



코로나바이러스감염증-19 (COVID-19) 환자들의 사망관련 인자에 대한 연구: 체계적 문헌고찰 및 메타분석

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Predictors of Mortality in Patients with COVID-19: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Most meta-analyses of risk factors for severe or critical outcomes in patients with COVID-19 only included studies conducted in China and this causes difficulties in generalization. Therefore, this study aimed to systematically evaluate the risk factors in patients with COVID-19 from various countries. **Methods:** PubMed, Embase, and Web of Science were searched for studies published on the mortality risk in patients with COVID-19 from January 1 to May 7, 2020. Pooled estimates were calculated as odds ratio (OR) with 95% confidence interval (CI) using the random-effects model. **Results:** We analyzed data from seven studies involving 26,542 patients in total in this systematic review and meta-analysis. Among the patients, 2,337 deaths were recorded (8.8%). Elderly patients and males showed significantly higher mortality rates than young patients and females; the OR values were 3.6 (95% CI 2.5–5.1) and 1.2 (95% CI 1.0–1.3), respectively. Among comorbidities, hypertension (OR 2.3, 95% CI 1.1–4.6), diabetes (OR 2.2, 95% CI 1.2–3.9), cardiovascular disease (OR 3.1, 95% CI 1.5–6.3), chronic obstructive pulmonary disease (OR 4.4, 95% CI 1.7–11.5), and chronic kidney disease (OR 4.2, 95% CI 2.0–8.6) were significantly associated with increased mortalities. **Conclusion:** This meta-analysis, involving a huge global sample, employed a systematic method for synthesizing quantitative results of studies on the risk factors for mortality in patients with COVID-19. It is helpful for clinicians to identify patients with poor prognosis and improve the allocation of health resources to patients who need them most.

KEYWORDS: COVID-19, SARS-CoV-2, mortality, comorbidity, systematic review, meta-analysis

The recent outbreak of coronavirus disease 2019 (COVID-19) is an emerging global health threat. Confirmed infections from the rapidly spreading COVID-19 surpassed 24,000,000 worldwide on August 28, 2020, and global deaths rose past 254,000 as COVID-19 spread across Europe and North America.¹⁾ In the last 20 years, we have faced a number of potentially deadly coronavirus outbreaks: Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which resulted in global case-fatality ratios of 11%

(916 deaths) and 34.4% (858 deaths), respectively.^{2,3)} According to current data, COVID-19 has a mortality rate of over 3.4%¹⁾, which is lower than previous coronavirus diseases; however, mortality rates of COVID-19 has shown diverse trends based on region or population, being potentially biased by incomplete outcome data.

The total population-level estimate of the case fatality rate is useful for understanding the average severity of an outbreak, but recognition of patients at risk of death within a population

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during an outbreak is also crucial. Information on the relative risk to different characteristics of patients, especially comorbidities, allows healthcare providers to focus on the most vulnerable and improve the allocation of health resources to those who require them most.

Due to the emergency and severity of the COVID-19 outbreak, the number of relevant studies have increased exponentially: 340 in January 30, 1,466 in February 24, and 6,022 in March 30.⁴⁾ The inundating amount of information regarding COVID-19 prompts the academic community to summarize meaningful results and extract comprehensive and reliable conclusions. Although there have been several meta-analyses of risk factors for severe or critical outcomes in patients with COVID-19,⁵⁻⁷⁾ most reviews only included the studies conducted in China, leading to a difficulty in generalization; therefore, a meta-analysis incorporating data from countries across the globe would be necessary, especially considering the fact the COVID-19 has already become a worldwide issue. In this context, this meta-analysis, employing a systematic method for synthesizing quantitative results, aims to provide the most current and comprehensive summary evidence of the association between the comorbidities and mortality in patients with COVID-19 worldwide.

Material and Methods

Literature search strategy

Two researchers separately searched PubMed, Embase, and Web of Science for studies on mortality risk in COVID-19

patients, published between 1 January 2020 and 7 May 2020. The following search terms were used: (“coronavirus disease 2019” OR “coronavirus disease-19” OR “COVID-19” OR “2019-nCoV” OR “SARS-CoV-2” OR “novel coronavirus”) AND (“death” OR “deaths” OR “mortality” OR “mortalities”). Duplicates and obviously irrelevant studies were excluded through initial screening of titles and abstracts, and the remaining articles were further reviewed according to inclusion and exclusion criteria. A flow diagram summarizing the study selection process is shown in Fig. 1.

Inclusion and exclusion criteria

According to the inclusion criteria, studies were eligible if they (1) investigated the association between underlying chronic diseases and mortality in patients with COVID-19; (2) used a prospective or retrospective cohort study design; (3) provided sufficient information to calculate OR and 95% CIs; and (4) were published only in English. Exclusion criteria were: (1) reviews, commentaries, or editorials; (2) in vitro or animal studies; or (3) studies on specific populations such as children. In instances of overlapping data, only the most recent and comprehensive data were included in the meta-analysis.

Study selection, data extraction and quality assessment

Two investigators separately selected publications and extracted data, and discrepancies were resolved by consensus. The following information was extracted from each study: name of the first author, publication year, study setting, patient age, percentage of male and diagnosis criteria of COVID-19.

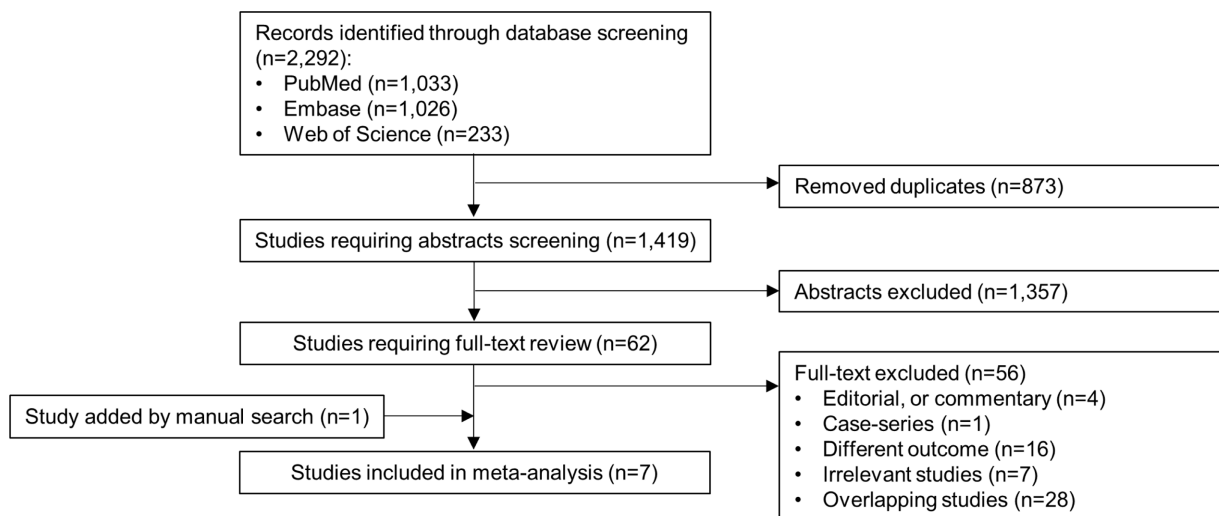


Fig. 1. Flow diagram of study selection.

Also, the number of death cases in each risk factor group was extracted. As all included studies were cohort studies, quality scores were evaluated by the Newcastle-Ottawa Quality Assessment Scale.⁸⁾

Statistical analysis

The strength of associations between mortality and risk factors was assessed using odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was analyzed by Z-test, and a p-value <0.05 was considered statistically significant. Heterogeneity between studies was assessed by a chi square-based Q test and I² test. A random-effects model (DerSimonian-Laird method) was applied to consider the heterogeneity within and between studies and to give a more conservative estimate of statistical confidence.⁹⁾ Publication bias was assessed using Begg's test and Egger's test. Sensitivity analysis was also performed based on quality of studies.

All statistical analyses were performed using R software (version 3.6.0; R Foundation for Statistical Computing,

Vienna, Austria) with 'meta' package. The review was written based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹⁰⁾

Results

Identification and characteristics of the included studies

A total of 2,292 records were identified from searches of three databases, and 873 duplicates were excluded. After removing 1,357 studies during title and abstract screening, 62 were selected for full-text review. Thereafter, 56 articles were excluded for the following reasons: editorial or commentary (n=4); case-series (n=1); different outcome (n=16); not investigating comorbidities (n=7); and overlapping studies (n=28). After adding one study through a manual search, seven studies were ultimately included for meta-analysis.¹¹⁻¹⁷⁾ Among 26,542 patients included in this meta-analysis, 2,337 patients died (8.8%). The main characteristics of included studies are listed in Table 1. Quality scores evaluated by the NOS ranged from 5 to 9.

Table 1. Characteristics of studies included in the meta-analysis

Study	Setting	Location	Enroll period	Sample size	Death (%)	Age (median, IQR)	Male (%)	COVID-19 diagnosis	NOS
Grasselli et al. [11]	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Milan, Italy	February 20 ~March 18, 2020	1,591	405 (25.5)	63 (56-70)	1,304 (82.0)	WHO interim guidance	8
Guan et al. [12]	575 hospitals (National Health Commission)	China	December 11, 2019 ~January 31, 2020	1,590	50 (3.1)	48.9 (mean)	904 (56.9)	WHO interim guidance	5
Mandeep et al. [13]	169 hospitals in 11 countries (Surgisphere)	USA, Canada, Spain, Italy, Germany, France, UK, Turkey, China, South Korea, Japan	December 20, 2019 ~March 15, 2020	8,910	515 (5.8)	49±16 (mean, SD)	5,339 (60.0)	Laboratory-confirmed of SARS-CoV-2	9
Miyashita et al. [14]	Mount Sinai Health System	NY, USA	March 1 ~April 6, 2020	5,688	555 (9.8)	NA	NA	Laboratory-confirmed of SARS-CoV-2	5
Nikpouraghdama et al. [15]	Baqiyatallah hospital	Tehran, Iran	February 19 ~April 15, 2020	2,968	239 (8.1)	56 (46-65)	1,955 (65.9)	Laboratory-confirmed of SARS-CoV-2 or clinically diagnosed based on CT	7
Richardson et al. [16]	12 Northwell Health acute care hospitals	NY, USA	March 1 ~April 4, 2020	5,700	553 (9.7)	63 (52-75)	3,437 (60.3)	Laboratory-confirmed of SARS-CoV-2	7
Tomlins et al. [17]	North Bristol NHS Trust	Bristol, UK	March 10 ~March 30, 2020	95	20 (21.1)	75 (59-82)	60 (63.2)	NA	7

IQR: interquartile range; COVID-19: Coronavirus disease 2019; NOS: Newcastle-Ottawa scale; WHO: World Health Organization; SARS-CoV-2: SARS-coronavirus 2; NA: not available; CT: computed tomography.

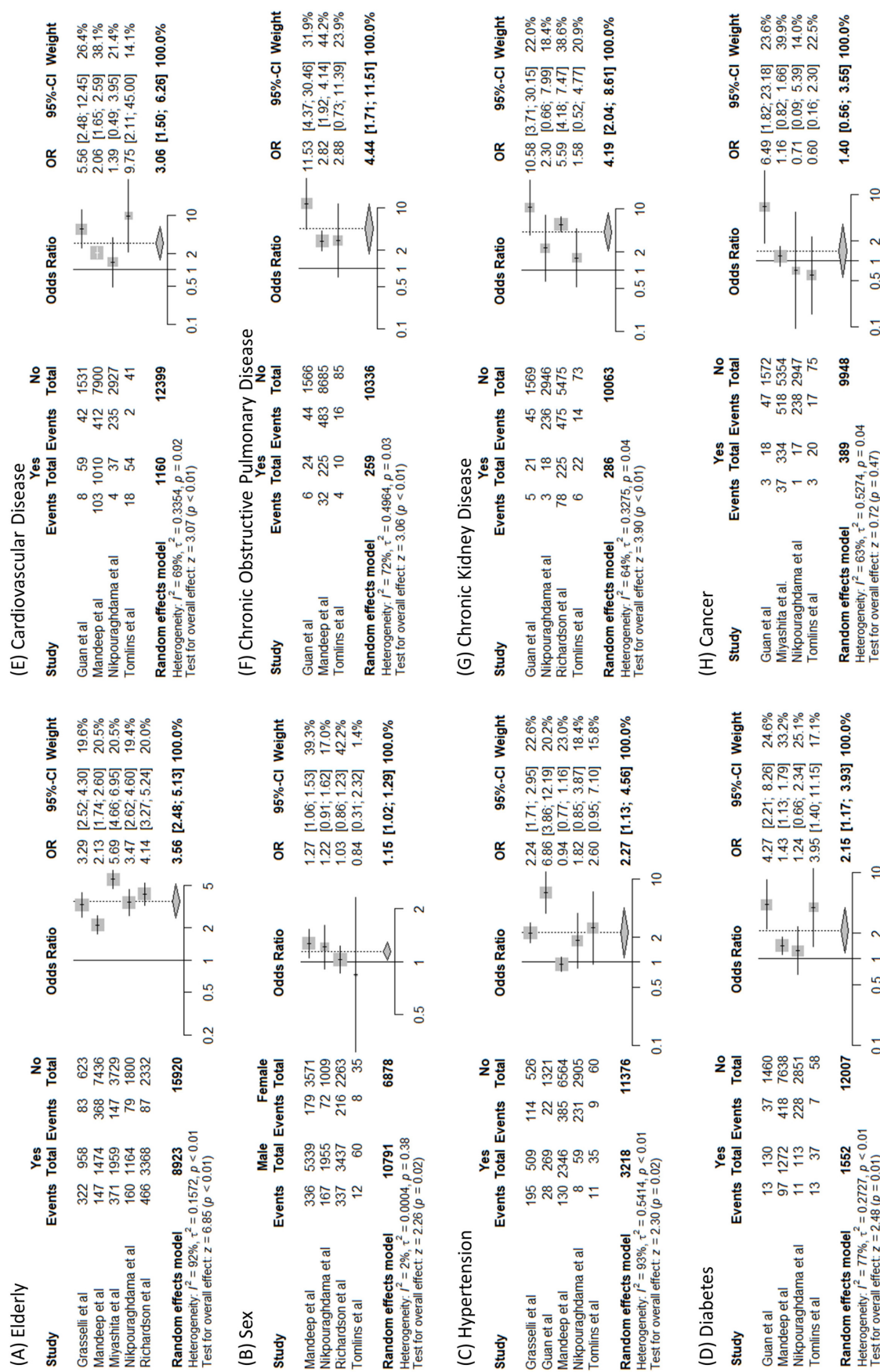


Fig. 2. Forest plots of the association between clinical characteristics and mortalities. (a) Elderly (b) Sex (c) Hypertension (d) Diabetes (e) Cardiovascular disease (f) Chronic obstructive pulmonary disease (g) Chronic kidney disease (h) Cancer.

Table 2. Sensitivity analysis of high-quality studies

	Number of studies	I ² (%)	Odds ratio (95% CI)	p-value
Elderly	4	85.5	3.15 (2.29-4.33)	<0.0001
Male	4	2.4	1.15 (1.02-1.29)	0.024
Hypertension	4	89.0	1.68 (0.91-3.09)	0.096
Diabetes	3	47.5	1.59 (1.01-2.49)	0.043
Cardiovascular disease	3	56.1	2.42 (1.13-5.19)	0.023
Chronic obstructive pulmonary disease	2	0	2.82 (1.95-4.09)	<0.0001
Chronic kidney disease	3	68.4	3.14 (1.29-7.65)	0.012
Cancer	2	0	0.63 (0.01-1.94)	0.424

Quantitative data synthesis

The meta-analysis results of the associations between mortality rates and clinical characteristics such as demographic factors and comorbidities are shown in Fig. 2. Except for sex, considerable heterogeneity was observed. Elderly patients (defined as >60 years in three studies^{11,15,16}) and >65 years in two studies^{13,14}) and males showed significantly higher mortality rate compared to young patients and females; the OR values were 3.6 (95% CI 2.5~5.1) and 1.2 (95% CI 1.0~1.3), respectively. Among comorbidities, hypertension (OR 2.3, 95% CI 1.1~4.6), diabetes (OR 2.2, 95% CI 1.2~3.9), CVD (OR 3.1, 95% CI 1.5~6.3), chronic obstructive pulmonary disease (COPD, OR 4.4, 95% CI 1.7~11.5), and chronic kidney disease (CKD, OR 4.2, 95% CI 2.0~8.6) were significantly associated with an increase in mortality. On the contrary, cancer was not a significant factor for mortality in patients with COVID-19.

Publication bias and sensitivity analysis

Both Begg's and Egger's test showed no evidence of publication bias ($p > 0.05$ for all analyses). The results of sensitivity analysis on high-quality studies (NOS ≥ 7) were shown in Table 2. When two studies of scores of 5 were excluded,^{12,14} significant associations for age, sex, diabetes, COPD, CVD, and CKD remained. For hypertension, a similar trend was observed, although statistical significance was not obtained (OR 1.7, 95% CI 0.9-3.1).

Discussion

The main findings of this meta-analysis are that older age, male, and presence of comorbidities (hypertension, diabetes, CVD, CKD, and COPD) were associated with higher mortality rates in patients infected by SARS-CoV-2. Sensitivity analysis

showed similar results, strengthening the findings.

We have confirmed that older age was associated with mortality in patients with COVID-19. Older age is a well-known risk factor for mortality in patients with coronavirus. A previous study using patients with SARS in Hong Kong concluded that patients who are older than 60 years old showed 5.1-fold (95% CI 2.3 to 11.3) increased risk of death than younger patients.¹⁸ Another study on risk factors of mortality for MERS showed that old age is an important risk factor for death.¹⁹ The exact mechanism is unknown; however, it can be predicted that aging leads to defects in T-cell and B-cell function and excessive production of type 2 cytokines. Hence, these abnormal age-dependent changes may result in a deficiency in the management of viral replication and an increase in pro-inflammatory responses.²⁰ In addition, males were associated with higher mortality rates among patients with COVID-19. A previous study suggested that while susceptibility to SARS-CoV-2 was similar in males and females, mortality risks were higher in men.²¹ This can be partially attributable to the angiotensin-converting enzyme 2 (ACE2) gene; recently, an *in vitro* study showed that cell entry of SARS-CoV-2 depends on ACE2.²² This was also reported in SARS patients; high expression of the ACE2 protein was associated with organ failure.²³ It is known that circulating ACE2 levels are higher in males than in females^{24,25}; therefore, male patients with COVID-19 can be more prone to mortality compared to females due to higher expressions of ACE2.

Among comorbidities, CKD was one of the prominent risk factors for mortality. A previous study with coronavirus-infected patients showed that renal dysfunction or high serum creatinine levels were associated with high risk of death.²⁶ Since the kidney is known to be an organ in which ACE2 is located, it was thought that ACE2 plays an important role in SARS-CoV-2 infection. A clinical study showed that SARS-

CoV-2 directly infected human kidney tubules, thereby causing acute renal failure in patients with COVID-19.²⁷⁾ This was also reported in SARS patients; high expression of the ACE2 protein was associated with organ failure.²³⁾ Meanwhile, CKD is known to be associated with some disorders of both the innate and adaptive immune system in such a form that there is a coexistence of both immune activation and immune suppression.²⁸⁾ Although the exact mechanism is not known, there is a close relation between the progressively defective immune system and mortality. Infectious diseases are the second most common causes of mortality after CVD in patients with CKD, contributing to 30-36% of deaths among patients on dialysis.²⁹⁻³¹⁾ Uremic toxins, nutritional deficiencies, and immunosuppressive medications also contribute to immune dysregulation, which are further complicated by renal replacement therapies.

It has been reported that the most frequent comorbidities in patients with COVID were in the following order: hypertension, diabetes, and CVD.³²⁾ Similarly, the most frequent comorbidity in patients who developed acute respiratory distress syndrome following SARS-CoV-2 infection was hypertension (27%) followed by diabetes (19%) and CVD (6%).³³⁾ It is unclear if there is a causal relationship between hypertension and COVID-19 because hypertension is extremely frequent in the elderly, and older patients could not only be at high risk of SARS-CoV-2 virus infection but also experience more severe forms and complications of COVID-19.³⁴⁾ Nevertheless, blood pressure control remains an important consideration for reducing disease burden.³⁵⁾ Meanwhile, ACE inhibitors and angiotensin receptor blockers, which are frequently used in patients with hypertension or CVD, could also affect the susceptibility to or outcomes of COVID-19, considering that SARS-CoV-2 binds to ACE2 in the lung to enter cells.³⁴⁾

Diabetes and uncontrolled glycemia were significant factors for severity and mortality in patients infected with various viruses including SARS-CoV and MERS-CoV.^{24,36)} While it is difficult to pinpoint the mechanism of the association between diabetes and outcomes from COVID-19 due to a lack of data, it was suggested that diabetes, a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities, can affect response to pathogens.³⁷⁾ Another plausible explanation is immune response impairment in diabetic patients. Poorly controlled diabetes has been linked to inhibited lymphocyte proliferative response to different kinds of stimuli as well as impaired monocyte, macrophage, and neutrophil dysfunction.^{37,38)}

Nevertheless, the evidence remains controversial regarding whether diabetes itself indeed affects susceptibility and outcomes from infections, or the cardiovascular and renal comorbidities that are frequently associated with diabetes are the main factors involved.³⁷⁾

For patients with CVD, viral illness can further damage myocardial cells through several mechanisms including direct myocardial injury by the virus, systemic inflammatory response, destabilized coronary plaque, and aggravated hypoxia.^{32,39-42)} Among these candidate mechanisms, acute myocardial injury is the most commonly reported complication in COVID-19. Studies showed that patients admitted to intensive care units or that have fatal illnesses have several-fold higher likelihood of troponin elevation, whereas the incidence of elevated troponin has been only 1-2% in patients with mild illness, not requiring intensive care unit admission.^{32,41,43)} This was supported by a previous autopsy study in patients who died due to SARS; the viral ribonucleic acid was detected in 35% of the autopsied human heart sample.⁴⁴⁾

COPD, which is characterized by chronic inflammation of the large airways, small bronchioles and destruction of the lung parenchyma, has the functional consequence of expiratory airflow limitation.⁴⁵⁾ It is not surprising that COPD was a poor prognosis of COVID-19, considering that pathogenic infections are a common cause of acute exacerbation of COPD, which can result in undesirable respiratory outcomes.⁴⁶⁾

There are several limitations to consider. First, there were not enough studies to perform subgroup analyses or meta-regression analyses. The second limitation was heterogeneity, which could not be fully accounted for. Third, due to the lack of individual-level data, adjusted estimates by clinically important risk factors could not be obtained. Nevertheless, incorporating literature conducted from various countries, this meta-analysis provides a reconciliation of inconsistent findings across such studies, presenting novel conclusions and issues worth considering for future research on COVID-19.

Conclusion

This meta-analysis employs a systematic method for synthesizing quantitative results of studies regarding the risk factors for mortality in patients with COVID-19. It is expected that determination of potential risk factors for mortality with their pooled OR could help clinicians to identify patients with poor prognosis on admission and improve the allocation of

health resources to patients who need them most.

Authors' contributions

All authors have contributed significantly to the work and have read and approved the manuscript for publication. WK, JM and KEL were responsible for the study concept and design. WK and JH participated in literature search. WK analyzed the data. WK, JM and KEL contributed to the manuscript writing and discussion.

Conflict of Interest

We declare no conflict of interest.

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