

Risk Factors for Mortality Among COVID-19 Patients in Asia: A Literature Review

Hoirun Nisa^{*}, Adi Setya Frida Utami, Anissa Dwi Oktaviani

Faculty of Health Sciences, State Islamic University (UIN) Syarif Hidayatullah
Jakarta, Indonesia

**Email: hoirun.nisa@uinjkt.ac.id*

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ABSTRACT

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. This virus was first discovered in Wuhan, China, in December 2019, and was declared an international public health emergency by WHO on January 30, 2020. The Asian region, especially Southeast Asia, is the second-ranked region with the highest deaths of COVID-19 patients. This study aimed to determine risk factors for mortality among COVID-19 patients in the Asian region. This study was a literature review. The articles were searched using the keywords "death COVID-19 in Asia" and "mortality factor COVID-19 Asia" in the electronic databases of Science Direct and PubMed. Results of this review showed that there were two main factors of mortality among COVID-19 patients in Asia: individual characteristics and comorbidities. COVID-19 patients with older age had a higher risk of COVID-19 death. Comorbidities of COVID-19 patients that caused the most deaths in COVID-19 patients were hypertension, diabetes mellitus and heart disease.

Keywords: Asia; COVID-19 patient; death risk for COVID-19

ABSTRAK

COVID-19 merupakan penyakit menular yang disebabkan virus SARS-CoV-2. Virus ini pertama kali ditemukan di Wuhan, China tanggal 31 Desember 2019 dan dideklarasikan sebagai kedaruratan kesehatan masyarakat tingkat internasional oleh WHO pada tanggal 30 Januari 2020. WHO menunjukkan bahwa wilayah Asia terutama Asia Tenggara menjadi wilayah peringkat ke 2 dengan kejadian kematian tertinggi. Penelitian ini bertujuan untuk mengetahui faktor-faktor yang mempengaruhi kejadian kematian COVID-19 di wilayah Asia. Penelitian ini menggunakan metode *literature review*. Pencarian literatur menggunakan kata kunci "death COVID-19 in Asia" dan "mortality factor COVID-19 Asia" di pangkalan data elektronik *Science Direct* dan *PubMed*. Hasil penelitian ini menunjukkan faktor risiko kematian pada pasien COVID-19 di Asia dikelompokkan menjadi dua faktor utama yaitu karakteristik individu dan komorbiditas. Pasien COVID-19 dengan usia yang lebih tua memiliki risiko kematian COVID-19 yang lebih tinggi. Penyakit penyerta pasien COVID-19

yang menjadi penyebab kematian terbanyak pada pasien COVID-19 adalah hipertensi, diabetes melitus, dan penyakit jantung.

Kata kunci: Asia; pasien COVID-19; risiko kematian COVID-19

INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (Zhou, 2020). Common symptoms are fever, tiredness, dry cough, nausea, diarrhoea and cannot smell (CDC, 2020). Severe symptoms include acute respiratory syndrome, pneumonia and kidney failure, leading to death. This virus is transmitted through infected droplets or contaminated surfaces (Kemenkes RI, 2020a). This virus was discovered in Wuhan, China, on December 31, 2019 (Kemenkes RI, 2020b). The spread of COVID-19 in various countries has been declared an international public health emergency by WHO since January 30, 2020 (Worldometer, 2020).

Globally, the total COVID-19 cases have been more than 34.8 million. The number of deaths due to COVID-19 has been reported to have reached more than 1 million confirmed cases on October 4, 2020. Based on data from newly reported and cumulative COVID-19 cases and deaths by WHO, it is revealed that the Asian region, especially Southeast Asia, is the second-ranked region with the highest mortality (WHO, 2020). In addition,

COVID-19 cases in the Asian region is also in line with the increasing number of deaths due to COVID-19. In the Southeast Asian region, new deaths within seven days until October 4, 2020, reached 8,456 deaths. In the Eastern Mediterranean region, it reached 2,804 deaths, and in the Western Pacific region, it reached 503 deaths due to COVID-19 (WHO, 2020). Previous research found that the multivariable regression analysis showed an increase in the probability of death among COVID-19 patients in hospitals with older age and the presence of sequential organ failure (Zhou et al., 2020a). Globally, the highest proportion of COVID-19 cases was 25-39 years, and approximately 50% of cases were in the 25-64-year age group. However, the risk of COVID-19 deaths increases with age, and 75% of deaths occur in the age of 65 years and over (WHO, 2020). This study reviewed risk factors for mortality among COVID-19 patients in the Asian region.

METHOD

This study used the Literature Review method for identifying, analyzing, evaluating, and interpreting all research

results that have been carried out completely, regularly and thoroughly (Kitchenham, 2004). Meanwhile, the approach used was a qualitative approach to synthesize research results that were descriptive qualitative. This method of synthesizing the results of qualitative research was called "meta-synthesis".

The literature search was conducted in September-November 2020 using the Science Direct and PubMed electronic databases. The keywords used in this study were "Death COVID-19 in Asia" and "Mortality Factor COVID-19 Asia". The articles were selected based on inclusion

and exclusion criteria. The search yielded 1,686 articles. After being excluded based on the inclusion and exclusion criteria, 29 articles were included in the analysis and 1,657 articles were excluded (Figure 1). The inclusion criteria were (1) articles with all types of research methods, (2) related to risk factors for death in COVID-19 patients, (3) published in December 2019-2020, (4) conducted in Asia, and (5) articles were fully accessible (full text). An article was excluded if (1) not published by an international journal and does not explain risk factors for death in COVID-19 patients, and (2) research was not conducted in Asia.

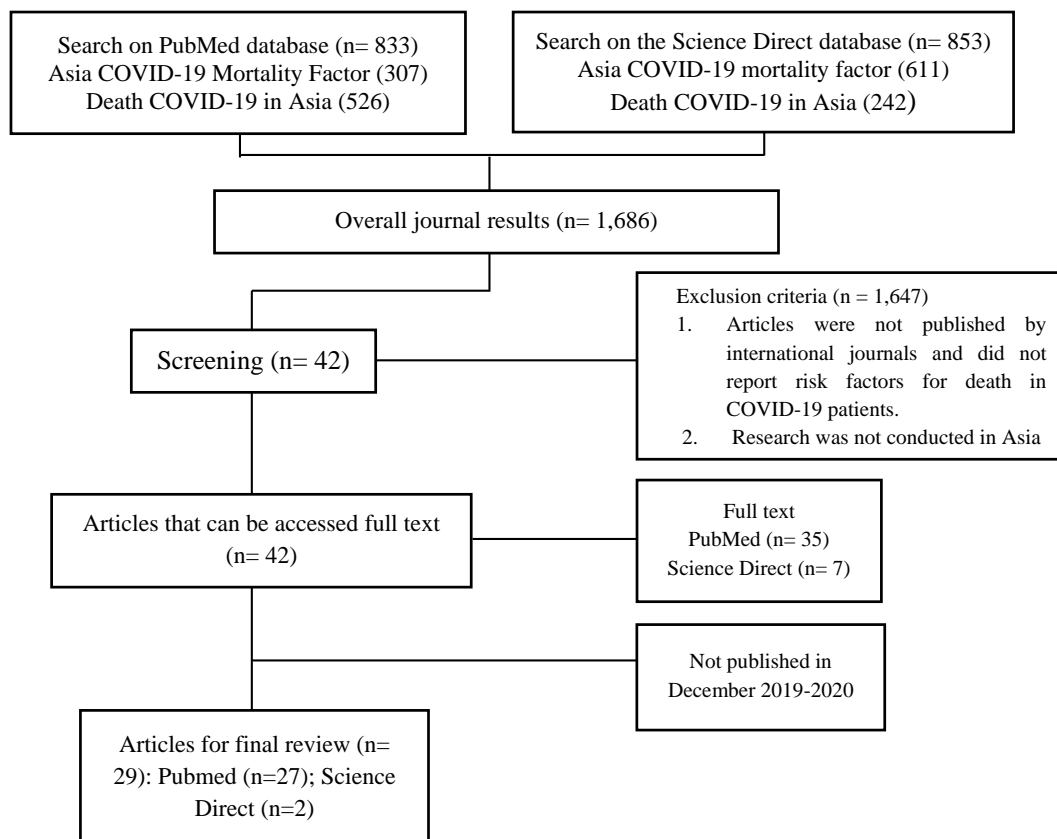


Figure 1. The articles selection process for review

RESULTS AND DISCUSSION

The articles search yielded 29 articles that met the inclusion criteria. The risk factors for death in COVID-19 patients in Asia were grouped into two main factors: individual characteristics and

comorbidities. The results of individual characteristics by age, gender, and the number of deaths among COVID-19 patients in Asia are illustrated in Table 1.

Table 1. Distribution of the frequency of deaths of COVID-19 patients in Asia in 2020

Researcher	Country	Study Design	Characteristics		Number of Deaths
			Age (Years)	Gender	
B. Zhang et al	China	Cohort Retrospective	< 60 (19.5%) 60 – 80 (56.1%) > 80 (24.4%)	Male (65.9%)	82 case
Lee et al	South Korea	Cross Sectional	< 60 (0%) 60 – 80 (60%) > 80 (40%)	Male (61.5%)	27 case
Alamdari et al	Iran	Cross-Sectional	70.58 ± 10.66	Male (77.8%)	63 case
Q. Li et al (Q. Li et al., 2020)	China	Cross Sectional	< 65 (65%) ≥ 65 (36%)	Male (100%)	209 case
Y. Li et al	China	Cohort Retrospective	< 65 (46.2%) ≥ 65 (53.8%)	Male (53%)	15 case
Gao et al	China	Cohort Retrospective	71 (67 – 77)	Male (63%)	35 case
Kim et al	South Korea	Cohort	< 60 (9.2%) 60 – 80 (46.1%) > 80 (44.6%)	Male (51%)	130 case
Guan et al	China	Cohort Retrospective	60.8 ± 13.4	Male (57.3%)	50 case
Pan et al	China	Cohort Retrospective	≤ 68 (47.2%) > 68 (52.8%)	Male (75.3%)	89 case
Chen et al	China	Case Series Retrospective	< 60 (17%) ≥ 60 (83%)	Male (73%)	113 case
K. Yang et al	China	Cohort	< 60 (43%) 60 – 80 (50%) > 80 (8%)	Male (73%)	40 case
Wei et al	China	Cohort	67 (61.0 – 80.5)	Male (100%)	3 case
Nasir, Farooqi et al	Pakistan	Studi Observasi Retrospektif	< 60 (50%) 60 – 80 (0%) > 80 (50%)	Male (75%)	4 case
Yu et al	China	Cohort	< 65 (30.7%) ≥ 65 (69.3%)	Male (70.7%)	212 case
X. Yang	China	Retrospective Observational	< 60 (37%) 60 – 80 (56%) > 80 (6%)	Male (66%)	32 case
We et al	China	Cohort	< 65 (80.1%) ≥ 65 (19.9%)	Male (63.7%)	44 case

Researcher	Country	Study Design	Characteristics		Number of Deaths
			Age (Years)	Gender	
Cheng et al	China	Cohort	63 (50 – 71)	Male (52.4%)	113 case
Zhou et al	China	Cohort Retrospective	69 (63 – 76)	Male (70%)	54 case
R.-H. Du et al	China	Cohort Prospective	6.35 ± 4.51	Male (54.1%)	21 case
Shi et al	China	Cohort	64 (21 – 95)	Female (50.7%)	57 case
Wang et al	China	Cohort Retrospective	< 60 (25%) 60 – 80 (75%) > 80 (0%)	Male (100%)	4 case
Albitar	China	Cohort Retrospective	< 65 (20%) ≥ 65 (80%)	Male (59.1%)	219 case
L. Zhang et al	China	Cohort Retrospective	62 (48 – 69)	Female (50.7%)	13 case
Guo et al	World	Cohort Retrospective	58.5 (14.66)	Male (48.7%)	43 case
Y. Du et al	China	Observational Retrospective	65.8 (14 – 86)	Male (72.9%)	85 case
Xie et al	China	Cohort Retrospective	60 (47 – 68)	Male (51.4%)	36 case
Sun et al	China	Case-Control Retrospective	72 (66 – 78)	Male (67.8%)	121 case
X. Yang et al	China	Cohort Retrospective	67 (59 – 75)	Male (65.5%)	234 case
Meng et al	China	Cohort Retrospective	< 60 (19.2%) 60 – 80 (56.1%) > 80 (24.4%)	Male (59.3%)	32 case

Table 1 shows that deaths from COVID-19 mainly occur in the age group over 60 years. In addition, most of the deaths occurred in male. The risk of death from COVID-19 is often associated with advanced age, and several studies reveal that age was significantly associated with COVID-19 mortality (Alamdari et al., 2020; Gao et al., 2020; Guo et al., 2020; Sun et al., 2020; Wei et al., 2020; Xie et al., 2020; X. Yang et al., 2020a; L. Zhang et al., 2020). Another study showed that those aged 80 years had a two times greater risk of dying from COVID-19 than those aged

49 years (Meng et al., 2020). In addition, another study found that those aged 65 years had a 3.765 times greater risk of dying from COVID-19 (R.-H. Du et al., 2020). It was found in another study that there was a correlation between age and risk of dying from COVID-19 OR 1.079 95% CI (1.064 – 1.095) (Albitar et al., 2020).

Increasing age causes various organ functions in the human body to decrease so that the elderly become an age group with an immune system that is susceptible to disease. A decreased immune system can

make the elderly susceptible to infection with various microorganisms, including the SARS-CoV-2 virus. In elderly COVID-19 patients, it can cause changes in respiratory anatomy and physiology, such as elasticity and lung capacity, leading to respiratory failure in patients. Thus, older age may be related to the higher risk of deaths from COVID-19.

Several studies have reported that the male have higher risk of deaths from COVID-19

with an OR of 1.607 CI 95% (1.002 – 2.576), meaning that the male group has a risk 1.6 times greater than the female group (Albitar et al., 2020). Another study found that gender was significantly associated (p-value < 0.05) with the incidence of COVID-19 deaths (Cheng et al., 2020; Guo et al., 2020; Kim et al., 2020; Pan et al., 2020; Sun et al., 2020; X. Yang et al., 2020b, 2020a; Yu et al., 2020). The higher risk of deaths in men might be related to men suffer from chronic diseases more than women.

Table 2. Description of factors contributing to death in COVID-19 patients in Asia in 2020

Researcher	Country	Risk Factors for COVID-19 Deaths
B. Zhang et al	China	Most of the patients who died had comorbidities (76.8%). Comorbid conditions included hypertension (56.1%), heart disease (20.7%), DM (18.3%), cerebrovascular disease (12.2%) and cancer (7.3%) (B. Zhang et al., 2020).
Lee et al	South Korea	Among comorbidities, diabetes (OR=4.74) and chronic lung disease (OR=8.33) were significantly associated with mortality (Lee et al., 2020).
Alamdari et al	Iran	Mortality rates were much higher among patients suffering from comorbidities such as diabetes, cancer and Chronic Kidney Disease (CKD) (Alamdari et al., 2020).
Q. Li et al	China	Cancer was significantly associated with the risk of dying in hospitals from COVID-19 (HR = 2.45 95% CI 1.04 – 5.76; p-value = 0.041) (Q. Li et al., 2020).
Y. Li et al	China	Hypertension was the most common comorbid (64.4%), followed by cardiovascular disease (13.6%) and cerebrovascular (9.1%) (Y. Li et al., 2020).
Gao et al	China	The dead from COVID-19 had a significant relationship with comorbidities, namely cardiovascular disease, respiratory disease, cerebrovascular disease and chronic kidney disease (p-value <0.001) (Gao et al., 2020).
Kim et al	South Korea	The highest proportion of comorbid COVID-19 patients had acute bronchitis (53.5%). COVID-19 patients had comorbidities, the highest odds ratio for death with sepsis (OR=3.60), heart failure (OR=3.17), kidney failure (OR=3.07), pneumonia (OR=2.29), diabetes mellitus (OR=1.82), ischemic heart disease (OR=1.71) and acute laryngitis (OR=1.71) (Kim et al., 2020).
Guan et al	China	The most comorbidity was hypertension (16.9%), followed by diabetes (8.2%). Diabetes (HR=1.59 (95% CI 1.03–2.45)) and hypertension (HR=1.58 (95% CI 1.07–2.32) were risk

Researcher	Country	Risk Factors for COVID-19 Deaths
		factors for reaching the composite endpoint (Guan et al., 2020).
Pan et al	China	ARDS was dominant in the death group. A total of 71.8% with ARDS complications died (Pan et al., 2020).
Chen et al	China	Chronic hypertension and other cardiovascular comorbidities were common in patients who died (48%) and (14%) (Chen et al., 2020).
K. Yang et al	China	Cancer patients who received chemotherapy within four weeks before symptom onset (OR = 3.51 [95% CI 1.16-10.59]; p = 0.026) were a risk factor for death during hospital admission (K. Yang et al., 2020).
Wei et al	China	All three deaths occurred in patients with acute myocardial injury (Wei et al., 2020).
Nasir, Farooqi et al	Pakistan	The cause of death was ARDS in all three patients with COVID-19 Associated Pulmonary Aspergillosis (CAPA) (Nasir et al., 2020).
Yu et al	China	An increased chance of dying from COVID-19 was associated with a history of diabetes (OR = 2.34, 95% CI = 1.45-3.76) (Yu et al., 2020).
X. Yang	China	The non-survivor group (died) had disease complications such as Acute Respiratory Distress Syndrome (ARDS), acute kidney injury, hyperglycemia, heart injury and impaired liver function (X. Yang et al., 2020b).
We et al	China	Risk factors associated with the development of ARDS to death (HR: 6,17; CI 95% 3,26-11,67) (Wu et al., 2020).
Cheng et al	China	COVID-19 patients with kidney disease had a significantly increased risk of death (Cheng et al., 2020).
Zhou et al	China	Patients had comorbidities, with hypertension being the most common (30.0%), followed by diabetes (19.0%) and coronary heart disease (8.0%) (Zhou et al., 2020b).
R,-H. Du et al	China	Patients who already had the cardiovascular or cerebrovascular disease (OR=2.464, 95% CI 0.755–8.044; p = 0.007) and cardiac troponin I 0.05 ng • mL 1 (OR=4.077, 95% CI 1.166–14.253; p <0.001) was associated with an increased risk of death from COVID-19 (R.-H. Du et al., 2020).
Shi et al	China	Heart injury was an independent risk factor for COVID-19 death in hospitals (Shi et al., 2020).
Wang et al	China	Pneumothorax was a frequent complication and cause of death in critically ill patients with COVID-19 (Wang et al., 2020).
Albitar	China	Patients with hypertension (OR, 3,576; 95% CI, 1,694–7,548) and patients with diabetes mellitus (OR, 12,234; 95% CI, 4,126–36,272) were independent risk factors for death among COVID-19 patients (Albitar et al., 2020).
L. Zhang et al	China	Patients with D-dimer levels ≥ 2.0 g/ml had a higher incidence of death when compared to those with D-dimer levels < 2.0 g/ml (HR=51.5, 95% CI: 12.9-206.7) (L. Zhang et al., 2020).
Guo et al	World	Myocardial injury was significantly associated with COVID-19 fatal outcome (Guo et al., 2020).

Researcher	Country	Risk Factors for COVID-19 Deaths
Y. Du et al	China	Hypertension, diabetes, and coronary heart disease are the most common comorbidities. Most patients died from multiple organ failure (Y. Du et al., 2020).
Xie et al	China	Dyspnea was independently associated with mortality in a multivariable analysis (HR = 2.60; 95% CI, 1.24-5.43; P = 0.01) (Xie et al., 2020).
Sun et al	China	Lower lymphocyte count (LYM) (p value=0.001) was independently associated with mortality in hospitalized COVID-19 patients (Sun et al., 2020).
X. Yang et al	China	Thrombocytopenia was common in COVID-19 patients and was associated with an increased risk of in-hospital death. The lower the platelet count, the higher the mortality (X. Yang et al., 2020a).
Meng et al	China	COVID-19 patients with cancer showed a significant increase in mortality (P < 0.0001). Cancer patients had a higher risk of death than non-cancer patients (OR=2.98, 95% confidence interval (95% CI) 1.76-5.06) (Meng et al., 2020).

Table 2 describes the comorbidities that related with deaths in COVID-19 patients in Asia in 2020. Based on Table 2, it was shown that death from COVID-19 was caused by age, but comorbidities were the main factors that might exacerbate or increase the risk of death for COVID-19 patients. Comorbidities are other illnesses experienced by patients before being infected with COVID-19. Patients who died from COVID-19 had at least one or more comorbidities. Comorbidities are often associated with an independent risk of death among COVID-19 patients. Several studies have shown that comorbidities such as hypertension, diabetes mellitus, heart disease, cardiovascular disease, cerebrovascular disease, kidney disease, and respiratory disease were significantly associated with the risk of death of COVID-19 patients. Another study also found that

cancer was significantly associated (p-value <0.05) with the risk of death among COVID-19 patients (Q. Li et al., 2020; Meng et al., 2020; K. Yang et al., 2020).

The study by Albitar et al (2020) found that the risk factor for death in COVID-19 patients with comorbid hypertension had a 3.576 times greater risk of death from COVID-19 than those without comorbid hypertension (OR, 3.576; 95% CI, 1.694-7.548) and patients with diabetes mellitus had a 12.234 times greater risk of death from COVID-19 than those without comorbid diabetes mellitus (OR, 12.234; 95% CI, 4.126-36.272) (Albitar et al., 2020). Patients with comorbidities such as hypertension or diabetes who were being treated were at higher risk of developing severe COVID-19 infection (Zhou et al., 2020b). In addition, death cases were also

found in patients with comorbid cardiovascular and cerebrovascular diseases (R.-H. Du et al., 2020).

Cardiovascular diseases such as hypertension are diseases in which the systolic and diastolic blood pressure rises more than normal. Hypertension will result in impaired oxygen perfusion to all body tissues. Hypertension can be caused by ischemia of heart tissue (coronary heart disease) and rupture of cerebral blood vessels (B. Zhang et al., 2020). Diabetes mellitus is a disease in which blood glucose levels rise more than usual (hyperglycemia). Diabetes mellitus can increase blood viscosity/clotting, which results in the retention of blood flow that functions as a carrier of oxygen and nutrients to all body tissues. Coronary heart disease is a disease of the heart's blood vessels and can cause ischemia or death of heart tissue.

The SARS-Cov-2 virus that causes COVID-19 is replicating, infecting the respiratory system. COVID-19 becomes severe when the infectious process attacks the lungs' alveoli (pneumonia). In the pathophysiology of the disease, the body will release various compounds, especially the immune system, to fight infection reactions, namely white blood cells and

lymphocytes. The body's immune system can enter the area of injury or infection through the bloodstream. Patients with hypertension and diabetes mellitus experience problems with the circulatory system. Circulatory disorders due to hypertension and diabetes mellitus make it difficult for white blood cells and lymphocytes to reach the wound area. This condition allows injury due to infection with the SARS-CoV-2 virus in lung tissue to spread.

On the other hand, the healing process of lung tissue injured due to COVID-19 infection has been delayed because the supply of oxygen and nutrients for wound healing is hampered. This condition occurs because tissue perfusion in patients with hypertension and diabetes mellitus has problems. If not treated promptly, all these conditions may increase the risk of a widespread infection, organ failure, and death in patients with severe COVID-19.

CONCLUSION

This review concluded that individual characteristics and comorbidities affect mortality from COVID-19. The older the individual, the higher the risk of death from COVID-19. Comorbidities such as hypertension, diabetes mellitus, heart disease, cardiovascular disease,

cerebrovascular disease, kidney disease, respiratory disease and cancer were associated with the risk of death in COVID-19 patients. The comorbidities that caused the most deaths in COVID-19 patients were hypertension, diabetes mellitus and heart disease. This review suggested improving COVID-19 prevention measures with special reference to an individual with older age and having comorbidities.

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