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REVIEW PAPER

Evaluation of predictors of mortality in patients with COVID-19: a systematic review and meta-analysis

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Evaluation of predictors of mortality in patients with COVID-19. In the present study, articles published from January 2019 to December 1, 2021, were reviewed in PubMed, Scopus, Web of Science, and EBSCO databases. A software program (Endnote X8) was utilized to manage electronic titles. The 95% confidence interval for Odds ratio and mean differences, fixed effect method, and Mantel–Haenszel or Inverse-variance formula were calculated. Meta-analysis in the present study was performed using Stata 16 software. A total of 281 articles were found within the beginning search. The full text of 42 articles was reviewed, and 32 articles were excluded due to lack of access to the complete content of the article and lack of relevance to the title and purpose of the article. Finally, ten studies were selected. The odds ratio of hypertension between Surviving and Deceased cases was 0.99 (OR, 0.99 95 % CI 0.82, 1.15; p=0.00). Odds ratio of other comorbidities such as cardiovascular, diabetes and respiratory comorbidities between Surviving cases and Deceased cases was (OR, 1.0 95 % CI 0.92, 1.84; p=0.00), (OR, 0.81 95 % CI 0.72, 1.27; p=0.00), (OR, 0.78 95 % CI 0.64, 1.05; p=0.00), respectively. Meta-analysis showed that comorbidities and fatigue increased mortality rate in COVID-19 patients, and the association of onset of symptoms to admission time with COVID-19 mortality was statistically significant.

KEYWORDS

COVID-19; mortality; predictors; comorbidities; clinical manifestations.

Introduction

In the current century, the outbreak of novel coronavirus infectious disease (COVID-19) has postured significant wellbeing dangers to the world's open health [1]. COVID-19 is now prevalent in most countries of the world. Most countries have high mortality in this disease [2,3]. Coronaviruses were found within the 1960s and proceeded to be examined until the mid-1980s [4]. The disease has symptoms such as fever, cough, headache, and shortness of breath, and its transmission humans and humans is very common [5]. The virus's incubation period is so long, takes between 2 and 14 days for the symptoms to appear. This feature increases the outbreak rate and makes it more challenging to prevent and control [6]. COVID-19 is susceptible to transmission from person to person and can be transmitted through respiratory droplets, direct contact with secretions containing the virus, and through the mouth, nose, and eyes [7]. Despite significant advances in disease control, infectious diseases are still of particular importance in epidemiology and health [8]. Therefore, identifying the different

dimensions of this disease in the form of at-risk groups according to the occurrence or non-occurrence of the disease can help prevent the disease and even accelerate the recovery of patients. The studies in this regard also indicated the importance of comparing the factors associated with individuals with COVID-19 disease. However, researchers' information on the various dimensions of the disease is being updated, and accurate information is scarce due to global geographical features. Therefore, for a more accurate analysis of such data, attention should be paid to the available data. According to the latest global statistics (November 28 2021), COVID-19 has infected 261,435,768 million people worldwide to date, of which more than 5,207,634 million have died. As of November 29 2021, a total of 7,772,799,316 vaccine doses have been administered [9]. Almost all countries have reported morbidity and mortality. However, determining the factors contributing to the increase in COVID-19 mortality is challenging and not well known. Although previous studies have been performed in this area, the severity of the disease has been considered more than the clinical outcome [10,11]. Several studies have examined the association between disease severity and mortality from COVID-19 with underlying diseases [12], laboratory findings [13], and its association with medications used [14]. However, further studies can help confirm the evidence and improve knowledge. Therefore, the purpose of this study was an evaluation of predictors of mortality in patients with COVID-19.

Method

Search strategy

The current review of previous studies used the PRISMA checklist to search for the studies [15]. PRISMA protocol consists of five stages: systematic literature search, studies selection, data evaluation, data extraction, and data classification. To achieve the overall aim of the study, in the first step, the studies published in the period from January 2019 to December 1, 2021, were reviewed in the databases of PubMed, Scopus, Web of Science, and EBSCO. Searches were performed with mesh terms:

Selection criteria

Randomized controlled trials studies, Prospective and retrospective cohort studies, observational studies included, and other study designs and specific patients were excluded. Data from selected articles were extracted based on years, study design, number of patients, and mean age. Two blind, and independent reviewers extracted the information from the abstract and full content of the articles to extract the data. Before the screening, kappa statistics were performed to confirm the level of agreement between the reviewers with higher kappa values (>0.80).

Data analysis

95 confidence intervals (CI) of Odds ratio or Risk ratio with fixed effect Model and Mantel-Haenszel procedure; 95 confidence intervals (CI) of mean differences with fixed effect model and Inverse-variance formula were calculated. The random-effects method was used to investigate potential heterogeneity between studies, and I^2 showed heterogeneity. Random effects were used to deal with potential heterogeneity, and I^2 values showed heterogeneity. I^2 values less than 50% indicate low heterogeneity ($p>0.05$), and high values indicate high heterogeneity ($p<0.05$). Statistical analysis and meta-analysis were performed with Software Version 16 (STATA Corporation).

Results

A add-up of 281 articles were found within the beginning search. After removing duplicates, entry criteria for the titles were applied to the remaining 267 articles, and a summary of the remaining articles was reviewed. In this step,

225 articles were excluded. In the next, the full text of 42 articles were reviewed, and 32 articles were excluded due to lack of access to the complete content of the article and lack of relevance to the title and purpose of the article. Finally, ten studies were selected.

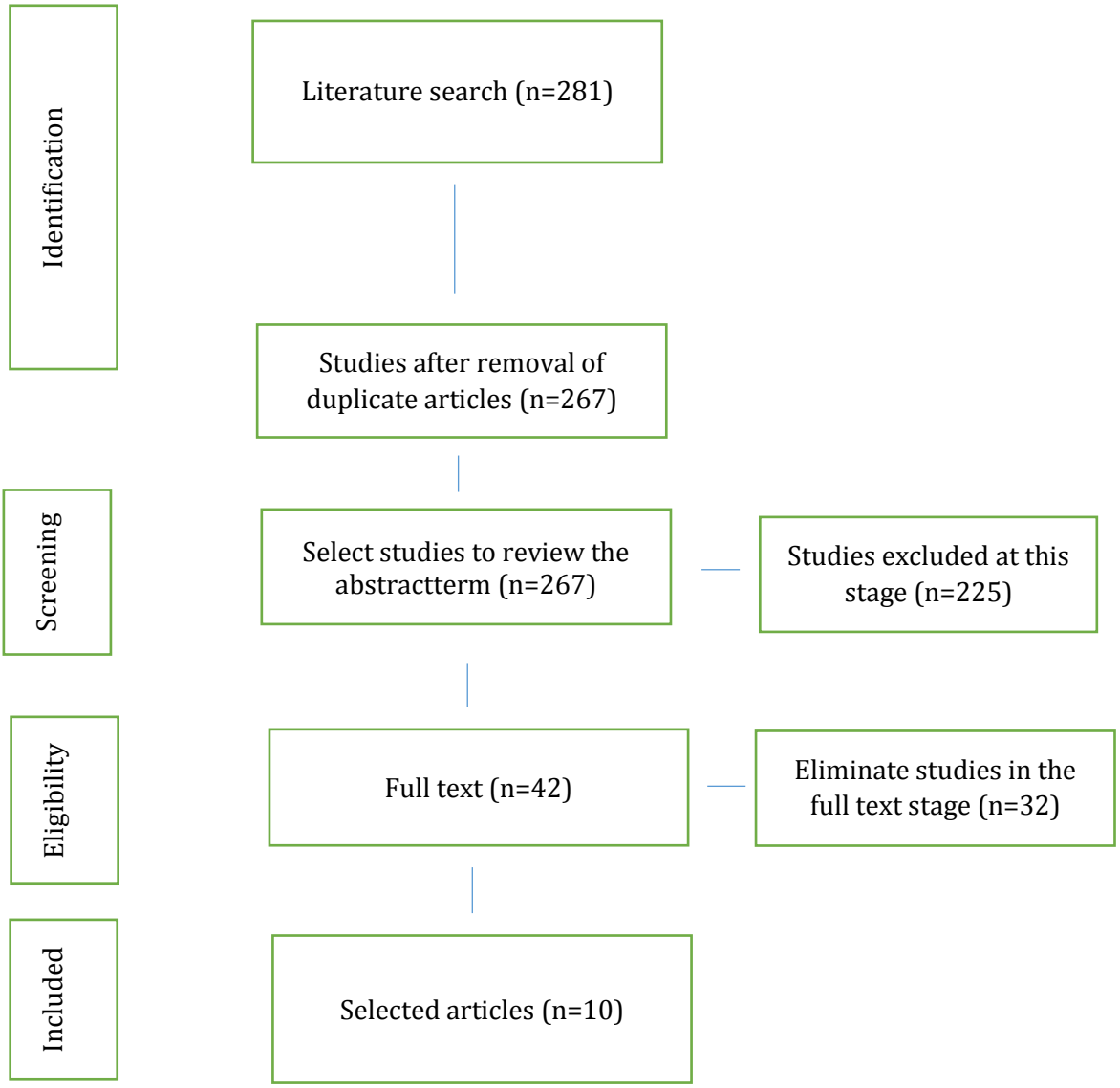

FIGURE 1 Flowchart of PRISMA

Characteristics

Ten studies (two observational retrospective studies, one prospective cohort study, and seven retrospective cohort studies) have been included in the present article. The number of Surviving patients was 1589 male and 1515 female. A total was 3104; the number of Deceased cases was 668 male and 343 female, a total of 1011 patients died (32.53%); with a mean age of 62.31 years. Table 1 summarizes studies for patient demographics, comorbidities, and clinical manifestations.

TABLE 1 Characteristics of included studies for meta-analysis

n	Study. Years	Study design	Number of patients				Mean of age	comorbidities				clinical manifestations			
			Surviving cases		Deceased cases										
			male	Female	male	Female		HTN	CC	D	RC	F	Fa	M	Di
1	Yang X et al., 2020 (16)	OR	14	6	21	11	59	18	5	9	4	51	40	6	2
2	Tang N et al.,2020 (17)	OR	82	80	16	5	54		75				NR		
3	Deng Y et al., 2020 (18)	RCs	51	65	73	36	69	58	16	26	25	189	57	13	33
4	Zhou F et al., 2020 (19)	RCs	81	56	38	16	56	58	36	15	6	151	44	29	9
5	Cao J et al., 2020 (20)	RCs	40	45	13	4	54	28	5	11	10	83	56	NR	11
6	Chen T et al., 2020 (21)	RCs	88	73	83	30	68	93	23	47	18	249	185	66	120
7	Richardson S et al., 2020 (22)	RCs	1095	1046	352	201	63	3026	966	1808	923	1734	-	-	-
8	Du RH et al., 2020 (23)	PCs	82	76	15	6	64.3	161	38	26	-	76	138	28	21
9	He XW et al., 2020 (24)	RCs	18	10	15	11	68.0	24	8	13	3	21	38	18	14
10	Li J et al., 2020 (25)	RCs	38	58	42	23	67.8	-	59	-	10	77	101	26	25

OR: Observational Retrospective; HTN: Hypertension; CC: cardiovascular comorbidities; D: Diabetes; RC: Respiratory comorbidities; F: Fever; Fa: Fatigue; M: Myalgia; Di: Diarrhea; SP: surviving patients;

Comorbidities

According to 2631/4115 patients (63.93%) had hypertension, 659/4115 patients (16.01%) had cardiovascular comorbidities, 2030/4115 patients (49.33%) had diabetes and, 1074/4115 patients (26.09 %) had respiratory comorbidities. Odds ratio of Hypertension between surviving cases and deceased cases was 0.99 (OR, 0.99 95% CI 0.82, 1.15; p=0.00) and low heterogeneity was observed (I^2 =13.79%; p=0.32) (Figure 2). This result showed hypertension had statistically significant association with mortality in COVID-19 patients. Odds ratio of other comorbidities such as cardiovascular, diabetes and respiratory comorbidities between surviving cases and deceased cases

was 1.0 (OR, 1.0 95% CI 0.92, 1.84; p=0.00) and low heterogeneity was observed (I^2 =16.79%; p=0.33), 0.81 (OR, 0.81 95% CI 0.72, 1.27; p=0.00) and low heterogeneity was observed (I^2 =18.70%; p=0.62) and 0.81 (OR, 0.78 95 % CI 0.64, 1.05; p=0.00) and low heterogeneity was observed (I^2 =15.71%; p=0.45), respectively. This result showed there was statistically significant association between comorbidities and mortality rate.

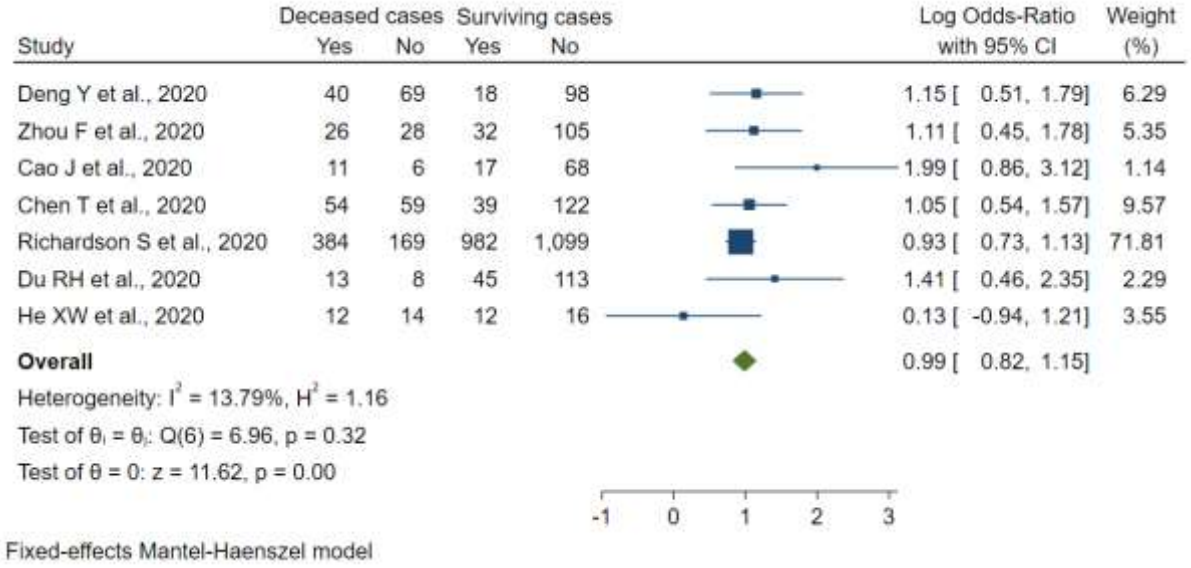

FIGURE 2 The forest plot showed hypertension between surviving cases and deceased cases

Association of patient demographics with COVID-19 mortality

Mean differences of age between surviving cases and deceased cases was 11.89 years (MD, 11.89 95% CI 10.27, 13.51; p=0.00), and high heterogeneity was observed (I^2 =72.63%; p=0.00) (Figure 3). This result revealed that age had a statistically significant association with mortality in COVID-19 patients.

Odds ratio of gender between male and female death was 0.37 (OR, 0.37 95 % CI 0.21, 0.53; p=0.00) and moderate heterogeneity was observed (I^2 =57.29%; p=0.01) (Figure 4). This result showed male gender had a statistically significant association with mortality in COVID-19 patients.

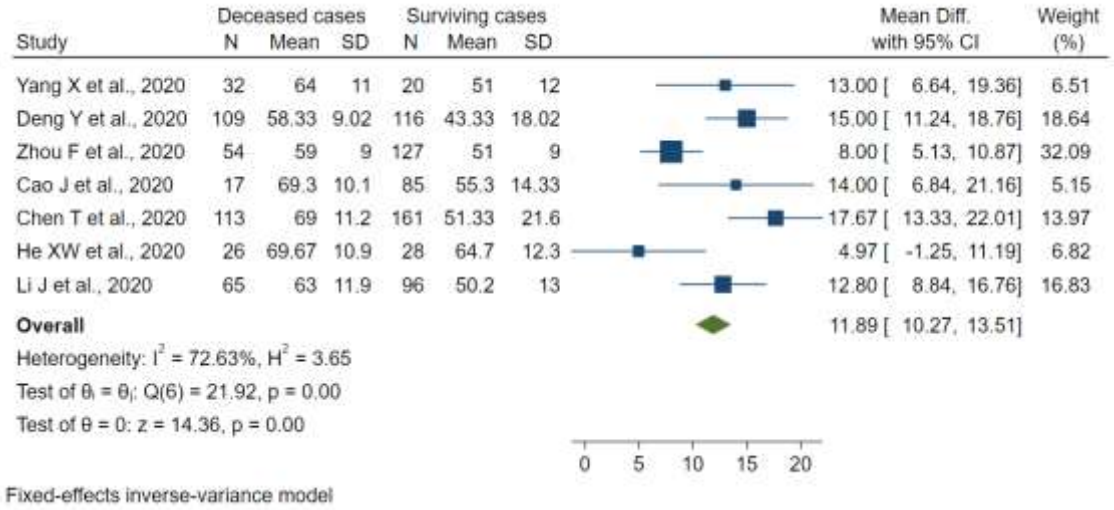

FIGURE 3 The forest plot showed mean differences of age between surviving cases and deceased cases

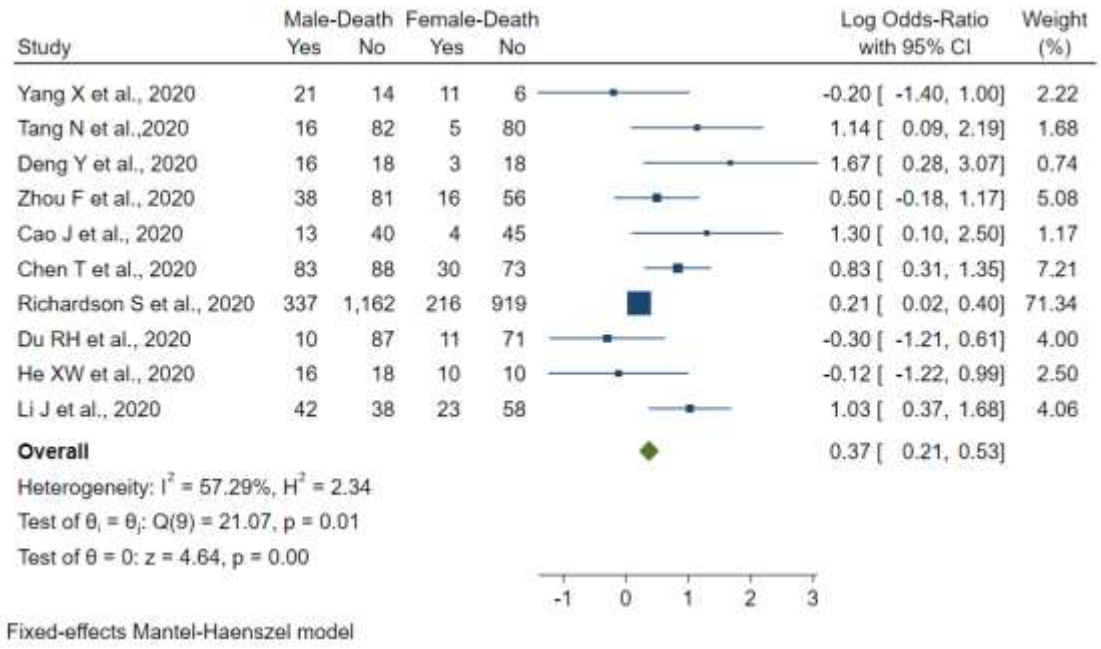

FIGURE 4 The forest plot showed odds ratio of gender between male and female death

Clinical manifestations

According to subgroup meta-analysis odds ratio of clinical manifestations such as fever, fatigue, myalgia and diarrhea between Surviving cases and Deceased cases was 0.59 (OR, 0.59 95 % CI 0.19, 0.99; p=0.33) and low heterogeneity was observed (I^2 =38.09%; p=0.14), 0.67 (OR, 0.67 95 % CI 0.36, 0.98; p=0.00) high heterogeneity reported (I^2 =78.93%; p=0.00), -0.04 (OR, -0.04 95 % CI -0.35, 0.27; p=0.90) and low heterogeneity found (I^2 =4.12%; p=0.39) and -0.03 (OR, -0.03 95 % CI 0.13, 0.46; p=0.94) and high heterogeneity was observed (I^2 =56.48%; p=0.00), respectively. Overall Odds ratio of clinical manifestations was 0.30 (OR, 0.30 95 % CI 0.13, 0.46; p=0.00) with moderate heterogeneity (I^2 =56.48%; p=0.00), the test of subgroup differences showed there was differences between subgroups, statistically significant association between fatigue and mortality rate (Figure 5).

Association of onset of symptoms to admission time with COVID-19 mortality

Mean differences of association of onset of symptoms to admission time with COVID-19 mortality between Surviving cases and Deceased cases was 1.39 (MD, 1.39 95 % CI 0.74, 2.04; p=0.00) with moderate heterogeneity (I^2 =53.63%; p=0.12) (Figure 6). Statistically significant association of onset of symptoms to admission time with COVID-19 mortality.

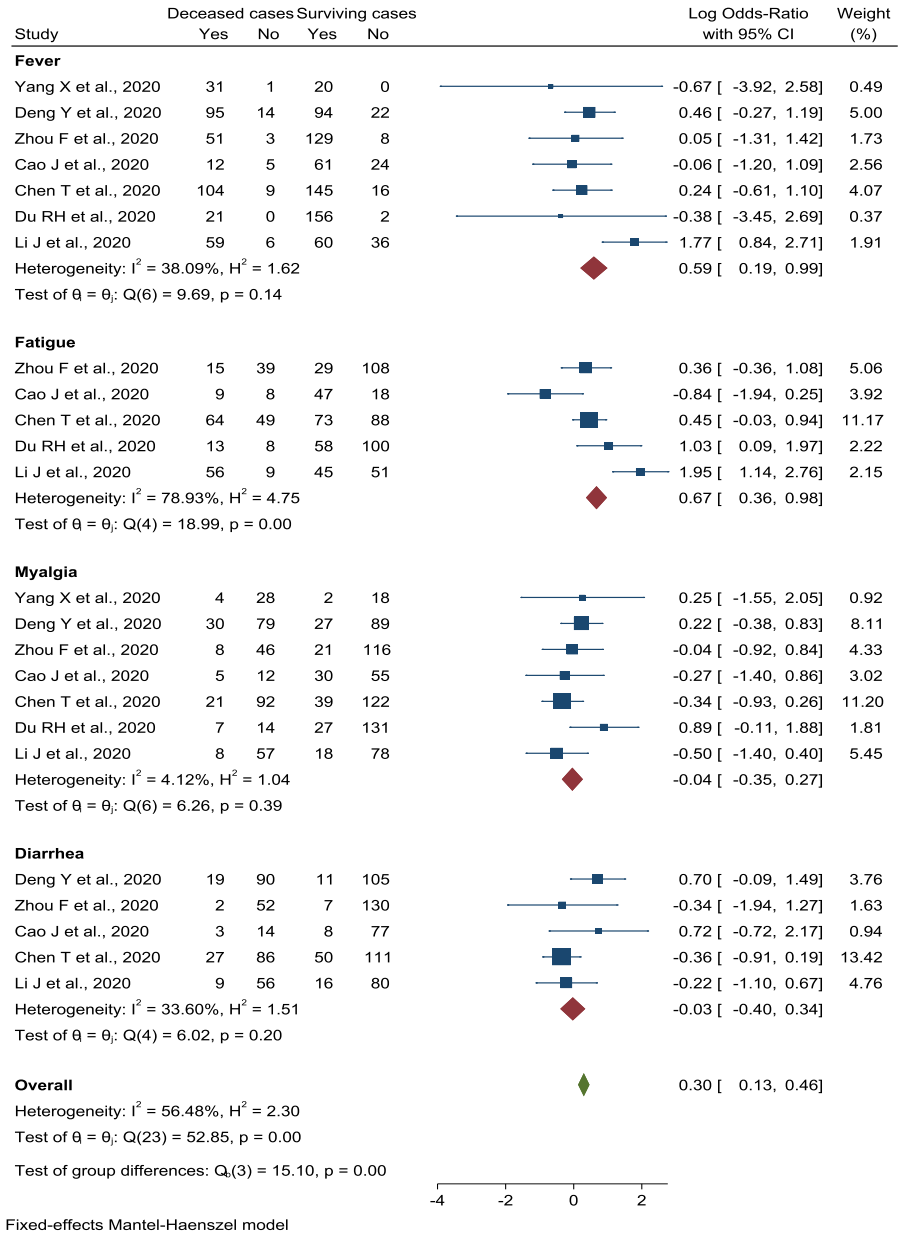

FIGURE 5 The forest plot showed the odds ratio of clinical manifestations between surviving cases and deceased cases

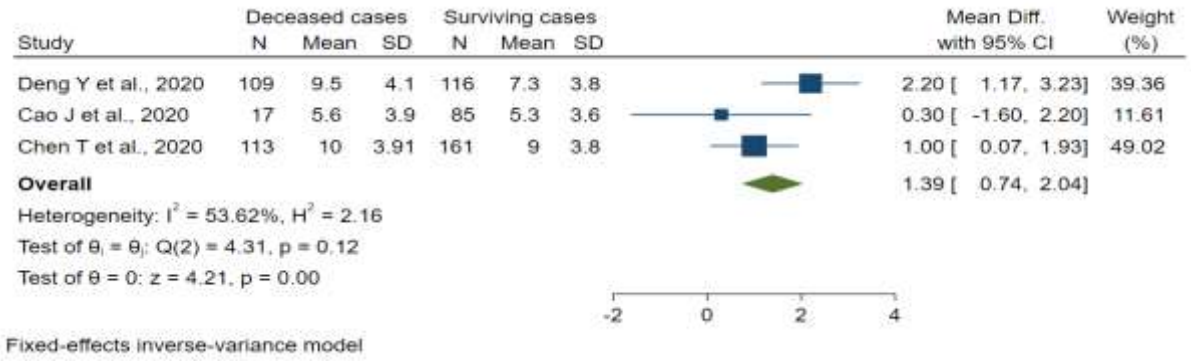

FIGURE 6 The forest plot showed association of onset of symptoms to admission time with COVID-19 mortality

Discussion

The purpose of the current study was an evaluation of predictors of mortality in COVID-19 patients. 32.53% of the total patients died; Mortality rates vary in different studies. The difference in the mortality rate of patients with COVID-19 may be due to the specialized services provided in the relevant center, the equipment used, and the time of diagnosis and referral to medical centers. According to Meta-analysis a significant relationship in terms of mean age and mortality. Usually, in the elderly, the severity of the disease is higher, and the underlying diseases are higher. These people need more care and therefore increase the risk of disease and subsequent death. According to Meta-analysis a significant relationship between mortality of men compared to women with COVID-19.

Moreover, the present study's findings showed that having underlying diseases increases the mortality rate. Having cardiovascular disease, diabetes, chronic neurological disease, chronic lung disease, and malignancy increases the chance of death. According to the results of other studies, patients with cardiovascular disease, followed by people with diabetes, chronic respiratory diseases, high blood pressure, and cancer, were most susceptible to the disease. The mean length of stay also showed that the number of patients who died was significantly longer. The present study's findings are consistent with the results of other meta-analysis studies [12-26] because meta-analysis showed that hypertension is a common underlying disease that is directly related to mortality in patients with COVID-19. High blood pressure increases the risk of death from COVID-19 disease. After high blood pressure, diabetes can significantly increase the risk of death from COVID-19 [27,28]. Previous studies have shown that diabetes and cardiovascular disease increase the incidence of SARS and MERS, which, like COVID-19, are acute respiratory syndrome, increasing the risk of SARS mortality by 11% and 8%, respectively. More than 50% of people with measles had underlying diabetes and hypertension, and more than 30% had underlying cardiovascular disease [29]. Diabetes can increase the risk of immune disorders, as many studies have shown that diabetes can disrupt the immune system by reducing the function of the immune system by disrupting neutrophil chemotaxis and the antibacterial activity of monocytes and phagocytosis, leading to increased infection [30]. Since smoking itself reduces the function of the immune system and increases the risk of cardiovascular disease and high blood pressure, scientists have been convinced since 1989 that smoking reduces the activity of natural killer cells (NK) and ultimately increases the risk of infections [31].

Conclusion

The study's limitations include the following: high heterogeneity between studies in the study of some variables. It is suggested that these limitations be removed in future studies to provide more substantial evidence. RCT studies were not found; few studies observed a link between predictors and death in COVID-19 that further studies are needed. Most studies have been done in China, with wind studies conducted worldwide to improve the comparison process.

Underlying diseases (hypertension, diabetes, and cardiovascular disorders) can increase the risk of developing Covid-19 disease and the death rate from these diseases. Comorbidities and fatigue increase mortality rate patients COVID-19 and association of onset of symptoms to admission time with COVID-19 mortality were statistically significant. To reduce mortality in patients with COVID-19, especially at-risk individuals, family members, and elderly caregivers need to know what medication they are taking and ensure access to the food and medical equipment needed. It is also critical to pay

particular consideration to elderly patients with underlying illnesses in medical care.

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