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Clinical Outcomes of Diabetic Patients with and without Hypertension Vaccinated with the Sinovac Vaccine

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Abstract

Diabetes and hypertension are the most common degenerative diseases found during the Covid-19 vaccination. Of the 1488 cases of patients exposed to the Covis-19 virus, 13.2% died with hypertension and 11.6% with diabetes. This study aims to evaluate the clinical outcomes of diabetic and diabetic patients with hypertension who have been vaccinated with the Sinovac vaccine. This study uses retrospective and prospective cohort methods for 5 months. Of the 300 patients, 56.3% were female patients with the majority of the ages coming from the 41 to 60 years old group (46.7%) and 47.6% from the >60 years age group. There was no significant association between the length of diagnosis of diabetic patients and diabetes with hypertension and clinical outcomes. There was an association between kidney failure and clinical outcomes with the death of 8 people (2.7%) in patients with stage 4 and 5 renal failure. There was no association between sociodemographics and clinical outcomes. In comorbidities with Diabetes Mellitus, 3.33% of patients die. From the results of the study, it is also known that patients diagnosed with the disease >10 years have a higher percentage of mortality compared to patients diagnosed <10 years.

Introduction

COVID-19 vaccination is a highly effective and cost-effective method to prevent illness caused by the SARS-CoV-2 virus. Vaccination also plays an important role in reducing the severity and death rate from COVID-19 globally, including in Indonesia. According to Our World In Data (2022), around 70.3% of the global population has received at least one dose of the COVID-19 vaccine, with a total of 13.48 billion doses injected. In Indonesia, vaccination began in January 2021 with the first dose for 1.3 million health workers and 21.5 million elderly people. As of July 22, 2023, about 86.88% of the population has received the first dose, 74.55% the second dose, 38.07% the third dose, and 1.89% the fourth dose. The SARS-CoV-2 virus attacks the immune system, so drugs and vaccines are essential. COVID-19 vaccination stimulates the formation of antibodies, reducing the risk of disease. However, vaccination can increase the Glomerular Filtration Rate (GFR) and urine protein levels in CKD patients, influenced by factors such as age, gender, comorbidities, and medications. Vaccination is also important for patients with comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease to reduce the risk of more severe diseases (Jackson et al., 2023).

Diabetes mellitus is a metabolic disorder in which the pancreas does not produce insulin effectively, leading to chronic hyperglycemia. This is a growing global health problem, with 537 million cases and 6.7 million deaths in 2021. Projections for 2024 estimate 783.2 million cases. In Indonesia, the prevalence of diabetes reached 10.6% with 19.47 million cases in 2021.

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Diabetes is often associated with hypertension, exacerbating complications, morbidity, and mortality. The prevalence of hypertension in people with diabetes is estimated to be 50-70%, with risk factors including age over 45, female gender, genetic factors, and obesity (Vasilev et al., 2022).

Hypertension, known as silent killers, often shows no obvious symptoms, but is characterized by systolic blood pressure above 140 mmHg and diastolic above 90 mmHg. Common symptoms include headaches, vertigo, heart palpitations, fatigue, vision problems, tinnitus, and nosebleeds. This causes 9.4 million deaths each year globally. In Indonesia, the mortality rate due to hypertension is 14.41 per 100,000 population, placing it in 87 out of 183 countries. In diabetic patients, hypertension can develop due to intravascular fluid resistance due to high blood glucose levels and damage to the vascular system (Jia & Sowers, 2021).

Vaccination can increase the production of RBD-specific anti-RBD-IgG, NAbs, and MBC. The CDC advises people with diabetes and hypertension who have received the Pfizer-BioNTech or Moderna vaccines to get a third shot, as they are likely to have compromised immunity and low antibody responses. Before vaccination, the patient's condition needs to be checked, including HbA1C below 58 mmol/mol and blood pressure below 180/110 mmHg. Additional tests such as blood sugar, creatinine, and electrolytes are recommended to monitor hyperglycemia, electrolyte balance, and risk of infection. The duration of diabetes of more than 10 years can worsen the clinical prognosis.

This study aims to evaluate the *clinical outcomes* of diabetic patients and hypertensive patients who have been vaccinated with the Sinovac vaccine with a focus on *the Clinical Outcome* of those receiving diabetes medication and hypertension medication for both conditions. This study is expected to provide valuable insights in care management for diabetic patients and diabetic patients with hypertension who have been vaccinated with the Sinovac vaccine.

Methods

Material

The materials used in this study consist of retrospective and prospective data. Retrospective data is secondary data in the form of patient medical records from April 2021 to December 2023. This data comes from research subjects that include diabetic patients (150 patients) and diabetic patients with hypertension (150 patients), both of whom are patients who have received two doses of the Sinovac vaccine. The information obtained is recorded on the clinical results research sheet. Meanwhile, prospective data consists of primary and secondary data. Primary data were obtained through interviews with the same research subjects based on retrospective secondary data, while prospective secondary data were medical records from January 2024 to May 2024 who were still undergoing therapy. During the interview, the researcher fills out a clinical result research form and takes informed consent from the patient or respondent. These two types of data were selected based on the inclusion criteria of the study.

Method

This study uses statistical data analysis with univariate, bivariate, and multivariable analysis approaches. Univariate analysis was conducted to observe the frequency of age, gender, BMI, comorbidities, and *Clinical Outcomes*. Bivariate analysis was used to test the relationship between independent variables such as age, sex, comorbidities, BMI and *Clinical Outcome* using the chi-square test for categorical variables in the initial dataset. All of these analyses were carried out using Statistical Product and Service Solutions (SPSS) software.

Prior to data collection, ethical approval had been submitted and had been obtained, which was issued by the University Health Research Ethics Committee of August 17, 1945 Jakarta on December 18, 2023 with ethics number 83/KEPK-UTA45JKT/EC/EXP/12/2023

Result and Discussion

The evaluation *of Clinical Outcomes* in diabetic and diabetic patients with hypertension was carried out in the period from April 2021 to May 2024 with the convenience sampling method used to select a total of 300 samples that met the inclusion criteria from the patient's medical record data. The results of the study showed that there was a characteristic relationship based on the sociodemographics of patients with *clinical outcomes* in patients accompanied by comorbidities which can be seen in Table 1.

Table 1. Relationship between Sociodemography and Comorbidities with Clinical Outcomes

Variable	Information	Clinical Outcome N (%)		Total	P value
		Live	Die		
Age	20 - 40	17 (5.7%)	0 (0%)	17 (5.7%)	0.780
	41- 60	131 (43.7%)	9 (3%)	140 (46.7%)	
	>60	135 (45.0%)	8 (2.7%)	143 (47.6%)	
	Total	**283 (94.3%)**	**17 (5.7%)**	**300 (100%)**	
Gender	Male	124 (41.3%)	7 (2.4%)	131 (43.7%)	1.000
	Female	159 (53%)	10 (3.3%)	169 (56.3%)	
	Total	**283 (94.3%)**	**17 (5.7)**	**300 100%)**	
BMI	Normal	171 (57%)	12 (4%)	183 (61%)	0.455
	Overweight	112 (37.3%)	5 (1.7%)	117 (39%)	
	Total	**283 (94.3%)**	**17 (5.7%)**	**300 (100%)**	
Comorbidities	DM	54 (18.3%)	10 (3.3%)	64 (21.6%)	0.000*
	DM+HPT	93 (31%)	0 (0%)	93 (31%)	
	DM+HPT+cholesterol	105 (35%)	3 (1%)	108 (36%)	
	DM+HPT+Heart	30 (10%)	4 (1.4%)	34 (11.4%)	
Total		**282 (94.3%)**	**17 (5.7%)**	**300 00%)**	

Based on the results of data analysis in Table 1 with the chi-square test on age variables, significant values of 0.780 were obtained, gender and BMI variables were obtained significant values of 1,000 and 0.455, and for comorbidity variables values were 0.000. Based on this value, because of the p> value of 0.05, it can be concluded that there is no relationship between age, gender, BMI, and the clinical outcome of the respondents. The Comorbidity Variable with Clinical Outcome gave significant results with a P value of 0.000.

Table 2. Long-Diagnosed Relationship with Clinical Outcomes

Long Diagnosed	Clinical Outcome (N %)		Total (N%)	*P-value*
	Live	Die		
<10 years	115 (38.3%)	4 (1.3%)	119 (39.7%)	0.206
>10 years	168 (56%)	13 (4.3%)	181 (60.3%)	
Total	**283 (94.3%)**	**17 (5.6%)**	**300 (100%)**	

Based on the data in Table 2, it can be seen that respondents with a long history of being diagnosed with diabetes and diabetes with hypertension for more than 10 years have a clinical outcome of 168 (56%) and those with less than 10 years as many as 115 (38.3%). Meanwhile, respondents with more than 10 years diagnosed with clinical outcomes died 13 (4.3%), and less than 10 years died 4 (1.3%). Based on these data, it can be seen that the percentage of diabetes and diabetes hypertension diagnosed for more than 10 years is higher in respondents with a clinical outcome who are alive when compared to respondents with clinical outcomes who die. Based on the results of data analysis with the chi square test, a significant value of 0.206 was obtained, based on this value, because of the p > value of 0.05, it can be concluded that there is no relationship between the time of diagnosis and the clinical outcome of the respondent.

Table 3. Relationship between Kidney Failure (EGFR) and Clinical Outcomes

EGFR (Kidney Failure)	Clinical Outcome (N%)		Total (N%)	*P-value*
	Live	Die		
Normal >90 (1)	120(40%)	3 (1.0%)	123(41%)	
Light 60-89 (2)	126(42.3%)	4 (1.3%)	130(43.3%)	
Medium 30-59 (3)	31(10.3%)	2 (0.7%)	33(11%)	0.000*
Weight < 29 (4,5)	6(2.0%)	8 (2.7%)	14 (4.7%)	
Total	283(94.3%)	17(5.7%)	300(100%)	

Based on the data in Table 3, it can be seen that the percentage of patients who die in diabetic and diabetic patients with hypertension vaccinated with the Sinovac vaccine due to kidney failure with severe egfr (stages 4 and 5), is higher than 2.7% compared to patients with kidney failure with moderate and mild egfr (stages 2 and 3) which is 2.0%. Based on the results of data analysis with the chi square test, a significant value of 0.000 was obtained. Based on this value, because of the p value of <0.05, it can be concluded that there is a relationship between kidney failure or EGFR and clinical.

In the group of patients over 60 years, it resulted a survival clinical outcome 45%, while in the age group 41-60 years, a survival clinical outcome 43.7% was obtained. The results of this study show that patients 60 years live more, because of maintenance of drug doses for geriatric patients and their diet and lifestyle are better, and also medical treatment and special attention from internist at the hospital. The study shows that treatment adherence in elderly patients has a significant relationship with their quality of life thereby increasing their survival rate. This is because patients over 60 years of age may benefit from more careful monitoring and adherence to treatment regimens, driven by awareness of their increased vulnerability to serious health events (Albadrani et al., 2024).

From this study the clinical outcome of patients who died in the 41-60 age group was 9 (3%) and over 60 years was 8 (2.7%). It is known that patients with adulthood and advanced age affect clinical outcomes because older age tends to be associated with a higher risk of diabetes and hypertension complications such as kidney failure, heart disease, and stroke. As we age, the body undergoes various physical and biological changes. The aging process causes reduced elasticity of blood vessels, increased arterial stiffness, and decreased kidney and heart function. This can worsen blood pressure control and blood sugar levels, which in turn increases the risk of complications (Dewi et al., 2020).

Patients with diabetes and hypertension have a higher risk of developing chronic complications such as coronary heart disease, stroke, and kidney failure. The age of 41-60 years is often the point at which these complications begin to appear or worsen significantly due to vascular damage and decreased function of vital organs. An unhealthy lifestyle such as an unbalanced diet, lack of physical activity, and smoking or alcohol consumption habits can increase the risk of health complications at this age. The age of 41-60 years is also often the point where chronic complications such as coronary heart disease, stroke, and kidney failure begin to appear or worsen significantly due to vascular damage and decreased function of vital organs, leading to death. Age is an important factor in epidemiological studies because it is closely related to the level of susceptibility, exposure to disease, frequency of disease occurrence, and determining the risk of developing certain diseases. Vaccines stimulate the immune system response that can cause side effects. Younger people generally have stronger immune systems, so they are likely to experience higher levels of immune responses and greater possible side effects to vaccines. Clinical trial data for COVID-19 vaccines shows that younger people tend to experience more side effects compared to older people (Arjita et al., 2023).

From 300 patient data, as many as 159 patients with sociodemographic characteristics of the female sex experienced a clinical outcome compared to male patients. This happens because female patients have a higher tendency to develop diabetes and hypertension caused by several factors such as hormonal and metabolic. In this factor, the hormone progesterone that changes

during the menstrual cycle, pregnancy, and menopause can affect the body's sensitivity to insulin and glucose metabolism. These changes can increase a woman's risk of developing insulin resistance and eventually type 2 diabetes. Women also tend to have higher body fat and lower muscle mass compared to men in the same proportion. This condition can contribute to an increased risk of diabetes and hypertension. Differences in the immune hormonal system by sex were observed at the beginning of puberty, during the period of reproductive development, suggesting that sex hormones are not the only cause of the immune system's different response to vaccines (Tandjungbulu et al., 2022).

The results of *the clinical outcome* of patients with death outcomes were also dominated by patients with the female gender as much as 3.3%. This is known because of the possible factor estrogen and progesterone in women. Where these hormones can affect speerti in a state of menopause, namely during menopause, estrogen levels naturally decrease drastically. This decrease can negatively impact cardiovascular health because estrogen has a protective effect on the heart and blood vessels. This condition can increase the risk of cardiovascular disease in women after menopause and women with obesity, hypertension, or coronary heart disease, will be more susceptible to hormonal changes that can affect cardiovascular health and glucose metabolism so that severe complications occur and reduced organ performance leading to death (Suprapto, 2021).

BMI (Body Mass Index) is a measurement used to evaluate a person's weight status based on height and weight. This study found no significant association between BMI and clinical outcomes, suggesting that both high and low BMI may contribute to diabetes and hypertension complications. These findings challenge the common perception that higher BMI is associated with worse clinical outcomes. Rather, this suggests that other factors, such as visceral fat and metabolic predisposition, may play a more important role in influencing the risk of developing complications associated with this condition. This research highlights the importance of understanding body composition beyond simply measuring BMI. Visceral fat, which surrounds internal organs, is particularly concerning because it is more metabolically active and can contribute to insulin resistance and inflammation, leading to a higher risk of cardiovascular complications. Therefore, individuals with a normal BMI but high levels of visceral fat still have a significant risk of adverse clinical outcomes. (Priyantini et al., 2022). Additionally, metabolic tendencies, such as genetic factors and an individual's metabolic rate, also physical activity can influence BMI. (Astuti et al., 2022) These factors can contribute to the development of diabetes and hypertension. regardless of overall body weight. This study suggests that healthcare providers should adopt a more comprehensive approach to assessing and managing this condition, taking into account not only BMI, diet, and physical activity, also other indicators of metabolic health. The risk of developing metabolic syndrome is 2.99 times greater high consumption of carbohydrates. Consumption High carbohydrates can be used by the liver to produce triglycerides. Triglycerides is the basic ingredient for the formation of fat. As a result, obesity occurs and causes disorders of bodily function that are at risk of occurring diseases such as Diabetes Melitus, coronary heart disease, and hypertension (Driyah et al., 2019).

The habit of people who often consume fast food and sugary drinks excessively, which is high in sucrose and fructose, has a significant impact on increasing body mass index (BMI). These foods tend to be high in calories with low nutritional value that do not provide satiety, increase total energy intake, and lead to unhealthy weight gain . In individuals with obesity and insulin resistance, hyperplasia of perivascular adipose tissue (PVAT) and proinflatival immune cell infiltration occurs. This contributes to vascular inflammation and impaired endothelial function. End-of-the-line dysfunction, triggered by adipocyte activity in obese individuals, leads to chronic subinflammatory conditions that affect the development of cardiovascular diseases, including atherosclerosis. Atherosclerosis in patients with diabetes mellitus interferes

with peripheral blood circulation, which can result in a decrease in the Ankle Brachial Index (ABI), indicating serious vascular complications in this condition (Priyantini et al., 2022).

Based on the results showing a p > value of 0.05 for the variables of sex, age, body mass index (BMI), and comorbidities, it can be concluded that there is no significant relationship between sex, age, BMI, and comorbidities with clinical outcomes in respondents. Nonetheless, Carhart-Harris & Nutt notes that patients with diabetes and hypertension may have an affected immune response, especially in the context of vaccination, which can be influenced by gender factors. However, the exact mechanism still requires further research to be understood thoroughly, including the potential role of vaccines and the variability of immune responses. In addition, the differences in the hormonal system and immune responses by sex seen during the period of puberty also show complexity in their effect on the immune system's response to vaccines (Klein & Pekosz, 2014).

Patients with comorbidities of diabetes mellitus and hypertension and cholesterol were the patients who dominated the clinical outcome in this study. This is because patients with hypertension, diabetes mellitus, and high cholesterol are often closely related to each other in terms of pathophysiology and risk factors as well as insulin resistance that occurs in type 2 diabetes that causes hypertension. High cholesterol often occurs in conjunction with diabetes and hypertension, where the pathophysiological processes of each of these conditions can affect and exacerbate each other.

Insulin resistance can cause hypertension through several mechanisms. First, insulin helps in regulating the amount of salt and water in the body. When cells don't respond well to insulin, this regulation is disrupted, which can lead to increased blood volume and blood pressure. In addition, insulin resistance can also affect blood vessel function and blood pressure regulation mechanisms. Thus, insulin resistance can be a risk factor for the development of hypertension. While insulin resistance is also related to changes in lipid metabolism, which can lead to increased levels of cholesterol and triglycerides in the blood. Insulin usually helps regulate the production and metabolism of fat in the body. When insulin resistance occurs, this system can be disrupted, which can lead to an increase in LDL cholesterol (bad cholesterol) and triglycerides, as well as a decrease in HDL cholesterol (good cholesterol). This condition is often seen in patients with type 2 diabetes, who also often have high cholesterol problems (Ichsan et al., 2021).

Patients with diabetes comorbidities accompanied by hypertension and cholesterol have better *clinical outcomes* (35%) than patients with other comorbidities. This is because patients with diabetes comorbidities accompanied by hypertension and cholesterol have comprehensive management including more intensive monitoring of blood glucose levels due to interrelated comorbidities. This is because the therapy used affects the effect of therapy and the possibility of DRP therapy in the patient. Periodic monitoring of the patient's blood pressure and cholesterol levels is the main concern in patients with this comorbid condition. Meanwhile, patients with diabetes mellitus without comorbidities have worse *clinical outcomes* than other comorbidities, which may occur due to the effects of diabetes that cause damage to large or small blood vessels. Thus increasing the risk of coronary heart disease, stroke and peripheral vascular disease resulting in serious organ failure at one time leading to death. Based on the p-value on the comorbidity variable with the results of *clinical outcomes* Where the p-value from the results of the relationship test using *chi-square* shows a relationship marked by *a p-value* of <0.05.

Patients with a diagnosis of more than 10 years dominated the population in this study. This is because patients with long-diagnosed diabetes tend to have poorer glycemic control, because in type 2 diabetes, especially long-standing ones, the body's cells become less responsive to the insulin produced by the pancreas. This phenomenon is called insulin resistance. As a result, the

body needs more insulin to regulate glucose levels in the blood. If insulin production is not enough to meet these needs or if insulin resistance is very high, glycemic control can be difficult. So the length of diagnosis in patients also affects the clinical outcomes. Insulin resistance that gets worse over time can lead to increased blood glucose levels, which are difficult to control even with proper treatment. Hypertension can worsen insulin resistance, making glycemic control more difficult. Patients who have had diabetes and hypertension for a long time may have more comorbidities and require more medications to manage. Both conditions, both diabetes and hypertension, can lead to oxidative stress and chronic inflammation in the body. Oxidative stress can damage the beta cells of the pancreas that produce insulin, while inflammation can interfere with blood glucose regulation. The combination of these two conditions can lead to more difficult blood sugar regulation (Apristina et al., 2023).

Meanwhile, 4.3% of patients with a diagnosis of more than 10 years had *outcome clinic* results that led to death. This is because patients with diabetes and hypertension who have been living with these conditions for more than 10 years tend to have a higher risk of developing long-term complications. These include coronary heart disease, heart failure, stroke, chronic kidney failure, diabetic retinopathy, neuropathy, and other vascular disorders hence these complications significantly increase the risk of death. Other factors include changes in the patient's response to medications and decreased adherence to the treatment plan (Nakagami & Morishita, 2018).

Based on the p-value of 0.125, it can be concluded that there is no significant relationship between the duration of diabetes diagnosis and the clinical outcomes of patients who also suffer from hypertension. Increased blood pressure in diabetic patients is caused by changes in endothelial function, which usually occur within a period of 0 to 10 years after diagnosis. Diabetes along with COVID-19 has a complex pathophysiological mechanism, which can accelerate the risk of thrombosis, ischemic and multi-organ complications, which also has an impact on the increase in mortality. Another study by Lim showed that coronavirus infection worsens inflammation and alters the immune system's response, resulting in difficulties in regulating blood sugar levels in diabetic patients. SARS-CoV-2 infection also increases the risk of thromboembolism and may lead to cardiorespiratory failure in diabetic patients compared to individuals without diabetes (Mogi, 2022).

This study showed that there was a significant relationship between kidney failure or EGFR and the *clinical outcomes* of respondents in diabetic and diabetic patients with hypertension who had been vaccinated with the Sinovac vaccine. More specifically, patients with kidney failure who had severe EGFR (stages 4 and 5) had a higher percentage (i.e. 2.7%) in terms of mortality compared to patients with moderate and mild EGFR (stages 1, 2, and 3). The existence of a significant correlation between kidney failure or decreased kidney function (characterized by low EGFR) and the clinical outcomes of diabetic patients who have been vaccinated with the Sinovac vaccine can be caused by several factors (Boroumand et al., 2022).

Diabetes and hypertension can directly cause damage to the blood vessels of the kidneys, which is very important in the process of filtering waste and excess fluid from the blood. In diabetes, high blood sugar levels over a long period of time can result in damage to blood vessels throughout the body, including the kidneys. Diabetic nephropathy, or kidney damage due to diabetes, can occur when the kidneys try to compensate by increasing the glomerular filtration rate (GFR) in the early stages, but then experience a gradual decline in function, leading to chronic kidney failure. In hypertension, high blood pressure can damage the blood vessels in the kidneys and reduce the ability of the kidneys to carry out the process of filtering waste effectively. As a result, high blood pressure is the main cause of the development of chronic kidney failure. In both of these conditions, the vascular damage that occurs to the kidneys can

lead to serious complications in kidney function, threatening the patient's overall health (Lim et al., 2021).

Conclusion

It can be concluded that on average, diabetic patients and diabetic patients with hypertension who have received the Sinovac vaccine can survive as much as 94.3% and those who die 5.7%. Of the patients who died, there were 8 people with stage 3 and 4 chronic kidney failure, which amounted to 2.7%. Of the 300 patients, 58% were female patients with most ages coming from the 41 to 60 years old group (55.3%). There was a significant relationship between comorbidities and clinical outcomes (p-value <0.001). From the results of the analysis, it was also known that patients diagnosed with >10 years of age had a mortality percentage of 4.3% compared to patients diagnosed <10 years of 1.3%.

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