ORIGINAL ARTICLE

Coronavirus Disease 2019 (COVID-19) Leads to Risen Hypertension Prevalence among Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Diabetes is the second most prevalent comorbidity of coronavirus disease 2019 (COVID-19) cases in Indonesia. Type 2 diabetes mellitus (T2DM) patients experience increased blood vessel remodeling, resulting in elevated peripheral arterial resistance. In addition to exacerbating the severity of T2DM, COVID-19 also increases hypertension risk. This study aimed to elucidate the effect of COVID-19 on hypertension prevalence among T2DM patients.
Methods: This research employed an analytical observational design, specifically the case-control study design. A total of 200 datasets were extracted from medical records covering the period from May 2020 to April 2022 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The inclusion criteria for the study samples were T2DM patients diagnosed by a doctor, as documented in their medical records, with no previous history of hypertension. The data were analyzed using the Chi-square test at a significance level of $p<0.05$ to determine the effect of COVID-19 on hypertension prevalence in T2DM patients.
Results: There were 100 T2DM patients without COVID-19 (30 with hypertension and 70 without hypertension) and 100 T2DM patients with COVID-19 (45 with hypertension and 55 without hypertension). The Chi-square test indicated an effect associated with COVID-19 on hypertension prevalence in T2DM patients, with $p=0.028$ and an odds ratio (OR) of 1.909.
Conclusion: The study suggests that COVID-19 infection increases the risk of hypertension in T2DM patients. Raising awareness of the complications of hypertension is important, particularly for high-risk individuals, such as T2DM patients who have a history of COVID-19.

Keywords: Diabetes mellitus; coronavirus disease 2019 (COVID-19); hypertension; D-dimer; diseases

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Highlights:
1. There has been no research examining the relationship between coronavirus disease 2019 (COVID-19) and the prevalence of hypertension complications, especially in type 2 diabetes mellitus (T2DM) patients.
2. This study highlights the importance of raising awareness regarding the finding that the incidence of COVID-19 increases the prevalence of hypertension in T2DM patients.

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INTRODUCTION

Since December 30, 2019, when the first outbreak was identified in Wuhan, China, cases of coronavirus disease 2019 (COVID-19) had been on the rise globally (World Health Organization, 2024). Almost all countries, including Indonesia, have been affected by the COVID-19 outbreak. The first two cases of COVID-19 in Indonesia were detected on March 2, 2020 (Putri, 2020). Since then, the number of COVID-19 cases around the country continued to increase, reaching 108,376 cases in July 2020 (Ministry of Health of the Republic of Indonesia, 2020). The COVID-19 Handling Task Force reported that along with the increasing number of COVID-19 cases, the number of deaths also continued to escalate to 33,183 by February 14, 2021 (BBC, 2021).

COVID-19 deaths are affected by comorbid diseases that compromise the immune system, thereby worsening the severity of the infection (Marzuki et al., 2021). The global prevalence of COVID-19 cases was found to be 57.7% with comorbidities and 42.3% without comorbidities (Nanda et al., 2021). Spanning a year and 11 months since the start of the COVID-19 pandemic until mid-early November 2021, a total of 249,343,498 COVID-19 cases were recorded around the world. During this period, 5,045,077 deaths were also documented, which accounted for 2% of the total cases. As of

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November 5, 2021, Indonesia reported 4,246,802 cases, with a mortality rate of 3.4% that constituted 143,500 deaths. The patients who died had comorbidities, such as hypertension, chronic heart or kidney disease, and chronic lung disease. Research has shown that 42 people per 1,000 COVID-19 cases suffer from diabetes mellitus as a comorbidity, with a mortality rate of 10% (Lienggonegoro, 2022).

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, affecting over 90% of all diabetic patients (American Diabetes Association, 2013). In 2015, there were approximately 415 million people with diabetes mellitus, with 98% affected by T2DM (International Diabetes Federation, 2015). In 2019, Indonesia ranked 7th globally for the prevalence of T2DM, comprising 10.7 million people. T2DM poses a challenge in COVID-19 cases. Diabetes has been recognized as the second most common comorbidity in COVID-19 cases in Indonesia. The death rate for COVID-19 cases increased 8.3 times in diabetic patients compared to non-diabetic patients (International Diabetes Federation, 2019; Tempo, 2020).

Patients with T2DM commonly have decreased cell function. The attachment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the angiotensin converting enzyme 2 (ACE2) receptor located on pancreatic islet cells results in elevated blood glucose levels during the acute phase of COVID-19. Additionally, this attachment induces insulin resistance in patients infected by the virus. These pathways enable COVID-19 to accelerate the severity of the disease in patients with T2DM (Hayden, 2020). Patients with T2DM experience increased blood vessel remodeling, resulting in elevated peripheral arterial resistance due to a stable surge in body fluids and osmolar adjustments due to hyperglycemia (Ohishi, 2018). Therefore, COVID-19 can potentially exacerbate cardiovascular disease. The binding of SARS-CoV-2 may lead to a depletion of ACE2, thus elevating the overall levels of angiotensin II within the system (South et al., 2020).

Blood pressure levels are elevated in individuals who have recovered from non-severe COVID-19 compared to those who have not been infected, indicating a notable hypertensive sequela (Schmidt-Lauber et al., 2023). In addition to increasing the severity of T2DM, COVID-19 can also theoretically increase the risk of hypertension. Against this background, this study aimed to investigate the effect of COVID-19 on the prevalence of hypertension among patients diagnosed with T2DM.

METHODS

This research was an analytical observational study conducted using a case-control design (Johnson, 2018). The sample data covered the period from May 2020 to April 2022, comprising 200 datasets selected out of 4,692 inpatient medical records at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. This study utilized the purposive sampling technique by implementing certain inclusion and exclusion criteria (Etikan et al., 2016). The research was conducted at Dr. Soetomo General Academic Hospital after obtaining a research permit and ethical approval, registered under number 0584/LOE/301.4.2/IX/2021 and issued on September 9, 2021. The inclusion criteria of this study comprised T2DM patients diagnosed by a doctor who exhibited no previous history of hypertension and had complete data in their medical records. The exclusion criteria were patients with diseases causing secondary hypertension, including adrenal disease, kidney disease, hyperthyroidism, hypothyroidism, coarctation of the aorta, sleep apnea, and long-term consumption of certain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral contraceptives, antidepressants, decongestants, narcotics, alcohol, and psychotropic substances. T2DM patients infected with COVID-19 served as the case group, whereas T2DM patients who were not infected with COVID-19 represented the control group.

The data obtained in this research were analyzed using the Chi-square test to determine the effect of COVID-19 on the prevalence of hypertension in T2DM patients. The relationship between the two variables was deemed significant according to the results of the Chi-square test, with a confidence interval (CI) of 95% and a significance level (α) below 0.05 (Pandis, 2016). The strength of the relationship between the variables was determined using the odds ratio (OR) test. The data processing in this study was conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) as the statistical data analysis tool. A p-value below 0.05 indicated the acceptance of H1 and the rejection of H0, demonstrating a significant relationship between the prevalence of hypertension and COVID-19 infection in T2DM patients. Conversely, a p-value higher than 0.05 implied the rejection of H1 and the acceptance of H0, signifying that there was no notable relationship between the prevalence of hypertension and COVID-19 infection in T2DM patients (Rana & Singhal, 2015).

RESULTS

This study involved a total of 200 T2DM patients, 100 of whom were not infected with COVID-19, and another 100 had a COVID-19 infection. The T2DM patients without COVID-19 consisted of 30 hypertensive individuals and 70 non-hypertensive individuals. Meanwhile, the T2DM patients with COVID-19 comprised 45 hypertensive individuals and 55 non-hypertensive individuals. The characteristic data obtained from the T2DM patients included sex, age, length of hospitalization, and hospital outcomes. The frequency distribution of the patients categorized by sex, age, length of hospitalization, and

Table 1. Frequency distribution of patients by sex

Sex	T2DM				T2DM+COVID-19				Total	
	HT		Non-HT		HT		Non-HT		n	%
	n	%	n	%	n	%	n	%		
Male	13	6.5%	29	14.5%	22	11%	31	15.5%	95	47.5%
Female	17	8.5%	41	20.5%	23	11.5%	24	12%	105	52.5%
Total	30	15%	70	35%	45	22.5%	55	27.5%	200	100%

Notes: T2DM=type 2 diabetes mellitus; T2DM+COVID-19=type 2 diabetes mellitus as a comorbidity in coronavirus disease 2019; HT=hypertension..

hospital outcomes can be seen in Tables 1, 2, 3, and 4, respectively.

Table 1 shows that among the T2DM patients without COVID-19, there were 13 (6.5%) males and 17 (8.5%) females who had hypertension. The T2DM patients who were not infected with COVID-19 and did not have hypertension consisted of 29 (14.5%) males and 41 (20.5%) females. Among the T2DM patients infected with COVID-19 and suffering from hypertension, there were 22 (11%) males and 23 (11.5%) females. In the meantime, the T2DM patients who were infected with COVID-19 and had hypertension included 31 (15.5%) males and 24 (12%) females.

Table 2 indicates that among the T2DM patients uninfected with COVID-19 and having hypertension, there were 2 individuals (1%) aged 26–35 years, 4 individuals (2%) aged 36–45 years, 8 individuals (4%) aged 46–55 years, 7 individuals (3.5%) aged 56–65 years, and 9 individuals (4.5%) aged over 65 years. Among the T2DM patients who were not infected with COVID-19 and had no hypertension, there were an individual (0.5%) in the age range of 17–25 years, 8 individuals (4%) in the age range of 36–45 years, 17 individuals (8.5%) in the age range of 46–55 years, 33 individuals (16.5%) in the age range of 56–65 years, and 11 individuals (5.5%) in the age range of >65 years. In the group of T2DM patients with COVID-19 and hypertension, there were 3 individuals (1.5%) aged 26–35 years, 5 individuals (2.5%) aged 36–45 years, 13 individuals (6.5%) aged 46–55 years, 19 individuals (9.5%) aged 56–65 years, and 5 individuals (2.5%) aged above 65 years. The T2DM patients who had COVID-19 and were not hypertensive included 3 individuals (1.5%) aged 26–35 years, 8 individuals (4%) aged 36–45 years, 21 individuals (10.5%) aged 46–55 years, 18 individuals (9%) aged 56–45 years, and 5 individuals (2.5%) aged over 65 years.

As shown by the data in Table 3, the T2DM patients

Table 2. Frequency distribution of patients by sex

Age	Mean	Median	T2DM				T2DM+COVID-19				Total	
			HT		Non-HT		HT		Non-HT		n	%
			n	%	n	%	n	%	n	%		
17–25	25	25	0	0%	1	0.5%	0	0%	0	0%	1	0.50%
26–35	31.5	31.5	2	1%	0	0%	3	1.5%	3	1.5%	8	4%
36–45	41.3	43	4	2%	8	4%	5	2.5%	8	4%	25	12.5%
46–55	51	51	8	4%	17	8.5%	13	6.5%	21	10.5%	59	29.5%
56–65	59.8	60	7	3.5%	33	16.5%	19	9.5%	18	9%	77	38.5%
>65	72.2	72	9	4.5%	11	5.5%	5	2.5%	5	2.5%	30	15%
Total			30	15%	70	35%	45	22.5%	55	27.5%	200	100%

Notes: T2DM=type 2 diabetes mellitus; T2DM+COVID-19=type 2 diabetes mellitus as a comorbidity in coronavirus disease 2019; HT=hypertension.

Table 3. Frequency distribution of patients according to the length of hospitalization

LoH	Mean	Median	T2DM				T2DM+COVID-19				Total	
			HT		Non-HT		HT		Non-HT		n	%
			n	%	n	%	n	%	n	%		
<4 days	2	2	14	7%	18	9%	3	1.5%	9	4.5%	44	22%
4–7 days	5	5	11	5.5%	31	15.5%	2	1%	8	4%	52	26%
>7 days	17	15	5	2.5%	21	10.5%	40	20%	38	18.5%	104	52%
Total			30	15%	70	35%	45	22.5%	55	27.5%	200	100%

Notes: LoH=length of hospitalization; T2DM=type 2 diabetes mellitus; T2DM+COVID-19=type 2 diabetes mellitus as a comorbidity in coronavirus disease 2019; HT=hypertension.

Table 4. Frequency distribution of patients according to the hospital outcomes

Outcomes	T2DM				T2DM+COVID-19				Total	
	HT		Non-HT		HT		Non-HT		n	%
	n	%	n	%	n	%	n	%		
Survival	28	14%	63	31.5%	32	16%	34	17%	157	78.5%
Mortality	2	1%	7	3.5%	13	6.5%	21	10.5%	43	21.5%
Total	30	15%	70	35%	45	22.5%	55	27.5%	200	100%

Notes: T2DM=type 2 diabetes mellitus; T2DM+COVID-19=type 2 diabetes mellitus as a comorbidity in coronavirus disease 2019; HT=hypertension.

Table 5. Results of the analysis using the Chi-square test

Diagnoses	T2DM		T2DM+COVID-19		p	OR
	n	%	n	%		
HT	30	30%	45	45%	0.028	1.909
Non-HT	70	70%	55	55%		
Total	100	100%	100	100%		

Notes: T2DM=type 2 diabetes mellitus; T2DM+COVID-19=type 2 diabetes mellitus as a comorbidity in coronavirus disease 2019; HT=hypertension; OR=odds ratio.

uninfected with COVID-19 and having hypertension endured a length of hospitalization of fewer than four days for 14 (7%) individuals, four to seven days for 11 (5.5%) individuals, and more than seven days for 5 (2.5%) individuals. The T2DM patients who were not infected with COVID-19 and had no hypertension demonstrated a length of hospitalization of fewer than four days for 18 (9%) individuals, four to seven days for 31 (15.5%) individuals, and longer than seven days for 21 (10.5%) individuals. The T2DM patients with COVID-19 and hypertension had the following lengths of hospitalization: fewer than four days for 3 (1.5%) individuals, four to seven days for 2 (1%) individuals, and more than seven days for 40 (20%) individuals. Among the T2DM patients who were infected with COVID-19 and did not have hypertension, the documented length of hospitalization was fewer than four days for 9 (4.5%) individuals, four to seven days for 8 (4%) individuals, and longer than seven days for 38 (18.5%) individuals.

The data shown in Table 4 indicated that among the T2DM patients who were uninfected with COVID-19 and had hypertension, a total of 28 (14%) individuals survived and were discharged from the hospital, whereas 2 (1%) individuals succumbed. Among the T2DM patients who were uninfected with COVID-19 and non-hypertensive, 63 (31.5%) individuals discharged from the hospital with favorable outcomes, while 7 (3.5%) individuals died. In the cohort of T2DM patients with COVID-19 and hypertension, 32 (16%) individuals were discharged alive from the hospital, whereas 13 (6.5%) individuals succumbed to the disease. Among the T2DM patients who were infected with COVID-19 and had no hypertension, 34 (17%) individuals were discharged alive from the hospital, and 21 (10.5%) individuals succumbed to the disease.

The data presented in Table 5 shows that among the T2DM patients who were uninfected with COVID-19, there were 30 (30%) hypertensive individuals and 70 (70%) non-hypertensive individuals. The T2DM patients infected with COVID-19 included 45 (45%) hypertensive individuals and 55 (55%) non-hypertensive individuals. The analysis of the effect of COVID-19 on the prevalence of hypertension in T2DM patients yielded a p-value of 0.028 and an OR value of 1.909, indicating a significant relationship between COVID-19 infection and the prevalence of hypertension in T2DM patients. An OR value of 1.909 indicated that T2DM patients infected with COVID-19 were at 1.909 times higher risk of developing hypertension than T2DM patients who were uninfected.

DISCUSSION

Diabetes mellitus causes a gradual deterioration in the patient's immune response. The immune response imbalance resulting from diabetes mellitus heightens the possibility of immune modulator dysregulation. This immune imbalance is viewed as a contributing factor for SARS-CoV-2 susceptibility in patients with diabetes mellitus and also exacerbates disease severity (Kulcsar et al., 2019; Lin et al., 2020). Diabetes mellitus leads to a reduction of the cluster of differentiation 3+ (CD3+) T cells, hence altering adaptive immunity and stimulating chronic inflammation. The number of lymphocytes and T-lymphocyte subtypes in diabetic patients was lower than in non-diabetic patients. Cluster of differentiation 4+ (CD4+) T helper type 1 (Th1) cells coordinate antigen presentation and immune response to various infections, such as by SARS-CoV-2, through the production of interferon gamma (IFN-γ). It has been discovered that SARS-CoV-2 induces lymphocytopenia by inducing apoptosis in cluster of differentiation 3 (CD3), cluster of differentiation 4 (CD4), and cluster of differentiation 8 (CD8) T cells, hence destroying circulating immunological cells. Furthermore, diabetes mellitus diminishes neutrophil phagocytosis, chemotaxis, and microbial eradication. Delayed action of Th1 cell-mediated immune response and delayed inflammation are two common types of adaptive immunity deficiencies observed in individuals with diabetes mellitus. The increased expression of ACE2 due to antidiabetic drugs may also increase the viral entry rate (Muniyappa & Gubbi, 2020; Sen et al., 2021).

ACE2 is the target for the binding mechanism of the SARS-CoV-2 during infection. It is known as an essential enzyme for the counterregulation of the renin-angiotensin-aldosterone system (RAAS). ACE2 binds to the extracellular membrane of cells in several organs. The tissues of the heart, kidneys, lungs, and intestines exhibit high levels of ACE2 expression. In addition, ACE2 has the ability to convert angiotensin II into angiotensin 1–7 (Ang 1–7). Vasoconstriction, salt retention, and fibrosis can be mitigated by angiotensin 1–7, thus counteracting the effects of angiotensin II (Vaduganathan et al., 2020).

COVID-19 has been found to exacerbate hypertension. SARS-CoV-2 occupying ACE2 can interfere with the function of the enzyme in the renin-angiotensin-aldosterone system. Angiotensin 1–7, a key molecule in the renin-angiotensin-aldosterone system, can be produced at a diminished rate due to the reduced efficiency of ACE2. Angiotensin II builds up as a result of the disruption of ACE2, which exerts a vasoconstrictive impact. This disruption affects the equilibrium of the blood pressure system, resulting in persistent hypertension (Alfhad et al., 2020).

Overactive inflammation and an imbalanced immune response in patients with diabetes mellitus have been associated with a proinflammatory condition and a weakened innate defense mechanism (Yang et al., 2020). Additionally, diabetes has been linked to increased susceptibility to infections and poor clinical outcomes, notably pneumonia and influenza (Hussain & do Vale Moreira, 2020). In T2DM, the blood vessel linings suffer damage due to elevated blood sugar levels, insulin resistance, and other metabolic irregularities. This damage occurs through multiple pathways, including oxidative stress, impaired endothelial function, increased platelet activity, and chronic inflammation (Ohishi, 2018). The risk of vascular injury, mortality, and morbidity in diabetic patients increases when these events are activated because they cause vasoconstriction and thrombus development (Tousoulis et al., 2013; Kaur et al., 2018; Li et al., 2021).

D-dimer levels are markedly increased during an inflammatory storm. Plasmin activation is the initial effect of an inflammation. Nevertheless, with the exacerbation of inflammation and the onset of hypoxia, hypoxia-triggered molecules can directly stimulate thrombin, while the activation of monocytes-macrophages prompts the secretion of substantial quantities of tissue factor. This action initiates exogenous coagulation pathways, potentially leading to a widespread hypercoagulable condition or even disseminated intravascular coagulation. Diabetic patients have considerably higher levels of D-dimer and fibrinogen, indicating that they are more prone to hypercoagulable conditions compared to people without diabetes (Guo et al., 2020).

The information gathered suggests that elevated D-dimer levels and the existence of coagulopathy could serve as the prognostic markers of worsened morbidity and mortality in hospitalized COVID-19 patients. Abou-Ismail et al. (2020) demonstrated that the laboratory assessments of COVID-19 patients were consistent with prothrombotic conditions, characterized by elevated levels of D-dimer, fibrinogen, factor VIII (FVIII), and von Willebrand factor (vWF), along with reduced antithrombin levels and thromboelastography (TEG) findings, reflecting a hypercoagulable state. In comparison to the non-diabetic group, the diabetic group exhibited considerably higher absolute neutrophil counts, C-reactive protein (CRP) levels, erythrocyte sedimentation rates (ESR), and D-dimer levels. In addition, the diabetic group had significantly lower counts of absolute lymphocytes, red blood cells, and hemoglobin compared to the non-diabetic group. These data suggest that COVID-19 patients with diabetes are at a higher risk of developing an uncontrolled exaggerated inflammatory response and hypercoagulable state, which may contribute to a poorer COVID-19 prognosis (Guo et al., 2020).

Elevated levels of D-dimer, a product of fibrin degradation, have been hypothesized to indicate increased intravascular thrombogenesis and fibrin turnover, potentially impacting endothelial cells. These processes accelerate the progression of oxidative stress (Kushner et al., 2024). Endothelial factors, such as nitric oxide and endothelin, can negatively affect vascular tone by decreasing nitric oxide bioavailability and elevating oxidative stress, leading to reduced vasodilation and increased blood pressure (Salvagno et al., 2024). Therefore, a prothrombotic condition may be responsible for the rise in blood pressure, as reflected by the positive correlation between blood pressure and D-dimer concentration. The concentration of D-dimer indicates the pathophysiology related to hypertension, which may dramatically increase the patient's risk of cardiovascular disease (Mukaz et al., 2023).

There is no previous research that has examined the relationship between COVID-19 and the prevalence of hypertension in patients with T2DM, which serves as the advantage of this study. This study excluded patients with a history of diseases that cause secondary hypertension to reduce bias. However, the research was conducted by collecting data from a single hospital, potentially leading to referral bias.

CONCLUSION

This study demonstrates an effect of the incidence of COVID-19 on the prevalence of hypertension in patients with type 2 diabetes mellitus (T2DM). The mortality rate for T2DM patients with COVID-19 and hypertension is higher compared to T2DM patients who are uninfected and non-hypertensive. COVID-19 prolongs the length of hospitalization of T2DM patients with hypertension. Enhanced awareness and attention are essential to mitigate the complications of hypertension, which may present in patients with diabetes mellitus who have a history of COVID-19.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ETHICS CONSIDERATION

The ethical clearance for this study was received from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, according to the letter of exemption under reference number 0584/LOE/301.4.2/IX/2021 dated September 9, 2021.

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AUTHOR CONTRIBUTION

All authors have contributed to all the processes in this research. AP had a role in conception and design, analysis and interpretation of the data, provision of funding, and collection and assembling of the data. R carried out the critical revision of the article for important intellectual content, provision of administrative, technical, or logistical support, and statistical expertise. AT provided final approval of the article as well as study materials or patients. DTPU drafted the article and provided administrative, technical, or logistic support.

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