Asymptomatic people with SARS-CoV-2 as unseen carriers of COVID-19: A systematic review and meta-analysis

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Abstract

Background

The asymptomatic patients with SARS-CoV-2 can act as an unseen carrier for magnifying the transmission of COVID-19.

Aims

This study was designed to appraise the burden of asymptomatic individuals and estimate their occurrence among different age groups and gender by reviewing the existing published data on asymptomatic people with COVID-19.

Methods

Three electronic databases: PubMed, Embase and Web of Science (WoS) were used to search studies as per the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the search was limited to English language. The study population of this review includes asymptomatic individuals infected by COVID-19. All original articles which have reported cases of the COVID-19 patients with no symptoms until 31 April 2020 were included in the study. Random effects model was applied to analyze pooled data on the prevalence of symptomless cases among total COVID-19 infected patients and also on different age groups and gender.

Results

In the meta-analysis of 16 studies, comprising 2,788 COVID-19 infected patients, the pooled prevalence of asymptomatic cases was 48.2% (95% CI, 30%-67%). Among the asymptomatic patients, 55.5% (95% CI, 43.6%-66.8%) were female and 49.6% (95% CI, 20.5%-79.1%) were children.

Conclusion

About half of the COVID-19 infected patients were asymptomatic cases. Children and females were more apparent to be asymptomatic patient of COVID-19 and could act as unseen carrier of SARS-CoV-2. Symptom based screening only, might fail to identify all SARS-CoV-2 infections escalating the threat of global spread of SARS-CoV-2. Therefore, mass surveillance system tracking asymptomatic cases is a pressing need of public health, paying special attention to female and young children, which could aid in prevention and containment of this unprecedented pandemic.

Background

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Coronaviruses are common infectious pathogens in the world, which mainly cause respiratory tract illnesses in humans. Only six different coronaviruses (HCoV-229E, HCoV-HKU1, HCoV-OC43, HCoV-NL63, SARS-CoV and MERS-CoV) were known to be contagious to humans until December 2019 [1, 2]. A cluster of fatal pneumonia cases of unknown etiology were presented in late December, 2019 in Wuhan, the Hubei province, China with all the patients epidemiologically associated with the wet-market where seafood, game and live animals were sold [3]. The etiological agent was identified to be the seventh coronavirus causing infection to humans and was initially referred as 2019 novel virus of coronaviridae family (2019-nCoV) [4]. As genome sequence of this new virus shared 79.5% homology with that of the SARS-CoV, the International Committee on Taxonomy of Viruses (ICTV) renamed 2019-nCoV as SARS-CoV-2 [5]. Consequently on 11 February 2020, World Health Organization (WHO) announced the name of the disease caused by the virus as Corona Virus Disease 2019 (COVID-19) [6]. In response to the rapid global spread, WHO declared it a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and labeled as a pandemic on 11 March 2020 [7].

The usual symptoms of COVID-19 infection include headache, fever, cough, fatigue, dyspnea, diarrhea and even conjunctivitis. The estimated incubation period of SARS-CoV-2 is 14 days, with maximum cases occurring approximately 4 to 5 days after exposure [8–10]. The clinical outcome of COVID-19 can vary from symptomless to severe SARS-like viral pneumonia, acute respiratory distress syndrome (ARDS), multi-organ dysfunction and even death. The conditions like old age, presence of co-morbid conditions such as hypertension and diabetes and coronary heart disease have been characterized as the major risk factors for the deaths of COVID-19 infected patients [11] with varied fatality rate ranging from 4–7%, with increment as progress of pandemic [12]. As of 26 May, 2020, there were 5,508,904 confirmed cases of COVID-19 with 346,612 deaths reported globally [13].

SARS-CoV-2 has been proven to be transmitted through the respiratory tract, mucosal surfaces (such as conjunctiva) and even gastrointestinal system [10, 14]. With the main mode of disease transmission being respiratory droplets [15], virus particle spread from aerosol, air droplet, hands contaminations, fomites and other objects too [8]. The cardinal route of transmission via aerosol exhaled by asymptomatic COVID-19 individuals during the act of breathing and speaking is well documented [16–19] and cases of familial transmission through asymptomatic patients have been reported from different countries [16, 20–25].

Asymptomatic patients with COVID-19 can propagate SARS-CoV-2 to another person unknowingly [26]. Moreover, the asymptomatic individuals frequently escape detection by public health surveillance systems. This increases the incidence of COVID-19 infection in the community. It has been anticipated that undiagnosed symptomless cases of COVID-19 infection were responsible for up to 79% of SARS-CoV-2 infections in Wuhan, China [19]. This unseen asymptomatic carrier of SARS-CoV-2 creates a massive hurdle in the prevention and containment of COVID-19 pandemic. Accurate understanding of true prevalence and demographic features of asymptomatic individuals may provide important clues in controlling the highly infectious viral disease. But demographic characteristics, clinical features as well

this study was designed to evaluate the burden of asymptomatic individuals and estimate their occurrence among different age groups and gender by summarizing the existing published data on asymptomatic people with COVID-19.

Methods

Search strategy and data sources

Electronic databases such as PubMed, Embase and Web of Science (WoS) were used to search studies following the PRISMA guideline [28]. PRISMA checklist (Table S1, Supplementary information (SI) file) was strictly followed while conducting this study. The following Medical Subject Headings (MeSH) terms and key words were used to search the published articles: "Novel coronavirus 2019", or "2019 nCoV", or "COVID-19", or "Asymptomatic carriers of COVID-19", or "Asymptomatic infections with COVID-19" and "SARS-CoV-2", where search was limited to articles published from January 1, 2020 to April 31, 2020 in English language.

Selection criteria

Authors (GS, PD, SB and DRJ) evaluated search results and determined the eligibility of studies independently and dissonance was resolved by discussion between the authors. Any discrepancy during the review of full articles was resolved with a vote of majority.

Eligibility criteria

We considered following inclusion criteria for this meta-analysis and review:

- Study populations included asymptomatic COVID-19 infected patients (Cases who were tested positive for SARS-CoV-2 nucleic acid test by RT-PCR but without symptoms while screening).
- Study designs included case-control study, prospective/retrospective cohort study and case reports. The inclusion criteria included:

The exclusion criteria set for this study were:

- Study without asymptomatic proportion of COVID-19 infected patients
- Review and opinion articles, published protocols, meta-analyses, editorials and cases published in other languages than English.

Study selection

The results of the initial search strategy were first screened for relevant articles by examining title and abstract. Then, full texts of relevant articles were inspected for inclusion and exclusion criteria. Studies

that reported asymptomatic proportion of COVID-19 infected patients were included for quantitative synthesis.

Data extraction

From the screened articles, items including first author, type of study- the publishing institution, date of publication, site of study, sample size, (Table 1) age and gender of patients, asymptomatic and symptomatic cases were recorded (Supplementary information (SI) File 1).

Table 1
Characteristics of the studies included for meta-analysis

S.N.	Study ID	Study period	Place of study	Total number of confirmed cases of COVID-19	Asymptomatic cases among confirmed cases [N (%)]
1.	Baggett et al. (2020) [54]	April 2020	Homeless Shelter in Boston, USA	147	129 (87.8%)
2.	Dong et al. (2020) [55]	January 16 to February 8, 2020	China	728	94 (12.92%)
3.	Hu et al. (2020) [39]	January 28 to February 9, 2020	The Second Hospital of Nanjing, China	24	24 (100%)
4.	Kimball et al. (2020) [52]	March 2020	Nursing Facility-King County, USA	23	13 (56.52%)
5.	Lu et al. (2020) [56]	January 28 to February 26, 2020	The Wuhan Children's Hospital, China	171	39 (22.81%)
6.	Meng et al. (2020) [53]	January 1 to February 23, 2020	Renmin Hospital of Wuhan University, China	58	58(100%)
7.	Mizumoto et al. (2020) [57]	February, 2020	Diamond Princess cruise ship, Yokohama, Japan	634	328 (51.74%)
8.	Nishiura et al. (2020) [58]	February 6, 2020	Japan	13	4 (30.8%)
9.	Pan et al. (2020) [59]	January 10 to March 10, 2020	China	26	26 (100%)
10.	Qiu et al. (2020) [60]	January 17 to March 1, 2020	Three hospitals in Zhejiang province, China	36	10 (28%)
11.	Song et al. (2020) [61]	January 26 to March 6, 2020	People's hospital of Dafou county, China	83	18(21.7%)
12.	Sutton et al. (2020) [62]	March 22 to April 4, 2020	Two hospitals in New York, USA	33	29 (87.9%)

S.N.	Study ID	Study period	Place of study	Total number of confirmed cases of COVID-19	Asymptomatic cases among confirmed cases [N (%)]
13.	Tao et al. (2020) [38]	January to March 2020	Chongqing Public Health Medical Center, Chongqing, China	167	20 (11.98%)
14.	Tian et al. (2020) [63]	January 20 to February 10, 2020	China	262	13 (4.9%)
15.	Wang et al. (2020) [64]	February 23, 2020	Third People's Hospital of Shenzhen, China	55	55 (100%)
16.	Zhou et al. (2020) [65]	March 4, 2020	Shanghai Public Health Clinic Centre, China	328	13 (3.96%)
Total				2,788	873

Outcome measurements

The primary finding in this study was the prevalence of symptomless cases (event rates) among COVID-19 infected patients. This study had also other secondary outcome measures including prevalence of asymptomatic cases among different gender and age, and prevalence of true asymptomatic cases. In case of secondary outcomes, the denominator was adjusted to asymptomatic cases to extract prevalence of asymptomatic cases in different age and gender.

Risk of bias (quality) assessment in individual studies

The potential risk of bias of each included studies was assessed according to Newcastle-Ottawa Scale (NOS) for observational studies (case-control, cohort, and cross-sectional studies). Studies were graded out of 10 points (stars) as shown in Table S2 (SI file). The mean score of two reviewers (GS, SB) was considered for the decision. Any variation in individual scores was checked and resolved by an author (DRJ). Since we did not find any standard cut off score, the studies scoring arbitrary value ≥ 6 were used for meta-analysis and review. This quality assessment was performed to assess the systematic error and external validity of studies and ultimately to reduce the risk of biases.

Publication bias assessment

The potential publication bias was assessed by plotting the standard error and precision with Logit event rate as funnel plots. The absence of publication bias among included studies was also confirmed by

Begg's (Begg and Mazumdar rank Correlation) and Egger's test (regression intercept) considering p -value > 0.05 indicating no publication bias.

Data analysis

All the statistical analysis were done using (Comprehensive Meta-Analysis version 3) statistical software (<https://www.meta-analysis.com/>). Percentages were calculated to describe the distributions of categorical variables. The prevalence of symptomless cases of COVID-19 infection was expressed as proportion and 95% confidence interval, using the random effects model, and was presented as Forest plot. Cochran Q test and inconsistency index (I^2) were used to detect heterogeneity among studies, with a p -value < 0.05 indicating significant heterogeneity. I^2 values of $< 25\%$, $25-75\%$ and $> 75\%$ indicate low, moderate and high heterogeneity respectively [29].

Subgroup analysis

Subgroup analysis was performed according to targeted patient age groups (children, adult and elderly), gender groups (male and female) and clinical outcome of asymptomatic cases (pre-symptomatic and true asymptomatic). Individuals of age less than 18 years were considered as children as recognized by the United Nations Convention on the Rights of the Child [30]. Asymptomatic cases not showing any typical symptoms associated with COVID-19 during the time of hospitalization were categorized into "True asymptomatic cases" and cases not showing any symptom during incubation period for up to 14 days but becoming symptomatic later were categorized into "pre-symptomatic cases". Studies that have reported age, gender and true cases of asymptomatic COVID-19 patients were only included in the subgroup analysis of respective age, gender, and clinical outcome of asymptomatic cases.

Results

Study selection

A total of 1,449 potentially relevant articles were retrieved using the search strategy. After removing 675 duplicates, remaining 774 articles were further assessed by title of study and abstract and 115 articles were included for the full-text appraisal. As shown in PRISMA flow diagram (Fig. 1), among them 16 articles [38, 39, 52–65] were included for the quantitative meta-analysis and 99 were excluded after full text review due to the lack of information about incidence of asymptomatic COVID-19 case.

Study characteristics

This systematic review included 16 studies that were published between January and April, 2020. Majority of the studies were from China ($n = 11$), two from Japan and three from the USA, including a total of 2,788 SARS-CoV-2 infected patients (Table 1). This review integrated cross sectional and observational cohort study.

The susceptibility of SARS-CoV-2 was higher in the male patients (54.4%) in comparison to the female patients (45.6%) in this study. Among the SARS-CoV-2 infected patients, 42.5% were children (≤ 18 years), 22.8% were adult (19–50 years) and 34.7% were elderly patients (≥ 51 years). Regarding the clinical characteristics, (873/2788) were asymptomatic cases and (1915/2788) were symptomatic cases with varying clinical symptoms including fever, cough, sore throat, myalgia, fatigue, headache, and dyspnea. Review of demographic and clinical features of COVID-19 patients is summarized in Table S3 (SI).

Meta-analysis of asymptomatic cases of COVID-19

The pooled prevalence of asymptomatic case of COVID-19 from a total of 2,788 confirmed SARS-CoV-2 infected patients in 16 studies was 48.2% (95% CI, 30–67%), with significant heterogeneity noted among studies ($p_{\text{script}} > 0.001$; $I^2 = 97.5$) (Fig. 2).

Subgroup analysis

Gender

Among 223 asymptomatic cases of COVID-19 in seven studies, 55.5% (95% CI, 43.6%–66.8%) were female and 44.5% (95% CI, 33.2–56.4%) were male (SI, Fig S1). Although there was no significant subgroup difference between male and female ($p = 0.199$) (data not shown), moderate heterogeneity was noted among the studies ($p < 0.001$; $I^2 = 58.9\%$) (Fig. 3).

Age

In a subgroup analysis of eight studies, among 318 asymptomatic cases of COVID-19, 49.6% (95% CI, 20.5–79.1%) were children (≤ 18 years), 30.3% (95% CI, 13–56%) were adult (19–50 years) and only 16.9% (95% CI, 7.8–32.9%) were elderly patients (≥ 51 years) (SI, Fig S2). Despite of insignificant subgroup difference according to age ($p = 0.142$), there was high heterogeneity among studies ($p < 0.001$; $I^2 = 85.1\%$) (Fig. 3).

Clinical outcome of asymptomatic cases of COVID-19

The pooled prevalence of symptomless cases of COVID-19 from a total of 1,277 confirmed SARS-CoV-2 infected patients in 10 studies was 39% (95% CI, 20.4–61.4%) (SI, Fig S3). The pooled prevalence of pre-symptomatic cases was 15.3% (95% CI, 7.2–29.6%). There was significant high heterogeneity among analyzed studies ($p < 0.001$; $I^2 = 95.6\%$) (Fig. 3).

Publication bias

The funnel plot (SI, Fig. 4) showed symmetry, demonstrating the absence of publication bias among the included studies. The Begg's (Begg and Mazumdar rank Correlation) and Egger's (regression intercept) tests also confirmed that there was no evidence of publication bias among the included studies for

prevalence of asymptomatic COVID-19 cases. Kendall's tau with continuity correction in Begg and Mazumdar rank Correlation (P (2-tailed) = 0.0884) Egger's regression intercept (P (2-tailed) = 0.7472) were insignificant. (SI, Table S4).

Discussion

The pooled prevalence of symptomless cases of COVID-19 was 48.2% in this meta-analysis of 2,788 infected patients. In a case series of 78 patients from 26 transmission cluster cases in Wuhan, China, similar estimate (42.3%) of COVID-19 infected patients were asymptomatic carriers [26]. However, considering the basic reproduction number (R_0) 2.5, Centers for Disease Control and Prevention (CDC) has estimated slightly low (35%) asymptomatic SARS-CoV-2 infection rate [31]. This indicates that the large numbers of asymptomatic cases of COVID-19 are prevailing in the community, seeding potential outbreak which requires vigilant control strategies to prevent the next episode of outbreak. Thus, use of masks and widespread testing for identification and quarantine of infected asymptomatic individuals are essential to combat the rapid spread of COVID-19 pandemic locally and globally [32].

Although SARS-CoV, SARS-CoV-2 and MERS belong to the same genus *Betacoronavirus*, differences in disease transmission and clinical features have been reported. SARS and MERS were mainly associated with nosocomial spread whereas SARS-CoV-2 is widely disseminated in the community [33]. The prevalence of symptomless infection was comparatively less in MERS and SARS, which was about 9.8% [34] and 13% [35] respectively. The reason for higher asymptomatic infection of COVID-19 could be related to the high replication efficiency of SARS-CoV-2, which replicate 3 times more rapidly compared to SARS-CoV. Thus SARS-CoV-2 can rapidly disseminate to the pharynx, from where it can be shed prior to the activation of innate immune response and production of symptoms [36]. Another contributing factor could be due to the less significant induction of host interferon and proinflammatory response, which also distinguishes it from SARS-CoV [36]. The proportion of symptomless cases of COVID-19 has gradually increased since its first outbreak in Wuhan, Hubei province, China [37]. One of the reasons behind this may be because of decreased toxicity of SARS-CoV-2 in the process of long chain of transmission [38].

The communicable period (interval from the first day of positive nucleic acid test to the first day of continuous negative test) of asymptomatic case of COVID-19 could be as long as a month [39]. Thus, asymptomatic patient may carry virus for a long period of time and potentially spread it to others silently. Potential SARS-CoV-2 transmission from asymptomatic individuals had been documented in many studies [23–25, 39]. In a study for assessing the viral load of SARS-CoV-2 in upper respiratory specimens of infected COVID-19 patients, high viral load was obtained among asymptomatic, pre-symptomatic and symptomatic patients, suggesting a high potential of transmission regardless of symptoms [40]. The biologic evidence for this is aided by a study conducted in a prolonged care facility where infectious SARS-CoV-2 was cultured from upper respiratory tract specimens of pre-symptomatic and asymptomatic patients even before six days to the development COVID-19 associated symptoms [41].

Among the total SARS-CoV-2 infected patients included in this study, 54.4% were male and 45.6% were female. This implies that the susceptibility of SARS-CoV-2 infection was higher in male compared to female. This might be explained by the presence of immune related gene on the X chromosome and sex hormones by which both immune responses: innate and adaptive can be influenced [42–44]. Females mount stronger both innate and adaptive immune responses compared to males (42) and therefore might be less susceptible to SARS-CoV-2 infection. Another contributing factor could be a higher likelihood of exposure to the virus in males due to occupational risk and more outdoor activities. Smoking behavior had also been linked to increased incidence of SARS-CoV-2 infection among males [45]. The gene expression of angiotensin - converting enzyme 2 (ACE2), which is a cell receptor for SARS-CoV-2, is significantly elevated in smokers [46]. Since smoking behavior is comparatively higher in males than in females in general, increased incidence of SARS-CoV-2 could have been observed in males.

Subgroup analysis of asymptomatic patients revealed that the children are the most predominant asymptomatic carrier of SARS-CoV-2 (49.6%), followed by adults (30.3%) and elderly (16.9%). The increased incidence of symptomless cases of COVID-19 in children could be related to both exposure and host factors. Children's immune system is not well developed, and it is speculated that maturity and binding ability of ACE2 in children is lower [47]. Additionally, children often experience many viral infections. Hence, it is possible that repeated viral exposure aids the immune system to respond against SARS-CoV-2 [48]. Meanwhile, elderly populations have a weakened immune system [49, 50] and less likely to be an asymptomatic carrier. In contrast, adult population most likely has stronger immune system to tackle with the infection and can remain as asymptomatic carrier. However, an in-depth mechanism for difference in asymptomatic manifestation among these three age groups (children, adult, and elderly) is yet to be explored.

The pooled prevalence of asymptomatic SARS-CoV-2 infection was observed to be higher in females (55.5%) than in males (44.5%) from subgroup analysis. Similarly, more women (66.7%) were observed to be asymptomatic cases in a case series done among 78 close contacts of COVID-19 patients in Wuhan, China [26]. Although there is no significant subgroup difference according to gender, higher prevalence of symptomless cases in female could be owing to less exposure and host factors in female. In comparison to male, female exhibit stronger innate, cellular, and humoral immune responses due to increased activation effects of female sex hormones and the presence of immune response genes on sex chromosomes [51]. These enhanced innate and adaptive immune responses could have contributed to the increased asymptomatic SARS-CoV-2 infection in females.

Asymptomatic COVID-19 infected patients (cases who were tested positive for SARS-CoV-2 nucleic acid test by RT-PCR but not showing any typical symptoms of SARS-CoV-2 infection while screening) were included in this meta-analysis. The reported prevalence of symptomless SARS-CoV-2 in this study consisted prevalence of both true asymptomatic patients (cases not showing any signs and symptoms at all during the period of hospitalization) and pre-symptomatic patients (cases not showing any symptom during incubation period for up to 14 days but becoming symptomatic later). Among total asymptomatic

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were pre-symptomatic cases. After 3 days of RT-PCR nucleic acid testing positive, pre-symptomatic cases showed mild COVID-19 related symptoms including fever, malaise, and cough [52, 53].

A recent review stated that, as the surveillance and contacts testing of the MERS progressed overtime, the rate of asymptomatic MERS infected patients increased up to 28.6% [34]. This increase in the asymptomatic infection of MERS was inversely proportionate to the case fatality rate. This clearly demonstrates the importance of mass surveillance and contact tracing in the detection of asymptomatic COVID-19 infected patients, reduction of fatality rate and control of similar respiratory infection of COVID-19. Transmission of COVID-19 through asymptomatic persons is the Achilles' heel of COVID-19 control and prevention strategies. Hence, mass testing of SARS-CoV-2 among asymptomatic persons should be broaden especially among amass living conditions like prisons, inpatients of hospitals, camps, nursing, and aged care facilities. To limit the rapid spread of this novel pandemic, screening and SARS-CoV-2 testing of asymptomatic carriers must be prioritized in the community level along with wakeful control strategies.

Several strengths of this study include comprehensive inclusion of 16 studies adding more precision to the estimation of the prevalence of asymptomatic SARS-CoV-2 infection. Subgroup analysis found that the children and female were the most likely asymptomatic carriers of SARS-CoV-2, highlighting the necessity of providing special attention to them for preventing and controlling this pandemic.

This study has few limitations. As asymptomatic patients in the community might have been unnoticed and missed from being detected, the pooled prevalence rate in this study might be under-reported. Moreover, most of the studies included in this analysis were from China and ethnic groups other than Chinese were minimal. More comprehensive studies including all ethnicity from wider communities are warranted in order to preclude a more precise estimate of the prevalence of symptomless SARS-CoV-2 carriers.

Conclusion

High prevalence of symptomless cases of COVID-19 had been reported, predominantly among children and female. This suggests that symptom based screening only, might fail to identify all SARS-CoV-2 infections escalating the threat of global spread of SARS-CoV-2. Thus, robust surveillance system tracking these asymptomatic cases is a pressing need of public health, paying special attention to female and young children which could help to deduct the risk of SARS-CoV-2 dissemination.

List Of Abbreviations

ACE2 Angiotensin Converting Enzyme 2

ARDS Acute Respiratory Distress Syndrome

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COVID-19 Corona Virus Disease 2019

HCoV-229E Human Coronavirus 229E

HCoV-HKU1 Human Coronavirus HKU1

HCoV-NL63 Human Coronavirus NL63

HCoV-OC43 Human Coronavirus OC43

ICTV International Committee on Taxonomy of Viruses

MERS-CoV Middle East Respiratory Syndrome Coronavirus

MeSH Medical Subject Headings

2019-nCoV 2019 Novel Coronavirus

PHEIC Public Health Emergency of International Concern

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis

RT-PCR Reverse Transcriptase Polymerase Chain Reaction

SARS-CoV Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2

USA United States of America

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information file.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

All persons who meet the authorship criteria are listed as authors. GT and DRJ designed the study. GT, PD and SB reviewed the literature, extracted data, provided the analysis and drafted the manuscript. DRJ, LBS, RT and BR revised and reviewed the manuscript. All the authors read and approved the final manuscript.

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References

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*. 2020;395(10224):565–74;doi:[1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8)
2. Qiang XL, Xu P, Fang G, Liu WB, Kou Z. Using the spike protein feature to predict infection risk and monitor the evolutionary dynamic of coronavirus. *Infect Dis Poverty*. 2020;9(1):1–8.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–33.
4. Livingston E, Bucher K, Rekito A. Coronavirus disease 2019 and influenza 2019-2020. *JAMA*. 2020;323(12):1122.
5. Gorbalenya AE, Baker SC, Baric RS, deGroot RJ, Drosten C, Gulyaeva AA, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020; 5:536–544. doi:10.1038/s41564-020-0695-z.
6. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report – 22. 2020.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=fb6d49b1_2. Accessed 8 May 2020.
7. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 51. 2020.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10. Accessed 8 May 2020.

8. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199–207.
9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.
10. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, 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):514-23.
11. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *EurRespir J*. 2020; 55:2000547. doi:10.1183/13993003.00547-2020].
12. Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, Quek SC. The many estimates of the COVID-19 case fatality rate. *The Lancet Infect Dis*. 2020;3099(20):30244;doi:10.1016/S1473-3099(20)30244-9
13. Johns Hopkins University and Medicine. Coronavirus resource center. <https://coronavirus.jhu.edu>. Accessed on 26 May 2020
14. To KK, Tsang OT, Chik-Yan Yip C, Chan KH, Wu TC, Chan JMC, et al. Consistent detection of 2019 novel coronavirus in saliva. *Clin Infect Dis*. 2020; doi:10.1093/cid/ciaa149.
15. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672-5.
16. Bai Y, Yao L, Wei T, Tian F, Jian DY, Chen L, Wang M. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020; 14;323(14):1406-7.
17. Morawska L, Cao J. Airborne transmission of SARS-CoV-2: The world should face the reality. *Environ Int*. 2020;139:105730.
18. Anderson EL, Turnham P, Griffin JR, Clarke CC. Consideration of the aerosol transmission for COVID-19 and public health. *Risk Anal*. 2020;40(5):902-7.
19. Asadi S, Bouvier N, Wexler AS, Ristenpart WD. The coronavirus pandemic and aerosols: Does COVID-19 transmit via expiratory particles? *Aerosol Sci Tech*. 2020;54(6):635-8.
20. Yu X, Yang R. COVID-19 transmission through asymptomatic carriers is a challenge to containment. *Influenza Other Respi Viruses*. 2020;14:474-5.
21. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the achilles' heel of current strategies to control COVID-19. *N Engl J Med*. 2020; 382(22):2158-60.
22. Tindale L, Coombe M, Stockdale JE, Garlock E, Lau WYV, Saraswat M, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. *medRxiv*. 2020; doi:10.1101/2020.03.03.20029983.
23. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-NCOV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382(10):970–1.
24. Yu P, Zhu J, Zhang Z, Han Y. A familial cluster of infection associated with the 2019 novel coronavirus indicating person-to-person transmission during the incubation period. *J Infect*

- Dis. 2020; 221(11):1757-61.
25. Qian G, Yang N, Ma AHY, Wang L, Li G, Chen X, et al. A COVID-19 transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis*. 2020; doi:10.1093/cid/ciaa316.
 26. Yang R, Gui X, Xiong Y. Comparison of clinical characteristics of patients with asymptomatic vs symptomatic coronavirus disease 2019 in Wuhan, China. *JAMA Netw Open*. 2020;3(5):e2010182. doi:10.1001/jamanetworkopen.2020.10182.
 27. Petrosilla N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect*. 2020;26(6):729-34.
 28. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
 29. Higgins JP, SG T. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-58.
 30. United Nations. United Nations General Assembly Session 44 Resolution 25. Convention on the Rights of the Child A/RES/44/25 November 20, 1989. https://www.un.org/ga/search/view_doc.asp?symbol=A/RES/44/25 Accessed May 20, 2020.
 31. Coronavirus Disease 2019: Pandemic Planning Scenarios. CDC. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html>. Accessed May 26, 2020.
 32. Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. *Science*. 2020; eabc6197; doi:10.1126/science.abc6197.
 33. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China—key questions for impact assessment. *N Engl J Med*. 2020;382(8):692-4.
 34. Al-Tawfiq JA, Gautret P. Asymptomatic Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: extent and implications for infection control: a systematic review. *Trav Med Infect Dis*. 2019;27:27-32.
 35. Wilder-Smith A, Telesman MD, Heng BH, Earnest A, Ling AE, Leo YS. Asymptomatic SARS coronavirus infection among health-care workers, Singapore. *Emerg Infect Dis*. 2005;11(7):1142-5.
 36. Chu H, Chan JF, Wang Y, Yuen TT, Chai Y, Hou Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. *Clin Infect Dis*. 2020;ciaa410, doi:1093/cid/ciaa410.
 37. Du Z, Xu X, Wu Y, Wang L, Cowling BJ, Meyers LA. Serial interval of COVID-19 among publicly reported confirmed cases. *Emerg Infect Dis*. 2020;26(6):1341-3.
 38. Tao Y, Cheng P, Chen W, Wan P, Chen Y, Yuan G, et al. High incidence of asymptomatic SARS-CoV-2 infection, Chongqing, China. *medRxiv*. 2020;2020.03.16.20037259. doi: 10.1101/2020.03.16.20037259
 39. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci*. 2020;63(5):706-11.

40. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020;382(12):1177-9.
41. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020; 382(22):2081-90.
42. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clin Rev Allergy Immunol*. 2019;56(3):308–21.
43. Klein SG and RS. Sex drives dimorphic immune responses to viral infections. *J Immunol*. 2017;198(5):1782–90.
44. Xie M, Chen Q. Insight into 2019 novel coronavirus — an updated intrim review and lessons from SARS-CoV and MERS-CoV. *Int J Infect Dis*. 2020;94:119–24. doi:[1016/j.ijid.2020.03.071](https://doi.org/10.1016/j.ijid.2020.03.071).
45. Rabi FA, Zoubi MA, Kasabeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: What we know so far? *Pathogens*. 2020;9(3):231. doi:10.3390/pathogens9030231
46. Chinwong D, Mookmanee N, Chongpornchai J, Chinwong S. A comparison of gender differences in smoking behaviors, intention to quit, and nicotine dependence among Thai University students. *J Addict*. 2018; 8081670:1-8. doi:[1155/2018/8081670](https://doi.org/10.1155/2018/8081670)
47. Ciaglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. *Front Pediatr*. 2020;8:206. doi: 10.3389/fped.2020.00206.
48. Ludvigsson JF. Systematic review of COVID-19 children shows milder cases and a better prognosis than adults. *Acta Paediatrica*. 2020;109:1088-95.
49. Montecino-rodriguez E, Berent-maoz B, Dorshkind K, Montecino-rodriguez E, Berent-maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. *J Clin Invest*. 2013;123(3):958–65.
50. Weiskopf D, Weinberger B, Grubeck-Loebenstien B. The aging of the immune system. *Transpl Int*. 2009;22(11):1041–50.
51. Klein SL. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. *Bioessays*. 2012;34(12):1050-9.
52. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, 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):377–81.
53. Meng H, Xiong R, He R, Lin W, Hao B, Zhang L, et al. CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. *J Infect*. 2020;81(1):e33-9.
54. Baggett TP, Keyes H, Sporn N, Gaeta JM. Prevalence of SARS-CoV-2 infection in residents of a large homeless shelter in Boston. 2020;323(21):2191-2.
55. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6);e20200702; doi:10.1542/peds.2020-0702.
56. Lu X, Zhang L, Du H, Zhang J, Li YY, QuJ, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382(17):1663-5.

57. Mizumoto K, Kagaya K, Zarebski A, Chowell G. 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):pii 2000180.
58. Nishiura H, Kobayashi T, Miyama T, Suzuki A, Jung SM, Hayashi K, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis*. 2020;94:154-5.
59. Pan Y, Yu X, Du X, Li Q, Li X, Qin T, et al. Epidemiological and clinical characteristics of 26 asymptomatic SARS-CoV-2 carriers. *J Infect Dis*. 2020;221(12):1940-7.
60. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis*. 2020;20(6):689-96.
61. Song H, Xiao J, Qiu J, Xin J, Yang H, Shi R, Zhang W. A considerable proportion of individuals with asymptomatic SARS-CoV-2 infection in Tibetan population. *medRxiv*.2020;doi:1101/2020.03.27.20043836.
62. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. *N Eng J Med*. 2020;382(22):2163-4.
63. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. *J Infect*. 2020;80(4):401-6.
64. Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical outcomes in 55 patients with severe acute respiratory syndrome coronavirus 2 who were asymptomatic at hospital admission in Shenzhen, China. *J Infect Dis*. 2020;221(11):1770-4.
65. Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. *Clin Microbiol Infect*. 2020; S1198-743X(20)30169-5. doi:[1016/j.cmi.2020.03.024](https://doi.org/10.1016/j.cmi.2020.03.024)

Figures

Figure 1

PRISMA flow diagram of screening process for the selection of studies for meta-analysis.

Heterogeneity: $I^2 = 97.5$, $\tau^2 = 2.119$, $p = 0.001$

* Random model

Figure 2

Forest plot showing asymptomatic infection rate in COVID-19 patients. The overall asymptomatic event rate was 0.48 (asymptomatic prevalence rate 48.2%).

Figure 3

Forest plot showing subgroup analysis of pooled clinical outcome, and gender and age based on prevalence of asymptomatic COVID-19 cases. The forest plot of event rates (ratios) showed higher prevalence of asymptomatic (0.39), female (0.56) and children (0.50) COVID 19 patients.

Supplementary Files

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