Frequency of underlying diseases, symptoms and mortality rate of COVID-19: a systematic review and meta-analysis

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Coronavirus disease 2019 (COVID-19) is known to be affected by underlying diseases of the respiratory system. In this meta-analysis, the keywords of COVID-19, underlying diseases, symptoms, and mortality were searched in national and international databases to obtain the related studies. The inclusion criteria were as follows: interventional, clinical, descriptive and cross-sectional, and studies focusing on COVID-19. This study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Eighteen studies were selected to be finally analyzed. The mean percentage of mortality was 14% ($I^2 = 98.9$, $P < 0.001$). The most common symptoms were fever (91%, $I^2 = 88.5$, $P < 0.001$) and cough (71%, $I^2 = 84.5$, $P < 0.001$), and the most frequent underlying diseases were hypertension (41%, $I^2 = 98.9$, $P < 0.001$), diabetes mellitus (18%, $I^2 = 88.7$, $P < 0.001$) and cardiovascular disease (11%, $I^2 = 87.7$, $P < 0.001$). Findings of present study suggest that individuals with underlying diseases have a higher rate of mortality following COVID-19 infection.

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019. At first, it was named SARS-CoV-2. Because of the rapid spread at the end of 2019, this virus was named COVID-19. On 30 January 2020, WHO has announced emergency condition [1,2]. Many reports suggested this virus is being spread in 26 countries. Consequently, the statistical and clinical data of affected persons are of high importance for WHO [3].

Based on COVID-19 studies, researchers have found COVID-19 patients were recognized with two clinical presentations: systemic and respiratory symptoms. Systemic symptoms included fever, dry cough, tiredness, sputum production, and headache. On the other hand, the respiratory symptoms comprised of rhinorrhea, sneezing, sore throat, pneumonia, and serious acute respiratory syndrome [4–6].

Based on present reports, this disease is easily spreading from one person to the others and its primary reservoir is not identified definitely. Scientists attempted to discover its genesis and concluded it was originally occurred in animals [6]. Spread from one person to other is mainly through direct contact or droplets, which spread by coughing or sneezing of patients infected with COVID-19 [6].

Consequently, prevention is the best solution. Therefore, people must utilize health and immunity considerations, including avoiding the face touching, putting on the face

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mask, keeping a safe distance with high-risk persons, and less going into crowded and closed-in places not having adequate ventilation. By employing these considerations, we will not be afflicted and the rate of spread is reduced considerably [6,7].

COVID-19 is routinely diagnosed by means of clinical symptoms obtained from computed tomography scan and chest X-ray examinations of suspected patients [4,5]. In regard to the rate of mortality, we could refer to respective studies, which reporting to be 10–35% [8,9]. Two months after its outbreak, 82 000 COVID-19 cases were diagnosed and the number of deceased patients was reported to be more than 2800 persons, mostly in China [1]. Results of another study showed that out of 99 afflicted patients 57 (58%) were hospitalized, 31 (31%) released, and solely 11 (11%) deceased [5].

High-risk persons have been those with compromised immune system as well as those with underlying illness and comorbidities such as renal, heart, and respiratory diseases and senescence [4,5].

The highest rate of this disease was reported in China, subsequently in Iran and then Italy. Iran has close relationships with China and the disease spread by this route. Shortly after its outbreak, a great number of people were being affected, unfortunately, some were deceased, and some others were recuperated and released.

Although there are a number of extensive studies performed by systematic review and meta-analysis methodology, given the complexity and many unknown aspects of the disease, the demand for such studies may be continued. One advantage of these studies is the validity of their results and, therefore, their results could be generalized [10,11]. With regard to various studies and the validity of the obtained data, it seems necessary to conduct a meta-analysis in order to provide a valid and precise scale for researchers and scholars. The present study was conducted by meta-analysis and systematic review methodology to evaluate the frequency of underlying diseases and symptoms in relation to the mortality rate of COVID-19.

Methods

The present systematic review and meta-analysis were conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol during 2019–2020 [12]. This study was performed in five steps in the following order: primary designing, searching data resources, collecting and considering articles in regard to inclusion criteria, assessment of articles, and finally, data statistical analysis. To inhibit publication bias, the searching process was performed by two investigators independently, and the acquired results were combined by this party.

Searching strategy

In order to obtain studies related to the research question, two investigators were independently performed a comprehensive searching in national and international academic sources (Scopus, PubMed, Cochrane, and Web of Science) and Google Scholar search engine. With reference to the research question, the following keywords were utilized to search the relevant articles: coronavirus, COVID-19, mortality, and comorbidity symptoms. At first, these keywords were considered separately. Subsequently, a combination of these keywords was used for searching. Finally, in order to find related articles, all references of obtained articles were also reviewed. Of these references, the pertinent and not-repetitiveness articles were selected and their full text was being prepared and provided by the investigators.

Inclusion criteria

For the meta-analysis, the inclusion criteria were the interventional articles and clinical, descriptive, and cross-sectional trials considering COVID-19.

Exclusion criteria

Articles with irrelevant information regarding the underlying conditions, symptoms, and mortality rate of COVID-19 were excluded from the study.

Assessment tools

Finally, full and comprehensive studies about COVID-19 were assessed.

Data extraction

Considered variables in every article were including corresponding anther, data and location of research, sample volume, COVID-19 mortality, COVID-19 symptoms, COVID-19 clinical symptoms, and recovery from COVID-19. These data were selected from final articles and thereupon introduced into a researcher-made checklist.

Statistical analysis

Considering combined data, publication bias and funnel plot were not implemented (as the number of final studies was less than 10). To calculate heterogeneity, the I^2 index was used. In various studies, this index was calculated for every variable of COVID-19, separately. With respect to lack of essential quality, lack of cohesion to the subject matter, incomplete reporting review paper, case reports, correspondence (letter to editor), and abstracts presented in seminars contained incomplete data.

Selection and assessment of articles quality

To assess the quality of articles, strengthening the reporting of observational studies in epidemiology statement (checklist) was applied [12,13]. Two authors dedicated 0–2 scores to every part, separately. Based on the obtained scores, in regard to quality, articles were divided into three categories: weak, moderate, and strong, with 1–15, 16–30, and 31–44 scores, respectively. Articles with the least 16 score were included in the meta-analysis.

Meaning fullness of heterogeneity of raider ($P < 001.0$), was used in the meta-analysis model with random effects in order to combine results of different studies. Data were analyzed using (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study characteristics

First, a list of all the titles and abstracts of the articles retrieved from the databases was prepared by the researchers. After hiding the details of the articles including journals' and authors' names, the full texts of the articles were provided to the researchers. The initial search resulted in 100 related articles of which 30 duplicates were excluded. In addition, 40 articles were excluded because of limited and incomplete results. By reviewing the full texts of the articles, 12 related articles were omitted due to the lack of necessary criteria. Finally, 18 articles enrolled for evaluation process (Fig. 1). According to the results of this study, the mean age of patients was 45.44 years. The overall sample size was 2720 rendering an average of 151 subjects per study.

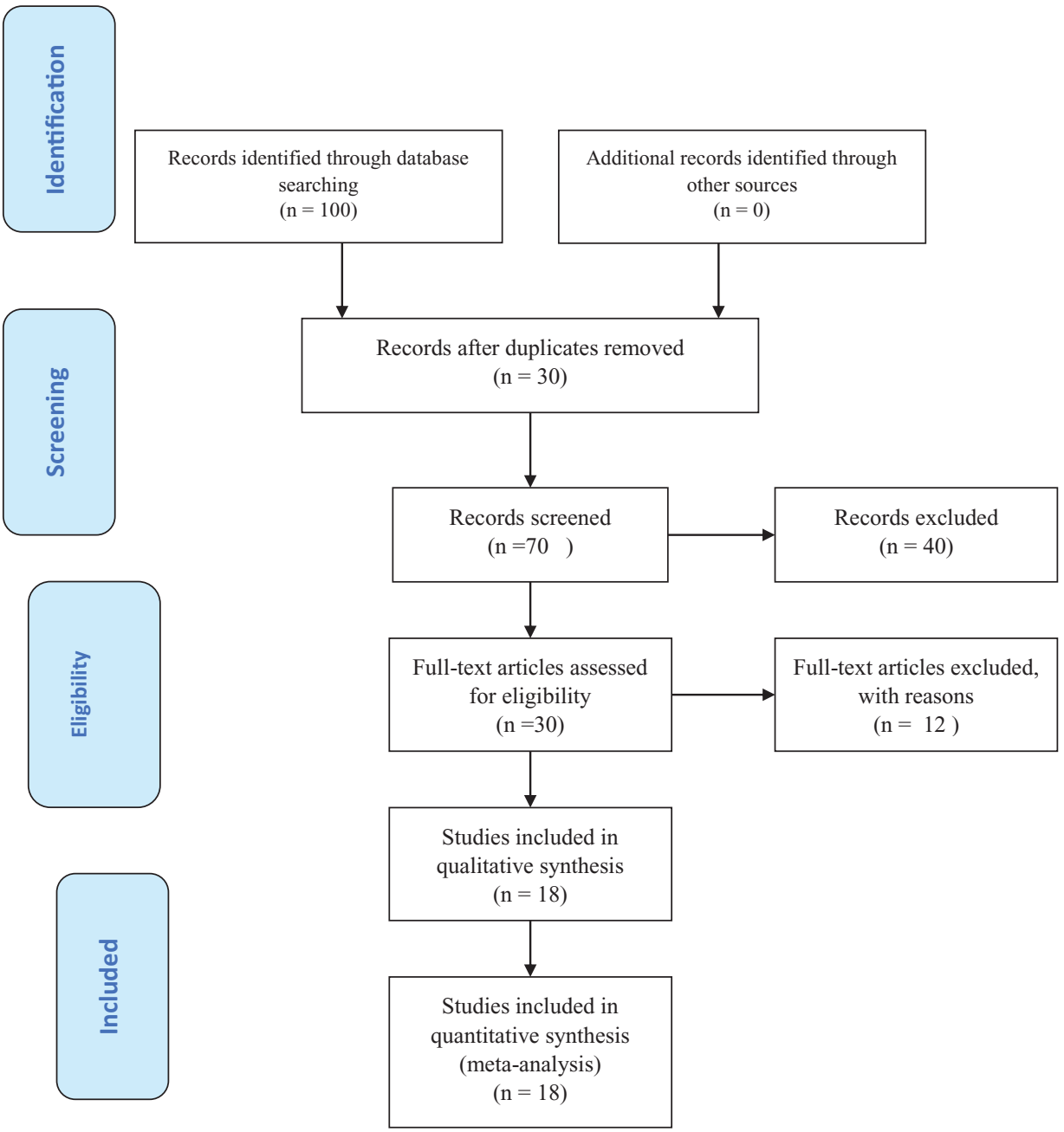

Fig. 1. The flowchart for the inclusion of studies in meta-analysis.

Table 1. The main characteristics of the included studies.

Variables	Subgroup	Articles (*N*)	%	95% CI	I^2	*P* value
Mortality	–	4	14	12–16	98.9	<0.001
comorbidities (%)	Hypertension	9	41	19–64	98.9	<0.001
	Diabetic	12	18	12–24	88.7	<0.001
	chronic pulmonary obstructive disease	9	6	3–9	91.3	<0.001
	Cardiovascular	9	11	6–16	87.7	<0.001
	Brain disease	4	17	9–25	66.1	0.031
	Other[a]	6	15	7–22	84	<0.001
Symptoms of the disease	Fever	16	91	87–95	88.5	<0.001
	Cough	16	71	65–77	84.5	<0.001
	Fatigue	10	46	32–60	97.1	<0.001
	Dyspnea	10	44	28–60	97.2	<0.001
	Sputum	8	29	18–39	90.6	<0.001

CI, confidence interval.
[a]Liver disease, digestive disease, kidney disease.

The characteristics of the reviewed articles have been presented in Table 1. The frequencies of underlying diseases, symptoms, and mortality rate of COVID-19 along with the significance levels and I^2 indices have been shown in Table 2.

Figures 2 and 3 show the forest plots of most common underlying diseases (i.e. hypertension and diabetes mellitus), and Figs. 4 and 5 demonstrate the forest plots related to the most frequent symptoms (i.e. fever and cough).

The publication bias in the data obtained here has been depicted in Fig. 6. The circle sizes exhibit the studies weights (larger circles reflect higher sample sizes and smaller ones represent lower sample sizes).

Meta-regression was performed to compare the COVID-19 based on different genders, sample sizes, and years of the studies. Meta-regression was also used to seek the heterogeneity reasons among the studies (Figs. 7 and 8).

Discussion

The aim of the present study was to evaluate the prevalence of underlying diseases, symptoms, and mortality rate of COVID-19 by a systematic review and meta-analysis. The I^2 heterogeneity index represents a numerical value, which is utilized as a substitute for the odd ratio to estimate the variance of statistically heterogeneous studies. In this regard, $I^2 \leq 25$ shows low heterogeneity, whereas I^2 values of 26–50%, 51–75%, and 76–100% indicate moderate, statistically significant, and high heterogeneities, respectively. In this study, the I^2 index was 96.5%, which shows a high heterogeneity [10,11].

The results of the present study revealed a mortality rate of 14%. Similar studies across the world have reported mortality rates ranging from 10 to 35% [8,9]. In one study on 99 patients with COVID-19 infection, 57 (58%) were hospitalized, 31 (31%) were discharged, and only 11 (11%) died of the infection [5]. These were consistent

Table 2. The prevalence of underlying diseases, symptoms, and mortality rate of COVID-19.

References	Author	Place	Year	Total (*N*)	Female (*N*)	Male (*N*)	Age
[13]	Liu	China	2020	73	32	41	41.6
[14]	Chen	China	2020	9	–	–	32.7
[15]	Zhou	China	2020	191	72	119	–
[16]	Yang	China	2020	149	68	81	–
[17]	Liu	China	2020	10	6	4	42.0
[2]	Shi	China	2020	81	39	42	–
[18]	Hish	Taiwan	2020	2	1	1	–
[19]	Chen	China	2020	17	–	–	62.8
[20]	Yang	China	2020	52	17	35	59.7
[21]	Sun	China	2020	482	201	281	46.0
[22]	Liu	China	2020	78	39	39	–
[23]	Huang	China	2020	41	11	30	49.0
[24]	Kui	China	2020	137	76	61	57.0
[25]	Liu	China	2020	12	4	8	53.0
[26]	Wang	China	2020	138	75	63	56.0
[27]	Zhang	China	2020	9	4	5	35.2
[28]	Guan	China	2020	1099	459	640	47.0
[29]	Zhang	China	2020	140	69	71	57.0

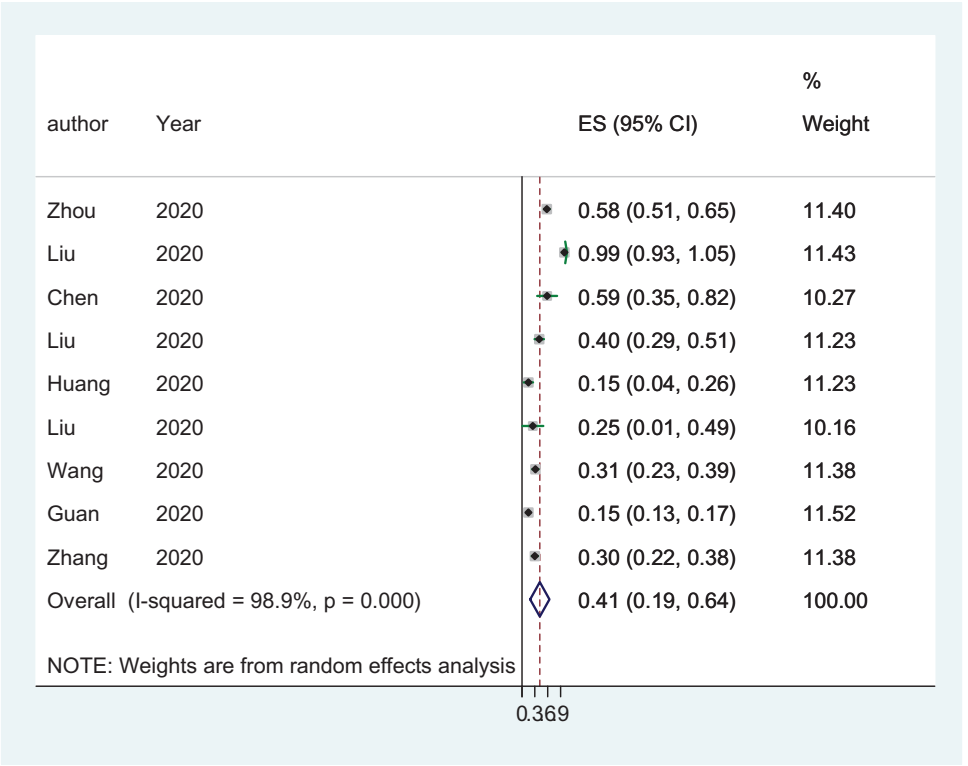

Fig. 2. Forest plot of Hypertension percentage with 95% confidence interval. The middle point of each line estimated the percentage of hypertension in individual studies. The diamond shows the total confidence interval of fear of fall in all the studies.

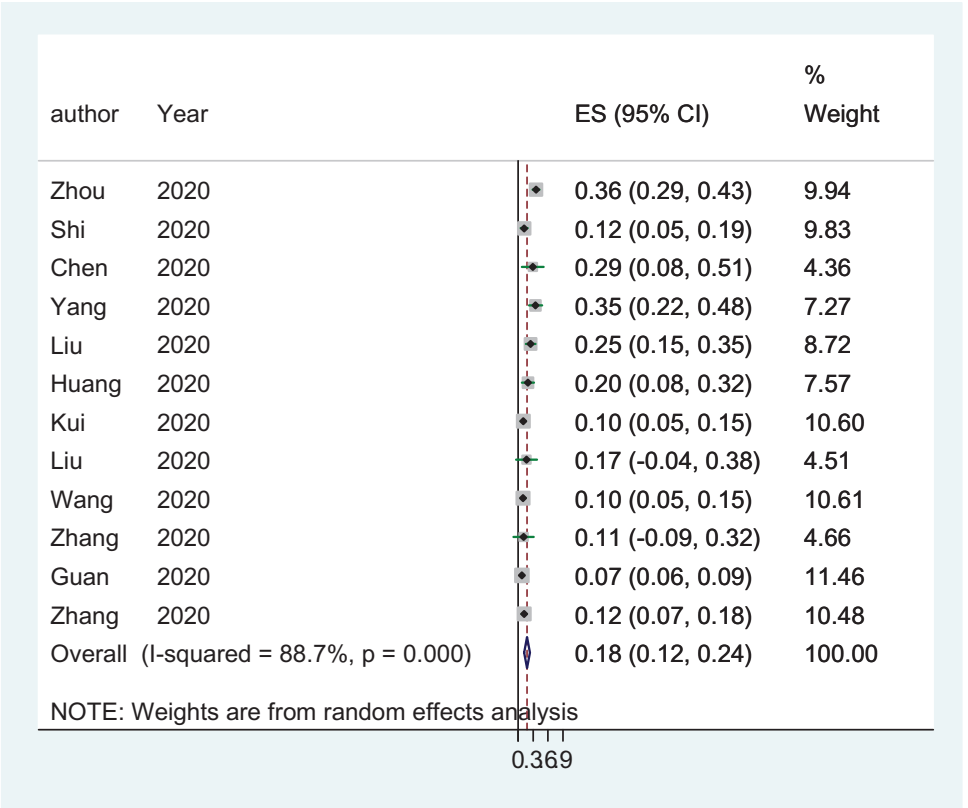

Fig. 3. Forest plot of diabetic percentage with 95% confidence interval. The middle point of each line estimated the percentage of diabetic in individual studies. The diamond shows the total confidence interval of fear of fall in all the studies.

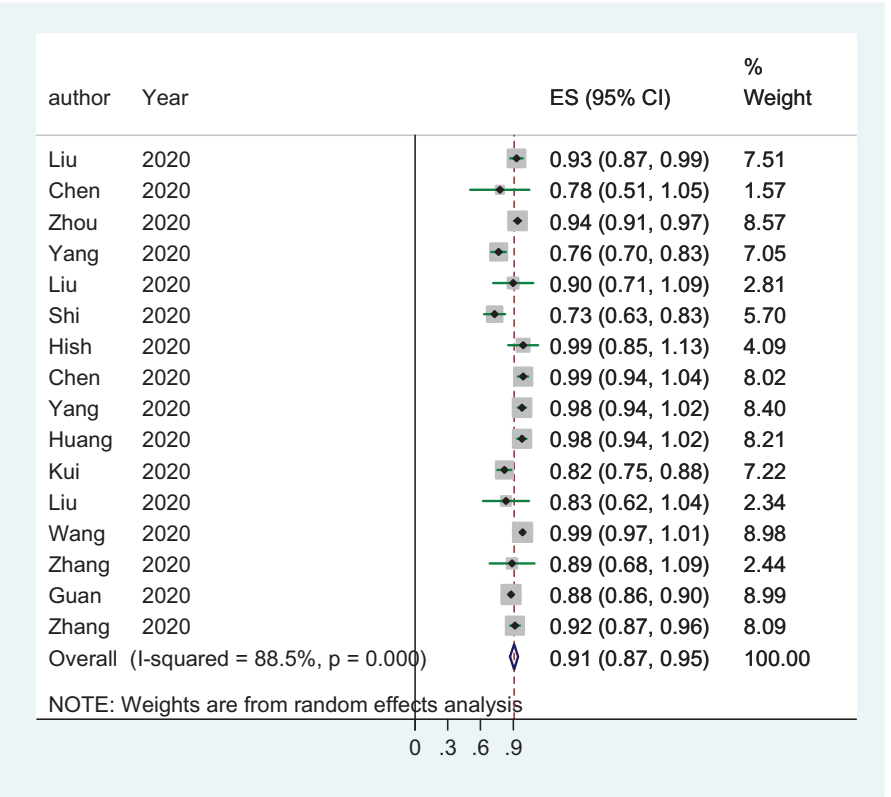

Fig. 4. Forest plot of fever percentage with 95% confidence interval. The middle point of each line estimated the percentage of fever in individual studies. The diamond shows the total confidence interval of fear of fall in all the studies.

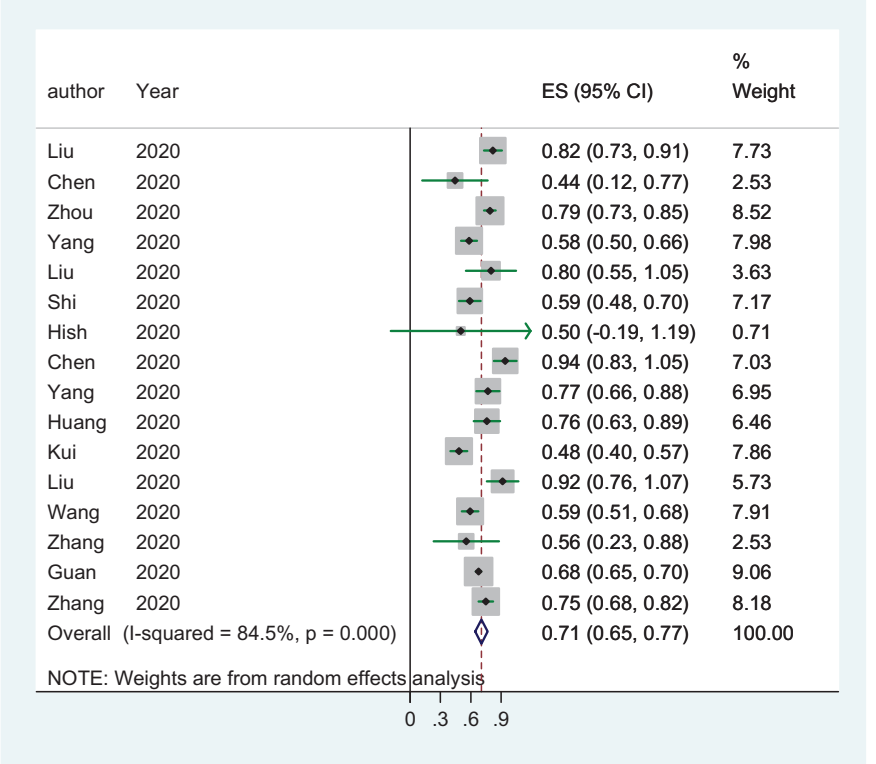

Fig. 5. Forest plot of cough percentage with 95% confidence interval. The middle point of each line estimated the percentage of cough in individual studies. The diamond shows the total confidence interval of fear of fall in all the studies.

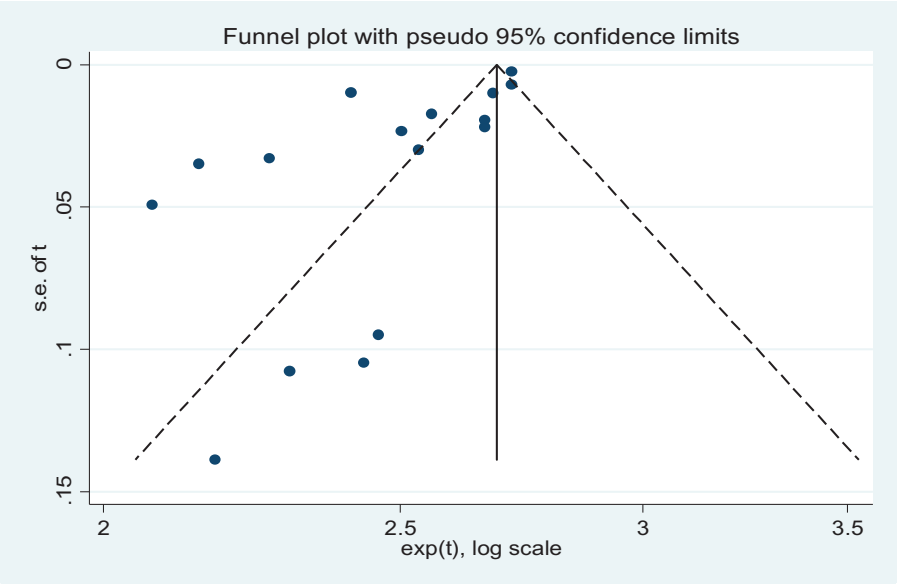

Fig. 6. Publication bias regarding COVID-19.

with the findings of the present study. It has also been highlighted in these studies that the disease is rapidly spreading and easily transmitted between individuals. Therefore, compliance with safety and health principles is of great importance.

Our results showed that hypertension, heart disease, diabetes mellitus, as well as respiratory and cerebral diseases were the most common comorbidities observed in COVID-19 affected patients. Various studies have shown that deceased patients had underlying diseases, such as hypertension, history of angiography, and diabetes mellitus. The presence of these underlying conditions including cardiac and cerebral diseases along with weakened immune system predisposes to the spread of the virus throughout the body and a higher probability of death [5,30–33]. In conclusion, the role of underlying diseases is important in this condition by increasing the mortality rate of COVID-19.

The results of the present study showed that fever, cough, fatigue, dyspnea, and sputum were the most prevalent symptoms. In similar studies on patients hospitalized with the definitive diagnosis of COVID-19, fever, cough, and dyspnea were more common than other signs and symptoms, which is in line with our results [4,5]. Accordingly, the above-mentioned symptoms can be considered as the main symptoms of COVID-19, and any

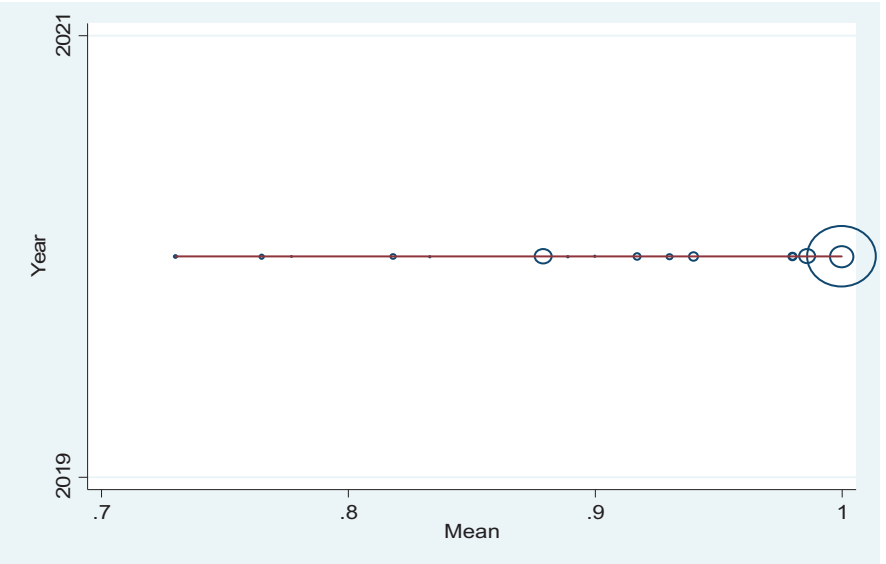

Fig. 7. The meta-regression of COVID-19 on studies years.

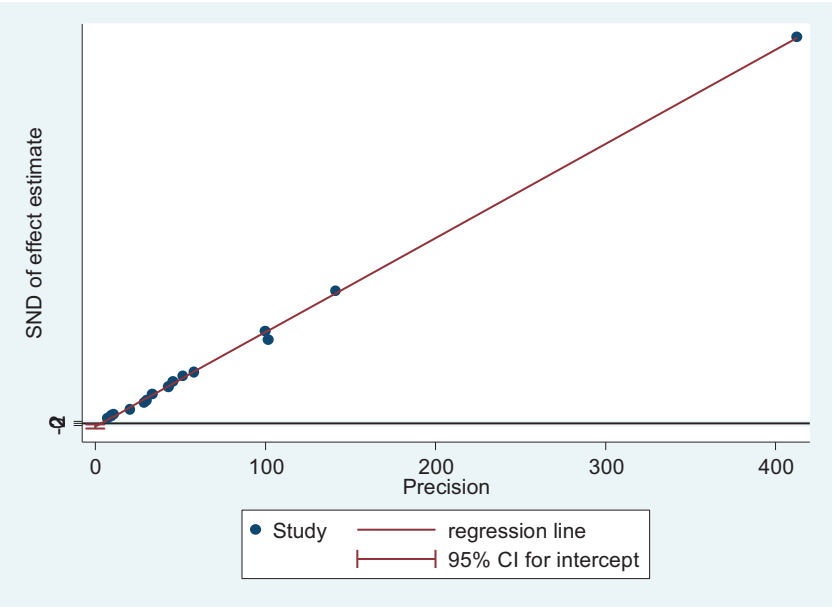

Fig. 8. The meta-regression of COVID-19 on studies sample size.

person with these symptoms should refer to the hospital and health center.

Early results regarding the clinical features of the COVID-19 in Iran also reveal similarities with the results of this meta-analysis. Although the underlying diseases, including cardiovascular diseases, hypertension, diabetes mellitus, malignancy, kidney injury, and chronic lung diseases were the most common risk factor of deceased among Iranian patients with COVID-19 [34,35]. As such, symptoms including dyspnea and cough, fatigue, as well as abnormal chest X-ray were the most reported symptoms in Iranian patients with COVID-19 [34,35].

Limitations

The variables studied in the studies were limited, and we could not properly analyze them. There were no comparisons between men and women, and only general data had been presented in some studies.

Conclusion and recommendations

The results of the present meta-analysis reveal that underlying diseases (hypertension, diabetes mellitus, and cardiovascular disease) are the major risk factors of mortality among the COVID-19 patients, hence, it could be used as a prognostic factor in infected patients. Therefore, such preventive measures, including social distancing, quarantine, and the use of the personal protection equipment (PPE) as well as early detection and treatment should be greater consideration in patients with underlying diseases.

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Conflicts of interest

There are no conflicts of interest.

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