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ORIGINAL PAPER

Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis

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Abstract

Objectives The main aim of this study was to find the prevalence of mortality among hospitalized COVID-19 infected patients and associated risk factors for death.

Methods Three electronic databases including PubMed, Science Direct and Google Scholar were searched to identify relevant cohort studies of COVID-19 disease from January 1, 2020, to August 11, 2020. A random-effects model was used to calculate pooled prevalence rate (PR), risk ratio (RR) and 95% confidence interval (CI) for both effect measures. Cochrane chi-square test statistic Q, I^2, and τ^2 tests were used to measure the presence of heterogeneity. Publication bias and sensitivity of the included studies were also tested.

Results In this meta-analysis, a total of 58 studies with 122,191 patients were analyzed. The pooled prevalence rate of mortality among the hospitalized COVID-19 patients was 18.88%, 95% CI (16.46–21.30), $p < 0.001$. Highest mortality was found in Europe [PR 26.85%, 95% CI (19.41–34.29), $p < 0.001$] followed by North America [PR 21.47%, 95% CI (16.27–26.68), $p < 0.001$] and Asia [PR 14.83%, 95% CI (12.46- 17.21), $p < 0.001$]. An significant association were found between mortality among COVID-19 infected patients and older age (> 65 years vs. < 65 years) [RR 3.59, 95% CI (1.87–6.90), $p < 0.001$], gender (male vs. female) [RR 1.63, 95% CI (1.43–1.87), $p < 0.001$], ICU admitted patients [RR 3.72, 95% CI (2.70–5.13), $p < 0.001$], obesity [RR 2.18, 95% CI (1.10–4.34), $p < 0.05$], hypertension [RR 2.08,95% CI (1.79–2.43) $p < 0.001$], diabetes [RR 1.87, 95% CI (1.23–2.84), $p < 0.001$], cardiovascular disease [RR 2.51, 95% CI (1.20–5.26), $p < 0.05$], and cancer [RR 2.31, 95% CI (1.80–2.97), $p < 0.001$]. In addition, significant association for high risk of mortality were also found for cerebrovascular disease, COPD, coronary heart disease, chronic renal disease, chronic liver disease, chronic lung disease and chronic kidney disease.

Conclusion This meta-analysis revealed that the mortality rate among COVID-19 patients was highest in the European region and older age, gender, ICU patients, patients with comorbidity had a high risk for case fatality. Those findings would help the health care providers to reduce the mortality rate and combat this pandemic to save lives using limited resources.

Keywords COVID-19 · Comorbidity · Mortality · Meta-analysis · Risk factors

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the most recently discovered RNA virus named coronavirus, formerly referred to as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [1]. It causes tract infections within the human and animal bodies present with fever, cough, cold, and sometimes patients may die due to acute respiratory distress syndrome or pneumonia [2]. Coronaviruses are a beta coronavirus that constitutes the subfamily Orthocoronavirinae, and family Coronaviridae. The name "coronavirus" is derived from Latin word corona, meaning as crown or wreath. Coronaviruses were first discovered in the 1930s in North Dakota with an acute respiratory tract infection of domesticated chickens [1]. Among seven coronavirus species that are identified to infect human beings and cause disease, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are generally mild,

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often cause normal cold side effects. Other three human coronaviruses, middle east respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produce potentially severe symptoms, which have been identified in 2012, 2002 and 2019 respectively [3, 4].

The first case of COVID-19 disease was identified on December 8, 2019, in Wuhan, the Hubei province of China by the Chinese Center for Disease and Prevention from the throat swab of a patient [5]. Since COVID-19 disease emergence first in China, it's rapidly become a worldwide threat and it's declared as a pandemic by World Health Organization (WHO). From that time, this disease has spread to 216 countries and territories around the world, with 20,995,433 confirmed cases and 760,774 deaths (World Health Organization statistics as on August 15, 2020) [6]. The case fatality rate is high for COVID-19 infection. Globally the death rate was 3.6% [6]. The highest confirmed number of cases was reported in the United States of America with 5,150,407 confirmed cases with 164,826 deaths. From the European region, the majority of confirmed cases/death was accounted from the Russian Federation, Spain, UK, Italy (912,823/15,498, 337,334/28 605, 313,802/46 706, 252,235/35 231) respectively. In the African region, the highest confirmed cases/death was found in South Africa (572,865/11 270) and in the Eastern Mediterranean region highest cases/death was found in Iran (336,324/19 162). From the South-East Asia region, India accounted for the highest number of cases/death (2,461,190/64 553). In Bangladesh, the confirmed number of cases was 269,115 with 3 557 deaths up to August 15, 2020 [6].

Patients with COVID-19 present primarily with various symptoms like fever, cough, dyspnea, myalgia, and fatigue [7, 8]. Although most of the COVID-19 infected patients are thought to be recovered after few days, male patients, older patients (age greater than 60 years) and patients with various chronic diseases may have fetal outcomes [9].

Several factors are responsible for the severity and mortality of COVID-19 disease. From different studies, it had been found that patients with comorbidities such as hypertension, diabetes mellitus, acute respiratory distress syndrome (ARDS), cardiovascular disease, cancer, COPD, asthma, renal disease, kidney disease, liver disease, hepatic disease, pneumonia, obesity, and also for the history of smoking were responsible for the development of the disease or death [10–14]. The mortality rate of COVID-19 patients were varied among the intensive care unit (ICU) and non-ICU patients and also for severe and non-severe patients. From different studies, it had been found that the mortality rate was higher among ICU admitted patients and severe patients compared to non-ICU and non-severe patients [15–17].

Low and middle-income countries like Bangladesh, COVID-19 disease is sort of a threat to health and economic sectors. Proper social distancing is not possible for a large number of populations, which is essential to prevent this disease because of having no proper treatment or medicine to treat coronavirus infected patients and vaccine to prevent it. Numerous requiring ICU care and mechanical ventilator, which is difficult to arrange for many developing countries [18]. Proper steps should be taken to prevent this disease and reduce the mortality rate. Several studies had reported the risk factors associated with death among COVID-19 patients [10–14]. In this study, we aimed to review the prevalence of mortality and the risk factors associated with mortality among coronavirus infected patients in the hospital and to summarize the available findings in a meta-analysis.

Methods

Search Strategy

A systematic search had been performed using the online databases of PubMed, Science Direct and Google Scholar for relevant publications from January 1, 2020, to August 11, 2020. Advanced search strategy with the following combined text heading as ("coronavirus" OR "COVID-19" OR "novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "Severe Acute Respiratory Syndrome related coronavirus") AND ("mortality" OR "death" OR "fatal outcome") AND ("risk factors") had been used to find out the potential paper. An initial search had been carried out followed by an analysis of the text words contained in Title/Abstract. A literature search had been done by two independent reviewers (FMN and MMI).

Study Eligibility Criteria

We included the articles assessing the association between age, gender, comorbidities and mortality risk factors from COVID-19 infection as the major outcomes of interest. Articles that reported SARS-CoV-2 infected patients confirmed by real time reverse transcriptase polymerase chain reaction (RT-PCR) were included. Studies that didn't report the prevalence of mortality among COVID-19 patients were excluded. For this analysis purpose, studies with only cohort study design were used. Randomized controlled trials, cross-sectional study, case–control study and case report study design were excluded. Editorials, systematic review articles, letters to editors and short communication were also excluded for this analysis. Studies that included only pediatric patients, pregnant women, surgery patients and patient co-infection with other diseases were excluded due to heterogeneous results found among those groups for coronavirus disease. Articles were written in English language and only human based studies were included. Only published and peer reviewed articles were included in the analysis. Unpublished articles were excluded due to data uncertainty. All the identified articles were investigated by hand and not recognized by electronic inquiry. Duplicate articles were found out and extracted at last. Titles and abstracts were searched by two independent researchers. Controversial matters were resolved after discussion.

Data Extraction Process and study Quality Assessment

Two reviewers independently screened full articles after an initial search by title and abstract for inclusion and exclusion criteria. The extracted data included: confirmation of SARS-CoV-2 infected patients, study design, time and place of data collections, author name, year of publication, country, the total number of reported cases, the total number of fatality cases, gender, age, comorbidities (e. g., hypertension, diabetes, cardiovascular disease, etc.). The results of this analysis were presented based on the PRISMA checklist [19]. Newcastle–Ottawa technique was used for the quality assessment of the included cohort studies [20]. Three major components were utilized to assess the quality of the included studies such as selection procedure of the study patients, coordination of efficient confounding variables and assessment of the outcome and the article's point with more than 5 were considered as high-quality publications among maximum 9 points [21].

Statistical Analysis

Data analysis was carried out using STATA version 16 and Microsoft Excel. The pooled prevalence rate (PR), risk ratio (RR) and 95% confidence interval (CI) for both of those were calculated using random effects model to pool weighted effect size as well as every individual study. PR was used to calculate the prevalence of mortality among hospitalized patients with COVID-19 and RR was used to calculate the risk of mortality. Random effects model was used in this analysis as there was substantial heterogeneity among the study results. In meta-analysis a random effects model assumes that the effect size of all studies is not uniform and may follow a distribution [22, 23]. For examining the between-study heterogeneity, chi-square test statistic (Q), and I^2 and τ^2 test were used in this analysis [23, 24]. Forest plot was used as a graphical representation of heterogeneity among the included studies. Substantive heterogeneity among the included studies result was identified by subgroup analysis based on continent. A sensitivity analysis was conducted to find the effect of a single study on the overall study result. Publication bias was detected by funnel plot [25].

Results

Search Results and Study Characteristics

A total of 2147 articles were identified from three databases PubMed, Science Direct and Google Scholar. After screening those articles by title and abstract, 340 articles were identified. Of those, 144 articles were selected for full text assessment. Among those, 58 articles with 122,191 participants reporting the mortality rate and risk factors of mortality among hospitalized patients with confirmed COVID-19 infection as a primary outcome were included. Rest of the 86 articles were excluded due to lack of proper information, study design and duplication. Finally, 58 cohort studies were included in this meta-analysis (Fig. 1). The characteristics of all the included studies were described in (Table 1).

Among the included studies, 26 studies were conducted in China [10–13, 26–47], 8 in USA [48–55], 7 in Italy [16, 56–61], 4 in Spain [14, 62–64], 2 in South Korea [65, 66], 2 in Mexico [67, 68], 1 in Bangladesh [69], 1 in Brazil [70], 1 in England [71], I in Greece [72], 1 in Iran [73], 1 in Kuwait [74], 1 in Switzerland [75], 1 in Turkey [76] and 1 in few European countries [77]. The sample size of the included studies varied from 16 to 51,633 patients and the mean age of the included patients varied from 41 years to 85.5 years. Prevalence of mortality among hospitalized coronavirus patients was reported in 58 studies and the risk of mortality was reported in 48 studies. The mortality rate among hospitalized patients varied from 0.6 to 61.5%.

Prevalence of Mortality Among Coronavirus Patients

Summary of this meta-analysis for the prevalence of mortality among hospitalized coronavirus patients and subgroup analysis with respect to continent were presented in Table 2. Total 58 studies with 122,191 patients were used to find the mortality rate. The prevalence of mortality among the hospitalized patients with COVID-19 disease was 18.88%, 95% CI (16.46–21.30), $z = 15.30$, $p < 0.001$ (Fig. 2). The subgroup analysis by continent revealed that the mortality of hospitalized patients with COVID-19 was the highest in Europe [PR 26.85%, 95% CI (19.41–34.29), $z = 7.07$, $p < 0.001$, $\tau^2 = 199.87$, $I^2 = 99.1\%$] followed by North America [PR 21.47%, 95% CI (16.27–26.68), $z = 8.08$, $p < 0.001$, $\tau^2 = 68.28$, $I^2 = 99.5\%$], Asia [PR 14.83%, 95% CI (12.46–17.21),

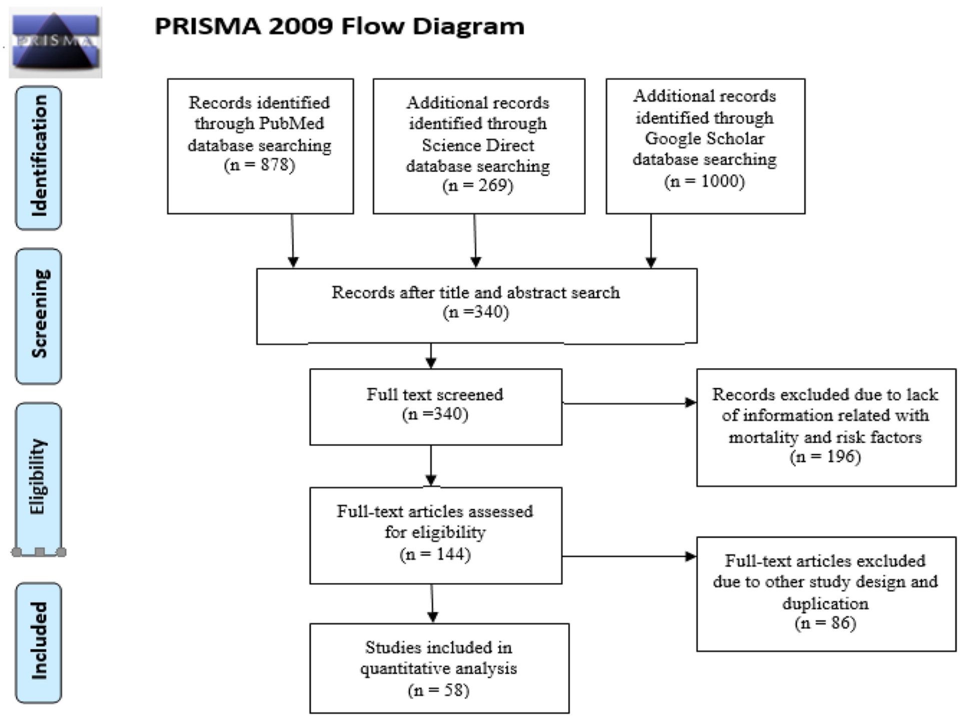

Fig. 1 PRISMA flowchart for search strategy and the process of selecting articles

z = 12.25, p < 0.001, τ^2 = 42.14, I^2=98.8%] and South America [PR 6.33%, 95% CI (5.28- 7.38), z = 11.83, p < 0.001] (Fig. S1).

Risk Factors of Mortality Among Coronavirus Patients

Risk of mortality among hospitalized COVID-19 patients is highly influenced by older age, male patients and patients with different comorbidities. Risk ratio (RR) was used as an effect measure to find the associated risk of mortality among hospitalized COVID-19 patients. Summary of this meta-analysis for the risk of mortality among COVID-19 patients were presented in Table 3. Among 58 studies, 48 studies with 60,623 patients were analyzed to get risk factors for mortality. Mortality among hospitalized COVID-19 patients with age > 65 years were 3.59 times more likely or 259% higher as compared to the patients with age < 65 years [RR 3.59, 95% CI (1.87–6.90), z = 3.84, p < 0.001] (Fig. S2). The risk of mortality among male patients with COVID-19 was 63% higher compared to female patients [RR 1.63, 95% CI (1.43–1.87), z = 7.15, p < 0.001] (Fig. S3). ICU admitted patients with COVID-19 was 3.7 times more likely to die compared to non-ICU patients [RR 3.72 (2.70–5.13), z = 8.01, p < 0.001] (Fig. S4).The risk of mortality among obese patients with COVID-19 was 118% higher compared to non-obese patients [RR 2.18, 95% CI (1.10–4.34), z = 2.22, p < 0.05] (Fig. S5). Mortality among COVID-19 patients with the history of smoking was 81% higher compared to the patients without the history of smoking [RR 1.81, 95% CI (0.99–3.33), z = 1.91, p < 0.1] (Fig. S6). Patients with hypertension was two times as high as patients with no hypertension to die [RR 2.08, 95% CI (1.79–2.43), z = 9.33, p < 0.001] (Fig. S7). Mortality among hospitalized COVID-19 patients with diabetes was 87% higher compared to the patients without diabetes [RR 1.87, 95% CI (1.23–2.84), z = 2.93, p < 0.001] (Fig. S8). The risk of mortality among the patients with cardiovascular disease was 2.5 times more likely than compared to the patients without cardiovascular disease [RR 2.51, 95% CI (1.20–5.26), z = 2.34, p < 0.05] (Fig. S9). Mortality of COVID-19 patients with cerebrovascular disease increased the risk by 165% compared to the patients without cerebrovascular disease [RR 2.75, 95% CI (1.54–4.89), z = 3.44, p < 0.01] (Fig. S10). Patients with asthma was two times as high as the patients without asthma to die due to COVID-19 disease [RR 1.96, 95% CI (0.89–4.33), z = 1.66, p < 0.01] (Fig. S11). Those patients with COPD was two times more likely to die compared to the patients with no COPD [RR 2.23, 95% CI (1.17–4.24), z = 2.44, p < 0.05] (Fig. S12). The risk of mortality was 131% higher among the hospitalized COVID-19 patients with cancer compared to the patients who have no cancer [RR 2.31, 95% CI (1.80–2.97), z = 6.51, p < 0.001] (Fig. S13). The risk of mortality among the hospitalized patients with coronary heart disease [RR 3.63, 95% CI (1.52–8.65), z = 2.90, p < 0.01] (Fig. S14), chronic renal disease [RR 3.82, 95% CI (2.17–6.73), z = 4.64, p < 0.01] (Fig.

Table 1 Characteristics table for included studies

Author [Ref]	Country	Study period	Study design	Sample size	Death	Quality score	Main findings
Hwang et al. (2020) [66]	South Korea	Feb 01-Mar 25	Retrospective	103	26	7	Age: Mean 67.62 ± 15.32, Male: 52/103, tested by RT-PCR
Mikami et al. (2020) [49]	USA	Mar 13-Apr 17	Retrospective	6493	806	7	Age: Median 59 (43–72), Male: 3538/6493, tested by RT-PCR
Zhao et al. (2020) [42]	China	Jan 13-Mar 4	Retrospective	539	125	7	Age: Median 59(43–69), Male: 255/539, tested by RT-PCR
Deng et al. (2020) [26]	China	Dec 29-Apr 17	Retrospective	11,793	78	7	Age: Median 45 (1–97), Male: 5950/11,793, tested by RT-PCR
Bello-Chavolla et al. (2020) [68]	Mexico	May 18	Retrospective	51,633	5332	6	Age: Mean 46.65 ± 15.83, tested by RT-PCR
Du et al. (2020) [34]	China	Dec 25-Feb7	Retrospective	179	21	7	Age: Mean 57.6 ± 13.7, Male: 97/179, tested by RT-PCR
Lee et al. (2020) [65]	South Korea	Feb 18-Mar 4	Retrospective	98	20	7	Age: Median 72 (68–79), Male: 44/98, tested by RT-PCR
Garcia et al. (2020) [77]	Europe	Apr 22	Retrospective	639	97	7	Age: Median 63 (53–71), Male: 447/639, tested by RT-PCR
Goicoechea et al. (2020) [63]	Spain	Mar 12-Apr 10	Retrospective	36	11	7	Age: Mean 71 ± 12, Male: 23/36, tested by RT-PCR
Chen et al. (2020) [27]	China	Jan 31	Retrospective	1590	50	8	Age: Median 69 (51–86), tested by RT-PCR
Yang et al. (2020) [40]	China	Jan 13-Mar 18	Retrospective	205	40	9	Age: Median 63(56–70), Male:96/205, tested by RT-PCR
Zhou et al. (2020) [13]	China	Jan 31	Retrospective	191	54	9	Age: Median 56, Male: 119/191, tested by RT-PCR
Zhang et al. (2020) [10]	China	Jan 11-Feb 6	Retrospective	663	25	7	Age: Median 55.6, Male: 321/663, tested by RT-PCR
Cheng et al. (2020) [45]	China	Feb 8-Mar 11	Retrospective	305	85	7	Age: Median 65 (52–71), Male: 184/305, tested by RT-PCR & CT
Yu et al. (2020) [11]	China	Jan 14-Feb 28	Retrospective	1464	212	7	Age: Median 64, Male: 736/1464, tested by RT-PCR
Sousa et al. (2020) [70]	Brazil	Apr 14	Retrospective	2070	131	7	Male: 1017/2070, tested by RT-PCR
Chilimuri et al. (2020) [55]	USA	Mar 9-Apr 9	Retrospective	375	160	7	Age: Median 63(52–72), Male: 236/375, tested by RT-PCR
Smith et al. (2020) [71]	England	Mar 1-Apr 22	Retrospective	346	117	7	Age: Male: 194/346, tested by RT-PCR
Cen et al. (2020) [12]	China	Feb 10	Retrospective	1007	43	9	Age: Median 61, Male: 493/1007, tested by RT-PCR
Redd et al. (2020) [48]	USA	Apr 2	Retrospective	318	32	6	Age: Mean 63.4 ± 16.4, tested by RT-PCR
Remes-Troche et al. (2020) [67]	Mexico	Apr 1-May 5	Retrospective	112	3	6	Age: Mean 43.72 ± 15, tested by RT-PCR
Hirsch et al. (2020) [51]	USA	Mar 1-Apr 5	Retrospective	5499	888	6	Age: Median 61, tested by RT-PCR
Li et al. (2020) [38]	China	Jan 26-Feb 5	Retrospective	545	90	8	Age: Median 60, tested by RT-PCR

Table 1 (continued)

Author [Ref]	Country	Study period	Study design	Sample size	Death	Quality score	Main findings
Rocio et al. (2020) [14]	Spain	Mar 10-Apr 12	Retrospective	501	36	7	Age: Median 52, Male: 317/501, tested by RT-PCR
Cummings et al. (2020) [54]	USA	Mar 2-Apr 1	Retrospective	257	101	8	Age: Median 62, tested by RT-PCR
Wang et al. (2020) [39]	China	Mar 30	Retrospective	339	65	9	Age: Median 71, Male: 166/339, tested by RT-PCR
Mostaza et al. (2020) [64]	Spain	Mar 1-Apr 21	Retrospective	404	145	7	Age: Mean 85.2 ± 5.3, Male: 221/404, tested by RT-PCR
Zhang et al. (2020) [29]	China	Jan 29-Feb 12	Retrospective	258	15	8	Age: Median 64, tested by RT-PCR
Halvatsiotis et al. (2020) [72]	Greece	Mar 10-Apr 13	Retrospective	90	26	7	Age: Median 65.5, Male: 72/90, tested by RT-PCR
Chen et al. (2020) [36]	China	Jan 3-Apr 9	Retrospective	681	104	7	Age: Median 65, Male: 362/681, tested by RT-PCR
Di Castelnuovo et al. (2020) [56]	Italy	Feb 19-May 23	Retrospective	3894	712	9	Age: Median 67, Male: 2403/394, tested by RT-PCR
Giacomellia et al. (2020) [57]	Italy	Feb 21-Mar 19	Retrospective	233	48	9	Age: Median 61, Male: 161/233, tested by RT-PCR
Saticia et al. (2020) [76]	Turkey	Apr 2-May 1	Retrospective	681	55	9	Age: Mean 56.9 ± 15.7, Male: 347/681, tested by RT-PCR
Nikpouraghdama et al. (2020) [73]	Iran	Feb 19-Apr 15	Retrospective	2964	239	7	Age: Mean 55.50 ± 15.15, Male: 1955/2964, tested by RT-PCR
Almazeedi et al. (2020) [74]	Kuwait	Feb 24-Apr 20	Retrospective	1096	19	7	Age: Median 41, Male: 888/1096, tested by RT-PCR
Bonetti et al. (2020) [61]	Italy	Mar 1-Mar 30	Retrospective	144	70	9	Age: Median 78 (64.2–84), Male: 95/144, tested by RT-PCR
Borghesi et al. (2020) [58]	Italy	Mar 4-Mar24	Retrospective	302	65	7	Age: Median 67 (57–77), Male: 194/302, tested by RT-PCR
Klang et al. (2020) [52]	USA	Mar 1-May 17	Retrospective	3406	1136	7	Male: 1961/3406, tested by RT-PCR
Covino et al. (2020) [60]	Italy	Mar1-Mar 31	Retrospective	69	23	9	Age: Median 84 (82–89), Male: 37/69, tested by RT-PCR
Zhang et al. (2020) [43]	China	Jan 20-Feb 29	Retrospective	409	102	7	Age: Median 65 (56–71), Male: 234/409, tested by RT-PCR
Imam et al. (2020) [50]	USA	Mar 1-Apr 17	Retrospective	1305	200	6	Age: Mean 61.0 ± 16.3, tested by RT-PCR
Wang et al. (2020) [30]	China	Jan 7-Feb 11	Retrospective	296	19	7	Age: Mean 65.6 ± 12.6, Male: 129/296, tested by RT-PCR
Chen et al. (2020) [31]	China	Jan 18-Mar 27	Retrospective	3309	307	7	Age: Median 62(49–69), Male: 1667/3309, tested by RT-PCR
Chen et al. (2020) [35]	China	Jan 1-Feb 15	Retrospective	660	82	7	Age: Median 55 (34–68), Male: 295/660, tested by RT-PCR
Shi et al. (2020) [37]	China	Jan 1-Mar 8	Retrospective	306	47	7	Age: Median 64(56–72), Male:150/306, tested by RT-PCR
Poblador-Plou et al. (2020) [62]	Spain	Mar 4-Apr 17	Retrospective	4412	771	7	Male:1821/4412, tested by RT-PCR

Table 1 (continued)

Author [Ref]	Country	Study period	Study design	Sample size	Death	Quality score	Main findings
Grasselli et al. (2020) [16]	Italy	Feb 20-Apr 22	Retrospective	3988	1926	9	Age: Median 63 (56–69), Male: 3188/3988, tested by RT-PCR
Gupta et al. (2020) [53]	USA	Mar 4-Apr4	Retrospective	2215	784	9	Age: Mean 60.5 ± 14.5, Male: 1436/2215, tested by RT-PCR
Luo et al. (2020) [41]	China	Jan 9-Mar 31	Retrospective	1018	201	7	Age: Median 61 (49–69), Male: 521/1018, tested by RT-PCR
Chen et al. (2020) [44]	China	Feb 3- Feb 20	Retrospective	73	20	9	Age: Median 66 (59–72), Male: 42/73, tested by RT-PCR
Yao et al. (2020) [32]	China	Jan 31-Mar 10	Retrospective	108	12	7	Age: Median 52 (37–58), Male: 43/108, tested by RT-PCR
Hou et al. (2020) [28]	China	Jan 21-Mar 9	Retrospective	101	5	6	Age: Mean 50.9 ± 20.1, tested by RT-PCR
Meng et al. (2020) [46]	China	Jan 18-Mar 27	Retrospective	109	32	7	Male: 61/109, tested by RT-PCR
Fattizzo et al. (2020) [59]	Italy	Mar 24-Apr 24	Retrospective	16	5	7	Age: Median 77 (27–94), Male: 10/16, tested by RT-PCR
Chen et al. (2020) [33]	China	Jan 20-Apr 4	Retrospective	1859	208	7	Age: Median 59 (45–68), Male: 934/1859, tested by RT-PCR
Charlotte et al. (2020) [75]	Switzerland	Mar 1-Apr 12	Retrospective	196	33	7	Age: Median 70 (60–80), Male:119/196, tested by RT-PCR
Xu et al. (2020) [47]	China	Jan 12-Feb 3	Retrospective	239	147	7	Age: Mean 62.5 ± 13.3, Male: 143/239, tested by RT-PCR
MOWLA et al. (2020) [69]	Bangladesh	May 2-May 15	Retrospective	100	10	7	Age: Mean 41.67 ± 16.26, Male: 63/100, tested by RT-PCR

Table 2 Mortality rate and subgroup analysis of mortality rate with respect to continents

Continent	No of Studies	Total no of patients	Pooled prevalence (95% CI)	Test for overall effect		Test for heterogeneity			
				z-value	p-value	Q statistic	p-value	τ^2	I^2
Overall	58	122,191	18.88 (16.46–21.30)	15.30	< 0.001	14,453.14	< 0.001	81.85	99.6%
Asia	32	33,286	14.83 (12.46–17.21)	12.25	< 0.001	2590.69	< 0.001	42.14	98.8%
Europe	15	15,270	26.85 (19.41–34.29)	7.07	< 0.001	1489.26	< 0.001	199.87	99.1%
South America	1	2070	6.33 (5.28–7.38)	11.83	< 0.001	0.00	–	–	0.00
North America	10	71,563	21.47 (16.27–26.68)	8.08	< 0.001	1731.79	< 0.001	68.28	99.5%

S15), chronic liver disease [RR 2.02, 95% CI (1.16–3.50), $z = 2.48$, $p < 0.05$] (Fig. S16), chronic kidney disease [RR 2.11, 95% CI (1.72–2.58), $z = 7.22$, $p < 0.001$] (Fig. S17), chronic lung disease [RR 2.22, 95% CI (1.47–3.35), $z = 3.80$, $p < 0.001$] (Fig. S18) were 263%, 282%, 102%, 111% and 122% higher compared to the patients without those disease respectively.

Forest plot was used as a graphical representation of heterogeneity among the study results (Fig. 2, Fig. S1–S18). The overall effect was represented by diamond and individual study effects were represented by squares with their respective 95% CI.

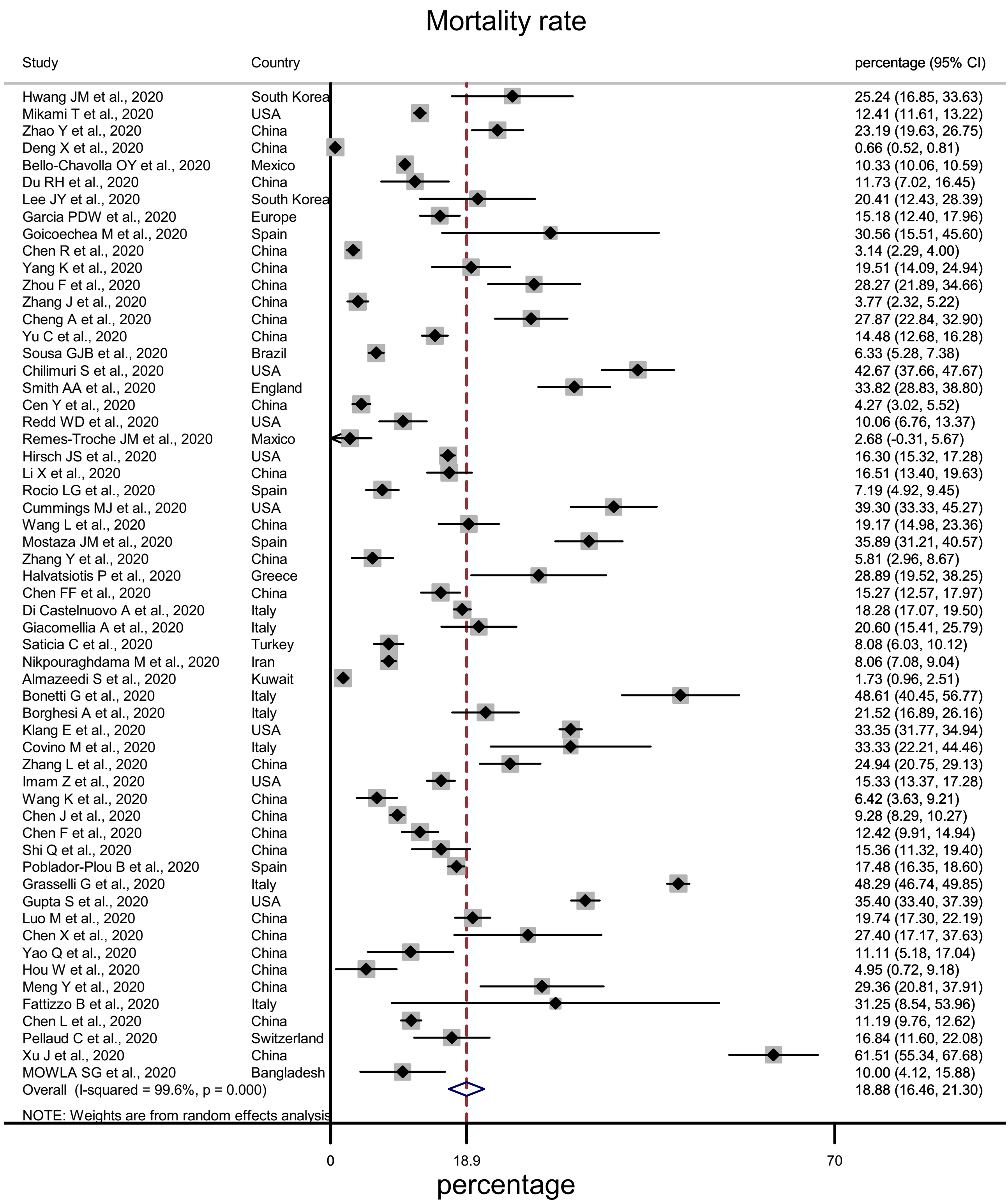

Fig. 2 Forest plot for the prevalence of mortality among the hospitalized COVID-19 infected patients

Table 3 Risk of mortality among hospitalized patients with COVID-19

Factors (Ref group)	No of Studies	Total no of patients	Pooled Risk Ratio (95% CI)	Test for overall effect		Test for heterogeneity			
				z-value	p-value	Q statistic	p-value	τ^2	I^2
Age (Age < 65 years)	13	25,872	3.59 (1.87–6.90)	3.84	< 0.001	16,651.02	0.000	1.40	99.9%
Gender (Female)	46	60,408	1.63 (1.43–1.87)	7.15	< 0.001	931.63	0.000	0.18	95.2%
ICU patients (non-ICU patients)	12	10,596	3.72 (2.70–5.13)	8.01	< 0.001	2403.48	0.000	0.29	99.5%
Obesity (No)	7	13,477	2.18 (1.10–4.34)	2.22	0.027	430.35	0.000	0.84	98.6%
Smoking (No)	10	13,598	1.81 (0.99–3.33)	1.91	0.056	1141.26	0.000	0.93	99.2%
Hypertension (No)	38	37,785	2.08 (1.79–2.43)	9.33	< 0.001	1602.32	0.000	0.21	97.7%
Diabetes (No)	35	35,411	1.87 (1.23–2.84)	2.93	< 0.001	11,774.33	0.000	1.55	99.7%
Cardiovascular disease (No)	16	8925	2.51 (1.20–5.26)	2.34	0.015	6445.68	0.000	2.24	99.8%
Cerebrovascular disease (No)	11	6069	2.75 (1.54–4.89)	3.44	0.002	1331.35	0.000	0.89	99.2%
Asthma (No)	7	12,410	1.96 (0.89–4.33)	1.66	0.097	226.11	0.000	1.09	97.3%
COPD (No)	19	22,384	2.23 (1.17–4.24)	2.44	0.015	6619.13	0.000	2.02	97.7%
Cancer (No)	15	21,622	2.31 (1.80–2.97)	6.51	< 0.001	321.34	0.000	0.20	95.6%
Coronary Heart disease (No)	11	10,851	3.63 (1.52–8.65)	2.90	0.004	12,620.11	0.000	2.16	99.9%
Chronic renal disease (No)	8	5635	3.82 (2.17–6.73)	4.64	< 0.001	727.04	0.000	0.63	99%
Chronic liver disease (No)	8	7090	2.02 (1.16–3.50)	2.48	0.013	101.30	0.000	0.45	95.3%
Chronic kidney disease (No)	16	24,450	2.11 (1.72–2.58)	7.22	< 0.001	568.74	0.000	0.15	97.4%
Chronic lung disease (No)	7	4108	2.22 (1.47–3.35)	3.80	< 0.001	184.51	0.000	0.295	96.7%

Sensitivity Analysis and Publication Bias

Sensitivity analysis was conveyed to identify the most influential study on the pooled summary effect and risk factors. From sensitivity analysis, it was found that the overall estimates and association of risk factors with COVID-19 mortality did not depend on a single study (Fig. S20–S21). Publication bias was detected by the funnel plot. Most of the variables showed evidence of publication bias (Fig. S19).

Discussion

From this meta-analysis, it had been found that the pooled prevalence of mortality among hospitalized COVID-19 patients was 18.88%. Subgroup analysis was conducted concerning for continent to find out the reason of variation among the mortality rate of COVID-19 patients due to geographical location. The highest mortality was found in Europe followed by North America and Asia. During this this meta-analysis, it was also found that older patients (> 65 years), male patients, obesity, patients with comorbidities such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease, COPD, cancer, coronary heart disease, chronic renal disease, chronic liver disease, chronic kidney disease and chronic lung disease were significantly associated with the risk of mortality among the hospitalized COVID-19 patients.

Though the case fatality rate of SARS-CoV-2 infection was lower than MERS-CoV and SARS-CoV infection, the total number of cases and death was higher for SARS-CoV-2 compared to MERS-CoV and SARS-CoV infection [78, 79]. From a systematic review, it had been found that the case fatality rate for COVID-19 infected patients was 5.6% compared to SARS (13%) and MERS (35%) infected patients [78].

The highest number of mortality for COVID-19 infection was observed in Europe. Among the the European region, the highest mortality was observed in Italy [16, 61] followed by Spain [63, 64]. The case fatality rate was also highest in USA [54, 55]. Compared to European and American countries, the case fatality rate was low in Asian countries. The mortality rate among COVID-19 patients in Bangladesh was 10% [69] followed by Iran and Kuwait 8.06% and 1.73% respectively [73, 74]. Among the Asian region, the highest mortality was found in China and South Korea [47, 66]. A large variation of prevalence of mortality was found among the Chinese population [13, 27, 32, 36, 41, 42, 47].

From several previous studies, older age was found as a potential risk factor for death among COVID-19 patients [50, 60]. Most of the older patients have several chronic diseases and less body fitness to fight with a viral infection, which may be one of the main reasons for fatal outcomes [60, 80]. Older age was also a risk factor for severity and mortality among SARS and MERS infected patients [81, 82]. Male patients with COVID-19 were more likely to die compared to female patients [35, 40, 55, 64]. Different sexual hormones could also be responsible for it. Mortality among male patients was also high for SARS and MERS infected patients compared to female patients [81, 82].

From this meta-analysis, it was found that obese patients with COVID-19 had a higher risk to die compared to non-obese patients. Consistent results were found from several studies [14, 70, 72]. The history of smoking among COVID-19 patients increased the risk of mortality. From a study, it was found that smokers had a 767% higher risk of mortality as non-smoker [32, 33, 74].

Several comorbidities were also responsible for the risk of mortality among hospitalized COVID-19 patients. Comorbid patients with COVID-19 had a high risk of disease severity, ICU admission, including death [83]. Hypertension was the most common underlining comorbidities among COVID-19 patients and the prevalence of mortality among hypertension patients due to COVID-19 was 58.3% [14, 30, 32, 69]. From our meta-analysis, it had been observed that mortality due to COVID-19 was 108% higher in the hypertension group compared to the non-hypertension group. The second most frequent comorbidity was diabetes and the prevalence of mortality among COVID-19 patients with diabetes was 49% [12, 30, 65, 69, 70]. We also observed that the rate of mortality due to COVID-19 infection among diabetes patients was 2 times as high as the patients with no diabetes.

We observed cardiovascular disease as a risk factor for death among COVID-19 infected patients. The previous data also seems to suggest that patients with cardiovascular disease are more likely to die in coronavirus infection [32, 34, 37, 43, 70]. A high rate of case fatality was found for cerebrovascular disease with 56.6% [70]. The prevalence of mortality among patients with asthma was 9.3% and had a higher risk of death compared to the patients with no asthma [69, 70, 72, 74]. From previous studies, it was found that the case fatality rate was high for hospitalized COVID-19 patients with COPD [30, 39, 69, 74]. The previous data seems to suggest patients with cancer are more prone to severe outcomes of COVID-19, including death [11, 32, 33, 69, 75]. Association between mortality among COVID-19 patients and increased chronic disease such as (cardiac, renal, liver, kidney and lung) were also found from several independent studies [13, 30, 32, 33, 37, 39, 42, 65, 66, 69, 70, 74].

The prevalence of mortality among COVID-19 patients admitted in the intensive care unit (ICU) was very high [13, 14, 37, 40, 60, 70]. From our analysis, it was observed that the case fatality rate was 272% higher for ICU admitted patients compared to non-ICU patients. A limited number of ventilation machines, skilled stuffs, and doctors, critical patients may be the main reason for this high risk of mortality. In developing countries, the number of ICUs are also limited.

The pathogenesis of COVID-19 is still unknown. Severity of the disease may depend on cytokine storms of the patients [84]. Acute respiratory distress syndrome is found at the early stages of COVID-19 infected patients and cytokine can lead to acute respiratory distress syndrome, which is one of the main reasons for fatality among the patients [9].

Findings from this analysis would help the policymakers of health care sectors to develop different strategies, management and stratified the patients according to risk for giving proper treatments and nursing with limited resources.

Limitations

This meta-analysis had some limitations. Articles only published in the English language were included in this analysis. The sample size of some included studies was very small which might not recognize uncommon factors. Biasness and high heterogeneity among the included studies was also found. Some risk factors could not be included due to data insufficiency. Evidence of publication bias was also found in the data. However, included studies showed good quality assessments.

Conclusion

This meta-analysis result revealed that the mortality rate among hospitalized COVID-19 patients was high and male gender, older aged patients, patients presented with comorbidities such as hypertension, diabetes, cardiovascular disease etc were highly associated with the risk of death among them. Those findings would help the health care providers or physicians to notice the risk of high mortality among the COVID-19 infected patients and take proper management strategies in health care sectors to reduce this high mortality rate and also combat this COVID-19 pandemic to save human lives.

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