sciences, 2020.
- 32. Mao, Z.Q., et al., *The enlightenment from two cases of asymptomatic infection with SARS-CoV-2: is it safe after 14 days of isolation?* International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases, 2020.
- 33. Lu, S., et al., Alert for non-respiratory symptoms of Coronavirus Disease 2019 (COVID-19) patients in epidemic period: A case report of familial cluster with three asymptomatic COVID-19 patients. Journal of Medical Virology, 2020.
- 34. Lu, D., et al., Asymptomatic COVID-19 infection in late pregnancy indicated no vertical transmission. J Med Virol, 2020.
- 35. Qiu, H., et al., Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. The Lancet Infectious Diseases, 2020.
- 36. Huang, L., et al., Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: A prospective contact-tracing study. J Infect, 2020.
- 37. Ma, Y., et al., *Characteristics of asymptomatic patients with SARS-CoV-2 infection in Jinan, China.* Microbes and Infection, 2020.
- 38. Dong, Y., et al., *Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China.* Pediatrics, 2020.
- 39. Luo, S.H., et al., A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). Chinese medical journal, 2020.
- 40. Ye, F., et al., *Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster.* Int J Infect Dis, 2020.
- 41. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ (Clinical research ed.), 2020. **369**: p. m1375.

- 42. Yongchen, Z., et al., Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. Emerging Microbes & Infections, 2020(just-accepted): p. 1-14.
- 43. Surveillances, V., *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
- 44. Pan, Y., et al., *Epidemiological and clinical characteristics of 26 asymptomatic SARS-CoV-2 carriers.*J Infect Dis, 2020.
- 45. Jiang, X.L., et al., *Transmission potential of asymptomatic and paucisymptomatic SARS-CoV-2 infections: a three-family cluster study in China*. J Infect Dis, 2020.
- 46. Bai, Y., et al., Presumed Asymptomatic Carrier Transmission of COVID-19. Jama, 2020.
- 47. Imai, K., et al., Clinical evaluation of an immunochromatographic IgM/IgG antibody assay and chest computed tomography for the diagnosis of COVID-19. Journal of Clinical Virology, 2020: p. 104393.
- 48. McGinnis, G.J., et al., *Rapid Detection of Asymptomatic COVID-19 by CT Image-Guidance for Stereotactic Ablative Radiotherapy*. J Thorac Oncol, 2020.
- 49. Arons, M.M., et al., *Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility*. N Engl J Med, 2020.
- 50. Kimball, A., et al., Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep, 2020. **69**(13): p. 377-381.
- 51. Gandhi, M., D.S. Yokoe, and D.V. Havlir, *Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19.* N Engl J Med, 2020.
- 52. Mayor, S., Covid-19: Nine in 10 pregnant women with infection when admitted for delivery are asymptomatic, small study finds. BMJ (Clinical research ed.), 2020. **369**: p. m1485.
- 53. Albano, D., et al., INCIDENTAL FINDINGS SUGGESTIVE OF COVID-19 IN ASYMPTOMATIC PATIENTS UNDERGOING NUCLEAR MEDICINE PROCEDURES IN A HIGH PREVALENCE REGION. J Nucl Med, 2020.
- 54. Poli, P., et al., *Asymptomatic case of Covid-19 in an infant with cystic fibrosis.* Journal of Cystic Fibrosis, 2020.
- 55. Day, M., Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ (Clinical research ed.), 2020. **368**: p. m1165.
- 56. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.*The New England journal of medicine, 2020. **382**(10): p. 970-971.
- 57. Asadollahi-Amin, A., et al., Lung Involvement Found on Chest CT Scan in a Pre-Symptomatic Person with SARS-CoV-2 Infection: A Case Report. Trop Med Infect Dis, 2020. **5**(2).
- 58. Samsami, M., et al., *COVID-19 Pneumonia in Asymptomatic Trauma Patients; Report of 8 Cases.* Arch Acad Emerg Med, 2020. **8**(1): p. e46.
- 59. Rodriguez-Morales, A.J., et al., *Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis.* Travel medicine and infectious disease, 2020: p. 101623-101623.
- 60. Al-Tawfiq, J.A. and P. Gautret, Asymptomatic Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: extent and implications for infection control: a systematic review. Travel medicine and infectious disease, 2019. 27: p. 27-32.
- 61. Cruz, A.T. and S.L. Zeichner, *COVID-19 in children: initial characterization of the pediatric disease.* Pediatrics, 2020.
- 62. Jia, H.P., et al., ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol, 2005. **79**(23): p. 14614-21.
- 63. Cai, J., et al., A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clinical Infectious Diseases, 2020.

- 64. Xiao, F., et al., *Evidence for gastrointestinal infection of SARS-CoV-2.* Gastroenterology, 2020. **158**(6): p. 1831-1833. e3.
- 65. Offord, C. *How (Not) to Do an Antibody Survey for SARS-CoV-2*. 2020 1/5/2020]; Available from: https://www.the-scientist.com/news-opinion/how-not-to-do-an-antibody-survey-for-sars-cov-2-
 - 67488?utm_campaign=TS_OTC_2020&utm_source=hs_email&utm_medium=email&utm_conte nt=87227297&_hsenc=p2ANqtz--OX79Py05lz3KB_wqDMHJfcVa3bRgNFKwz-ImL1fxCEQ_fZwMR1zxNctcNqGZAYwBFm8PrGdjQib1gWD3oZ0NWpLCEaw&_hsmi=87227297.
- 66. Zhou, P., et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020. **579**(7798): p. 270-273.
- 67. Bendavid, E., et al., *COVID-19 Antibody Seroprevalence in Santa Clara County, California.* medRxiv, 2020: p. 2020.04.14.20062463.
- 68. Younes, N., et al., *Challenges in Laboratory Diagnosis of the Novel Coronavirus SARS-CoV-2.* Viruses, 2020. **12**(6): p. 582.

Table 1: Characteristics and summary data of included studies

Country	Type of the 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. 30 patients started to show few clinical symptoms (after 3-14 days).	Persistent negative CT findings. 15 patients had CT scan positive (after 3–6 days) for COVID-19 pneumonia.	[18]
China (Guangzhou)	Correspondence	5	2 (40%)	3-years old male 33-years old woman	1 male 1 female	Normal lymphocyte counts. Positive qRT-PCR results.	Normal chest CT images	[19]
China (Guangzhou)	Research letter		7	Age range: 21- 56-year-old	4 males 3 females	Positive for SARS-CoV-2 by RT-PCR	The 56-year old patient showed multiple ground-glass-like high-density shadows on both lungs.	[20]
China (Guangdong)	Research article (familial cluster)	5	1 (20%)	10-year-old	Male	RT-PCR positive for SARS- CoV-2. Lymphopenia, thrombocytopenia, and increased	Ground-glass lung opacities	[21]

					C-reactive protein and lactate dehydrogenase levels		
F	Research article -	58	The average age of patients was 42.60±16.56 years old	26 male 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 (GGO) in 55 (94.8%) with peripheral in 44 (75.9%) distribution, unilateral location in 34 (58.6%) and mostly involving one or two lobes in 38 (65.5%)	[22]
]	Research letter - (familial	5	37-year-old wife 7-year-old	2 females 1 male	Throat swab specimens tested for SARS-CoV-2 were positive by	Abnormal chest CT scans showing features	[23]
	clsture)		fraternal twins 62-year-old grandfather 64-year-old	Twins gender not determined	PCR except for one patient, who tested negative on 4 consecutive throat swab specimen tests for SARS-CoV-2 but whose stool specimen was positive for SARS-	consistent with SARS-CoV-2 infection in one of the twins	
_	Case report -	1 (diagnosed as	grandmother 56-years	Male	CoV-2 RT-PCR of SARS-CoV-2 and	CT scan was negative	[24
		advanced lung adenocarcinoma)			IgM were negative, while his serological IgG antibody to SARS-CoV-2 were positive		

China (Wuhan)	Case report	-	1	8-year-old	Female	No clinical symptoms or decreased lymphocyte count.	Normal chest CT image	[25]
						Positive for SARS-CoV-2 IgG.		
China	Research	1012	30 (3%)	The median age	-	Positive RT-PCR for SARS-	Small patchy opacities	[26]
(Wuhan)	article			50-year old		CoV-2. During follow up from	(38.7%) and ground-	
				ranging from 16		admission to the end, fever	glass opacities (55.4%)	
				to 89 years		occurred in 6, with cough in 8,		
						myalgia in 3, dyspnoea in 2,		
						nasal congestion in 1, and		
						abdominal pain in 1. 14 of 1012		
						patients (1.4%) remained		
						asymptomatic during the whole		
						follow up		
China	Research article	155	51 (33%)	-	-	Positive RT-PCR for SARS-CoV-	CT showed no signs of	[27]
(Wuhan)						2	viral pneumonia	
China (Hubei)	Letter to the	-	25	Average age 42.2	17 males	16 of the patients recovered	Two-thirds of the patients	[28]
	Editor			(28–73)	8 females	without any symptoms. Nine	had involvement of a	
						patients developed a mild cough	single lobe, and two-thirds	
						and/or other symptoms.	had only a ground-glass	
							density shadow. The least	
							common CT finding was	

interlobular septal thickening

China (Hubei)	Case report	-	1	3 months	Male	No nasal congestion and snot, no cough, no shortness of breath, no cyanosis, no nausea, vomiting, and diarrhea, 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	[29]
China (Shanghai)	Letter to the Editor	328	13 (3.9%)	Mean age was 51.8 years (range: 25-80 years).	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 function, renal function, and coagulation function were within the normal range. No fever. Positive RT-PCR for SARS-CoV-2	A patient has developed signs, such as pneumonia on chest CT	[30]
China (Nanjing)	Research article)	24 screened due to close Contact with COVID-19 patients	Cases with symptoms after diagnosis (n=5) 53.0 (23.0 -65.0)	8 males and 16 females	Five cases (20.8%) developed symptoms (fever, cough, fatigue, etc.) during hospitalization. 5 (20.8%) presented stripe shadowing in the lungs. The	Twelve (50.0%) cases showed typical CT images of the ground-glass chest	[31]

				Cases without symptoms after diagnosis (n=19) 32.0 (15.0 - 57.0)		remaining 7 had no symptoms during hospitalization. 4 patients had C-reactive protein level ≥10 mg/liter		
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 (ESR), C-reactive protein and three items of myocardial enzyme spectrum were all negative	Chest CT scan was negative for both	[32]
China	Short	- 🔨	3	-	Patient 1:	No fever, cough, and	Patient 1: multiple patchy	[33]
(Guangdong)	communication				not	expectoration during	and ground glass shadows	
					determined	hospitalization.	with uneven density and	
					Patient 2:		fuzzy edge in the outer	
					female		zone of both lungs	
					Patient 3:			
					male			

China (Anhui)	Short communication	-	1	22- year- old pregnant woman	Female	No cough, dyspnea, or diarrhea was noted.	CT reexamination showed a small amount of pleural effusion on both sides	[34]
China (Zhejiang)	Research article (observational cohort study)	36	10 (28%)	Age range: 0–16 years with mean 8·3 years	-	Decreased lymphocytes, high levels of procalcitonin, D-dimer, and creatine kinase MB	-	[35]
China (Hefei)	Prospective contact-tracing study	-	1	22-year-old	Male	<u>-</u>	Lung infiltrates	[36]
China (Jinan)	Research article	47	11 (23.4%)	Median age: 23 years, ranging from 1 to 60 years	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) had increased lymphocyte count. High D-dimmer levels, C-reactive protein and ESR.	4 (36.4%) showed bilateral involvement and 3 (27.3%) showed unilateral involvement	[37]
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 is positive.	The chest imaging is normal.	[38]

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 suggested that she was very likely a healthy carrier.	-	[39]
China	Research article (familial cluster)	5	2 (40%)	28-year-old 23-years old	Males	Patients were afebrile without any clinical signs. On days 3 through 5 of hospitalization, the 23-years old man developed fever and cough symptoms. Other laboratory examinations showed increasing C-reactive protein	Chest CT images showed no abnormalities On days 3 through 5 of hospitalization, the 23-years old man chest CT scans showed ground-glass opacities in the lungs	[40]
China	News journal article	166	130 (78%)	-	-	-	-	[41]
China	Research article	21	5 (20.8%)	25 (10–61) years	3 males 3 females	RT-PCR positive for SARS-CoV-2. Only 1 case generated SARS-CoV-2 specific antibody responses.	-	[42]
China	Research article	72,314	889 (1.2%)	Most were aged 30–79 years	-	Positive viral nucleic acid test results but without any COVID19 symptoms	-	[43]

China	Research article	-	26	median age is	16 males	RT-PCR positive for SARS-	Nine patients with normal	[44]
	(hospitalized			29.5 years	10 females	CoV-2. C-reactive protein and	CT scans, 10 patients with	
	patients)					lymphocytes count were normal	typical manifestations	
						in all patients. Three patients had	(patch-like, ground-glass	
						reduced albumin and two patients	opacities distributed in the	
						with slightly elevated creatinine	extrapulmonary zone),	
						levels	seven patients with	
							changes in a unilateral	
							lung, and three patients	
					>		with changes in bilateral	
							lungs.	
China	Familial cluster	8	3 (37.5%)	35-year-old	Female	RT-PCR positive for SARS-CoV-	Ground-glass opacities	[45]
	study			53-year-old		2. No clinical symptoms	except in the infant	
				3-month-old				
				infant				
China	Research letter	6	1 (16.6%)	20-year-old	Female	RT-PCR positive for SARS-CoV-	Normal chest CT image	[46]
						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.		

Japan (Cruise	Donid	634	229 (51 70/)	Famala, aga	212 famala	SARS CoV 2 mositive by DCD		[14]
Ship)	Rapid communication	034	328 (51.7%)	Female: age ranged 0–59 years. Males: not determined	313 female 321 male	SARS-CoV-2 positive by PCR	-	[14]
Japan	Research article	112	38 (33.9%)	Age ranged (61.5–73.75) years	22 females 16 males	RT-PCR positive for SARS-CoV-2. IgM was detected in 27.8%, of the specimens collected 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 %).	[47]
USA (Texas)	Case report	-		63-year-old	Female	SARS-Cov2 nasopharyngeal swab RT-PCR resulted 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	[48]
USA (Washington)	Research article	48	27 (56%)	Age mean 75.9	14 females 13 males	real-time reverse-transcriptase polymerase chain reaction (rRT- PCR) to test all samples. 15 reported no symptoms and 12 reported only stable chronic symptoms. Fifteen (56%) residents who were asymptomatic	-	[49]

_								
						at the time of testing had		
						documented cognitive impairment		
USA	Synopsis	23	13 (57%)	Age mean 80.7	-	The reverse transcription—	-	[50]
(Washington)						polymerase chain reaction (RT-		
						PCR) testing cycle threshold (Ct)		
						values indicated large quantities		
						of viral RNA		
USA	Editorial	48	27 (56%)		<u>()</u>	RT-PCR positive for SARS-	-	[51]
(Washington)						CoV-2		
USA (New	News journal	33	29 (87.9%)	-	Pregnant	RT-PCR positive for SARS-	-	[52]
York)	article				Females	CoV-2		
USA (New	Case series	43	14 (32.6%)	Maternal age	Pregnant	PCR-confirmed SARS-CoV-2	-	[8]
York)				ranged from 20	females	8 patients developed fever		
				to 39 years with a		ranging from 37.9°C to 39.2°C		
				mean age of 26.9		during admission in the hospital.		
				years old		during durings on in the nospital		
Italy (Brescia)	Report	Patients	7	Median age 64.6	2 males	RT-PCR positive for SARS-CoV-	Patient 3: chest CT	[53]
	(Incidental	with		years old (Range:	5 females	2	showed a suspicious	
	Findings)	different		55-79) years			retrosternal lymph node	
		types of					but no lung pathology.	
		cancer						

							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	
Italy	Case report	-	1	1 month	Male	Real-time PCR confirmed	-	[54]
						infection		
						The infant is a cystic fibrosis		
						patient. He never developed a		
						fever or any signs of infection.		
Italy	News journal	3300	90 (2.7%)	-	-	RT-PCR positive for SARS-	-	[55]
	article					CoV-2		
Germany	Correspondence	-	4	Patient 1: 33-	Patient 1:	RT-PCR positive for SARS-	-	[56]
				year-old	male	CoV-2		
Iran (Tehran)	Case report	<u>-</u>	1	44-year-old	Male	RT-PCR positive for SARS-	Patchy ground-glass	[57]
						CoV-2	opacity in the upper lobe	
							of the right lung	

Iran	Case report	multiple	8	49.71 ±13.13	62.5%	None of the patients had COVID-	Pneumonia in chest CT	[58]
		trauma		(range: 34–67)	male	19 symptoms at the time of	scan	
		patients		years		admission to the hospital.		
		admitted				DT DCD assisting for CADC CaV		
		to				RT-PCR positive for SARS-CoV-		
		hospital				2. Laboratory results showed 4		
						(50%) patients with slight		
						increase in C-reactive protein		