Open Access Research Article

The 1st Cirebon International Health Symposium: Faculty of Medicine, Universitas Swadaya Gunung Jati
Update on Non-Communicable Diseases: Global Perspective on Health Challenges and Innovation

Correlation between Hypertension and the Severity of Diabetic Retinopathy in Diabetes Mellitus Patients at Waled Regional General Hospital: A Cross-Sectional Study

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DOI: 10.35898/ghmj-741077

ABSTRACT

Background: Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels and resulting from deviations in either insulin secretion, insulin action, or both. Prolonged hyperglycemia can lead to various complications, including diabetic retinopathy. The main risk factors for developing diabetic retinopathy are uncontrolled diabetes mellitus, hypertension, and dyslipidemia.
Aims: To determine the correlation between hypertension and the severity of diabetic retinopathy in diabetes mellitus patients at Waled Regional General Hospital, Cirebon, from 2020 to 2023.
Methods: This study used an analytical observational method with a cross-sectional design. We collected data from the medical records of patients with diabetic retinopathy at Waled Regional General Hospital from 2020 to 2023. This study employed total sampling as its sampling technique. We performed univariate analysis to determine the frequency distribution of the samples and bivariate analysis using the Spearman correlation test.
Results: Out of 50 diabetic retinopathy patients, the majority suffered from proliferative diabetic retinopathy (PDR), with 22 (44%) patients. The most common blood pressure level among the patients was grade 2 hypertension, with 19 (38%) patients. The bivariate analysis in this study showed a P-value of 0.091 and an r-value of 0.242.
Conclusion: There is no significant correlation between hypertension and the severity of diabetic retinopathy in diabetes mellitus patients at Waled Regional General Hospital from 2020 to 2023, with a positive correlation direction (p-value: 0.091 and r-value: 0.242).

Keywords: *Diabetic Retinopathy, Diabetes mellitus, Hypertension.*
Received: 25 September 2024 **Reviewed:** 16 October 2024 **Revised:** 30 November 2024 **Accepted:** 12 December 2024

1. Introduction

Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels and resulting from deviations in either insulin secretion, insulin action, or both (PERKENI, 2021). According to the WHO, around 422 million people worldwide suffer from diabetes mellitus. In the Southeast Asia region, including Indonesia, more than 96 million people suffer from diabetes mellitus (World Health Organization, n.d.). The International Diabetes Federation (IDF) shows that 537 million people aged 20-79 suffer from diabetes mellitus, representing 10.5% of the global population in that age group. The International Diabetes Federation estimates that by 2030, the number of people with DM will increase to 643 million (11.3%) and continue to rise to 783 million (12.2%) by 2045 (International Diabetes Federation, 2021). According to data from the Republic of Indonesia's Ministry of Health, there were 713,783 instances of diabetic retinopathy in the country in 2018, with West Java province having the highest number at 131,846 cases (Kementerian Kesehatan RI, 2018). The prevalence of diabetes mellitus patients in Cirebon Regency is 2,358 cases (Kementerian Kesehatan RI, 2018).

Prolonged hyperglycemia in diabetes mellitus can lead to various macrovascular and microvascular complications. One of the microvascular complications of diabetes is diabetic retinopathy. Retinal dysfunction is the underlying cause of this illness, which may result in blindness. Diabetes mellitus patients are at higher risk of developing retinopathy, and the risk increases with the duration of DM (Sudoyo, 2017). The World Health Organization (WHO) states that diabetic retinopathy is the cause of blindness in 4.8% of the 39 million blind people worldwide. This number is expected to increase rapidly alongside the growing number of diabetes patients. The global prevalence of diabetic retinopathy is 34.6%, while in Indonesia, the general prevalence is 43.1%, with 26.1% of cases being sight-threatening (Persatuan Dokter Spesialis Mata Indonesia, 2018).

Diabetic retinopathy can be classified based on the severity of changes in the small blood vessels of the retina and whether or not there is new blood vessel growth. The Early Treatment Diabetic Retinopathy Research Study Group (ETDRS) classifies diabetic retinopathy into two stages: NPDR (Non-Proliferative Diabetic Retinopathy) and PDR (Proliferative Diabetic Retinopathy). In NPDR, only minor changes are found in the small blood vessels of the retina. Fundus abnormalities that may be observed in NPDR include microaneurysms or intraretinal abnormalities known as intra-retinal microvascular abnormalities. These minor changes can lead to perfusion impairment, stimulating the proliferation of new blood vessels. The formation of new blood vessels is a hallmark of PDR (Persatuan Dokter Spesialis Mata Indonesia, 2018).

The main risk factors for diabetic retinopathy are uncontrolled diabetes mellitus, hypertension, and dyslipidemia (Yau et al., 2012). Hypertension can increase oxidative stress and inflammation. Increased production of reactive oxygen species (ROS) can lead to genetic abnormalities and mRNA production, which may result in cell apoptosis, particularly in pericytes and retinal endothelial cells (Shaniaputri et al., 2022). Hypertension is a common comorbid condition in DM, occurring in 40%-60% of type 2 DM patients (Ayutthaya & Adnan, 2020) Vascular Endothelial Growth Factors (VEGF) receptors can be overexpressed in people with diabetes mellitus, which can damage the endothelium of the retinal blood vessels. VEGF can bind directly to vascular endothelial cells, causing increased vascular permeability and forming ischemic neovascularization in diabetic retinopathy. VEGF will also stimulate the expression of Intracellular Adhesion Molecule-I (ICAM-I), which triggers the formation of bonds between leukocytes and blood vessel endothelium. This binding causes damage to the blood-retinal barrier, thrombosis, and retinal capillary occlusion (Nirmala Dewi & Vitresia, 2019). This study aims to investigate the potential correlation between hypertension and the severity of diabetic retinopathy in patients with diabetes mellitus at Waled Cirebon Regional Hospital, as there is currently no research on this issue in Cirebon.

2. Methods

Study design

This study used an analytical observational method with a cross-sectional design to examine the correlation between hypertension and the severity of diabetic retinopathy in diabetes mellitus patients at Waled Regional General Hospital from 2020 to 2023.

Populations and Samples

The study population is diabetic retinopathy patients diagnosed with Type 2 Diabetes Mellitus who visited Waled Cirebon Regional Hospital from 2020 to 2023. This study used a total sampling technique. The inclusion criteria in this study were the complete data, especially blood pressure in medical record of diabetic retinopathy patients at Waled Cirebon Regional Hospital in the period of January 2020 to December 2023. The study's exclusion criteria included diabetic retinopathy patients with dyslipidemia, patients with eye abnormalities that could interfere with examination or diagnosis, and medical records lacking information on blood pressure and the severity of diabetic retinopathy diagnosis. The total sample consisted of 50 patients out of 92 patients who met the inclusion and exclusion criteria

Data Collection

Data were collected from diabetic retinopathy patients' medical records, the data including demographic information such as age and gender, diabetic retinopathy classification from based on its severity (non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy with diabetic macula edema, proliferative diabetic retinopathy with diabetic macula edema), and blood pressure measurements based on JNC VIII (normal, pre-hypertension, grade 1 hypertension, grade 2 hypertension). There is no cutoff used for the patient's age. The data collection for this study is shown in Figure 1.

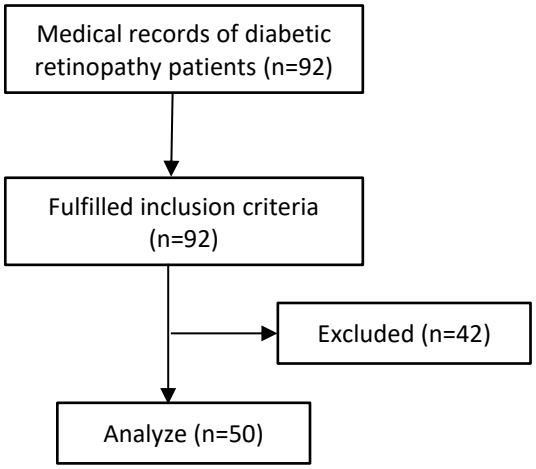

Figure 1. Consort Diagram.

Measurements

Independent Variables: Hypertension, defined according to blood pressure readings, divided into categories such as normal, pre-hypertension, grade 1 hypertension, and grade 2 hypertension. ***Dependent Variable***: Severity of diabetic retinopathy, classified as NPDR, PDR, NPDR with DME, and PDR with DME.

Statistical techniques

Acquired data were then analyzed using univariate statistics (distribution and percentage) to describe patient demographics (gender, age, complications) and clinical characteristics. The bivariate analysis used the Spearman correlation test to determine the correlation between hypertension and the severity of diabetic retinopathy. Spearman correlation test is reliable in this study because the data is not normally distributed. If the significance value is less than 0.05, there is a relationship between the two variables, whereas if the significance value is greater than 0.05, there is no relationship between them.

Ethical Clearance

This study has been ethically approved by the Ethic Committee of Waled Hospital with number, No. 000.9.2/032/KEPK/V/2024 on May 6th 2024.

3. Results

Patient's characteristics

In this study, it was found that the majority of patients, based on gender, were female, with 41 patients (82%). The table concludes that the average age of the subjects was 54.2 years, with the largest age group in the 45-60 age range (middle-aged), with 41 patients (82%). All 50 diabetic retinopathy patients in the study experienced complications of type 2 diabetes mellitus (100%). This study revealed that Proliferative Diabetic Retinopathy (PDR), which affected 22 out of 50 patients (44%), had the highest severity distribution of diabetic retinopathy. Based on blood pressure results, the majority of diabetic retinopathy patients (19 patients, or 38%) had stage 2 hypertension. The median, minimum, and maximum systolic and diastolic blood pressures were 140 (110-210) and 84 (70-110). Figure 2 shows the blood pressure percentage based on the severity of diabetic retinopathy among the respondents.

Table 1. Frequency Distribution of Patient's characteristics

Variables	n	%
Gender (n=50)		
Male	9	18%
Female	41	82%
Age (n=50)	54.2 ± 6.3*	
25-44 years old (*young age)*	2	4%
45-60 years old (*middle age)*	41	82%
61-75 years old (*elderly age)*	7	14%
Complications (n=50)		
DM type 1	0	0%
DM type 2	50	100%
Clinical Classification (n=50)		
NPDR	16	31%
PDR	22	44%
NPDR with DME	10	20%
PDR with DME	2	4%
Hypertension (n=50)	(Systolic 140 (110-210))** (Diastolic 84 (70-110))**	
Normal	6	12%
Pre-hypertension	16	32%
Hypertension grade 1	9	18%
Hypertension grade 2	19	38%

*Mean ± Standard deviation

**Median (minimum-maximum)

Bivariate analysis

Bivariate analysis was conducted using the Spearman correlation test to determine the relationship between independent and dependent variables. If the significance value is less than 0.05, there is a relationship between the two variables, whereas if the significance value is greater than 0.05, there is no relationship between the two variables. In Table 2, the study samples with normal blood pressure totaled 6, consisting of 3 NPDR (Non-Proliferative Diabetic Retinopathy) and 3 PDR (Proliferative Diabetic Retinopathy) cases. In the prehypertension group, there were 16 individuals, with 6 classified as NPDR, 7 as PDR, and 3 NPDR with DME (Diabetic Macular Edema). Among those with stage 1 hypertension, there were 9 people: 3 NPDR, 2 PDR, and 4 NPDR with DME. The largest group was those with stage 2 hypertension, totaling 19 individuals: 4 NPDR, 10 PDR, 3 NPDR with DME, and 2 PDR with DME. The results of the Spearman correlation test showed a p-value of 0.091 (>0.05), indicating that there was no correlation between hypertension and the severity of diabetic retinopathy. The correlation coefficient was 0.242, which suggests a very weak correlation, but the direction of the relationship was positive, meaning the two variables were correlated in the same direction.

Table 2. Correlation between Hypertension and the Severity of Diabetic Retinopathy

Variables	Diabetic Retinopathy						
Hypertension	NPDR	PDR	NPDR with DME	PDR with DME	Total	Correlation coefficient (r)	p-value
Normal	3 (6%)	3 (6%)	0 (0%)	0 (0%)	6 (12%)		
Pre-hypertension	6 (12%)	7 (14%)	3 (6%)	0 (0%)	16 (32%)	0.242	0.091
Hypertension grade 1	3 (6%)	2 (4%)	4 (8%)	0 (0%)	9 (18%)		
Hypertension grade 2	4 (8%)	10 (20%)	3 (6%)	2 (4%)	19 (38%)		
Total	16 (32%)	22 (44%)	10 (20%)	2 (4%)	50 (100)		

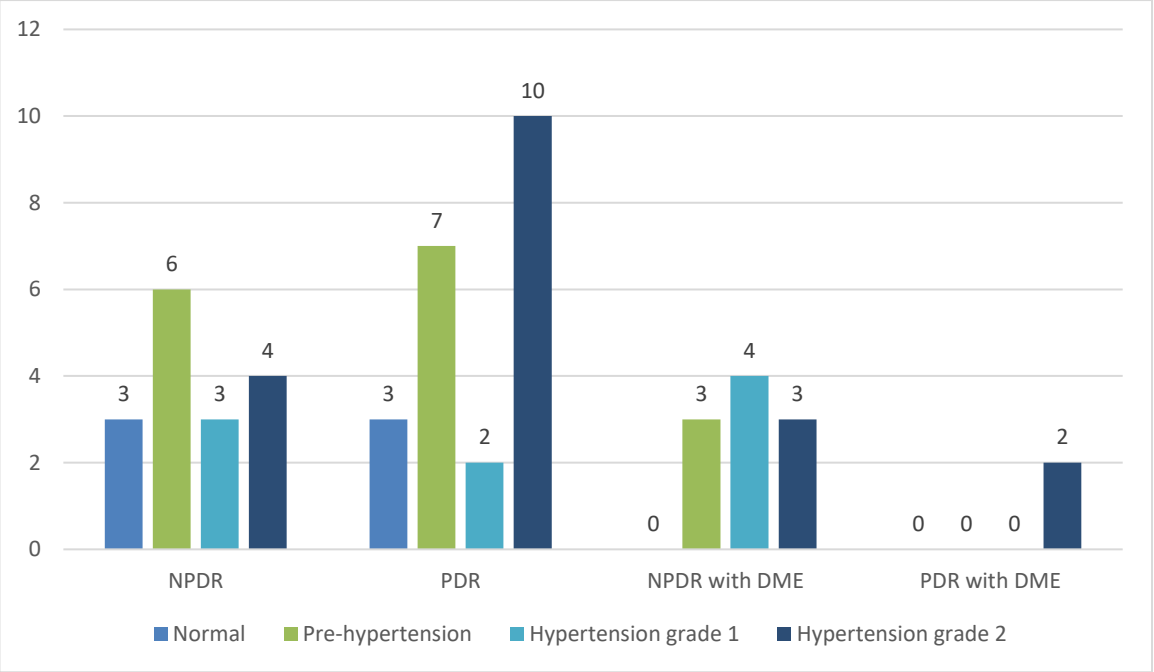

Figure 2. Blood pressure percentage based on the severity of diabetic retinopathy.

4. Discussion

Patient's Characteristics

In this study, it was found that most diabetic retinopathy patients at Waled Cirebon Regional Hospital from 2020-2023 had type 2 diabetes, were middle-aged (45-60 years old), were female, and had stage 2 hypertension, and the most common retinopathy classification was PDR (proliferative diabetic retinopathy), also, there is no relationship between hypertension and the severity of diabetic retinopathy.

The majority of patients with diabetic retinopathy in this study were female, with 41 out of 50 patients (82%). This is in accordance with the research by Karisman et al. in 2024 on diabetic retinopathy patients at JEC-ORBITA Makassar in 2022, where 528 of the 882 patients (59.9%) were female. The higher prevalence of diabetic retinopathy in women is due to estrogen levels, which play a role in diabetes mellitus. This hormone affects body composition, energy metabolism, vascular function, and inflammatory response. Elevated estrogen levels can

reduce leptin, which regulates appetite suppression in the hypothalamus. This leads to uncontrolled food intake, causing excessive fat accumulation and high blood sugar due to reduced peripheral tissue sensitivity to insulin (Farhani et al., 2023; Reubun Ririn Jihan S et al., 2022).

One of the risk factors for diabetic retinopathy is age The age group of 45-60 years dominated the diabetic retinopathy patients in this study. This is in accordance with the study by Fathia Farhani, Zulfachmi Wahab, and Yanuarita Tursinawati in 2023 at Cicendo Eye Hospital Bandung, where 64 out of 70 diabetic retinopathy patients (91.4%) were over 40 years old. At this age, individuals are more likely to develop diabetic retinopathy due to the decline in bodily functions associated with cell apoptosis in various organs as a result of aging. Retinal apoptosis is accelerated by inflammatory reactions and increased oxidative stress. Owing to the fact that the insulin resistance, beta-cell dysfunction, and glucose intolerance are linked to aging, those with diabetes mellitus over 40 are more likely to develop diabetic retinopathy (Hertapanndika et al., 2020).

In this study, all diabetic retinopathy patients at Waled Hospital from 2020 to 2023 had type 2 diabetes mellitus (50 patients, or 100%). This finding is consistent with the study by Angelina, Ari, and Ida Bagus in 2022 on diabetic retinopathy patients at RSUP Sanglah Eye Clinic, where all 80 patients had type 2 diabetes mellitus. The most prevalent form of diabetes, known as type 2 diabetes mellitus, is typified by insulin resistance and decreased beta-cell activity in insulin secretion. Prolonged hyperglycemia causes histopathological changes in blood vessels, leading to retinal capillary occlusion. Over time, diabetic patients experience retinal toxicity, which affects the death of retinal nerves and blood vessels (Farhani et al., 2023; Utami Dyah Rahayu et al., 2017).

The subjects with the highest diabetic retinopathy severity in this study were PDR (44%). This is in accordance with the study by Aisyah Primaputri et al. in 2022, which found that PDR patients made up 68% (57 out of 83 patients). PDR is an advanced stage of diabetic retinopathy that occurs when major retinal blood vessels become occluded, characterized by neovascularization. This is caused by damage to retinal pericytes, which disrupts blood flow and leads to ischemia. Factors influencing the progression of diabetic retinopathy include diabetes duration, HbA1c levels, and delayed diagnosis (Lamy Manao et al., 2021; Wang et al., 2017).

In this study, 19 out of 50 diabetic retinopathy patients (38%) had stage 2 hypertension (systolic ≥160 mmHg and/or diastolic ≥100 mmHg), while 16 patients (32%) had prehypertension (systolic 120-139 mmHg and/or diastolic 80-89 mmHg). The results for prehypertension and stage 2 hypertension were not significantly different. A similar study by Dyah Rahayu Utami et al. in 2017 on diabetic retinopathy found that 33.3% of patients (25 out of 75) had prehypertension and 30.7% (23 out of 75) had stage 1 hypertension. Prolonged hypertension is a risk factor for microvascular complications in diabetes mellitus, including those affecting the blood vessels in the retina, such as diabetic retinopathy. This is because oxidative stress and chronic inflammation are factors in hypertension (Li et al., 2021).

Correlation between Hypertension and the Severity of Diabetic Retinopathy

The correlation test between hypertension and diabetic retinopathy in this study yielded statistically non-significant results, with a p-value of 0.091 (>0.05) and a correlation coefficient of 0.242. This indicates a very weak relationship, and the direction of the relationship shows a positive correlation. The result is different from the research by Min Zhang et al. in 2023, which showed a correlation between hypertension and the severity of diabetic retinopathy in diabetes mellitus patients. However, the outcome of this study agrees with that of a study done in 2022 by Rizky Febrian, Sulistyani, Budi Hermawan, and Sahilah Ermawati. In that study, the Spearman correlation test between hypertension and diabetic retinopathy found a p-value of 0.219, which means there was no significant relationship between the two variables.

In this study, it was found that there is a positive correlation (r=0.242), meaning that if one variable increases, the other does as well Therefore, the greater the number of hypertension patients among those with diabetic retinopathy, the more severe the retinopathy will be. One of the ways that diabetes mellitus (DM) and hypertension interact is through the Renin Angiotensin-Aldosterone System (RAAS), which regulates blood sugar levels. An increase in RAAS in diabetic people can result in hypertensive disorders. Diabetes and hypertension together impact the retina's microvascular health, releasing retinal pericyte cells (Trika et al., 2024).

The findings of this study differ from those of Lei Liu et al. in 2020, who found a correlation between hypertension and the severity of diabetic retinopathy. The study included a larger participant population, consisting of 2189 patients from Chinese, Malays, and Indian backgrounds. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or self-reported diagnosis of hypertension, while diabetes was defined as random glucose concentration > 11.1 mmol/L, HbA1c ≥ 6.5%, and self-reported use of anti-diabetic medication, if previously diagnosed. That study used multivariate analysis. The differences in the sample size, study population, setting, and methodology could explain discrepancies between those two studies.

The non-significant results of this study may indicate that hypertension is not the only factor that can develop the severity of diabetic retinopathy. Other factors that were not examined include elevated LDL levels, which can lead to the accumulation of atherosclerotic plaques in blood vessels, including the small vessels in the retina (Raflin Sinaga & Dharma, 2023). Additionally, HbA1c control plays a role since HbA1c levels above 6.5% increase the risk of microvascular complications, including diabetic retinopathy, while stable blood glucose levels help reduce pressure on the retinal blood vessels. Another factor is the duration of diabetes, which triggers complications in type 2 diabetes mellitus, including macrovascular and microvascular complications such as diabetic retinopathy. Since this study did not evaluate these risk factors, the severity of diabetic retinopathy does not statistically significantly correlate with hypertension (Primaputri et al., 2022).

These findings might have important clinical implications for the healthcare providers managing patients with diabetic retinopathy to keep control of their blood pressure, LDL levels, and HbA1c to minimize the severity of diabetic retinopathy.

Limitation

There are several potential limitations in this study. First, this study used secondary data from medical records of diabetic retinopathy patients. Hence, other risk factors cannot be identified due to limited data from medical records, such as duration of diabetes, blood glucose level, and lipid profile. Other limitations are the relatively small sample size.

5. Conclusion

There is no significant correlation between hypertension and the severity of diabetic retinopathy in diabetes mellitus patients at Waled Regional General Hospital from 2020 to 2023, with a positive correlation direction (p-value = 0.091, r = 0.242). In the future studies, it is suggested to do the study with larger sample sizes to explore the causal relationship between hypertension and diabetic retinopathy severity, also exploring other risk factors such as HbA1c, dyslipidemia and duration of diabetes so that the study is more relevant.

Conflict of Interest

No potential conflict of interest in this study.

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Cite this article as:

Trinanda, S. K., Sisprihattono, B., & Astuti, W. (2024). Correlation between Hypertension and the Severity of Diabetic Retinopathy in Diabetes Mellitus Patients at Waled Regional General Hospital: A Cross-Sectional Study. *GHMJ (Global Health Management Journal)*, *7*(4), 279–286. https://doi.org/10.35898/ghmj-741077