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REVIEW

Case fatality rate of COVID-19: a systematic review and meta-analysis

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Keywords

Case fatality rate • COVID-19 • Meta-analysis • Epidemic • Epidemiology

Summary

Objective. *The ongoing novel coronavirus disease 2019 (COVID-19) is the leading cause of morbidity and mortality due to its contagious nature and absence of vaccine and treatment. Although numerous primary studies reported extremely variable case fatality rate (CFR) of COVID-19, no review study attempted to estimate the CFR of COVID-19. The current systematic review and meta-analysis were aimed to assess the pooled CFR of COVID-19.*
Methods. *Electronic databases: PubMed, Science Direct, Scopus, and Google Scholar were searched to retrieve the eligible primary studies that reported CFR of COVID-19. Keywords: ("COVID-19"OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2"OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR (("Wuhan" AND ("coronavirus" OR "coronavirus")) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("mortality "OR "mortality" OR ("case" AND "fatality" AND "rate") OR "case fatality rate") were used as free text and MeSH term in searching process. A random-effects model was used to estimate the CFR in this study. I^2 statistics, Cochran's Q test, and T^2 were used to assess the functional heterogeneity between included studies.*
Results. *The overall pooled CFR of COVID 19 was 10.0%(95% CI: 8.0-11.0); $P < 0.001$; $I^2 = 99.7$). The pooled CFR of COVID-19 in general population was 1.0% (95% CI: 1.0-3.0); $P < 0.001$; $I^2 = 94.3$), while in hospitalized patients was 13.0% (95% CI: 9.0-17.0); $P < 0.001$, $I^2 = 95.6$). The pooled CFR in patients admitted in intensive care unit (ICU) was 37.0% (95% CI: 24.0-51.0); $P < 0.001$, $I^2 = 97.8$) and in patients older than 50 years was 19.0% (95% CI: 13.0-24.0); $P < 0.001$; $I^2 = 99.8$).*
Conclusion. *The present review results highlighted the need for transparency in testing and reporting policies and denominators used in CFR estimation. It is also necessary to report the case's age, sex, and the comorbidity distribution of all patients, which essential in comparing the CFR among different segments of the population.*

Introduction

The ongoing coronavirus 2019 (COVID-19) was initially reported from Wuhan, China, in December 2019. After few weeks, it has been involved in several countries and became a significant global public health problem [1-3]. World Health Organization (WHO) designated COVID-19 as a pandemic disease on March 11, 2020 (WHO, situational Report-52). The most known symptoms of COVID-19 are fever, cough, shortness of breathing, and occasional watery diarrhea [4]. Even though COVID-19 often causes mild symptoms compared to other respiratory infections, it can cause severe illness in certain groups of people, such as the elderly and people with major underlying health problems (cardiovascular disease and diabetes) [5].
There are two key parameters to understand the epidemiological features of an outbreak or epidemic. These are primary reproduction numbers (R_0) and case-fatality rates (CFR) [6, 7]. The R_0 is an epidemiologic metric that has been used to assess the infectiveness of the agents that cause an outbreak. This index explains the average number of new cases generated from an infected person. The higher amount of R_0 indicates the highest transmissibility of the infection agent. An estimated R_0 of the COVID-19 virus is 3.32, which means one infected case can transmit the virus to 3 to 4 susceptible individuals [8]. CFR is another essential index that helps to understand the epidemiological characteristics of an outbreak. The CFR of COVID-19 is defined as the number of deaths in COVID-19 cases divided by the total number of people infected by COVID-19 [9]. Previously reported CFR of COVID-19 is highly variable. The primary cause of this heterogeneity could be varied as a result of surveillance systems sensitivity. Surveillance system sensitivity low due to more than 80% of cases does not show symptoms of the disease or show mild symptoms. Thus, cases missed by the surveillance system are not considered in the denominator and could lead to overestimation of CFR [10, 11]. Several primary studies have been conducted to estimate the CFR of COVID-19 across the world and reported extremely heterogeneous

magnitude. However, no review study has attempted to estimate pooled CRF of COVID-19 from the available literature to understand better the nature of an outbreak and the virulence of the disease. Thus, the current study was aimed to estimate pooled CFR of COVID-19 from primary studies reported from different countries using systematic review and meta-analysis.

Materials and methods

Search strategy

This systematic review and meta-analysis were performed to estimate pooled CRF of COVID-19 from the primary studies published in international electronic databases. Electronic databases: PubMed, Scopus, Science Direct, and Google Scholar were searched to retrieve eligible studies that were conducted to estimate CFR of COVID-19. Keywords: ("COVID-19"OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2"OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR (("Wuhan" AND ("coronavirus" OR "coronavirus")) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("mortality "OR "mortality" OR ("case" AND "fatality" AND "rate") OR "case fatality rate") were used in free text and MeSH terms.

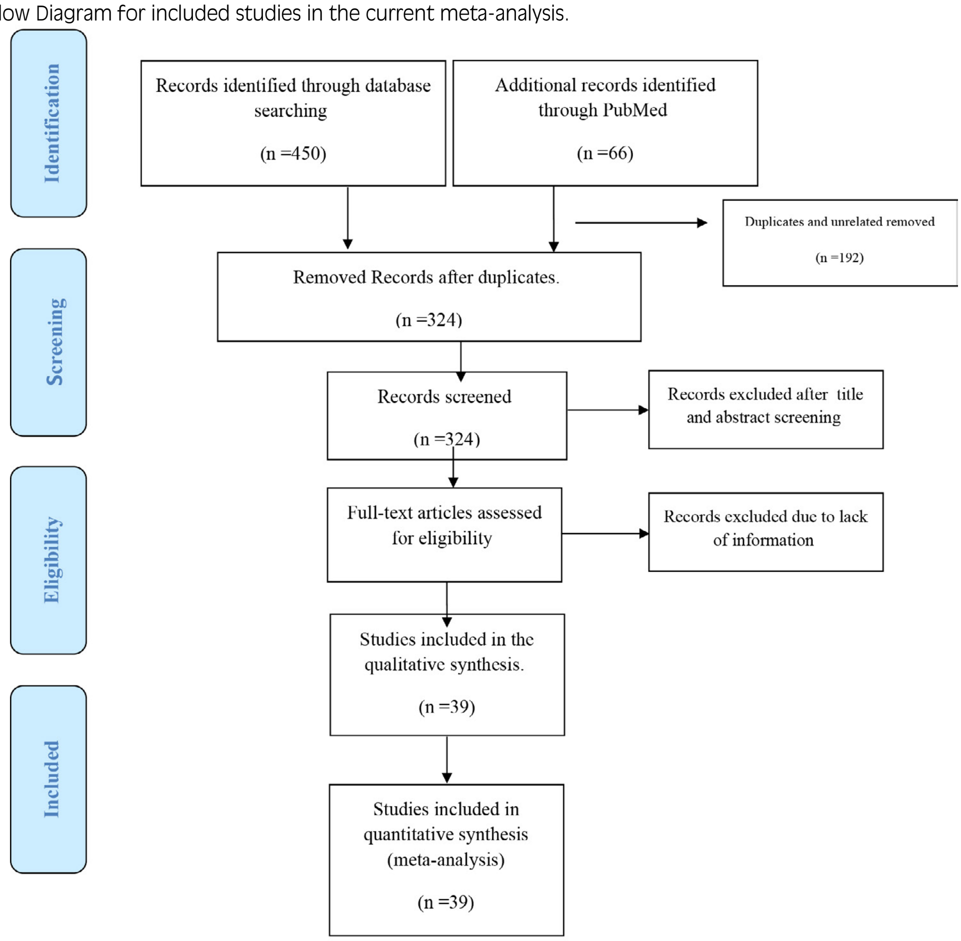
Study selection and data extraction

All studies published in 2020 and reported CFR for COVID-19 were included in this review (Fig. 1). From each included study, extracted information on the first author's name, the country from where the study was reported, year of study, sample size, type of study, age, gender, comorbidity, and CFR with a 95% confidence interval (Tab. I and II).

Statistical analysis

Cochran's Q test's heterogeneity in the CFR of COVID-19 between different studies was assessed with a significance level of $P < 0.1$ and I^2 statistic with values > 75% [12]. A random-effects meta-analysis model was used to estimate pooled CFR because of the presence of high heterogeneity ($I^2 = 99.7\%$ and Cochran's Q ($p < 0.001$). The univariate meta-regression model was used to assess the effect of sample size on the heterogeneity of pooled CFR. Publication bias was evaluated by Beggs and Eggers tests. Also, the risk of bias analysis performed using the Newcastle-Ottawa Scale for observational studies [13]. Data were analyzed by STATA v 11 (StataCorp, College Station, TX, USA).

Fig. 1. PRISMA Flow Diagram for included studies in the current meta-analysis.



Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/med of age	Study design (randomization, blinding)	Study based	CFR estimation
Wang et al. (2020) [13]	China	138	Both	58	Retrospective single-center case series	Hospitalized	0.043
Grasselli et al. (2020) [14]	Italy	1591	Both	63	Retrospective, case series	ICU, Hospitalized, Total	0.26
Grasselli et al. (2020) [14]	Italy	786	Both	64<=	Retrospective, case series	ICU, Hospitalized	0.36
Grasselli et al. (2020) [14]	Italy	795	Both	<=63	Retrospective, case series	ICU, Hospitalized	0.15
Guo et al. (2020) [15]	China	187	Both	58.5	Retrospective, single-center case series	Hospitalized	0.23
Wei et al. (2020) [16]	China	1975	Both		Cross-sectional	Unknown	0.0284
Yin et al. (2020) [17]	China	449	Both	65.1	Retrospective-cohort	Hospitalized	0.298
Chen et al. (2020) [18]	China	99	Both	55.5	Retrospective, single-center study	Hospitalized	0.11
Xiaobo Yang et al. (2020)[19]	China	52	Both	59.7	Retrospective observational	ICU, Hospitalized	0.615
Zhou et al. (2020) [20]	china	191	Both	56	Retrospective cohort	Hospitalized	0.2827
Barrasa et al. (2020) [21]	Spain	48	Both	63	Cross-sectional	ICU, Hospitalized	0.13
Tang et al. (2020) [22]	China	179		67	Retrospective case-control	Hospitalized	0.288
Lei et al (2020) [23]	China	34	Both	55	Retrospective review patient	Hospitalized, Total	0.206
Lei et al (2020) [23]	China	15	Both	55	Retrospective review patient	ICU admitted	0.467
Lei et al (2020) [23]	China	19	Both	47	Retrospective review patient	Hospitalized	0
Shim et al. (2020) [5]	South-Korea	6284	Both	NR	Cross-sectional	General Population, Total	0.007
Shim et al. (2020) [5]	South-Korea	2345	Male	NR	Cross-sectional	General Population	0.011
Shim et al. (2020) [5]	South-Korea	3939	Female	NR	Cross-sectional	General Population	0.004
Li et al (2020) [24]	China	279	Both	56	Ambispective cohort study	Hospitalized	0.011
Li et al (2020) [24]	China	269	Both	65	Ambispective cohort study	ICU admitted	0.325
Tian et al. (2020) [25]	China	262	Both	47.5	Retrospective	Hospitalized	0.009
Tian et al. (2020) [25]	China	46	Both	61.4	Retrospective	Hospitalized	0.065
Tian et al. (2020) [25]	China	216	Both	44.5	Retrospective	General Population	0
Liu et al. (2020) [26]	China	56	Both	NR	Retrospective study	Hospitalized, Total	NR
Liu et al. (2020) [26]	China	18	Both	68	Retrospective study	Hospitalized	0.0556
Liu et al. (2020) [26]	China	38	Both	47	Retrospective study	Hospitalized	0.0526
Liu et al. (2020) [27]	China	245	Both	43.95	Retrospective cohort	Hospitalized	0.1347
Lei et al (2020) [28]	China	20	Both	43.2	Cross-sectional	Hospitalized	0
Sun et al. (2020) [29]	China	288	Both	44	Cross-sectional	Unknown	0.135

▶

Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/med of age	Study design (randomization, blinding)	Study based	CFR estimation
Mei et al (2020) [30]	World	96580	Both		Cross-sectional	Unknown	0.0363
Cao et al. et al. (2020) [31]	China	199	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.161
Cao et al. (2020) [31]	China	99	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.152
Cao et al. (2020) [31]	China	100	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.17
Bhatraju et al. (2020) [32]	USA	24	Both	64	Retrospective case series	Hospitalized	0.5
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	53	Both	64	Cohort	Hospitalized	0.13
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	34	Both	67	Cohort	Hospitalized	0.18
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	19	Both	53	Cohort	Hospitalized	0.05
Liang et al. (2020) [34]	China	1590	Both	48.9	Retrospective cohort	General Population	0.031
Liang et al. (2020) [34]	China	647	Both	55.1	Retrospective cohort	General Population	0.073
Liang et al. (2020) [34]	China	943	Both	44.6	Retrospective cohort	General Population	0.003
Gao et al. (2020) [35]	China	54	Both	60.4	Cohort	Hospitalized	0.333
Du et al. (2020) [36]	China	109	Both	70.7	Multi-center observational	ICU	0.661
Du et al. (2020) [36]	China	51	Both	68.4	Multi-center observational	ICU	0.706
Du et al. (2020) [36]	China	58	Both	72.7	Multi-center observational	Hospitalized	0.620
Xiao-Wei Xu et al. (2020) [37]	China	62	Both	41	Retrospective study	Hospitalized	0
Cai et al (2020) [38]	Hong-Kong	298	Both	47.5	Retrospective study	General Population, Total	0.01
Cai et al (2020) [38]	Hong-Kong	240	Both	41	Retrospective study	General Population	0
Cai et al (2020) [38]	Hong-Kong	58	Both	62.5	Retrospective study	General Population	0.052
Cao et al. (2020) [39]	China	102	Both	54	Cohort	Hospitalized	0.167
Liu et al. (2020) [40]	China	137	Both	57	Retrospective	Hospitalized	0.118
Young et al. (2020) [41]	Singapore	18	Both	47	Case-series	Hospitalized, Total	0
Young et al. (2020) [41]	Singapore	12	Both	37	Case-series	Hospitalized	0
Young et al. (2020) [41]	Singapore	6	Both	56	Case-series	Hospitalized	0
Wang et al. (2020) [42]	China	69	Both	42	Retrospective review patient	Hospitalized	0.075
Jian Wu et al. (2020) [2]	China	80	Both	46.1	Retrospective	Hospitalized	0

▶

Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/ med of age	Study design (randomization, blinding)	Study based	CFR estimation
McMichael et al. (2020) [43]	USA	167	Both	72	Cross-sectional	General Population	0.21
Yanli Liu et al. (2020) [44]	China	383	Both	46	Retrospective cohort	Hospitalized	0.128
Yanli Liu et al. (2020) [44]	China	68	Both	52	Retrospective cohort	Hospitalized	0.309
Yanli Liu et al. (2020) [44]	China	315	Both	43	Retrospective cohort	Hospitalized	0.089
Chen et al. (2020) [45]	China	203	Both	54	Retrospective case series	Hospitalized	0.128
Ning Tang et al. (2020) [46]	China	183	Both	54.1	Cross-sectional	Hospitalized	0.115
Morteza Abdullatif Khafaie et al. 2020 [47]	World	337570	Both		Retrospective-cohort	Unknown	0.0434
Huang et al. (2020) [48]	China	41	Both	49	Prospective	Total	0.15
Huang et al. (2020) [48]	China	13	Both	49	Prospective	ICU	0.38
Huang et al. (2020) [48]	China	28	Both	49	Prospective cohort	Hospitalized	0.04
Wei-Jie Guan et al. (2020) [49]	China	926	Both	45	Retrospective	General Population	0.001
Wei-Jie Guan et al. (2020) [49]	China	173	Both	52	Retrospective	General Population	0.081
Nikpouraghdam et al. (2020) [1]	Iran	2964	Both	55.5	Retrospective	Hospitalized	0.086
Nikpouraghdam et al. (2020) [1]	Iran	2964	Both	55.5	Retrospective	General Population	0.018

Tab. II. The estimated case fatality rate of COVID-19 in different subgroups.

Group	Pooled estimation (%)	95% CI	Q	I^2 (%)
General population	1.00	1.0-3.0	P < 0.001	94.3
Hospitalized patients	13.0	9.0-17.0	P < 0.001	95.6
ICU admitted	37.0	24.0-51.0	P < 0.001	97.8
Unknown	4.0	3.0-5.0	P < 0.001	97.8
≤ 50	3.0	0.0-6.0	P < 0.001	93.7
> 50	19.0	13.0-24.0	P < 0.001	98.1
Unknown	2.0	1.0-3.0	P < 0.001	99.8
Overall	10.0	8.0-11.0	P < 0.001	99.7

Results

Figure 1 depicts the study selection procedure. A total of 516 records were retrieved through electronic databases search, and 324 identified articles after removing 192 pieces due to duplication and irrelevance for the review purpose. The second stape 236 articles were excluded after the title and abstract screeded for the inclusion and exclusion criteria. Of the remaining 88 articles, 49 articles were excluded due to a lack of relevant information or not original articles. Finally, 39 articles reported CFR of COVID-19 were included in the final analysis (Fig. 1 and Table 1).

The Median and IQR(Interquartile range) of reported CFR rate were 8.7%(23.0-1.0). The Minimum and Maximum reported CFR were 0 and 70.6% respectivly (Fig. 2). The overall pooled estimated CFR of COVID-19 was 10.0% (95% CI: 8.0-11.0; $P < 0.001$, $I^2 = 99.7$) (Fig. 2). The pooled estimated CFR of COVID-19 among general population was 1.0% (95% CI: 1.0-3.0; $P < 0.001$, $I^2 = 94.3$), while in hospitalised patients 13.0% (95% CI: 9.0-17.0; $P < 0.001$, $I^2 = 95.6$) (Fig. 2). The pooled estimated CFR of COVID-19 in the patients admited to ICU was 37.0% (95% CI: 24.0-51.0; $P < 0.001$, $I^2 = 97.8$), and in patients younger than 50 years 3.0% (95% CI: 0.0-6.0; $P < 0.001$, $I^2 = 99.2$), while the CFR was 19.0% (95% CI: 13.0-24.0; $P < 0.001$, $I^2 = 99.8$) in patients older than 50 years (Fig. 2 and Table 2). Based

Fig. 2. The forest plot of estimated case fatality rate of COVID-19 in different subgroups.

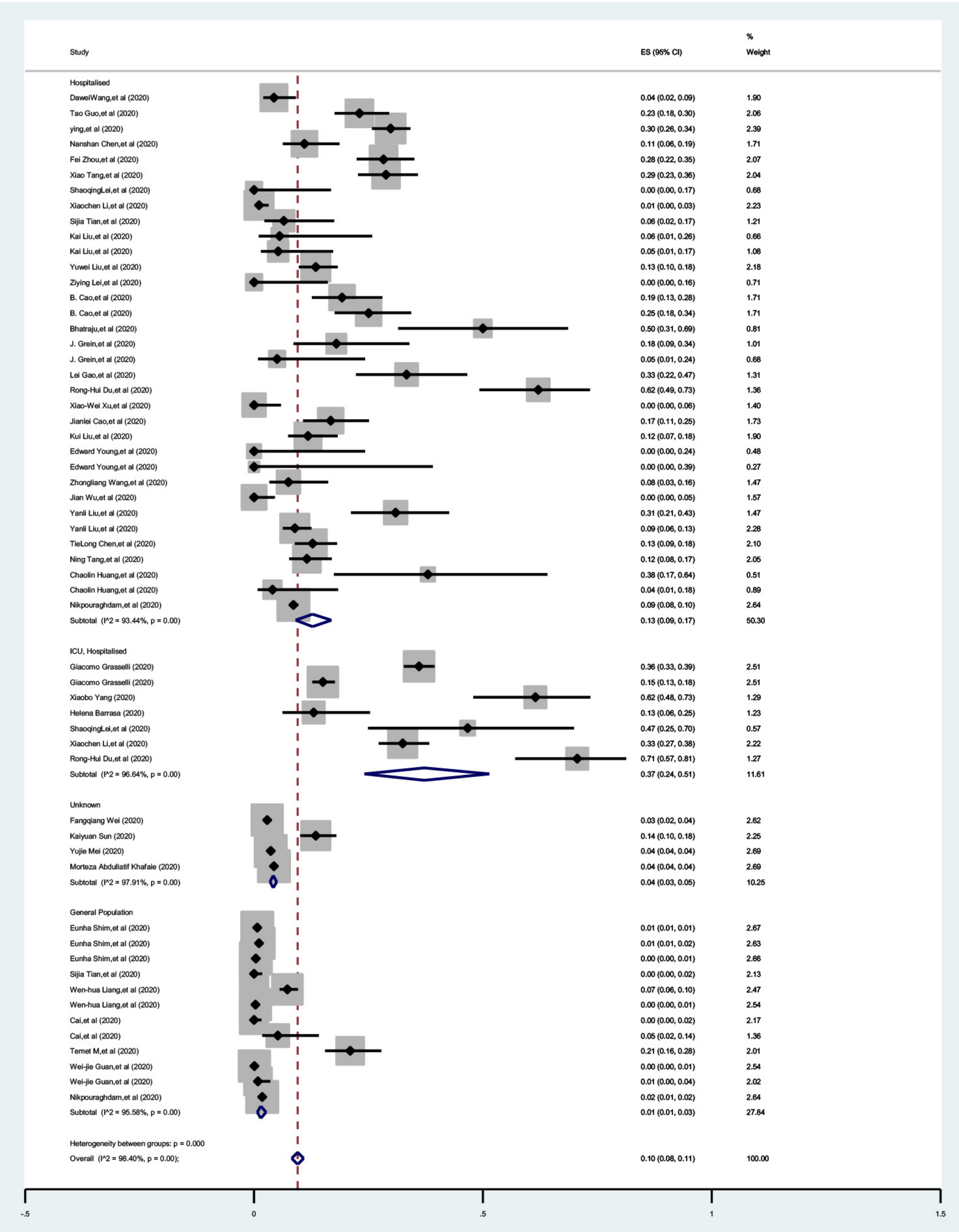
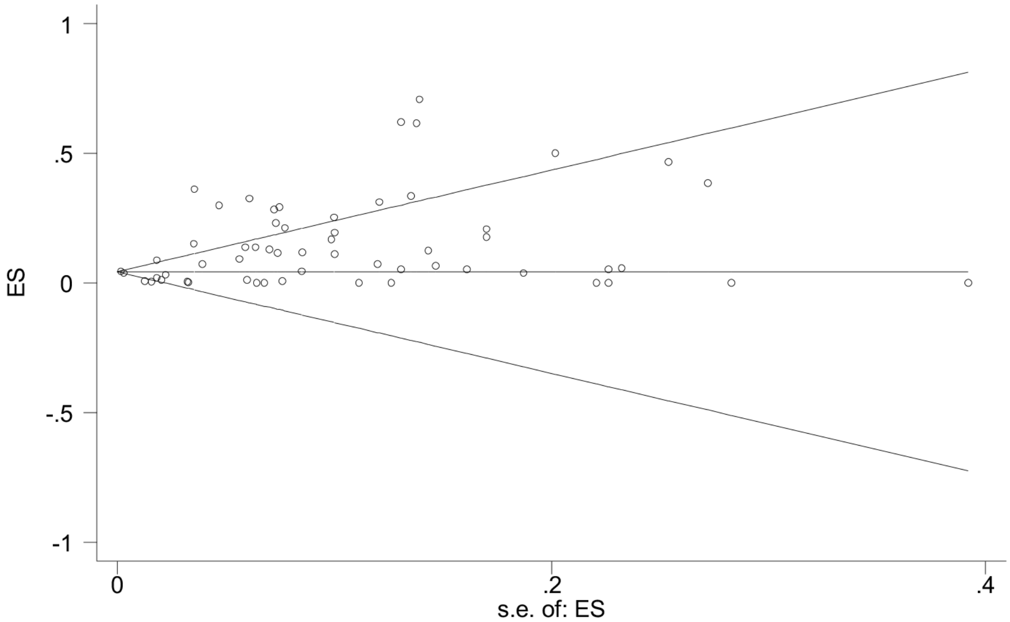


Fig. 3. The beggs funnel plot to assess publication bias.



on Beggs test there was no publication bias(P = 0.2), but the Eggers tests was shown the presence of publication bias (P < 0.001). Moreover, based on metaregresion regression analysis, ample size was not significantly associated with heatrogeneity of pooled estimated CFR (P = 0.31) (Fig. 3).

Discussion

The present study systematically reviewed the available literature to estimate the overall pooled CFR COVID-19 and specific subpopulations in patients admitted in hospital, ICU, and old. Based on 39 studies that fulfilled this study, the overall estimated pooled CFR of COVID-19 was 10.0%. The pooled CRF was only 1.0% in the general population, while 29% in patients admitted in ICU and 15% in hospitalized patients.

Although there is limited information on COVID-19 CFR, some primary studies have been reported CFR in different countries with various target populations. For example, the studies reported from Italy have indicated a 9.26% CFR of COVID-19 [47, 50]. Moreover, studies reported from Spain and France have reported 6.16 and 4.21% CFR, respectively [47, 50]. Furthermore, a study reported from Iran shown that 7.9% of CFR, while the study reported from Turkey indicated 2.0% CFR of COVD-19 [47, 50]. Compared to the previous studies cited above, our meta-analysis finding, based on primary studies reported from different countries, indicated CFR with a wide range. This difference between our CFR with its broad range and the previous study could be due to the target population difference.

Moreover, it might be due to case/death finding and reporting capacity between the countries where the primary studies were reported. Furthermore, case and death reporting in some countries might be influenced by political decisions. Thus, these probable reasons could affect the overall estimation of CFR, which could impact the actual epidemiological feature of the disease. CFR of COVID-19 ranges between 4 and 11% among hospitalized adult patients in different countries based on previous studies [51]. The present study showed that high (13%) CFR in hospital admitted patients. The present study was also revealed that CFR in patients admitted to ICU was 37%. In contrast to our findings, a case series study reported from Seattle indicated high CFR (50%) among critically ill patients [32]. Moreover, a study reported from Washington state the highest CFR (67%) in patients admitted to ICU. Thus the health background of patients admitted to ICU could be an essential factor related to death [52]. For example, among patients admitted to ICU in Washington, 86% have comorbidities such as chronic kidney disease and congestive heart failure [52]. High CFR among patients admitted to ICU is mainly attributable to comorbidities and old age, which exacerbate the morbidity that leads to poor outcomes in patients admitted to ICU. Patients with comorbidities and old age demand great attention to recover from COVID-19, and more evidence requires better understanding to inform health care [32].

The present meta-analysis revealed a significant difference in CFR in the age group younger than 50 years and older (3.0 *vs* 19%). In Italy, CFR was 52.3 in patients more aged than 80 years and 35.6 in 70-79 years old [9]. Similarly, in Chinese, CFR was high among the most aging patients [53]. Besides CFR differences in age groups, the overall CFR reported from Italy (7.2%) is substantially higher than in China (2.3%) [9, 53]. The difference in CFR is not only related to age, rather other factors such as. Occupation, gender, and clinical

comorbid could be contributed to high CFR in the old age group. A better method to preventing possible misconceptions about age effect on CFR in COVID-19 patients direct age adjustment could be a solution.
Several factors could affect on mortality of COVID-19 in different settings due to health system capacity, age variation, the burden of chronic diseases, perception regarding COVID-19, and other unknown factors. For instance, the majority of COVID-19 confirmed cases in Italy are in old proportion. Moreover, most deaths due to COVID-19 in Italy are among geriatric, male patients with comorbidity [9]. In addition, the number of symptoms the cases shown is probably affected by death due to COVID-19. For example, some patients have only one or three main symptoms of COVID-19, but some patients reveal more than three symptoms which most probably affects the death due to COVID-19. Thus, advanced, in-depth analyses are required to explore the effect of the number of signs on fatalities associated with COVID-19.
Prior findings suggested that CFR of COVID-19 seems to be less deadly compared to Bird flu, Ebola, SARS, and MERS , However, it becomes a global economic and public health concern [47, 54]. In most patients, COVID-19 shows mild symptoms, which hid the burden of the disease and facilitate transmission in the community rapidly [47]. Thus, media should play a significant role in enhancing health literacy because the unique characteristics of COVID-19 make the general community at risk. Some undetected or delayed cases could probably lead to underestimation of CFR of COVID-19. Underestimation could be linked to the level of the general public and politicians' preparedness and mitigation.

Conclusions

The pooled estimate CFR of COVID-19 in this review is considerably high and differs between different patient groups. The CFR was higher in patients admitted in ICU and older than 50 years. Moreover, the present review results highlighted the need for transparency in testing and reporting policies and denominators used in CFR estimation. It is also necessary to report the case's age, sex, and comorbidity distribution of all patients, which is essential in comparing the CFR among different population segments.

Ethics statement

Ethics clearance was not sought because this review was based on published articles.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

YA and MS: conception of the idea, data analysis, Manuscript writing, HHT, AAGH and MJ: searching, data extraction, manuscript writing. All authors read and approved the final manuscript.

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