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Review

The epidemiological and radiographical characteristics of asymptomatic infections with the novel coronavirus (*COVID-19*): A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Objectives: The role of asymptomatic infections in the transmission of COVID-19 have drawn considerable attention. Here, we performed a meta-analysis to summarize the epidemiological and radiographical characteristics of asymptomatic infections associated with COVID-19.
Methods: Data on the epidemiological and radiographical characteristics of asymptomatic infections were extracted from the existing literature. Pooled proportions with 95% confidence intervals were then calculated using a random effects model.
Results: A total of 104 studies involving 20,152 cases were included. The proportion of asymptomatic individuals among those with COVID-19 was 13.34% (10.86%–16.29%), among which presymptomatic and covert infections accounted for 7.64% (4.02%–14.04%) and 8.44% (5.12%–13.62%), respectively. The proportions of asymptomatic infections among infected children and healthcare workers were 32.24% (23.08%–42.13%) and 36.96% (18.51%–60.21%), respectively. The proportion of asymptomatic infections was significantly higher after 2020/02/29 than before (33.53% *vs* 10.19%) and in non-Asian regions than in Asia (28.76% *vs* 11.54%). The median viral shedding duration of asymptomatic infections was 14.14 days (11.25–17.04). A total of 47.62% (31.13%–72.87%) of asymptomatic infections showed lung abnormalities, especially ground-glass opacity (41.11% 19.7%–85.79%).
Conclusions: Asymptomatic infections were more commonly found in infected children and healthcare workers and increased after 2020/02/29 and in non-Asian regions. Chest radiographical imaging could be conducive to the early identification of asymptomatic infections.

Introduction

COVID-19 was first reported in December 2019 and has spread rapidly worldwide (Chen et al., 2020). The infectivity of COVID-19, which has a basic reproduction number *(R0)* ranging from 2 to 6.7, was estimated to be much higher than that of influenza, severe acute respiratory syndrome *(SARS)*, and middle east respiratory syndrome *(MERS)* (Wu et al., 2020; Zhao et al., 2020; Tang et al., 2020). Asymptomatic infections among patients with COVID-19 have been reported, including presymptomatic and covert infections; these are differentiated according to whether related clinical symptoms appear during follow-up (Wu, 2020). On the "Diamond Princess" cruise ship, 189 asymptomatic individuals were identified among the total number of 1723 travellers tested, as of 17 February 2020 (Wikipedia, 2020). Recently, asymptomatic infections in the transmission of COVID-19 have drawn considerable attention. In previous studies, evidence for secondary cases caused by asymptomatic carriers has been identified (Bai et al., 2020; Rothe et al., 2020; Yu et al., 2020). Among the skilled nursing facilities in the United States, 56% (27/48) of cases were asymptomatic, and the median Ct values of reverse

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transcription-polymerase chain reaction *(RT-PCR)* were similar in covert, presymptomatic, and symptomatic infections, thus indicating substantial viral shedding from asymptomatic individuals (Arons et al., 2020). Quantitative estimation showed that 56.1% of transmission occurred during the presymptomatic period (Casey et al., 2020). When taking asymptomatic carriers into account, the *R0* of COVID-19 could be up to 15.4 (range: 5.5–25.4) (Aguilar et al., 2020). Therefore, asymptomatic infections should be considered as a source of COVID-19 infections that plays a significant role in the spread of the virus.

However, many studies have indicated that there are inconsistencies in the proportion of asymptomatic individuals with COVID-19 infection. A study based on the Diamond Princess cruise ship reported a considerable proportion of asymptomatic infections (Wikipedia, 2020). In addition, on 1 April 2020, the China National Health Commission reported that 130 of 166 new COVID-19 infections were asymptomatic (Day, 2020a). Nonetheless, a previous study indicated that the proportion of truly asymptomatic infections appears to be relatively low and does not appear to be a major driver of transmission (Day, 2020b). Hence, in this study, we systematically pooled data from existing literature to quantify the proportion of asymptomatic individuals, including presymptomatic and covert infections, among those with COVID-19 to describe their epidemiological and radiographical characteristics. Our findings could be conducive to the development of prevention and control strategies for asymptomatic individuals.

Materials and methods

Our meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols *(PRISMA-P)* guidelines (Hutton et al., 2015).

Search strategy and selection criteria

A comprehensive systematic literature search of studies published from 1 January 2020 to 13 May 2020 was conducted through a series of databases including PubMed, medRxiv, bioRxiv, Web of Science, Cochrane, China National Knowledge Infrastructure *(CNKI),* SinoMed, Wangfang and VP. The search terms were “severe acute respiratory syndrome coronavirus 2”, “COVID-19”, “SARS-CoV-2”, “asymptomatic”, “presymptomatic”, “covert infection” and related terms. Further details are shown in Supplementary Table 1.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) the subjects included in the study were positive for COVID-19, as detected by RT-PCR or serum antibody; (ii) the asymptomatic individuals were those with presymptomatic and covert infections. Asymptomatic individuals were defined as persons who had no COVID-19-related clinical symptoms, but positive RT-PCR or serum antibody results were detected. Presymptomatic infections were defined as persons who were asymptomatic with positive RT-PCR or serum antibody results at the early phase of infections and then developed COVID-19-related clinical symptoms during follow-up. Covert infections were defined as persons who did not show any COVID-19-related clinical symptoms during the whole course, but RT-PCR or serum antibody detection was positive (Wu, 2020). In this meta-analysis, some of the potential eligible studies were not explicit about the definition of asymptomatic, presymptomatic and covert infections; in these cases, we made decisions based on the authors' descriptions; (iii) studies with sample sizes $\geq$20 participants; and (iv) studies with sufficient data to calculate the proportion of asymptomatic infections with COVID-19 (the number of asymptomatic infections/the total number of *RT-PCR* or serum antibody positives).

The exclusion criteria were as follows: (i) studies that included only patients with symptomatic COVID-19; (ii) duplicated publication data; and (iii) case reports, reviews, and studies without original data (*e.g.*, modeling studies).

Screening, data extraction and quality assessment

Seven reviewers (CC, DY, HL, DL, YZ, XF and CD) performed an initial screening of titles and abstracts to exclude studies that clearly contained no asymptomatic patients with COVID-19 or no suitable data for asymptomatic proportion calculation. All retained full-text articles were scrutinized against the eligibility criteria by two independent reviewers (TG and LL). Disagreements and uncertainties in the studies screened and selected were resolved by consensus by all authors. The collected data included basic study information (*e.g.*, first author, titles), study population (*e.g.*, close contact, cluster, family cluster, epidemiological investigation), the numbers of asymptomatic and total infections, the numbers of covert and presymptomatic infections (data were available when the studies completed follow-up), demographic data (*e.g.*, age, sex), the time of viral shedding, and radiographical findings (*e.g.*, abnormal lung findings, ground-glass opacity *(GGO)*). If a study included more than one independent study population, each of them was extracted as a separate dataset in the meta-analysis. Data extraction from each study was performed by two independent investigators (XL and CH). Disagreements and uncertainties in the data extraction were resolved by consensus by all authors. The scale recommended by the Agency for Healthcare Research and Quality (Meyers, 2012) was used for quality assessment of the included studies. The scale consists of 11 items, and each item was assigned 1 point if the condition was fulfilled. According to the total score, the studies were categorized into low (0–3), moderate (4–7) and high quality (8–11). The articles and citations were managed in EndNote (version X9).

Statistical analysis

The viral shedding duration is presented by the median and interquartile range *(IQR)* in the original papers; the ranges provided were converted to means and standard deviations *(SDs)* by using an online tool (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) developed by Luo et al. (2018). Then, the median viral shedding duration of asymptomatic infections was estimated, and its 95% confidence intervals *(CI)* were reported. The proportion of asymptomatic infections was pooled, and their 95% CIs were reported with variance transformed to a normal distribution by arcsine transformation or Freeman-Tukey double arcsine transformation (Barendregt et al., 2013). The heterogeneity among each study was assessed by $I^{2,}$ and when $I^2 > 50\%$, a random-effects model was chosen; otherwise, a fixed-effects model was used (Ades et al., 2005). Data from studies grouped according to study-level characteristics were compared using subgroup analyses. Potential publication bias was appraised by funnel plot and Egger weighted regression (Peters et al., 2006). Sensitivity analysis, which excluded preprint studies, was used to evaluate the robustness and reliability of the overall pooled proportion. R version 3.2.3. was used to perform the data clearing and analyses.

Results

Search results

Our literature searches identified 3322 records. After duplicates were removed, the titles and abstracts of 1755 published articles were screened, and then the eligibility of 229 full-text articles was assessed. Of these, 66 studies had no available/original data for asymptomatic infections, 30 studies had sample sizes less than 20 subjects, 15 studies only described asymptomatic infections but could not calculate the proportion of asymptomatic infections, and 14 publications presented duplicated study data. Finally, 104 studies, containing 105 datasets with 20,152 cases, were included in the meta-analysis (Figure 1). Further details are shown in Supplementary Table 2.

Proportion of asymptomatic individuals with COVID-19 infections

The proportion of asymptomatic individuals among those with COVID-19 was 13.34% (95% CI: 10.86%–16.29%) (Supplementary Figure 1A). Among the COVID-19 infections, the proportion of covert infections was 8.44% (95% CI: 5.12%–13.62%) (Supplementary Figure 1B) and the proportion of presymptomatic cases was 7.64% (95% CI: 4.02%–14.04%) (Supplementary Figure 1C) (Table 1).

Subgroup analysis of the asymptomatic individuals with COVID-19

Among the infections with COVID-19, infected children were more likely to be asymptomatic (32.24%; 95% CI: 23.08%–42.13%) than adults (9.66%; 95% CI: 5.54%–14.76%) and elderly individuals (7.98%; 95% CI: 5.4%–11.02%) (Supplementary Figure 2A). In the infected health-care workers, the proportion of asymptomatic infections accounted for 36.96% (95% CI: 18.51%–60.21%) (Supplementary Figure 2B). Asymptomatic infections were more likely to be found in COVID-19 clusters (16.15%; 95% CI: 9.35%–26.46%), close contacts of patients (15.58%; 95% CI: 6.17%–34.12%) and epidemiological investigations (12.80%; 95% CI: 10.09%–16.11%) (Supplementary Figure 2C). The proportion of asymptomatic infections showed significant differences in study periods and regions. Compared to the studies conducted before 2020/02/29, the proportion of asymptomatic infections was significantly higher in studies published after 2020/02/29 (33.53% *vs* 10.19%) (Supplementary Figure 2D), and the proportion was also significantly higher in non-Asian regions than that in Asian regions (28.76% *vs* 11.54%) (Supplementary Figure 2E) (Figure 2).

Viral shedding and radiographical findings among asymptomatic individuals with COVID-19

When considering asymptomatic infections, the median viral shedding duration was estimated to be 14.14 days (95% CI: 11.25–17.04 days) (Supplementary Figure 3A) (Figure 3A). Among the asymptomatic infections, 47.62% (95% CI: 31.13%–72.87%) showed lung abnormalities. The most common abnormalities were ground-glass opacity 41.11% (95% CI: 19.7%–85.79%), followed by unilateral pneumonia 30.95% (95% CI: 22.22%–43.12%) and bilateral pneumonia 27.13% (95% CI: 17.28%–42.59%) (Supplementary Figure 3B), (Figure 3B).

Subgroup analysis of presymptomatic infections among those with COVID-19

Presymptomatic individuals were more likely to be found in cluster infections (29.99%; 95% CI: 15.33%–50.34%) (Supplementary Figure 4A). The proportion of presymptomatic patients was higher in studies published after 2020/02/29, with proportions of 28.47% *vs* 3.53% (Supplementary Figure 4C), and was also higher in non-Asian regions than in Asian regions, with proportions of 28.47% *vs* 3.92% (Supplementary Figure 4E) (Figure 4A).

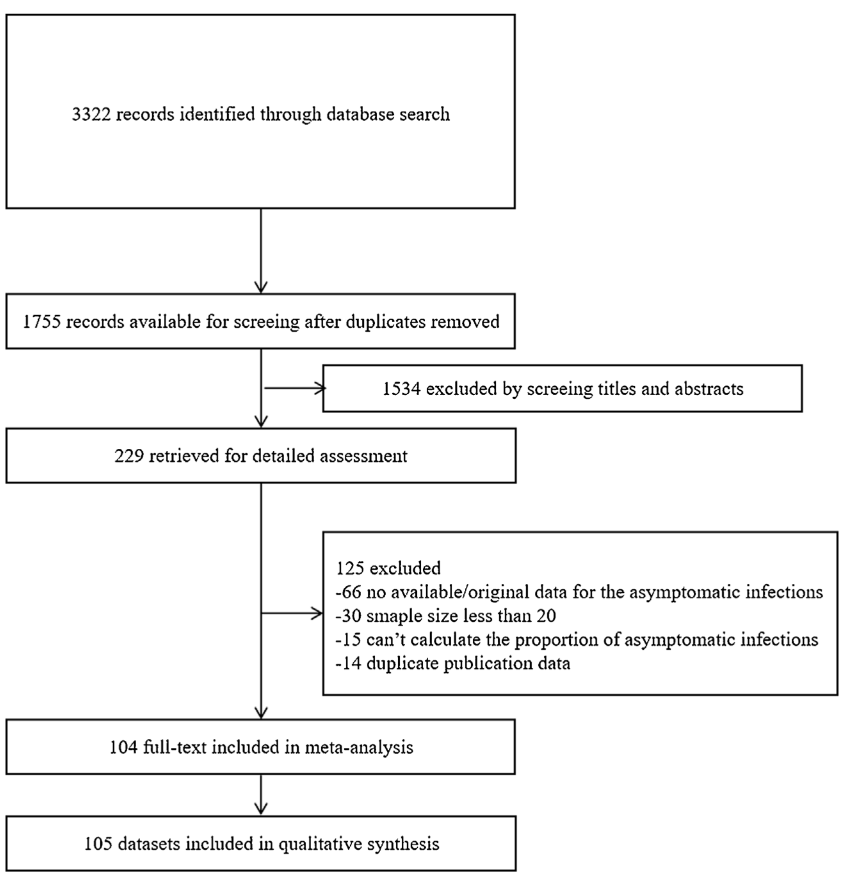

Figure 1. Flow diagram of the study selection process used for this meta-analysis.

Table 1
The proportions of asymptomatic individuals among patients with COVID-19.

Characteristics	Number of studies	Sample sizes	Proportions (95% CI)	Heterogeneity (I^2)
Asymptomatic	104	20,152	13.34% (10.86%–16.29%)	95.70%
Covert infection	20	3586	8.44% (5.12%–13.62%)	92.80%
Presymptomatic	18	2750	7.64% (4.02%–14.04%)	93.70%

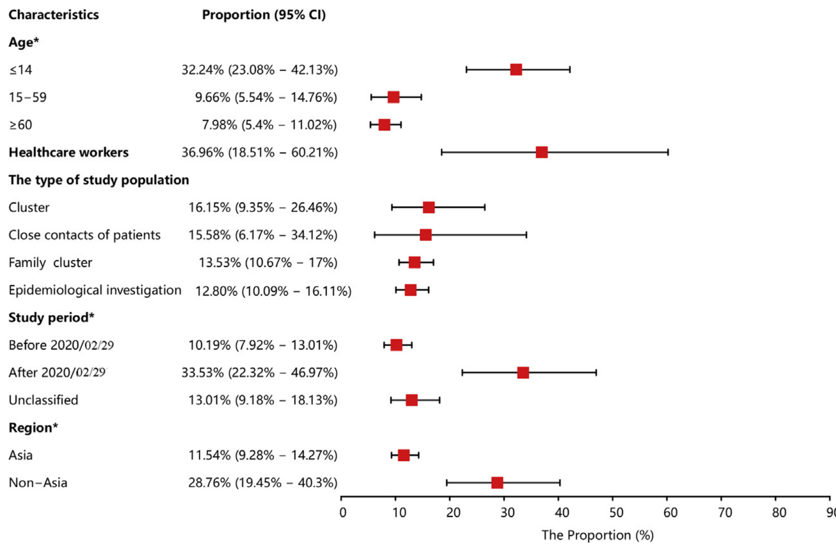

Figure 2. Subgroup analysis of asymptomatic individuals among COVID-19 infections. *Statistical differences between subgroups (P < 0.05).

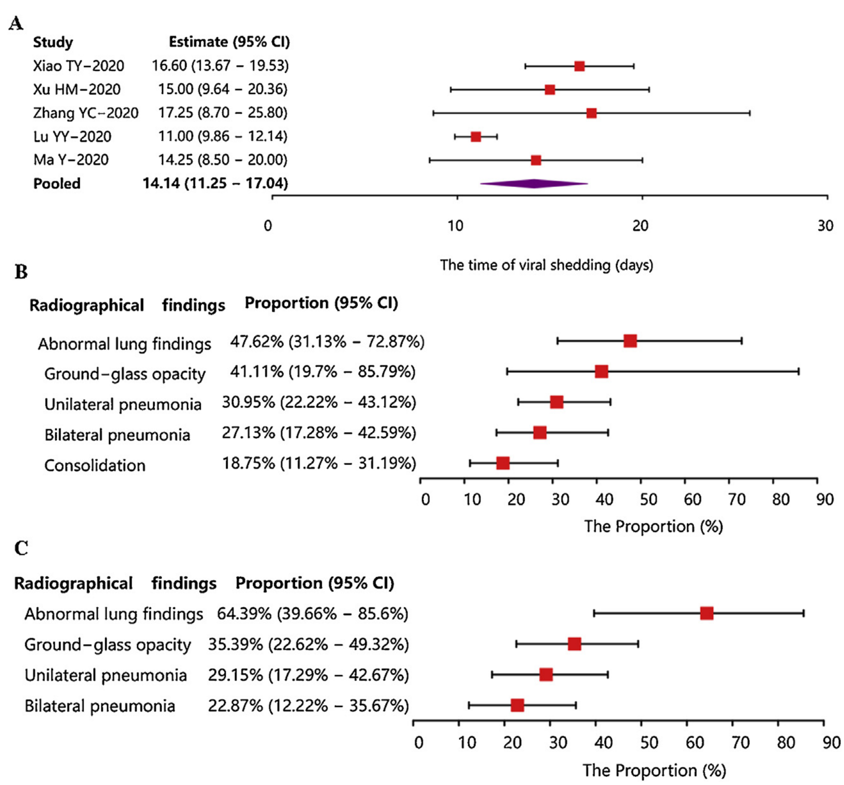

Figure 3. Viral shedding and radiographical findings among asymptomatic and covert infections with COVID-19. (A) The time of viral shedding among the asymptomatic individuals. (B) Radiographical findings among asymptomatic individuals. (C) Radiographical findings among covert infections.

Subgroup analysis of covert infections among those with COVID-19

Covert infections were also more likely to be found in cluster infections (14.81%; 95% CI: 7.41%–27.43%) (Supplementary Figure 5A). The proportion of covert infections was higher in studies published after 2020/02/29, with proportions of 13.80% *vs* 7.40% (Supplementary Figure 5B) and was also higher in non-Asian regions than in Asian regions, with proportions of 13.80% *vs* 6.91% (Supplementary Figure 5C) (Figure 4B). Among the covert infections, 64.39% (95% CI: 39.66%–85.6%) showed lung abnormalities. The most common abnormalities were ground-glass opacity (35.39%; 95% CI: 22.62%–49.32%), followed by unilateral pneumonia (29.15%; 95% CI: 17.29%–42.67%) and bilateral pneumonia (22.87%; 95% CI: 12.22%–35.67%) (Supplementary Figure 6) (Figure 3C).

Publication bias and sensitive analysis

The shapes of the funnel plots were relatively symmetrialc (Supplementary Figure 7). Egger-weighted regression was also conducted and yielded a P-value of 0.8805 ($P > 0.05$), thus indicating that no obvious publication bias was evident. When preprint studies were excluded from the meta-analysis, the pooled proportion estimate was 11.77% (95% CI: 9.15%–15.01%), while the overall proportion with preprints included was estimated to be 13.34% (95% CI: 10.86%–16.29%); the 95% CIs of the pooled proportions overlapped. In the subgroup analysis, no significant difference was found between the pooled proportions estimated among preprint studies and peer-reviewed published articles ($P = 0.0681 > 0.05$) (Supplementary Figure 8). Therefore, we consider that the results of our study were stable and that the inclusion of preprinted articles had no obvious impact on the results.

Discussion

Asymptomatic infection with COVID-19 has caused wide concern for preventing a possible epidemic rebound. Understanding asymptomatic infections is conducive to assessing the prevalence, transmission rate, and case fatality rate *(CFR)* of COVID-19 infection, as well as to developing measures for containing COVID-19 epidemics. However, we know very little about the epidemiological characteristics, especially the proportion of asymptomatic infections among those with COVID-19. Two studies previously pooled published data and attempted to determine the proportion of covert infections among COVID-19 patients. In the Byambasuren study, five studies were included that contained 413 cases; the proportion of covert infections was estimated to be 16% (Byambasuren et al., 2020). In the study conducted by Nelson Aguirre-Duarte, eight studies were included that contained 156 cases; the proportion of covert infections was estimated to be 29% (Buitrago-Garcia et al., 2020). There was a significant discrepancy between these two studies, and the sample sizes of the included articles appeared to have a marked impact on the results. In our study, we performed a large-scale meta-analysis that included 104 studies with 20,152 COVID-19 infections from 12 countries. The overall proportion of asymptomatic individuals among those with COVID-19 was estimated as 13.34%. Actually, among asymptomatic individuals, some infections were essentially presymptomatic infections, a transient asymptomatic state during the incubation period before clinical symptoms. Our results

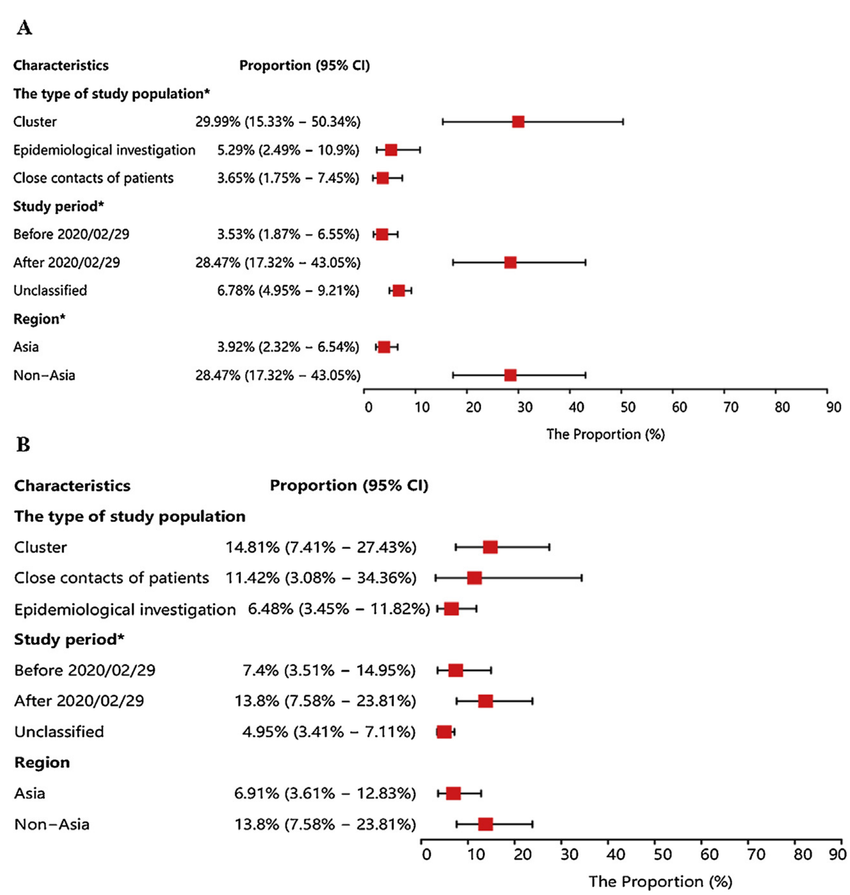

Figure 4. Subgroup analysis of presymptomatic and covert infections among COVID-19 infections. *Statistical differences between subgroups ($P < 0.05$). (A) Subgroup analysis of presymptomatic individuals among COVID-19 infections. (B) Subgroup analysis of covert infections among COVID-19 infections.

indicated that the proportion of presymptomatic infections among those with COVID-19 was estimated at 7.64%, while approximately 8.44% were covert infections that were asymptomatic throughout the disease course and extended follow-up.

We noticed that the proportion of asymptomatic infections in children was apparently higher than that in adults and elderly individuals. In a review of 72,314 cases in China, children younger than 10 years accounted for less than 1% of the cases (Wu and McGoogan, 2020), and most of the infected children appeared to have a mild clinical course (Lu et al., 2020a). Despite being mild or asymptomatic, prolonged viral shedding in the respiratory tract and stool was observed in these cases. After the onset of illness, the duration of SARS-CoV-2 RNA shedding in nasopharyngeal/throat swabs and feces ranged from 6 to 22 days and at least 2 weeks to more than 1 month, respectively (Cai et al., 2020; Xu et al., 2020). A previous study reported that the median viral shedding duration among covert, presymptomatic, and symptomatic infections, was 12.1, 16.6 and 16.6, respectively (Zhang et al., 2020). In this study, the median viral shedding duration among asymptomatic individual was estimated to be 14.14 days. Although some studies have argued that the clearance of the virus in asymptomatic individuals was faster than in symptomatic individuals (Zhang et al., 2020; Lu et al., 2020b), RNA-negative conversion still occurred at least two weeks from onset. Due to the long duration of viral shedding and the lack of visible features, asymptomatic individuals should be deemed an epidemiologically significant source of infection. A high proportion of asymptomatic individuals was also found in infected healthcare workers. Several reasons might contribute to this phenomenon. First, most affected healthcare workers were young adults, who only showed mild or moderate clinical symptoms (Cheng et al., 2020; Lai et al., 2020). Second, healthcare workers, known to be a high-risk group for COVID-19 (Folgueira et al., 2020), are tested urgently and intensively after exposure; therefore, infection is more likely to be identified at the presymptomatic stage. In our study, the proportion of asymptomatic infections, including covert infections, among COVID-19 patients increased after 2020/02/29. This result indicated that the virulence of COVID-19 appears to be declining. The CFR for COVID-19 was estimated at 2.58%, significantly lower than that for SARS-CoV (10%) and MER-CoV (35%) (WHO, 2004; WHO, 2016; Biswas et al., 2020). It appears that during the evolution of COVID-19, the virus tends to persistently and adaptively circulate among the population. This would also provide more opportunities for producing new mutant viruses that adapt to human hosts during long-term interactions between humans and COVID-19 (Issa et al., 2020). The increase in the proportion of asymptomatic infections and covert infections reduces the harm of COVID-19 to humans. This might also explain why the proportion of asymptomatic infections and covert infections in non-Asian regions was higher than that in Asian regions because studies conducted in non-Asian regions were mostly conducted after 2020/02/29.

To contain the COVID-19 epidemic, effective measurements should be taken not only for detecting symptomatic cases but also for identifying asymptomatic infections. However, there are more challenges for the prevention and control of asymptomatic infections with COVID-19. Currently, the main prevention and control strategies for asymptomatic infections consist of three aspects. First, asymptomatic infections should be efficiently detected. Epidemiological investigations and close contact tracing must be conducted promptly among confirmed, suspected and imported cases (Adhikari et al., 2020). Second, population-based surveillance and testing should be intensified. Several seroprevalence studies have been conducted among healthcare workers (Folgueira et al., 2020; Rivett et al., 2020). It has been reported that weekly testing of asymptomatic healthcare workers could reduce transmission by 16%–23% (Imperial College COVID-19 Response Team, 2020). Third, for individuals, it is necessary to maintain personal protection, a safe social distance, good personal hygiene, and wear face masks in crowded areas (Gasmi et al., 2020). Our results could be used to provide a quantified understanding of the proportion of asymptomatic individuals among COVID-19 infections and the specific population that is prone to asymptomatic infection. The estimated proportions of asymptomatic individuals among those with COVID-19 infections might be incorporated into modeling studies for the design of management policies and the determination of risk management implications. Lía Mayorga's reported that if 45% of the asymptomatic infections could be detected and isolated, and 50% of presymptomatic infections could be detected within three days of becoming infectious, then there would be no need for quarantine, and the *R0* could be reduced by half (Mayorga et al., 2020). Effective isolation and detection strategies for asymptomatic infections can have an important impact on the COVID-19 epidemic. The observed epidemiological characteristics of asymptomatic infections could help us target populations that might have higher proportions of asymptomatic infections. Meanwhile, it was indicated in our study that nearly half of the asymptomatic infections (47.62%) had lung abnormalities, and among the covert infections, 64.39% had lung abnormalities. Therefore, chest radiographical screening could serve as an effective supplementary method to identify asymptomatic infections in the early stage of disease.

This study has several limitations that need to be considered. First, most of the included studies did not categorize asymptomatic infections into covert and presymptomatic infections. This may have led to bias when estimating the proportion of covert and presymptomatic infections. Second, high statistical heterogeneity was found; this may be related to study regions, study populations, study periods, and sample sizes. Third, the majority of the studies were conducted in China; thus, regional differences need to be considered. Therefore, it would be better to incorporate as many studies as possible with a broad geographic scope to obtain a more comprehensive understanding of the proportion of asymptomatic infections among COVID-19 patients.

Conclusion

This was a large-scale study of the epidemiological characteristics and radiographical findings of asymptomatic infections with COVID-19. We included 104 studies with 20,152 COVID-19 infections from 12 countries. The overall proportion of asymptomatic individuals among those with COVID-19 infections was estimated to be 13.34%. Among the asymptomatic individuals, the proportions of presymptomatic and covert infections were estimated at 7.64% and 8.44%, respectively. Infected children are more likely to become asymptomatic infections, while a high proportion of asymptomatic infections were found in infected healthcare workers. The infection spectrum of COVID-19 appears to be changing, while the proportion of asymptomatic infections, including covert infections, among those with COVID-19 infections, increased after 2020/02/29. The median viral shedding duration among the asymptomatic individual was estimated to be 14.14 days. Furthermore, long-term viral shedding, and the lack of visible features, make asymptomatic infections epidemiologically significant in the transmission of COVID-19. In terms of the prevention and control of asymptomatic infections, chest radiographical examination could be conducive to the early identification of those with asymptomatic infections.

Authors' contributions

SY, LJ L, CZ and RH designed the study. CC, DY, HL, DL, YZ, XF, CD, GT, LL, XL, and CH collected data. CC analyzed data. JW and CZ

checked the data and results. CZ and CC interpreted data and wrote the report. SY, LJ L, CZ and RH revised the report from preliminary draft to submission. CC revised the report according to journal review comments. SY and CZ supervised the study. All authors have read and approved the manuscript.

Conflict of interest disclosure

The authors have no conflicts of interest relevant to this article to disclose.

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Ethical approval

Ethical approval has not required for this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.01.017.

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