

# RISK FACTORS FOR MORTALITY IN PATIENTS WITH COVID-19: A SYSTEMATIC REVIEW

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## ABSTRACT

**Background:** SARS-CoV-2, a new strain of the coronavirus, caused a global outbreak of fatal acute pneumonia. Globally, WHO has recorded 709,511 deaths from COVID-19, and the number is increasing. This study aimed to determine the risk factors for mortality in COVID-19 patients.

**Subjects and Method:** A systematic review was conducted by searching for articles from ScienceDirect, PubMed, SpringerLink, Scopus, and Google Scholar databases. The inclusion criteria were open access, English-language, and full-text articles published in journals between December 2019 and Mei 2020. The keywords were (*Coronavirus Disease 2019 AND clinical characteristics AND epidemiological characteristics AND comorbidities*) OR (COVID-19 AND *clinical characteristics AND epidemiological characteristics AND comorbidities*). A total of eight articles was reviewed to answer the research question. The data were analyzed by PRISMA flow chart.

**Results:** Based on the reports from China and Korea, a total of 1,314 (100%) COVID-19 patients who died was aged  $\geq 60$  years with comorbidity, in which 845 (64%) were male patients. Before the death of patients, the increase D-dimer level of  $\geq 1 \mu\text{g}/\text{mL}$  and Sequential Organ Failure Assessment (SOFA) score of  $\geq 4$  was reported. It indicated the occurrence of multi-organ failure and Acute Respiratory Distress Syndrome (ARDS). Most of the comorbidities were hypertension, diabetes mellitus, and cardiovascular diseases.

**Conclusion:** Risk factors for mortality in COVID-19 patients include age at  $\geq 60$  years, male, and presence of comorbidity. The clinical features are D-dimer levels  $\geq 1 \mu\text{g}/\text{mL}$ , high SOFA score ( $\geq 4$ ), and ARDS. Comprehensive efforts are needed to identify risk factors early and conduct effective treatment timely to reduce the mortality of COVID-19 patients.

**Keywords:** SARS-CoV-2, COVID-19, risk factors, mortality, comorbidity

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## BACKGROUND

Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2, which is thought to have originated from bats (Chan et al., 2020; Shereen et al., 2020). SARS-CoV-2 infection in humans was first detected in

Wuhan City, Hubei Province, China, in mid-December 2019, which spread rapidly in China and almost worldwide. Studies showed transmission between humans through droplets and direct contact with sufferers (Carlos et al., 2020;

Wang et al., 2020). The SARS-CoV-2 infection causes acute pneumonia, multi-organ failure, and even death (Hui et al., 2020). Globally, the Crude Mortality Ratio (the number of reported deaths divided by reported cases) was estimated to be 3-4% (WHO, 2020a). WHO has designated COVID-19 as a global pandemic with 18,902,735 confirmed cases with a total of 709,511 deaths as of 7 August 2020 (WHO, 2020b).

Symptoms of COVID-19 are fever, dry cough, fatigue, malaise, shortness of breath, headache, nausea, vomiting, and diarrhea (Chan et al., 2020). The disease's severity is categorized into asymptomatic and symptomatic, which includes the spectrum of mild, severe, critical or fatal to death (Gutiérrezocampo et al., 2020). The risk of COVID-19 transmission can occur through direct contact with an asymptomatic carrier (Bai et al., 2020; Chan et al., 2020). Until now, the severity reported was mostly mild symptoms (Carlos et al., 2020).

Various studies and case reports showed that the risk of severe infection to death increases in the elderly, mostly men. Comorbidities include hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer (WHO-China Joint Mission, 2020). This study aimed to conduct a synthesis of various study results and case reports to determine the risk factors for death in

COVID-19 patients through systematic reviews.

## **SUBJECTS AND METHOD**

### **1. Study Design**

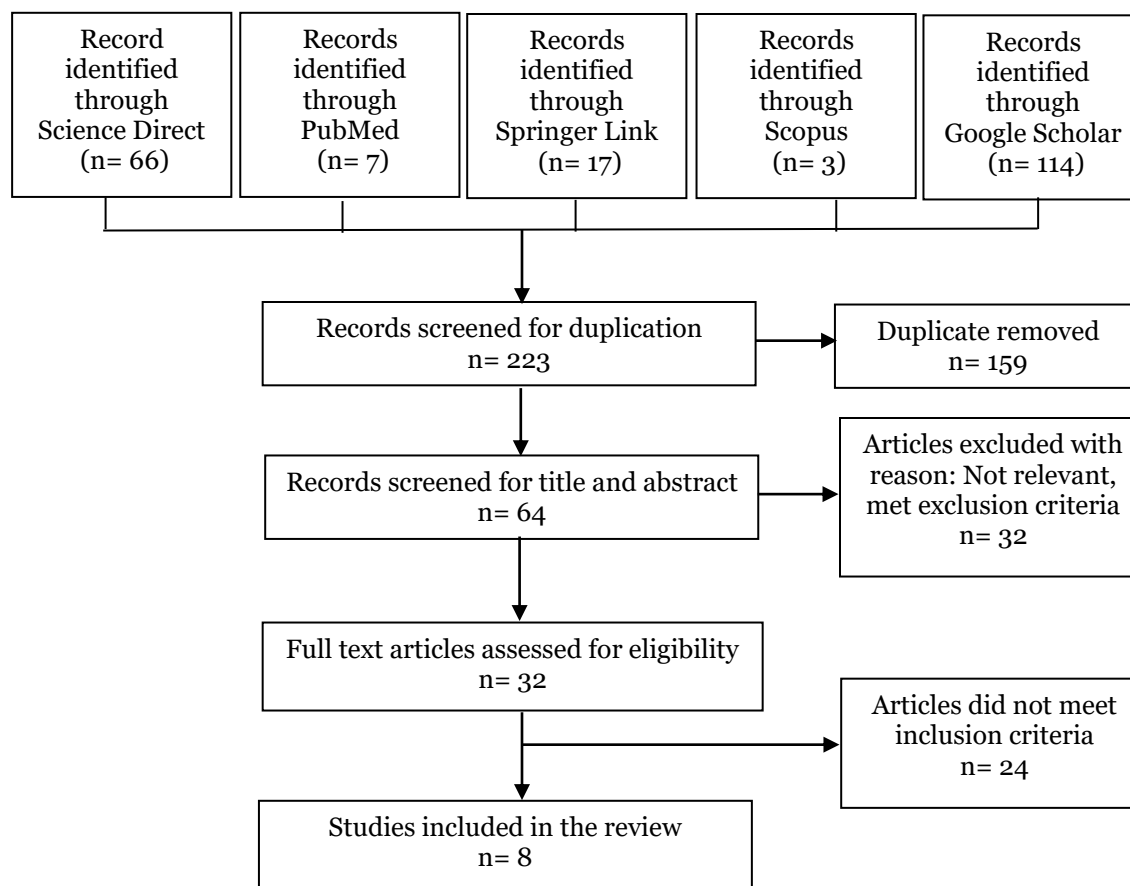
This study was a systematic review to determine the risk factors for death in COVID-19 patients. Articles were searched from database including Science Direct, PubMed, Springer Link, Scopus, and Google Scholar with keywords (Coronavirus Disease 2019 AND clinical characteristics AND epidemiological characteristics AND comorbidities) OR (COVID-19 AND clinical characteristics AND epidemiological characteristics AND comorbidities).

### **2. Inclusion and Exclusion Criteria**

The inclusion criteria included journal articles in English, open access, published between December 2019 to early 2020 with the scope of Global Health and Public Health. The design studies included were quantitative observational study results and case reports of deaths of COVID-19 patients. The exclusion criteria included journal articles that did not meet the inclusion criteria.

### **3. Data Extraction**

Journal articles in the filtered database were further identified based on the results of relevant studies. All journal articles that meet the inclusion criteria were summarized in the tabulation matrix.



**Figure 1. PRISMA Flow Chart**

## RESULTS

In the 8 journal articles analyzed, the median age of 1,314 patients dying from COVID-19 was 60 years or older, and 845 of them were male. The risk of death is increased in comorbid patients. The most common comorbidities were hypertension, diabetes mellitus, and cardiovascular disease. The reports from 4 articles showed that there was an increase in d-dimer levels of more than 1  $\mu\text{g} / \text{mL}$  in COVID-19 patients before death, and 2 journal articles showed a high SOFA score of 4 or more as an indication of multiorgan failure. 6 of the 8 journal articles mentioned before the death of

COVID-19 patients experiencing multi-organ failure and ARDS. The article searched results showed in Table 1.

## DISCUSSION

SARS-CoV-2 was identified as a new pathogen causing the global pandemic of acute pneumonia COVID-19. Of the 8 journal articles reviewed, risk factors for death from COVID-19 were associated with gender, age, presence of comorbid, and ARDS as well as clinical features of increased d-dimer levels and high SOFA scores. A total of 1,314 (100%) COVID-19 patients died aged 60 years or over, 845 (64%) among them were male.

**Table 1.** Article search results

No	Author (Year)	Title	Journal	Design study	Population, Study Time and Location	Results
1.	Zhou et al. (2020)	Clinical course and risk factors for mortality of adult in-patients with COVID-19 in Wuhan, China: a retrospective cohort	The Lancet	Cohort	191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital), from 29 Dec 2019 to 31 Jan 2020, Wuhan China	54 Patients (28.3%) died, the disease spectrum of 42 patients (78%) was critical, 100% due to multi-organ failure, 44 patients (81%) d-dimer level greater than 1 µg / mL, 50 patients (93%) had ARDS, exacerbated by comorbid Median SOFA score 4-5, Median age of the patient died 69 years, 38 patients (70%) were male, 36 patients (67%) were comorbid, most hypertensive 26 patients (48%), diabetes 17 patients (31%), coronary heart 13 patients (24%).
2.	Tu et al. (2020)	Clinicolaboratory study of 25 fatal cases of COVID - 19 in Wuhan	PubMed	Retrospective cohort	174 patients from Wuhan University Zhongnan Hospital, from 3 Jan to 24 Feb 2020, Wuhan China	25 patients (14.4%) died, 25 critical / fatal patients 14 patients (56%) due to multi-organ failure, ARDS, 24 patients (96%) d-dimer level greater than 1 µg / mL, Median age of the patient died 70 years, 19 patients (76%) were male, patients with comorbid, most hypertension 12 patients (48%), cardiovascular-cerebrovascular 8 patients (32%) and diabetes 6 patients (24%).
3.	Wu et al. (2020)	Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China	Journal of the American Medical Association	Cohort retrospective	201 patients from Jinyintan Hospital, from 25 Dec 2019 to 13 Feb 2020, Wuhan China	44 patients died of ARDS - multi-organ failure and level d - dimer more than 1 µg / mL, Median age of male patients was 68.5 years, 29 patients (65.9%) were male, patients with comorbid, the most hypertensive 16 patients (36.4%), diabetes 11 patients (25%) and cardiovascular 4 patients (9.1%).

4.	CDC Korea (2020)	Analysis on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020	Journal of Korean Medical Science	Analysis of KCDC daily press release and briefing contents from national / local government press conferences	54 fatal cases Covid-19, 10 Mar 2020, Korea	54 patients died spectrum of 54 critical/ fatal patients. 33 patients died with a median age of 75.5 years (61.1%), 49 males (90.7%). The most comorbid found 32 patients (59.3%) with cardiovascular disease (hypertension and heart), followed by 16 diabetic patients (29.6%), and 10 neurological diseases patients (dementia and stroke) (18.5%).
5.	Zhi et al. (2020)	The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China	PubMed	Cross-Sectional	72,314 cases of COVID-19 reported from China's Infectious Disease Information System, 11 Feb 2020, China	1,023 patients (2.3% of 44,672 positive cases of COVID-19) died with spectrum of disease showed 1,023 critical patients, age ranges were: <ul style="list-style-type: none"> <li>• 309 patients (30.2%) aged 60 to 69 years</li> <li>• 312 patients (30.5%) aged 70 to 79 years</li> <li>• 208 patients (20.3%) aged ≥80 years</li> </ul> The majority of 653 (63.8%) patients were male. The most occurred comorbid was hypertension (39.7%), followed by 92 patients with cardiovascular disease (22.7%) and 80 patients with diabetes (19.7%).
6.	Wang et al. (2020)	Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China	Journal of Medical Virology	Data Analysis	17 deaths due to COVID-19 reported by the National Health Commission's briefing on the pneumonia epidemic situation, 22 Jan 2020, China	17 patients died with organ failure and comorbidities. The median age was 75 years. It was reported 13 patients (76.5%) male, 11 patients (64.7%) with comorbid: 7 hypertensive patients (63.6%), 5 diabetic patients (45.5%), 5 cerebrovascular disease patients (45.5%), and 5 patients (29.4%) with history of surgery.

7.	Yang et al. (2020)	Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China : a single-centered, retrospective, observational study	The Lancet	Retrospective cohort	52 critical ICU COVID-19 patients from Wuhan Jin Yin-tan hospital, End of Dec 2019 to 26 Jan 2020, China	32 patients (61.5%) died with ARDS and organ failure. The median SOFA score was 6. The median age was 64.6 years. The majority male patients= 21 (66%), and 16 patients (50%) had comorbidities. The most patients had cerebrovascular disease = 7 patients (22%), followed by diabetes = 7 patients (22 %), and chronic cardiac disease = 3 patients (9%).
8.	Wang et al. (2020)	Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up	Journal of Infection	Retrospective cohort	339 COVID-19 patients over 60 years of age from Renmin Hospital of Wuhan University, from 1 Jan to 6 Feb 2020, China	65 patients (19.2%) died with a spectrum of disease. 60 patients (92.3%) were critical with organ failure complications and d-dimer level of more than 1 µg/ mL. 56 patients (87.5%) had ARDS. The median age was 76 years. The majority of patients were male = 39 (60%). The most comorbid found was 32 hypertensive patients (50%), 21 cardiovascular disease patients (32.8%), 11 diabetic patients (17.2%), and 10 cerebrovascular disease patients (15.6%).

The epidemiological data for the COVID-19 China Center Disease Control showed that the Case Fatality Rate (CFR) of male patients (2.8%) was higher than that of women (1.7%). This difference was associated with differences in the immune response based on sex and age (He et al., 2020).

Immunological differences based on sex contribute to variations in infectious disease susceptibility, response to viruses and disease malignancy (Fischer et al., 2015; Lotter and Altfeld, 2019). In general, women have a stronger and more adaptive immune response than men. This is related to the production of hormones sex as well as differences in the number of genes related to immunity found on the X chromosome (Ortona et al., 2019). Based on age, both men and women in the elderly showed a decreased ability to activate a strong immune response, especially against new antigens (Giefing K et al., 2015; Koff and Williams, 2020). SARS-CoV-2 infects body cells through the ACE2 receptor (Vignera et al., 2020). Several studies had shown that the spectrum of severe COVID-19 to death occurs in elderly comorbidities and most men are associated with ACE2 levels, viral load in the body and immunity (Vignera et al., 2020; Koff and Williams, 2020). ACE2 levels in women are higher than men because the ACE2 gene is attached to the X chromosome, and tends to decrease with age (Bastolla, 2020).

Clinically SARS-CoV-2 infection causes 2 phases of the immune response, including the incubation stage and the mild stage. A specific adaptive immune

response is needed to destroy the virus and prevent disease progression to a severe stage. In conditions of impaired immunity or decreased immune response, the virus will spread and cause tissue damage, especially in organs with high ACE2 expression (Shi et al., 2020). ACE2 is a protective protein in the body that catalyzes the conversion of angiotensin II to angiotensin (1-7). Angiotensin (1-7) plays a role in vasodilation, lowers blood glucose levels, lowers blood pressure, inhibits cell proliferation, protects damage to the endothelium of blood vessels, protects the cardiovascular system, protects the lungs from acid aspiration or sepsis and other physiological functions (Cure and Cumhur, 2020).

ACE2 is found in the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, large intestine, skin, lymph glands, thymus, bone marrow, spleen, liver, kidney, brain, pulmonary alveolar epithelial cells, small intestine enterocytes, endothelial cells arteries and veins, smooth muscle cells, are mostly expressed in epithelial cells of the lung and small intestine. SARS-CoV-2 infection causes degradation of the ACE2 receptor, then confuses ACE2 protein expression. Death occurs when the ACE2 level drops below a critical threshold before the body's immune system is able to control the virus population (Bastolla, 2020). In studies using mice infected with SARS-CoV-2, excess ACE2 protein expression helped viral replication and increased disease severity and death (Zhang et al., 2020). SARS-CoV-2 infection disrupts the immune response causing a cytokine storm in which immune

cells invade healthy tissue and leave fluid, white blood cells, pus, mucus, and detritus of cells that are destroyed. In the end, there is leakage of blood vessels and blood clots, hypotension, and organ failure (Wadman et al., 2020).

Blood clots can occur in the lungs (pulmonary embolism) or arteries characterized by increased d-dimer levels of more than 1 µg / mL. A high SOFA score (4 or more) indicates multi-organ failure (respiration, coagulation, liver, cardiovascular, central nervous system, and kidneys). Another consequence of the rapid viral load and the strong pro-inflammatory cytokine/ chemokine response is the induction of apoptosis in epithelial and pulmonary cells. Apoptosis of endothelial cells and epithelial cells damages the lung microvascular and alveolar epithelial cells causing leakage of blood vessels and alveolar edema, which eventually leads to hypoxia in the body, decreased oxygen levels in the blood and the patient has difficulty breathing (ARDS) (Ye et al., 2020). In the 8 journals reviewed, the most comorbid were hypertension, diabetes mellitus, and cardiovascular disease. The combination of comorbid and COVID-19 increases the risk of severity and death due to damaged vascular vessels and low ACE2 levels (Bastolla, 2020; Wadman et al., 2020).

Under normal body conditions, there is a balance in the renin angiotensin system (RAS) in which angiotensin converting enzyme (ACE) works against ACE2 (Sanchis-Gomar et al., 2020). In patients with hypertension, diabetes mellitus, and cardiovascular disease, drug therapy is carried out to in-

crease the expression of the ACE2 protein (Cure and Cumhur Cure, 2020; Fang et al., 2020). However, it got worse because the binding of SARS-CoV-2 to ACE2 increased viral load and disrupted the immune system (cytokine storm) and weakened ACE2 regulation, further leading to changes in the ACE/ ACE2 balance to the dominant ACE/ Ang II / AT1 regulation, where Ang II then triggers pulmonary vasoconstriction, inflammation, oxidative organ damage and eventually develops into ARDS which results in death (Sanchis-Gomar et al., 2020).

Based on the results of the systematic reviews of the 8 journal articles above, it is concluded that the risk factors for death in COVID-19 patients include age 60 years or more, mostly men, the presence of comorbid and ARDS and the clinical picture of an increase in d-dimer levels of more than 1 µg / mL and a high SOFA score of 4 or more. These risk factors were associated with differences in immunity based on sex and age, low ACE2 levels in the elderly and men, high expression of ACE2 protein in comorbid patients, and high viral load in the body. The mortality of COVID-19 patients can be reduced with efforts to detect risk factors early and treat them quickly and accurately. Further studies need to be done to get a more accurate picture of the risk factors for death from COVID-19.

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#### **AUTHOR CONTRIBUTION**

Authors contributed to the concept, design, analysis, and discussion of data.

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#### CONFLICT OF INTEREST

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There was no conflict of interest in this study.

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