

# The Impact of Hypertension Severity on Mortality Rate in Covid-19: A Literature Review

Alyssa Mutia Mutiara<sup>a</sup>, Rahmania Kemala Dewi<sup>b\*</sup>, Pradana Zaky Romadhon<sup>c</sup>

<sup>a</sup> alyssa.mutia.mutiara-2020@fk.unair.ac.id

<sup>a</sup>Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

<sup>b</sup>Forensic medicine and medicolegal science, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

<sup>c</sup>Department of internal medicine, Faculty of Medicine, Airlangga University, Surabaya 60132, Indonesia

## Abstract

Background: On January 30, 2020, the 2019 coronavirus epidemic (2019-nCoV) was assessed as potentially harmful to humans by the World Health Organization (WHO). On the same date, the WHO also stated that 7,818 cases had been reported and 170 deaths had been recorded. On March 11, 2020, WHO published that the coronavirus disease outbreak was categorized as a pandemic. (WHO, 2021) The Indonesian state recorded that the first Indonesian citizen who was declared infected with COVID-19 came from Depok City on March 2, 2020 COVID-19 patients with comorbid or comorbid diseases have a higher mortality rate compared to patients without congenital diseases. One of the most common comorbidities found in COVID-19 patients is hypertension. The prevalence of COVID-19 patients with hypertension reached 56.6%.

Keywords: Hypertension, Mortality, Covid-19

## 1. Introduction

Coronavirus is an infectious disease that targets the human respiratory system caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). (Rothan & Byrareddy, 2020) This disease originated in China, precisely in Wuhan City, in late December 2019, where the Chinese government found new pneumonia cases with unknown causes. Based on the results of epidemiological studies, it is thought that there is a link between this disease and animals (zoonosis). The Chinese state determined that the trigger for the incident was the new coronavirus. Which we now know as SARS-CoV-2 (1)

On 30 January 2020, the 2019 coronavirus (2019-nCoV) epidemic was rated as potentially dangerous to humans by the World Health Organization (WHO). On the same date, WHO also stated that 7,818 cases had been reported and 170 deaths had been recorded. On 11 March 2020, WHO published that the coronavirus disease outbreak was categorised as a pandemic. (WHO, 2021) The country of Indonesia recorded the discovery of the first Indonesian citizen who was declared infected with COVID-19 from Depok City on 2 March 2020 (1).

In comorbid hypertension, there is increased expression of ACE-2 receptors, making it more susceptible to COVID-19 infection. The vascular system, electrolyte balance and blood pressure are regulated by ACE-2. SARS-CoV-2 using ACE2 receptors results in reduced effectiveness of ACE-2 which inhibits the formation of angiotensin thus disrupting blood pressure homeostatis and causing vasoconstriction and worsening the condition of high blood pressure.6 In SARS-CoV-2 infection, angiotensin II in lung tissue increases so that vascular permeability also increases which can result in pulmonary oedema characterised by pneumonia and shortness of breath. This can lead to Acute Respiratory Distress Syndrome (ARDS) with a risk of death. In patients with comorbid hypertension, there can be immune disorders that cause cytokine storms, leading to complications of multi-organ failure leading to death (2).

This study aims to determine the magnitude of the relationship between hypertension and COVID-19 death by calculating the Hazard Ratio Adjusted (HRA<sub>adjusted</sub>), after being controlled with confounding variables, namely other variables that can interfere with the relationship between comorbid hypertension and death in COVID-19 cases. This can provide a scientific basis in prioritising the prevention of COVID-19 in groups of people with hypertension.

## 2. Method

This literature review was made by collecting, reviewing, and citing related journals. The journals were obtained through searches from the Google Scholar and Pubmed search engines. The keywords used in the search include "Hypertension", "Covid-19 mortality". The journals used were published in the range of 2015-2023. From the search results, 15 journals were obtained and reviewed.

## 3. Result

The literature search through the data base obtained 15 articles that will be reviewed in this study. A summary of the articles reviewed in this study can be seen in Table 1.

Table.1 Summary of articles reviewed

Title	Author	Objective	Design	Sampling	Main Finding
Relationship between Hypertension and Mortality of Covid-19 Patients in South Tangerang	Choirunnisaa, Helda, 2021 (3)	To determine the relationship between hypertension with mortality of Covid-19 patients in South Tangerang	Case-control analytic study using secondary data from the epidemiological tracing (PE) of the South Tangerang City Health Office in March 2020-July 2021. South Tangerang in March 2020-July 2021.	688 samples	The results of bivariate analysis showed that patients with Covid-19 patients who have hypertension have a risk of 9.15 (95%CI 5.80-14.74) times to experience death compared to Covid-19 patients who do not have hypertension
The Relationship between Hypertension and Mortality Rate of Covid-19 Patients at RSUD DR. Slamet Garut in 2020-2021	Luciyati et al, 2023 (1)	To analyse the association of hypertension with the mortality rate of covid-19 patients at RSUD dr. Slamet Garut in 2020-2021.	Cross sectional	117 people	Data were analysed using the Chi-Square Test which was conducted using SPSS 25 software. There is no relationship between hypertension and mortality of COVID-19 patients ( $p=0.0870$ ).
Associations of Comorbid Hypertension with Mortality in Confirmed Cases of COVID-19 in DKI Jakarta, March-August 2020	Wulandari et al, 2021 (2)	To determine the magnitude of the association between hypertension and COVID-19 death by calculating the Hazard Ratio Adjusted (HRAjusted), after controlling for confounding variables, namely other variables that can interfere with the relationship between comorbid hypertension and death in COVID-19 cases.	Retrospective cohort	1918 samples	COVID-19 cases with comorbid hypertension have a 2.2 times risk of death compared to COVID-19 cases without comorbid hypertension (HR 2.2 $P_v < 0.001$ 95% CI 1.66-3.87) after controlling for confounding variables of comorbid chronic renal failure, age group, clinical symptoms of shortness of breath, malaise and pneumonia.
Association of Hypertension with All-Cause Mortality among Hospitalized Patients with COVID-19	Rodilla et al, 2020 (4)	The main objective of this study was to analyse whether HT is an independent risk factor for of death as a hard endpoint in patients hospitalised for SARS-CoV-2 in Spain. More specifically, it sought to examine the effect of previous treatment	A cross-sectional, observational, retrospective, multicentre study analysing 12226 patients requiring hospitalisation in 150 health centres in Spain included in the national SEMI-COVID-19 Network	12226 patients	Multivariate analysis showed that after adjusting for gender (male, OR: 1.5, $p=0.0001$ ), age tertile (second and third tertile, OR: 2.0 and 4.7, $p=0.0001$ ), and Charlson Comorbidity Score index (second and third tertile, OR: 4.7 and 8.1, $p=0.0001$ ), hypertension was significantly predictive of all-cause mortality when this comorbidity was treated with angiotensin converting enzyme inhibitors (ACEI) (OR: 1.6, $p=0.002$ ) or other than renin-

		with ACEI/ARB on these patients. In addition, the relationship between HT and ACEI/ARB and admission and/or assisted intensive care unit (ICU) ventilation was analysed. ventilation analysed			angiotensin inhibitors. enzyme inhibitors (ACEI) (OR: 1.6, p = 0.002) or other than renin-angiotensin-aldosterone blockers
Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study	Gao et al, 2020 (5)	To determine whether hypertension treatment affects the mortality of patients diagnosed with coronavirus disease 2019 (COVID-19).	Retrospective	2877 patients	Results showed that patients with RAAS inhibitor use tended to have a lower risk of death (relative risk 0.65, 95% CI 0.45-0.94, P = 0.02).
Association of Hypertension with Severity and Mortality in Hospitalized Patients with COVID-19 in Wuhan, China: A Single-centered, Retrospective Study	Deng et al, 2021 (6)	To determine the association between hypertension and severity/death in hospitalised patients with COVID-19 in Wuhan, China.	Restrospective	337 patients	Patients with hypertension showed a significantly higher proportion of severe cases (69 [61.6%, 95%CI:52.5%-70.8%] vs. 117 [52.0%, 95%CI:45.4%-58.6%] in severe patients and 23 [19.3%, 95%CI:12.9%-28.1%] vs. 27 [12.0%, 95%CI:7.7%-16.3%] in critical patients, p=0.0014) and a higher mortality rate. 27 [12.0%, 95%CI: 7.7%-16.3%] in critical patients, p=0.0014) and higher mortality rates (20 [17.9%, 95%CI: 10.7%- 25.1%] vs. 20 [8.9%, 95%CI: 5.1%-12.6%, p=0.0202). In addition, hypertensive patients showed abnormal levels of various indicators, such as lymphopenia, inflammation, heart, liver, kidney, and lung function on admission. The hypertensive group still showed higher levels of TnT and creatinine towards hospital discharge.
Hypertension and Risk Factor to Mortality in Coronavirus Disease (Covid-19)	Oliveira et al, 2023 (7)	The aim of this study was to assess whether hypertension is considered a risk factor for mortality in adult patients with COVID-19 hospitalised for acute respiratory distress syndrome (ARDS).	Retrospective	134 patients	Two hundred and two consecutive patients were admitted for mild or moderate COVID-19-related ARDS and were included in this study. The mean age of the studied population was 69.1 ± 14.8 years. Of these, 130 patients (64.4%) were male. The mean BMI was 29.9 ± 6 kg/m <sup>2</sup> . Hypertension occurred in 134 patients, equivalent to 67% of the studied population. 35.8% of patients had diabetes and 10.45% had dyslipidaemia. Among the hypertensive patients, 58 (74%) died, with a relative risk of 1.45 (CI 0.96-2.2).
The effect of resistant hypertension on in-hospital mortality in patients	Isik, et al 2022 (8)	In this study, we aimed to examine the influence of in-hospital ResHT on mortality in patients hospitalised for	Retrospective	1897 patients	In multivariable analysis, ResHT was independently associated with a significantly increased risk of inpatient death due to COVID-19, while no significant increased risk was

hospitalized with COVID-19		COVID-19.			observed with RegHT [respectively, Odds Ratio (OR) = 2.013, Confidence Interval (CI) 1.085-3.734, p=0.026 and OR=1.194, CI 0.795-1.794, p=0.394].
COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study	Huang et al, 2020 (9)	This study aims to explore the influence of hypertension on disease progression and prognosis in patients with coronavirus disease 2019 (COVID-19).	Retrospective	310 patients	The number of neutrophils and lactate dehydrogenase, fibrinogen, and D-dimer levels in hypertensive patients were significantly higher than those in non-hypertensive patients (P < 0.05). However, multivariate analysis (adjusted for age and sex) failed to show that hypertension was an independent risk factor. COVID-19 mortality or severity.
The association between blood pressure levels and mortality in critically ill patients with COVID-19 in Wuhan, China: a case-series report	Geng et al, 2021 (10)	To determine the relationship between blood pressure levels and mortality of critically ill patients with Covid -19	Study case	123 patients	There is a significant relationship between stage 3 hypertension patients and the death of patients when critical who suffer from Covid-19
Symptoms and comorbidities affecting mortality of COVID-19 positive patients in East Jakarta, March-September 2020	Adisasmita & Drew, 2021 (11)	To identify risk factors that increase the risk of mortality in the	Retrospective cohort	8393 samples	Multivariate data analysis with logistic regression found that male gender increased the RR of mortality by 2.15 (95% IK: 1.47-3.14), age ≥60 years by 4.49 (95% IK: 3.05-6.63), presence of respiratory tract symptoms by 2.17 (95% IK: 1.26-3.72), presence of symptoms outside the respiratory tract by 2.47 (95% IK: 1.43-4.29), history of hypertension by 2.45 (95% IK: 1.46-4.10) and history of chronic renal failure by 3.33 (95% IK: 1.27-8.68).
Symptoms and comorbidities affecting mortality of COVID-19 positive patients in East Jakarta, March-September 2020	Fanani et al, 2022 (12)	To examine the relationship between comorbidities and mortality rates with COVID-19. Identifying the relationship of these comorbidities will certainly help educate comorbid patients to be more careful.	Retrospective	677 samples	The statistical test results showed a significant relationship between comorbidities (p=0.000), cardiovascular disease (p=0.000), hypertension (p=0.000), diabetes mellitus (p=0.000) with the mortality rate of COVID-19 patients. This study shows that many COVID-19 patients die in women aged 51-60 years, working.
Factor Analysis of Mortality with Covid-19 Comorbid Diseases	Satria et al, 2020 (13)	To analyze comorbid diseases as risk factors for death from COVID-19 at Bhakti Dharma Husada Hospital Surabaya	Retrospective	358 samples	358 patients were infected with COVID-19 and confirmed by nose and/or throat swabs. 66 patients (18%) died from COVID-19. 60.6% were male (OR 1.87, P 0.041), 22.7% were >64 years old (OR 2.097, P 0.041), and 83.3% had comorbid risk factors. Diabetes mellitus (30.3%) (OR 4.348, P 0.000), and cardiovascular disease (10.6%) (OR 4.319, P 0.016) were the highest risk factors for death in COVID-19.
Hypertension as a Single Comorbidity is a Risk Factor for COVID-19 Mortality: A Case-Control Study	Salha et al, 2023 (14)	Analyzed the risk factors for hypertension in COVID-19	Case control	322 samples	COVID-19 patients died in the elderly as many as 151 people (93.8%), 83 women (51.5%) and had comorbid hypertension 87

		mortality by controlling for age and gender.			people (54%). Comorbid hypertension in the case group was 87 people (54.0%), while the control group was 24 people (14.9%). Hypertension has a significant relationship with COVID-19 mortality ( $p=0.000$ ) with OR 6.711. The conclusion of this study is that COVID-19 patients with a single comorbid hypertension have a 6 times higher risk of dying than other patients of the same age and gender.
Risk of hospitalization and mortality associated with uncontrolled blood pressure in patients with hypertension and COVID-19	Zhou et al, 2021(15)	The role of uncontrolled blood pressure (BP) on the severity of COVID-19 in hypertensive patients is unclear. We evaluated the association between uncontrolled blood pressure and the risk of hospitalization and/or mortality in patients with hypertension from a large integrated healthcare system in the US.	Retrospective cohort	12548 patients	Among 12,548 hypertensive and COVID-19 patients (mean age = 60 years, 47% male), 63% had uncontrolled blood pressure ( $\geq 130/80$ mm Hg) before COVID-19. Twenty-one percent were hospitalized or died within 30 days of COVID-19 infection. Uncontrolled blood pressure was not associated with higher hospitalization or mortality. (adjusted rate ratio for blood pressure $\geq 160/100$ mm Hg vs $< 130/80$ mm Hg = 1.00 [95% CI: 0.87, 1.14]; blood pressure 140-159/90-99 mm Hg vs $< 130/80$ mm Hg = 1.02 [95% CI: 0.93, 1.11]). These findings were consistent across different age groups, antihypertensive drug treatment, as well as risk of atherosclerotic cardiovascular disease.

#### 4. Discussion

Choirunnisaa, Helda, 2021 (3) The results of bivariate analysis showed that Covid-19 patients who had hypertension were at risk of 9.15 (95% CI 5.80-14.74) times experiencing death compared to Covid-19 patients who did not have hypertension. Hypertension is an inflammatory disease characterized by endothelial dysfunction. This can lead to an increased risk of severity and death.<sup>17</sup> In addition, hypertensive patients have higher ACE 2 expression, which increases the risk of death from Covid-19 infection. ACE 2 is a receptor for the virus that causes Covid-19 which is found in several specific organs that can cause organ failure.

Luciyati et al, 2023 (1) Using Chi-Square analysis, statistical analysis revealed that there was no significant correlation between hypertension and mortality of COVID-19 patients, with a significance value of 0.087 ( $p > 0.05$ ). In some patients, hypertension generally does not stand alone but together with other comorbidities, so the relationship between hypertension and mortality of patients suffering from COVID-19 independently is difficult to determine. These results are also in line with research conducted by Azhar et al who found that there was no relationship between comorbid hypertension and the risk of death in Covid-19 patients. His research revealed that the chance of death for COVID-19 patients who have comorbid hypertension is 0.4 times greater than those who do not die. It can be said that Covid-19 patients who have comorbid hypertension have a chance of dying almost equal to the chance to stay alive or recover.

Wulandari et al, 2021 (2) COVID-19 cases with comorbid hypertension have a 2.2 times risk of death compared to COVID-19 cases without comorbid hypertension (HR 2.2  $P < 0.001$  95% CI 1.66-3.87) after controlling for confounding variables comorbid chronic renal failure, age group, clinical symptoms of shortness of breath, malaise and pneumonia. Angiotensin-Converting Enzyme 2 (ACE2) binds to the S-protein of SARS-CoV-2 so that the virus can enter cells and replicate. ACE2 receptors are abundant in the cardiovascular system, nasopharynx, and lungs. In cases of comorbid hypertension, there is an increased expression of ACE2 receptors, making it more susceptible to COVID-19 infection. The binding of SARS-CoV-2 with ACE2 results in reduced expression of ACE2 on the cell surface, thus blocking the cell's ability to reduce angiotensin II to angiotensin. The disrupted angiotensin production causes the vasodilator effect to not be maximized so that the condition of COVID-19 patients with comorbid hypertension can become more severe.

Rodilla et al, 2020 (4) Multivariate analysis showed that after adjusting for gender (male, OR: 1.5,  $p = 0.0001$ ), tertile age (second and third tertile, OR: 2.0 and 4.7,  $p = 0.0001$ ), and Charlson Comorbidity Index score (second and third tertile, OR: 4.7 and 8.1,  $p = 0.0001$ ), hypertension significantly predicted all-cause mortality when this comorbidity was treated with angiotensin converting enzyme inhibitors (ACEI) (OR: 1.6,  $p = 0.002$ ) or other than renin-angiotensin-aldosterone blockers (OR: 1.3,  $p = 0.001$ ) or angiotensin II receptor blockers (ARB) (OR: 1.2,  $p = 0.035$ ). First, a previous diagnosis of HT increased the risk of all-cause mortality in COVID-19 patients requiring hospitalization by approximately 20% and was independent of age and other cardiovascular comorbidities, such as heart failure and atrial fibrillation. In line with most studies, our results support the observation that COVID-19 patients are generally older and more fragile than the general population, as confirmed by the use of different scores reflecting concurrent chronic diseases. In our study population, we observed that the higher the Charlson corrected Comorbidity Index score, the higher the all-cause mortality. However, its specific association between HT and COVID-19 remains controversial. Some studies associate the presence of HT with poorer outcomes in COVID-19, whereas others consider HT only as a potential confounding factor in the actual, causal relationship between age, cardiovascular disease, and increased mortality from COVID-19.

Gao et al, 2020 (5) results show that patients with the use of RAAS inhibitors tend to have a lower risk of death (relative risk 0.65, 95% CI 0.45-0.94,  $P = 0.02$ ). So far, there is little clinical evidence to suggest that antihypertensive drugs can affect the prognosis of COVID-19. Despite the lack of evidence, the European Society of Cardiology (ESC) Hypertension Council recommends physicians and patients should continue treatment with antihypertensive drugs as usual therapy. Our analysis showed that patients with antihypertensive treatment prior to hospital admission had a lower mortality rate compared to those without hypertension treatment. These data support the ESC recommendation that patients should not stop or change their antihypertensive treatment unless instructed by a physician.

Deng et al, 2021 (6) Patients with hypertension showed a significantly higher proportion of severe cases (69 [61.6%, 95%CI:52.5%-70.8%] vs. 117 [52.0%, 95%CI:45.4%-58.6%] in severe patients and 23 [19.3%, 95%CI:12.9%-28.1%] vs. 27 [12.0%, 95%CI:7.7%-16.3%] in critical patients,  $p = 0.0014$ ) and a higher mortality rate (20 [17.9%, 95%CI:10.7%-25.1%] vs. 20 [8.9%, 95%CI:5.1%-12.6%,  $p = 0.0202$ ). In addition, hypertensive patients showed abnormal levels of various indicators, such as lymphopenia, inflammation, heart, liver, kidney, and lung function at admission. The hypertensive group still showed higher levels of TnT and creatinine. Nevertheless, hypertension was still an independently associated risk factor of death after adjustment for the effect of bacterial infection (OR: 2.029, 95%CI: 1.035-3.976,  $p < 0.05$ ), and clinicians should pay more attention to secondary bacterial infection in the group with arterial hypertension regarding the higher CRP level. However,



TnT and creatinine levels of the hypertensive group were unusually higher than those of the normotensive group during hospitalization and at the time of approaching discharge, which implies that more aggressive clinical management regarding cardiac and renal injury may be required for COVID-19 patients with hypertension. It has been observed that components of the renin-angiotensin system may play a pathogenic role in COVID-19 as ACE2 acts directly on hypertension and hypertensive disease. Transmission of SARS-CoV-2.4 The balance of the RAS pathway may determine the occurrence of tissue injury, especially to the heart and kidneys.<sup>20</sup> Our data underscore the influence of hypertension on the severity of COVID-19, especially cardiac and renal injury

Oliveira et al, 2023 (7) Two hundred and two consecutive patients were admitted for mild or moderate COVID-19-related ARDS and were included in this study. The mean age of the population studied was  $69.1 \pm 14.8$  years. Of these, 130 patients (64.4%) were male. The mean BMI was  $29.9 \pm 6$  kg/m<sup>2</sup>. Hypertension occurred in 134 patients, equivalent to 67% of the studied population. 35.8% of patients had diabetes and 10.45% had dyslipidemia. Among the hypertensive patients, 58 (74%) died, with a relative risk of 1.45 (CI 0.96-2.2).

Isik, et al 2022 (8) In multivariable analysis, ResHT was independently associated with a significantly increased risk of hospitalization for death due to COVID-19, while no significant risk increase was observed with RegHT [respectively, Odds Ratio (OR) = 2.013, Confidence Interval (CI) 1.085-3.734,  $p = 0.026$  and OR = 1.194, CI 0.795-1.794,  $p = 0.394$ ]. ReHT causes macrovascular and microvascular end-organ (target organ) damage, leading to adverse clinical outcomes. Macrovascular damage is caused by vascular calcification and arterial stiffness in a large number of vessels. Carotid intima-media thickness increases, aortic plaques develop, and peripheral arterial disease is seen. Microvascular damage occurs through remodeling of small arteries. The magnitude of remodeling is associated with a worse prognosis. It was observed that the media/lumen ratio (eutrophic index of remodeling) increased in tissue samples taken from small arteries. Microalbuminuria is another vascular complication of ResHT and is an early biomarker. It indicates intrarenal vascular dysfunction. Cerebral microangiopathy is a vasculopathy in patients with long-term ReHT. Systolic blood pressure and signs of hypertensive vasculopathy such as pulse pressure and peripheral and central pulse wave velocity are associated with cerebral microangiopathy in patients with long-term ReHT.

Huang et al, 2020 (9) Neutrophil and lactate dehydrogenase counts, fibrinogen, and D-dimer levels in hypertensive patients were significantly higher than in nonhypertensive patients ( $P < 0.05$ ). However, multivariate analysis (adjusted for age and gender) failed to show that hypertension was an independent risk factor for COVID-19 mortality or severity. Increasing clinical data suggest an association between worsening COVID-19 and cytokine storms, such as increased levels of IL-6, interleukin-7, granulocyte-macrophage colony stimulating factor, and tumor necrosis factor  $\alpha$ . It's worth noting that previous clinical studies have found that increases in these cytokines are also associated with the development of hypertension. An important example is that IL-6 has been observed to be closely associated with the poor prognosis of patients with COVID-19, which is also one of the important cytokines regulating the immune inflammatory response in hypertension. In addition, in hypertensive patients with COVID-19, due to an imbalance in the renin-angiotensin system (RAS), the NADH/NADPH oxidase system may be activated by excessive inflammatory reactions or large amounts of cytokines, resulting in cell damage and vasoconstriction, exacerbating lung damage in COVID-19 and leading to a poor prognosis.

Geng et al, 2021 (10) There is a significant relationship between stage 3 hypertension patients and the death of patients when critical who suffer from Covid-19. Adisasmita & Drew, 2021 (11) Multivariate data analysis with logistic regression found that male gender increased the RR of mortality by 2.15 (95% IK: 1.47-3.14), age  $\geq 60$  years by 4.49 (95% IK: 3.05-6.63), presence of respiratory tract symptoms by 2.17 (95% IK: 1.26-3.72), presence of external respiratory tract symptoms by 2.47 (95% IK: 1.43-4.29), history of hypertension by 2.45 (95% IK: 1.46-4.10) and history of chronic renal failure by 3.33 (95% IK: 1.27-8.68).

Male gender increased the risk of mortality compared to females (RR 2.15, 95% IK: 1.47 - 3.14). These findings are similar to the study conducted by Noor and Islam. In their meta-analysis study, the mortality risk of men was 1.63 (1.43-1.87) times higher than women. The difference in hormone levels between men and women is theorised to be the reason why men are more prone to death. Through immuno-modulating effects, oestrogen positively affects the female immune system to fight infection. Higher expression of ACE2 receptor levels is also theorised to increase COVID-19 viral load in the male population.

Fanani et al, 2022 (12) The results of the statistical test obtained a significant relationship between comorbidities ( $p=0.000$ ), cardiovascular disease ( $p=0.000$ ), hypertension ( $p=0.000$ ), diabetes mellitus ( $p=0.000$ ) with the mortality rate of COVID-19 patients. This study shows that many COVID-19 patients died in women aged 51-60 years, working. Hypertension has an influence on the incidence of COVID-19 to fall to death as much as 2.5x higher than patients who do not have comorbid hypertension. There was a prevalence of patients with hypertension in COVID-19 of 2,552 patients and 748 patients experienced severity (Liu et al., 2020). The most common comorbidity found in patients with COVID-19 is hypertension, which is 25.6%.

Satria et al, 2020 (13) 358 patients were infected with COVID-19 and confirmed by nose and/or throat swabs. 66 patients (18%) died from COVID-19. 60.6% were male (OR 1.87,  $P 0.041$ ), 22.7% were  $>64$  years old (OR 2.097,  $P 0.041$ ), and 83.3% had comorbid risk factors. Diabetes mellitus (30.3%) (OR 4.348,  $P 0.000$ ), and

cardiovascular disease (10.6%) (OR 4.319, P 0.016) were the highest risk factors for death in COVID-19.

Salha et al, 2023 (14) COVID-19 patients died aged elderly as many as 151 people (93.8%), 83 women (51.5%) and had comorbid hypertension 87 people (54%). Comorbid hypertension in the case group was 87 people (54.0%), while the control group was 24 people (14.9%). Hypertension has a significant relationship with COVID-19 mortality ( $p=0.000$ ) with an OR of 6.711. The conclusion of this study is that COVID-19 patients with a single comorbid hypertension have a 6 times higher risk of dying than other patients of the same age and gender.

Zhou et al, 2021(15) Among 12,548 hypertensive and COVID-19 patients (mean age = 60 years, 47% male), 63% had uncontrolled blood pressure ( $\geq 130/80$  mm Hg) before COVID-19. Twenty-one per cent were hospitalised or died within 30 years of COVID-19 infection. Uncontrolled blood pressure was not associated with higher hospitalisation or mortality (adjusted rate ratio for blood pressure  $\geq 160/100$  mm Hg vs  $< 130/80$  mm Hg = 1.00 [95% CI: 0.87, 1.14]; blood pressure 140-159/90- 99 mm Hg vs  $< 130/80$  mm Hg = 1.02 [95% CI: 0.93, 1.11]). These findings were consistent across different age groups, antihypertensive drug treatment, as well as atherosclerotic cardiovascular disease risk.

## 5. Conclusion

The risk of COVID-19 death with comorbid hypertension was 2.2 times compared to COVID-19 cases without comorbid hypertension, after controlling for comorbid confounding variables, namely chronic renal failure, age group, clinical symptoms of shortness of breath, malaise / weakness and pneumonia. Therefore, people with comorbid hypertension should be prioritised for special attention in the prevention and management of COVID-19 including the priority of COVID-19 vaccination to avoid severity that can lead to death. COVID-19 prevention, early detection, and management programmes need to consider special attention to vulnerable groups including people with comorbid hypertension. Future research can be carried out to see the relationship between deaths in patients with COVID-19 who suffer from comorbid hypertension with COVID-19 vaccination status and the relationship between deaths in patients with COVID-19 with comorbid hypertension with the status of antihypertensive drug administration.

## References

- Lucyati A, Pratama AS, Warnasouda SY. Hubungan Hipertensi Dengan Tingkat Mortalitas Pasien Covid-19 Di Rsud Dr . Slamet Garuttahun 2020-. 2023;4(September):3677–84.
- Wulandari EW, Ronoatmodjo S, Salama N. Hubungan Komorbid Hipertensi dengan Kematian pada Kasus Konfirmasi COVID-19 di DKI Jakarta, Maret-Agustus 2020. *J Ilmu Kesehat Masy*. 2021;10(04):287–98.
- Choirunnisa, Heida. Hubungan Hipertensi dengan Mortalitas Pasien Covid-19 di Tangerang Selatan Choirunnisa a\* Association of Hypertension with Mortality among Covid-19 Patients in South Tangerang. *J Epidemiol Kesehat Indones*. 2021;5(2):67–74.
- Rodilla E, Saura A, Jiménez I, Mendizábal A, Pineda-Cantero A, Lorenzo-Hernández E, et al. Association of hypertension with all-cause mortality among hospitalized patients with COVID-19. *J Clin Med*. 2020;9(10):1–12.
- Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J*. 2020;41(22):2058–66.
- Deng YP, Xie W, Liu T, Wang SY, Zan YX, Wang MR, et al. Association of diabetes with severity and mortality in hospitalized patients with COVID-19 in Wuhan, China: a single-centered, retrospective study. *Arch Endocrinol Metab*. 2021;65(5):596–608.
- Oliveira MA de, Haddad A, Godomiczer A, Garcia TR, Sten C, Moisés FP, et al. Hypertension and Risk Factor To Mortality in Coronavirus Disease (Covid-19). *J Hypertens*. 2023;41(Suppl 3):e191.
- Işık F, Çap M, Akyüz A, Bilge Ö, Aslan B, İnci Ü, et al. The effect of resistant hypertension on in-hospital mortality in patients hospitalized with COVID-19. *J Hum Hypertens*. 2022;36(9):846–51.
- Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, et al. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. *Hypertens Res [Internet]*. 2020;43(8):824–31. Available from: <http://dx.doi.org/10.1038/s41440-020-0485-2>
- Geng L, He C, Kan H, Zhang K, Mao A, Zhang C, et al. The association between blood pressure levels and mortality in critically ill patients with COVID-19 in Wuhan, China: a case-series report. *Hypertens Res [Internet]*. 2021;44(3):368–70. Available from: <http://dx.doi.org/10.1038/s41440-020-00594-x>
- Drew C, Adisasmita AC. Gejala dan komorbid yang memengaruhi mortalitas pasien positif COVID-19 di Jakarta Timur, Maret-September 2020. *Tarumanagara Med J*. 2021;3(1):42–51.
- Fanany AI, Askitosari TD, Hanum PS. Komorbid (Hipertensi, Diabetes Melitus, Penyakit Kardiovaskular) dan Kematian Pasien Covid-19. 2022;11(November).
- Satria RMA, Tutupoho RV, Chalidyanto D. Analisis Faktor Risiko Kematian dengan Penyakit Komorbid Covid-19. *J Keperawatan Silampari*. 2020;4(1):48–55.
- Salha Z, Endang Suherlan, Heni Muflihah. Hipertensi sebagai Komorbid Tunggal Merupakan Faktor Risiko Kematian COVID-19: Case-Control Study. *Bandung Conf Ser Med Sci*. 2023;3(1):1000–6.
- An J, Zhou H, Luong TQ, Wei R, Mefford MT, Harrison TN, et al. Risk of hospitalization and mortality associated with uncontrolled blood pressure in patients with hypertension and COVID-19. *Int J Cardiol Cardiovasc Risk Prev [Internet]*. 2021;11:200117. Available from: <https://doi.org/10.1016/j.ijcrp.2021.200117>