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Magnitude of asymptomatic COVID-19 cases throughout the course of infection: A systematic review and meta-analysis

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Abstract

Background

Asymptomatic SARS-CoV-2 infections are responsible for potentially significant transmission of COVID-19. Worldwide, a number of studies were conducted to estimate the magnitude of asymptomatic COVID-19 cases. However, there is a need for more robust and well-designed studies to have a relevant public health intervention. Synthesis of the available studies significantly strengthens the quality of evidences for public health practice. Thus, this systematic review and meta-analysis aimed to determine the overall magnitude of asymptomatic COVID-19 cases throughout the course of infection using available evidences.

Methods

We followed the PRISMA checklist to present this study. Two experienced review authors (MA and DBK) were systematically searched international electronic databases for studies. We performed meta-analysis using R statistical software. The overall weighted proportion of asymptomatic COVID-19 cases throughout the course infection was computed. The pooled estimates with 95% confidence intervals were presented using forest plot. Egger's tests were used to assess publication bias, and primary estimates were pooled using a random effects model. Furthermore, a sensitivity analysis was conducted to assure the robustness of the result.

Results

A total of 28 studies that satisfied the eligibility criteria were included in this systematic review and meta-analysis. Consequently, in the meta-analysis, a total of 6,071 COVID-19 cases were included. The proportion of asymptomatic infections among the included studies ranged from 1.4% to 78.3%. The findings of this meta-analysis showed that the weighted pooled proportion of asymptomatic COVID-19 cases throughout the course of infection was 25% (95%CI: 16–38). The leave-one out result also revealed that the weighted pooled average of asymptomatic SARS-CoV-2 infection was between 28% and 31.4%.

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Abbreviations: COVID-19, The 2019 Novel Coronavirus Disease; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; Sever SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization; CI, Confidence Interval.

Conclusions

In conclusion, one-fourth of SARS-CoV-2 infections are remained asymptomatic throughout the course infection. Scale-up of testing, which targeting high risk populations is recommended to tackle the pandemic.

Background

The novel coronavirus disease 2019 ("COVID-19") caused by sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now established a global pandemic [1]. The pandemic is a challenge for both developed and developing countries causing huge stress on the healthcare system of all countries [2]. Up to February 20, 2021; there were more-than 110 million total COVID-19 cases with more-than two million deaths, worldwide [3]. As studies reported, the early sign of the COVID-19 is pneumonia [4]. In addition, of COVID-19 patients who developed signs and symptoms, the most frequently reported symptoms was fever followed by cough [5].

Asymptomatic and presymptomatic COVID-19 cases are responsible for potentially significant transmissions, and this makes a challenge to control the pandemic [6]. Approximately, half of individuals with positive test results don't have any symptoms at the time of testing [7]. Additionally, about one-fifth of SARS-CoV-2 infections are remained asymptomatic throughout the course infection. One study indicated that the viral shedding coronavirus is peaked on before symptom onset [8]. This indicates that a substantial proportion of transmission probably occurred before first symptoms in the primary case. Another studies conducted in Singapore and China revealed that about 6.4%, and 12.6% of COVID-19 cases were attributed to asymptomatic transmission, respectively. Consequently, asymptomatic transmission expected to occur 1–3 days before symptom onset of source patients [9].

The serial interval and incubation period are the two main epidemiological parameters that suggests for presymptomatic transmission of COVID-19. When the average serial interval of COVID-19 is shorter than the average incubation period, some proportion of cases are attributed to presymptomatic transmission [10]. Accordingly, an observational study which aimed to provide the epidemiological parameters of COVID-19 using seven countries data revealed that the mean incubation period and serial interval were 7.44 days and 6.70 days, respectively [11].

Globally, a number of studies were conducted to determine the magnitude of asymptomatic SARS-CoV-2 infection. However, there is a need for more robust and well-designed studies to have relevant public health intervention. Studies vary depending on the number of participants recruited, the type of design employed and the country in which the study conducted [12, 13]. Combined findings of existing studies significantly strengthen the quality of evidences for public health practice. Since the biological, clinical and epidemiological characteristics of COVID-19 didn't well known, this well design and appropriately performed study is needed to have a solid evidence-based intervention. The findings of this study will have a potential role to inform policymakers and stakeholders to combat the pandemic. Thus, this systematic review and meta-analysis aims to determine the pooled magnitude of asymptomatic COVID-19 cases throughout the course of infection using existing evidences.

Methods

Searching for studies

The study follows the preferred reporting items for systematic review and meta-analysis (PRISMA) to present this study. The search was done by two experienced review authors (MA

and MAA) from international electronic databases (Google Scholar, PubMed, Science Direct, Web of Science, and CINAHL). In addition, we searched from the reference lists of the included studies to identify any other studies that may have been missed by our search strategy. We used the following search terms: "magnitude" OR "prevalence" AND "asymptomatic" OR "presymptomatic" OR "silent" AND "transmission" AND "coronavirus OR "COVID-19" OR "novel coronavirus" OR "SARS-CoV-2". Our search was performed between the 1st of June and the 9th of December, 2020. Finally, all studies were imported into reference management software (Mendeley desktop).

Inclusion criteria

Estimates reported: all observational studies reported the magnitude of asymptomatic COVID-19 cases throughout the course of infection

Study setting: worldwide

Population: all age group

Publication status: all published, and unpublished articles

Language: only studies reporting using English language

Publication date: published from the 1st of January to the 9th of December, 2020

Exclusion criteria

Articles that was not report the outcome of interest, case reports and review studies were excluded.

Outcome variable and data extraction

The outcome variable of this study was the magnitude of true asymptomatic SARS-CoV-2 infection. Asymptomatic SARS-CoV-2 infection is defined as an individual without a history of clinical signs and symptoms throughout the course of infection. Two experienced review authors (MA and LY) extracted all essential data from the included studies using a predesigned data extraction form. The data extraction form organized as; the last name of the first author, the country of the study conducted, data collection period, sample size, magnitude of asymptomatic COVID-19 cases. Any inconsistencies in the data extraction process were decided through discussion involving all authors.

Quality assessment

Two review authors (LY and TYB) were assessed the risk of bias of the included articles. The Newcastle Ottawa Scale (NOS) adapted for cross-sectional studies was used to evaluate the quality of studies [14]. This tool organized from three major sections. Consequently, the first section scored on the basis of one to five stars focuses on the methodological quality of each study. The second segment of the tool evaluates the comparability of the study groups with a maximum possibility of two stars to be given. The last section of the tool is concerned with the outcomes and statistical analysis of the included studies with a maximum possibility of three stars to be given. Each author rated the quality of each article. Any inconsistent report between the two reviewers was decided by taking the average score of the two reviewers'. Finally, the assessed articles with a score of less than six out of ten were considered as achieving low quality.

Data processing and analysis

After extracting all essential data using Microsoft Excel, data were exported to R statistical software for further analysis. In-consistency among the reported magnitude of asymptomatic

SARS-CoV-2 infection was assessed using I^2-index [15]. To estimate the weighted pooled magnitude of asymptomatic COVID-19 cases, a random-effect meta-analysis with an estimation of DerSimonian and Laird method was performed. The publication bias was assessed using a tool known as a funnel plot. Funnel plot asymmetry was also tested by using Egger's and Beggs' tests [16]. Furthermore, leave-one-out meta-analysis was conducted to assure the robustness of the result. Leave-one-out analysis involves performing a meta-analysis on each subset of the studies obtained by leaving out exactly one study. This shows how each individual study affects the overall estimate of the rest of the studies.

Results

Search results

Fig 1, shows the flow chart diagram describing the selection of studies included in the systematic review and meta-analysis. Our search resulted with a total of 8,260 studies. Consequently, 134 articles were eligible for screening after excluding duplication. Ninety six articles were excluded after reading the title and abstract. After carefully assessed the text in the included studies, ten articles were removed due to not extractable result and the outcome of interest. Finally, in this study, we included a total of 28 studies that satisfied the eligibility criteria.

Description of the included studies

The detail description of the included studies are presented in (**Table 1**). In this systematic review and meta-analysis, a total of 28 studies with a total COVID-19 cases of 6,071 COVID-19 included. The smallest sample size was 23 [17], while the largest sample size was 712 [18]. Nearly half (48.3%) of the included studies were conducted from China.

Magnitude of asymptomatic COVID-19 cases

Of the included studies, the proportion of asymptomatic SARS-CoV-2 infections ranged from 1% to 81%. Consequently, our meta-analysis showed that the weighted pooled truly asymptomatic COVID-19 cases was 25% (95%CI: 16–38) (**Fig 2**). **Table 2,** shows the sensitivity analysis of the study. The minimum weighted pooled proportion (28%) of SARS-CoV-2 was found by removing article [22], while the maximum proportion (31.4%) was obtained after removing the study [28]. The issue of publication bias was assessed by graphic inspection of funnel plot and using the rank correlation test. Even though, the funnel plot looks asymmetrical (**Fig 3**), the rank correlation test showed that no relationship between the effect size and its precision (P-value = 0.4).

Discussion

COVID-19 pandemic remains a major public health problem worldwide. Currently, there is no enough evidences to recommend any specific medication for the treatment of COVID-19. Presymptomatic and asymptomatic SARS-CoV-2 infections are capable to transmitting the virus, and this makes challenging to prevent and control the pandemic. Previous evidences showed that SARS-CoV-2 infections are spread more rapidly compared with Sever Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [45]. Previous studies suggest that contact and symptom based screening might fail to identify all potential SARS-CoV-2 infections. The current study was aimed to determine the overall magnitude of asymptomatic COVID-19 cases throughout the course of infection.

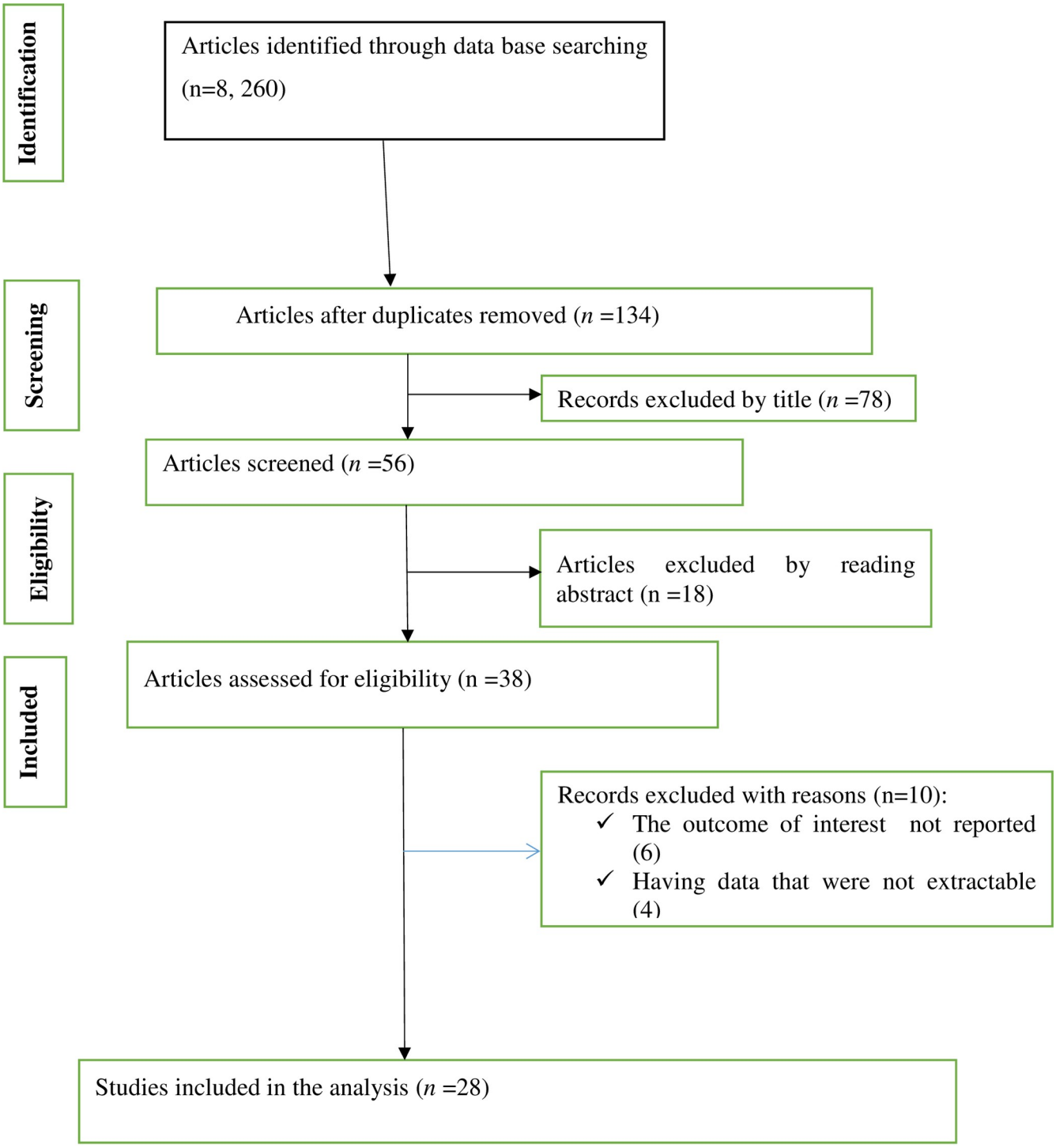

Fig 1. Flow chart diagram describing the selection of studies included in the systematic review and meta-analysis on the magnitude of truly asymptomatic SARS-CoV-2 infection, 2020.

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We computed the overall weighted proportion of COVID-19 cases who hadn't developed signs and symptoms throughout the course of infection. Accordingly, one-fourth (25% (95% CI: 16–38)) of COVID-19 cases were asymptomatic throughout the course of infection. This

Table 1. Descriptions of the included studies conducted on the proportion of asymptomatic SARS-CoV-2 infection, 2020.

No.	First author	Country	Study period	Total cases	Asymptomatic cases
1.	An et al [19]	China	April, 2020 *	25	16
2.	Arons et al [20]	USA	March 13 to 20,2020	48	3
3.	Chun et al [21]	South Korea	January 23 to March 31, 2020	89	16
4.	Day et al [22]	China	April 1,2020 *	166	130
5.	Feaster et al [23]	USA	April, 2020 *	631	257
6.	Inui et al [24]	Japan	February 7 to 28,2020	104	76
7.	Keeley et al [25]	Argentina	March, 2020 *	128	104
8.	Kimball et al [17]	USA	March 13,2020 *	23	3
9.	Kong et al [26]	China	January 25 to February 20,2020	511	100
10.	Lavezzo et al [27]	Italy	February 23 to March 8, 2020	102	44
11.	Ling et al [28]	China	January 23 to February 18, 2020	295	4
12.	Long et al [29]	China	February 6, 2020 *	178	37
13.	Luo et al [30]	China	February 21, 2020 *	83	8
14.	Ma et al [31]	China	Jan 23 to March 10,2020	47	11
15.	Meng et al [32]	China	Jan 1 and Feb 23, 2020	58	42
16.	Mizumoto et al [33]	Japan	February 20,2020 *	634	328
17.	Moriarty et al [18]	Japan	February to March 2020	712	331
18.	Nishiura et al [34]	Japan	February 12, 2020 *	565	235
19.	Noh et al [35]	North Korea	March, 2020 *	199	53
20.	Rivett et al [36]	United kingdom	April, 2020 *	30	17
21.	Tabata et al [37]	Japan	Feb 11 to Feb 25, 2020	104	33
22.	Tian et al [38]	China	Feb 10, 2020 *	262	13
23.	Wan et al [39]	China	February 20,2020 *	78	2
24.	Wong et al [40]	Brunei	April 24, 2020 *	138	16
25.	Xu et al [41]	China	January 18 to February 26, 2020	342	15
26.	Zhao et al [42]	China	February 21,2020 *	160	4
27.	Zhou et al [43]	China	March 4, 2020 *	328	10
28.	Zhou et al [44]	China	Jan 23 to March 3,2020	31	9

*study period was not clearly stated.

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result is comparable with previous study conducted on the asymptomatic SARS-CoV-infections. However, this result is lower than previous studies conducted on asymptomatic SARS-CoV-2 infection [6, 7]. The possible reason for this variation might be asymptomatic COVID-19 cases considered in the previous studies will develop sign and symptoms during hospitalization period. A study conducted in Barcelona, Spain revealed that more-than two-third of SRAS-CoV-2 infections are asymptomatic at the time of testing [46].

We also compared the proportion of asymptomatic SARS-CoV-2 infections with previously emerged coronavirus outbreaks. A study that reports the role of asymptomatic patients in the transmission of MERS-CoV showed that one-fourth (25.1%) of MERS-CoV were asymptomatic [47]. Though, one study showed that small number of SARS-CoV cases are asymptomatic, unlike COVID-19, sever acute respiratory syndrome could be controlled by effective isolation of symptomatic patients [48]. One study also showed that nearly half of SARS-CoV patients were asymptomatic throughout the course hospitalization [49]. This inconsistency might be due to the difference in clinical severity between COVID-19 cases, MERS and SARS-CoV [50].

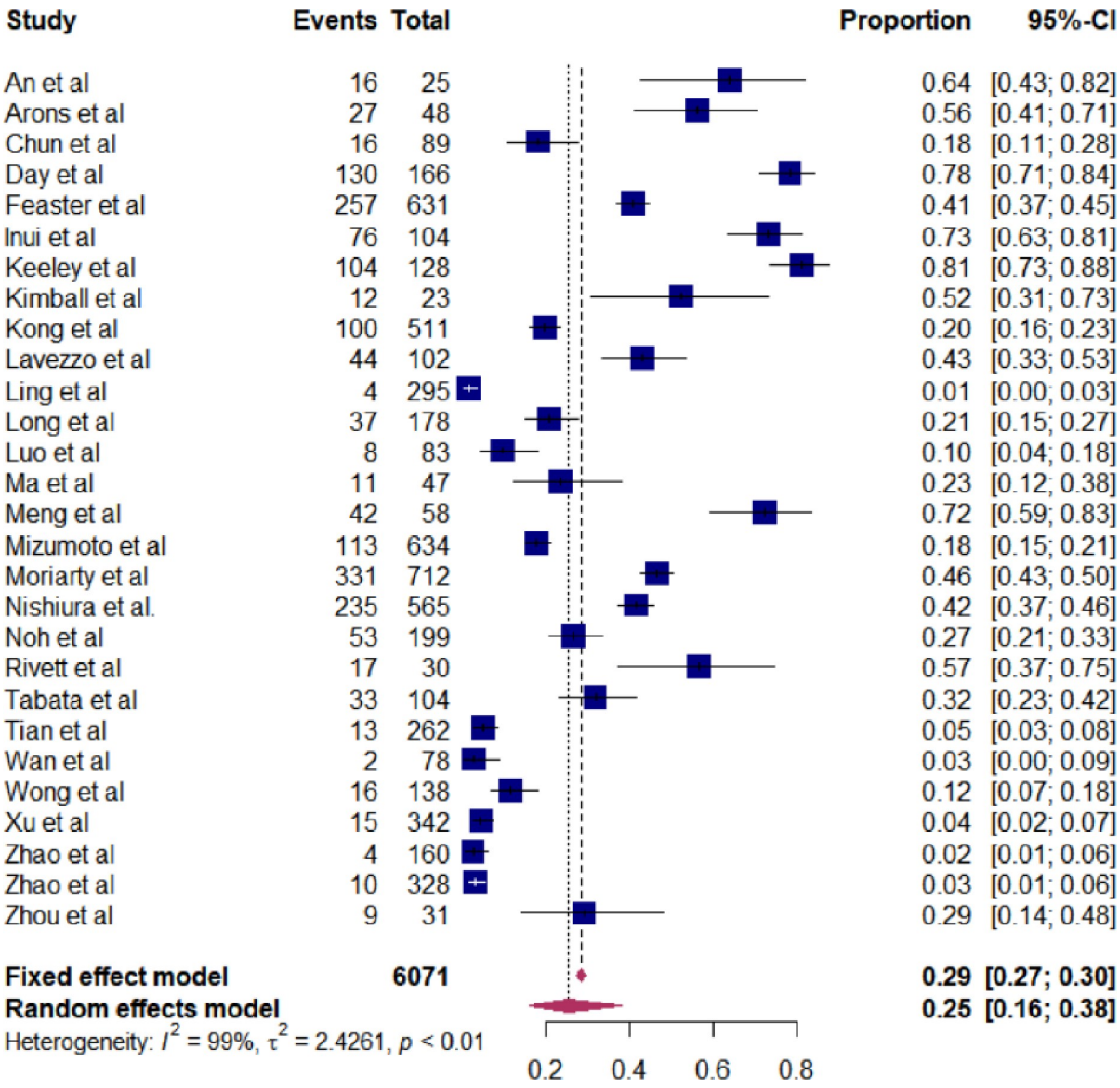

Fig 2. Forest plot that shows the weighted pooled proportion of asymptomatic SARS-CoV-2 infection using available studies, 2020.

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Limitation

The current study has a number of limitations. Firstly, the majority of the included studies had relatively small sample size which may decrease the power of the study. Secondly, the review was limited to only articles published in the English language. Lastly, since the included articles are limited to few countries, it may not represent the global figure of asymptomatic SARS-CoV-2 infection.

Conclusions

In conclusion, one-fourth of SARS-CoV-2 infections are remained asymptomatic throughout the course infection. Scale-up of testing, which targeting high risk populations is recommended to tackle the pandemic.

Table 2. The sensitivity analysis to estimate the pooled proportion of truly asymptomatic SARS-CoV-2 infection, 2020.

No.	Study omitted	Pooled proportion (95%CI)	No.	Study omitted	Pooled proportion (95%CI)
1.	An et al	28.7 (18.9, 39.6)	15.	Meng et al	28.4 (18.8,39.0)
2.	Arons et al	28.9 (19.0, 39.9)	16.	Mizumoto et al	30.3 (20.1,41.6)
3.	Chun et al	30.3 (20.1,41.5)	17.	Moriarty et al	29.2 (19.2,40.4)
4.	Day et al	28 (18.6,38.5)	18.	Nishiura et al	29.4 (19.3,40.6)
5.	Feaster et al	29.4 (19.3,40.6)	19.	Noh et al	30.0 (19.8,41.2)
6.	Inui et al	28.3 (18.7,38.9)	20	Rivett et al	29.0 (19.1,39.9)
7.	Keeley et al	27.9 (18.6,38.3)	21.	Tabata et al	29.8 (19.6,41.0)
8.	Kimball et al	29.1 (19.2,40.2)	22.	Tian et al	31.1 (20.9,42.1)
9.	Kong et al	30.3 (20.1,41.5)	23.	Wan et al	31.2 (21.2,42.2)
10.	Lavezzo et al	29.4 (19.3,40.5)	24.	Wong et al	30.6 (20.5,41.8)
11.	Ling et al	31.4 (21.5,42.5)	25.	Xu et al	31.1 (21.1,42.1)
12.	Long et al	30.2 (20.0,41.5)	26.	Zhao et al	31.3 (21.3,42.2)
13.	Luo et al	30.7 (20.6,41.9)	27.	Zhou et al	31.2 (21.2,42.2)
14.	Ma et al	30.1(19.9,41.3)	28.	Zhou et al	29.8 (19.7,41.1)

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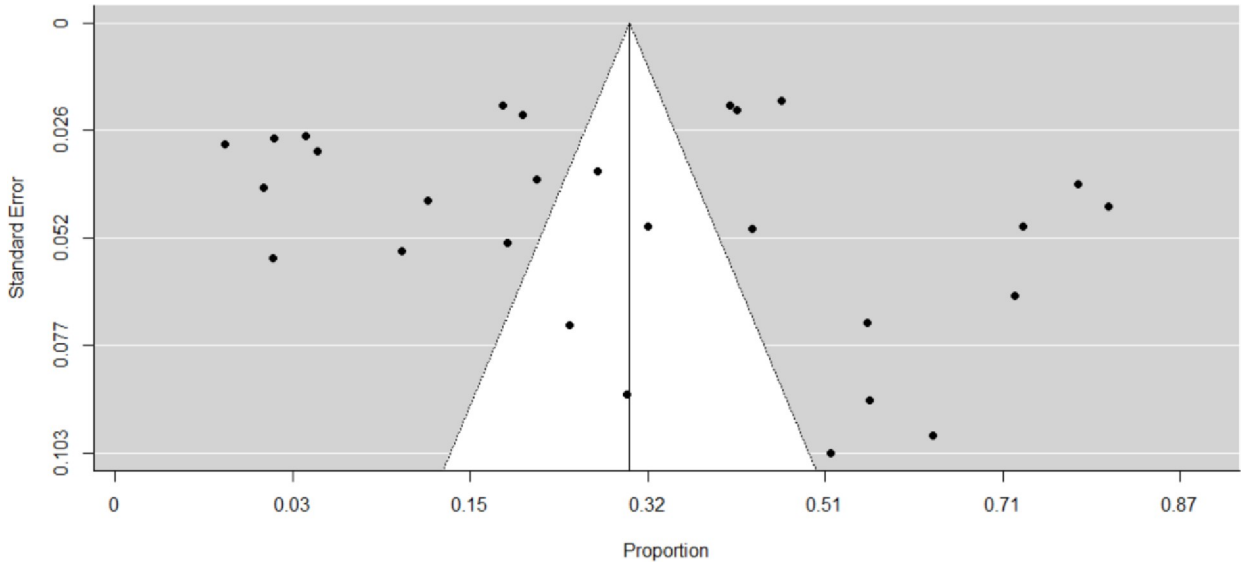

Fig 3. Funnel plot to check the publication bias of the included studies conducted on truly asymptomatic SARS-CoV-2 infection, 2020.

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Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Table. Individual effect sizes of the included studies conducted on truly asymptomatic SARS-CoV-2 infection, 2020.
(DOCX)

Author Contributions

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Writing – review & editing: Muluneh Alene, Leltework Yismaw, Moges Agazhe Assemie, Belayneh Mengist, Bekalu Kassie, Tilahun Yemanu Birhan.

References

1. WHO. media briefing on COVID-19–11 March 2020. Accessed from https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020.
2. The world bank.The Global Economic Outlook During the COVID-19 Pandemic: A Changed World, June 8,2020. accessed from https://www.worldbank.org/en/news/feature/2020/06/08/the-global-economic-outlook-during-the-covid-19-pandemic-a-changed-world.
3. JHONS HOPKINS coronavirus resource center.COVID-19. Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).
4. Rafiq D, Batool A, Bazaz MA. Three months of COVID-19: A systematic review and meta-analysis. Reviews in Medical Virology. 2020 May 18:e2113. https://doi.org/10.1002/rmv.2113 PMID: 32420674
5. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The Prevalence of Symptoms in 24,410 Adults Infected by the Novel Coronavirus (SARS-CoV-2; COVID-19): A Systematic Review and Meta-Analysis of 148 Studies from 9 Countries. Avail. https://doi.org/10.1371/journal.pone.0234765 PMID: 32574165
6. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. International Journal of Infectious Diseases. 2020 Jun 17. https://doi.org/10.1016/j.ijid.2020.06.052 PMID: 32562846
7. Syangtan G, Bista S, Dawadi P, Rayamajhee B, Shrestha LB, Tuladhar R, et al. Asymptomatic people with SARS-CoV-2 as unseen carriers of COVID-19: A systematic review and meta-analysis.
8. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature medicine. 2020 May; 26(5):672–5. https://doi.org/10.1038/s41591-020-0869-5 PMID: 32296168
9. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2—Singapore, January 23–March 16, 2020. Morbidity and Mortality Weekly Report. 2020 Apr 10; 69 (14):411. https://doi.org/10.15585/mmwr.mm6914e1 PMID: 32271722
10. Du Z, Xu X, Wu Y, Wang L, Cowling BJ, Meyers LA. Serial interval of COVID-19 among publicly reported confirmed cases. Emerging infectious diseases. 2020 Jun; 26(6):1341. https://doi.org/10.3201/eid2606.200357 PMID: 32191173
11. Ma S, Zhang J, Zeng M, Yun Q, Guo W, Zheng Y, et al. Epidemiological parameters of coronavirus disease 2019: a pooled analysis of publicly reported individual data of 1155 cases from seven countries. Medrxiv. 2020 Jan 1.

12. Alene M, Yismaw L, Berelie Y, Kassie B, Yeshambel R, Assemie MA. Prevalence and determinants of unintended pregnancy in Ethiopia: A systematic review and meta-analysis of observational studies. PloS one. 2020 Apr 7; 15(4):e0231012. https://doi.org/10.1371/journal.pone.0231012 PMID: 32255774

13. Alene M, Assemie MA, Yismaw L, Gedif G, Ketema DB, Gietaneh W, et al. Patient delay in the diagnosis of tuberculosis in Ethiopia: a systematic review and meta-analysis. BMC infectious diseases. 2020 Dec; 20(1):1–9.

14. Newcastle-Ottawa Scale customized for cross-sectional studies In. available from https://static-content.springer.com/esm/. . ./12889_2012_5111_MOESM3_ESM.doc.

15. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical Microbiology and Infection. 2014 Feb 1; 20(2):123–9. https://doi.org/10.1111/1469-0691.12494 PMID: 24320992

16. van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. BMC medical research methodology. 2014 Dec 1; 14(1):70. https://doi.org/10.1186/1471-2288-14-70 PMID: 24884381

17. 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, Mar.

18. Moriarty LF. Public health responses to COVID-19 outbreaks on cruise ships—worldwide, February–March 2020. MMWR. Morbidity and mortality weekly report. 2020; 69. https://doi.org/10.15585/mmwr.mm6912e3 PMID: 32214086

19. An P, Song P, Wang Y, Liu B. Asymptomatic patients with novel coronavirus disease (COVID-19). Blood. 2020 Apr 13; 3:12–0.

20. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. New England journal of medicine. 2020 Apr 24.

21. Chun JY, Baek G, Kim Y. Transmission onset distribution of COVID-19 in South Korea. medRxiv. 2020 Jan 1.

22. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate.

23. Feaster M, Goh YY. High Proportion of Asymptomatic SARS-CoV-2 Infections in 9 Long-Term Care Facilities, Pasadena, California, USA, April 2020. Emerging Infectious Diseases. 2020 Jul 2; 26(10).

24. Inui S, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, et al. Chest CT findings in cases from the cruise ship "Diamond Princess" with coronavirus disease 2019 (COVID-19). Radiology: Cardiothoracic Imaging. 2020 Mar 17; 2(2):e200110.

25. Keeley AJ, Evans CM, De Silva TI. Asymptomatic SARS-CoV-2 infection: the tip or the iceberg?. Thorax. 2020 Aug 1; 75(8):621–2. https://doi.org/10.1136/thoraxjnl-2020-215337 PMID: 32580993

26. Kong W, Wang Y, Hu J, Chughtai A, Pu H, of Sichuan CR. Comparison of clinical and epidemiological characteristics of asymptomatic and symptomatic SARS-CoV-2 infection: A multi-center study in Sichuan Province, China. Travel Medicine and Infectious Disease. https://doi.org/10.1016/j.tmaid.2020.101754 PMID: 32492485

27. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. medRxiv. 2020 Jan 1.

28. Ling Z, Xu X, Gan Q, Zhang L, Luo L, Tang X, et al. Asymptomatic SARS-CoV-2 infected patients with persistent negative CT findings. European journal of radiology. 2020 May 1; 126. https://doi.org/10.1016/j.ejrad.2020.108956 PMID: 32199142

29. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature medicine. 2020 Jun 18:1–5. https://doi.org/10.1038/s41591-020-0965-6 PMID: 32555424

30. Luo SH, Liu W, Liu ZJ, Zheng XY, Hong CX, Liu ZR, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus. Chinese medical journal. 2020 May 5; 133(9):1123–5. https://doi.org/10.1097/CM9.0000000000000798 PMID: 32149768

31. Ma Y, Xu QN, Wang FL, Ma XM, Wang XY, Zhang XG, et al. Characteristics of asymptomatic patients with SARS-CoV-2 infection in Jinan, China. Microbes and Infection. 2020 May 7. https://doi.org/10.1016/j.micinf.2020.04.011 PMID: 32387682

32. 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. Journal of Infection. 2020 Apr 12. https://doi.org/10.1016/j.jinf.2020.04.004 PMID: 32294504

33. 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 Mar 12; 25(10):2000180.

34. 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). International journal of infectious diseases. 2020 M. https://doi.org/10.1016/j.jebdp.2020.101499 PMID: 33303095

35. Noh JY, Yoon JG, Seong H, Choi WS, Sohn JW, Cheong HJ, et al. Asymptomatic infection and atypical manifestations of COVID-19: comparison of viral shedding duration. The Journal of Infection. 2020 May 21. https://doi.org/10.1016/j.jinf.2020.05.035 PMID: 32445728

36. Rivett L, Sridhar S, Sparkes D, Routledge M, Jones NK, Forrest S, et al. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. Elife. 2020 M. https://doi.org/10.7554/eLife.58728 PMID: 32392129

37. Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, et al. Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. The La. https://doi.org/10.1016/S1473-3099(20)30482-5 PMID: 32539988

38. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. Journal of Infection. 2020 Feb 27.

39. Wan R, Mao ZQ, He LY, Hu YC. Evidence from two cases of asymptomatic infection with SARS-CoV-2: Are 14 days of isolation sufficient?. International Journal of Infectious Diseases. 2020 Jun 1; 95:174–5. https://doi.org/10.1016/j.ijid.2020.03.041 PMID: 32251796

40. Wong J, Abdul Aziz AB, Chaw L, Mahamud A, Griffith MM, Ying-Ru LO, et al. High proportion of asymptomatic and presymptomatic COVID-19 infections in travelers and returning residents to Brunei. Journal of Travel Medicine. 2020 May 5.

41. Xu T, Huang R, Zhu L, Wang J, Cheng J, Zhang B, et al. Epidemiological and clinical features of asymptomatic patients with SARS-CoV-2 infection. Journal of medical virology. 2020 Apr 28.

42. Zhao D, Wang M, Wang M, Zhao Y, Zheng Z, Li X, et al. Asymptomatic infection by SARS-CoV-2 in healthcare workers: a study in a large teaching hospital in Wuhan, China. International Journal of Infectious Diseases. 2020 Aug 3.

43. Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. Clinical Microbiology and Infection. 2020 Mar 28.

44. Zhou R, Li F, Chen F, Liu H, Zheng J, Lei C, et al. Viral dynamics in asymptomatic patients with COVID-19. Int J Infect Dis. 2020 May 11; 96:288–90. https://doi.org/10.1016/j.ijid.2020.05.030 PMID: 32437933

45. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned?. Internationa. https://doi.org/10.1093/ije/dyaa033 PMID: 32086938

46. Borras-Bermejo B, Martínez-Gómez X, San Miguel MG, Esperalba J, Antón A, Martin E, et al. Asymptomatic SARS-CoV-2 Infection in Nursing Homes, Barcelona, Spain, April 2020. Emerging Infectious Diseases. 2020 Ju.

47. Al-Tawfiq JA, Gautret P. Asymptomatic Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: extent and implications for infection control: a systematic review. Travel medicine and infectious disease. 2019 Jan 1; 27:27–32. https://doi.org/10.1016/j.tmaid.2018.12.003 PMID: 30550839

48. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proceedings of the National Academy of Sciences. 2004 Apr 20; 101(16):6146–51. https://doi.org/10.1073/pnas.0307506101 PMID: 15071187

49. Chan PK, Ip M, Ng KC, Chan RC, Wu A, Lee N, et al. Severe acute respiratory syndrome–associated coronavirus infection. Emerging infectious diseases. 2003 Nov; 9(11):1453. https://doi.org/10.3201/eid0911.030421 PMID: 14718090

50. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related?. Clinical Microbiology and Infection. 2020 Mar 28.