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Research Article

# Lipid Profile in Type 2 Diabetes Mellitus Patients With and Without Diabetic Retinopathy

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**ABSTRACT**
**Background:** Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both. **Objective:** To analyze differences in the proportion of lipid profile categories in type 2 DM patients with and without diabetic retinopathy. **Methods:** This was a hospital-based cross-sectional study with 45 samples. The independent variables assessed were the lipid profile, including LDL, HDL, triglycerides, and total cholesterol levels. The dependent variable assessed was the incidence of diabetic retinopathy. The analysis used were univariate and bivariate (Chi-square and Fisher exact). **Results:** The prevalence of diabetic retinopathy was 37.8%, consist of 17.8% of NPDR and 20% of PDR. There were significant differences in the proportion of LDL categories (p=0.007) and total cholesterol (p=0.038) in type 2 DM patients with and without diabetic retinopathy, and there were no significant differences in the proportion of HDL categories (p=0.719) and triglycerides (p=1) in type 2 DM patients with and without diabetic retinopathy. **Conclusion:** There were significant differences in the proportion of LDL categories and total cholesterol in type 2 DM patients with and without diabetic retinopathy.

**Keywords:** diabetic retinopathy, insulin, lipid profile, total cholesterol

## 1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both [1]. The World Health Organization (WHO) reported that in 2019, diabetes was the direct cause of 1.5 million deaths, and 48% of all deaths due to diabetes occurred before the age of 70 years [2]. Diabetes mellitus can cause further microangiopathic complications, such as diabetic retinopathy. Diabetic retinopathy is microangiopathic damage as a result of diabetes, starting from non-proliferative diabetic retinopathy (NPDR) with several stages to proliferative diabetic retinopathy (PDR) [3]-[4]. The global prevalence of diabetic retinopathy is estimated at 35.4%. In Indonesia, the prevalence of diabetic retinopathy among DM patients was reported as 43.1% in Yogyakarta and 24.7% in Bandung [5, 6, 7].

One of the risk factors for the development and progression of diabetic retinopathy is the lipid profile levels in DM patients, including levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and total cholesterol [8]. Insulin resistance in DM can cause dyslipidemia, which is characterized by an increase in LDL, triglycerides, total cholesterol, and a decrease in HDL [9]. Lipid profile levels are known to be associated with the incidence of diabetic retinopathy. Reduced bioavailability of nitri oxide, caused by high lipid levels, can lead to endothelial dysfunction. This endothelial dysfunction is believed to contribute to the pathophysiology of diabetic retinopathy, particularly in damaging the blood-retinal barrier and forming retinal exudates [10].

A study in RSUP Dr. M. Djamil Padang, reported a significant association between LDL levels and the severity of diabetic retinopathy, an increase in the severity of diabetic retinopathy at high LDL levels [11]. A

significant association between HDL and the incidence of diabetic retinopathy in type 2 DM patients has been reported in a study in Purwokerto, with the result indicating that DM patients who have low HDL have a greater risk of developing diabetic retinopathy [8]. Different from these studies, a study at RSUPN Dr. Cipto Mangunkusumo reported that there was no significant relationship between plasma lipid profile and diabetic retinopathy [12]. Therefore, this study aims to see differences in the proportion of lipid profile categories in type 2 DM patients with and without diabetic retinopathy.

## 2. Methods

This was a hospital based cross-sectional study conducted at Arifin Achmad General Hospital, Riau. This study aimed to analyze the differences in the proportion of lipid profile categories in type 2 DM patients with and without diabetic retinopathy. The population in this study consisted of type 2 DM patients undergoing eye examinations at the Eye Clinic. Inclusion criteria for this study were type 2 DM patients aged 18 and above. Exclusion criteria included patients with opacity in the refractive media and those with retinal disorders other than diabetic retinopathy.

The independent variables studied were lipid profiles, including levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and total cholesterol. LDL and triglycerides levels were categorized as normal if <150 mg/dl and high if ≥150 mg/dl. HDL levels were categorized as normal if ≥40 mg/dl and low if <40 mg/dl. Total cholesterol levels were categorized as normal if <200 mg/dl and high if ≥200 mg/dl. The dependent variable studied was the incidence of diabetic retinopathy categorized as normal and diabetic retinopathy.

Univariate analysis was done to examine the frequency distribution of each variable. Bivariate analysis using Chi-square and Fisher exact tests was done to analyze the differences in the proportion of lipid profile categories in type 2 DM patients with and without diabetic retinopathy. Statistically significant differences in proportions indicated an association between lipid profiles and the incidence of diabetic retinopathy. Prevalence ratio (PR) values were used to assess the strength of the association between study variables with significant results.

## 3. Results

This study was conducted at the Eye Clinic of Arifin Achmad General Hospital of Riau from April to September 2023. A total of 103 samples were initially obtained for the study, but 58 samples were excluded due to incomplete data on lipid profile variables. Therefore, the total number of samples examined in this study was 45. The characteristics of the samples are shown in Table 1 and Table 2.

**Table 1.** Sample characteristics based on age, gender, visual acuity, and diabetic retinopathy severity

| Variables | Samples (n=45) |
|---|---|
| Age (year) | |
| Mean ± SD | 57,8 ± 8 |
| Gender | |
| Male | 10 (22,2%) |
| Female | 35 (77,8%) |
| Visual Acuity | |
| Normal (6/6 to ≤6/12) | 15 (33,3%) |
| Mild vision impairment (6/12 to ≤6/18) | 4 (8,9%) |
| Moderate vision impairment (6/18 to ≤6/60) | 15 (33,3%) |
| Severe vision impairment (6/60 to ≤3/60) | 2 (4,4%) |
| Blindness (worse than 3/60) | 9 (20%) |
| Diabetic Retinopathy Severity | |
| Normal | 28 (62,2%) |
| NPDR | 8 (17,8%) |
| PDR | 9 (20%) |

Based on Table 1, samples comprised of 10 (22,2%) males and 35 (77,8%) females, with mean age of 57,8 years. A larger number of samples do not have diabetic retinopathy when compared to those diagnosed with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

**Table 2.** Sample characteristics based on lipid profiles

| Variables | Samples | | |
|---|---|---|---|
| | Normal (n=28) | Diabetic Retinopathy (n=17) | Total (n=45) |
| LDL (mg/dl) | | | |
| Normal | 21 (75%) | 5 (29,4%) | 26 (57,8%) |
| High | 7 (25%) | 12 (70,6%) | 19 (42,2%) |
| HDL (mg/dl) | | | |
| Normal | 21 (75%) | 14 (82,4%) | 35 (77,8%) |
| Low | 7 (25%) | 3 (17,6%) | 10 (22,2%) |
| Triglycerides (mg/dl) | | | |
| Normal | 16 (57,1%) | 9 (25,9%) | 25 (55,6%) |
| High | 12 (42,9%) | 8 (47,1%) | 20 (44,4%) |
| Total Cholesterol (mg/dl) | | | |
| Normal | 15 (53,6%) | 3 (17,6%) | 18 (40%) |
| High | 13 (46,4%) | 14 (82,4%) | 27 (60%) |

Table 2 shows that according to the lipid profile categories, the categories of LDL, HDL, and triglycerides for the total sample are predominantly in the normal category. Meanwhile, the total cholesterol category for the total sample is predominantly in the high category. Samples with diabetic retinopathy more common in the high category for LDL, triglycerides, and total cholesterol. In contrast, samples without diabetic retinopathy more frequently fall into the normal category for LDL, triglycerides, and total cholesterol. The HDL category for both samples with and without diabetic retinopathy is more common in the normal category.

The mean HDL levels in the total sample were found to be in the normal range (≥40 mg/dl), while the mean total cholesterol levels in the entire sample were high (≥200 mg/dl). The mean values for LDL and triglycerides levels across the total sample were not normally distributed, so median values were used, and they were found to be in the normal range (<150 mg/dl).

The mean HDL levels in the diabetic retinopathy and non-diabetic retinopathy groups were within the normal range, 49 mg/dl and 50 mg/dl respectively. While, the mean total cholesterol levels in the diabetic retinopathy group were higher at 242 mg/dl (high) compared to the non-diabetic retinopathy group, which was 179 mg/dl (normal). The mean LDL and triglycerides levels in the two groups cannot be compared as the data distribution is not normal.

**Table 3.** Difference in Proportions of LDL Categories in Type 2 DM Patients with and without Diabetic Retinopathy.

| LDL Categories | Diabetic Retinopathy | | | | Total | | p | *Prevalence Ratio* (PR) |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Diabetic Retinopathy | | | | | |
| | n | % | n | % | n | % | | |
| Normal | 21 | 80,8 | 5 | 19,2 | 26 | 100 | 0,007 | 3,3 |
| High | 7 | 36,8 | 12 | 63,2 | 19 | 100 | | |
| Total | 28 | 62,2 | 17 | 37,8 | 45 | 100 | | |

Based on Table 3, it can be observed that in the samples with normal LDL category, more individuals do not have diabetic retinopathy. In contrast, among the samples with high LDL category, more individuals have diabetic retinopathy.

The bivariate analysis results using the *Chi-square* test show a p-value of 0.007 (p<0.05), indicating there is a significant difference in the proportions of LDL categories in type 2 DM patients with and without diabetic retinopathy, with a Prevalence Ratio (PR) value of 3.3.

**Table 4.** Difference in proportions of HDL categories in Type 2 DM patients with and without diabetic retinopathy

| HDL Categories | Diabetic Retinopathy | | | | Total | | p | *Prevalence Ratio* (PR) |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Diabetic Retinopathy | | | | | |
| | n | % | n | % | n | % | | |
| Normal | 21 | 60 | 14 | 40 | 35 | 100 | 0,719 | 0,75 |
| Low | 7 | 70 | 3 | 30 | 10 | 100 | | |
| Total | 28 | 62,2 | 17 | 37,8 | 45 | 100 | | |

Based on Table 4, it can be observed that among samples with normal HDL category, more samples do not have diabetic retinopathy. Similarly, a higher number of samples with low HDL categories also do not have diabetic retinopathy.

A bivariate analysis was conducted using the *Fisher exact* test because the variable data did not meet the *Chi-square* test requirements. The results of the *Fisher exact* test show a p-value of 0.719 (p>0.05), indicating there is no significant difference in the proportions of HDL categories in type 2 DM patients with and without diabetic retinopathy.

**Table 5.** Difference in Proportions of Triglycerides Categories in Type 2 DM Patients with and without Diabetic Retinopathy

| Triglycerides Categories | Diabetic Retinopathy | | | | Total | | p | *Prevalence Ratio* (PR) |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Diabetic Retinopathy | | | | | |
| | n | % | n | % | n | % | | |
| Normal | 16 | 64 | 9 | 36 | 25 | 100 | 1 | 1,1 |
| Tinggi | 12 | 60 | 8 | 40 | 20 | 100 | | |
| Total | 28 | 62,2 | 17 | 37,8 | 45 | 100 | | |

Based on Table 5, it can be observed that among samples with normal triglycerides categories, more individuals do not have diabetic retinopathy. Similarly, among samples with high triglycerides categories, a higher number also do not have diabetic retinopathy.

The bivariate test using the *Chi-square* test show a p-value of 1 (p>0.05), indicating there is no significant difference in the proportions of triglycerides categories in type 2 DM patients with and without diabetic retinopathy.

**Table 6.** Difference in Proportions of Total Cholesterol Categories in Type 2 DM Patients with and without Diabetic Retinopathy

| Total Cholesterol Categories | Diabetic Retinopathy | | | | Total | | p | *Prevalence Ratio* (PR) |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Diabetic Retinopathy | | | | | |
| | n | % | N | % | n | % | | |
| Normal | 15 | 83,3 | 3 | 16,7 | 18 | 100 | 0,038 | 3,1 |
| High | 13 | 48,1 | 14 | 51,9 | 27 | 100 | | |
| Total | 26 | 62,2 | 15 | 37,8 | 45 | 100 | | |

Based on Table 6, it can be observed that among samples with normal total cholesterol category, more individuals do not have diabetic retinopathy. In contrast, among samples with high total cholesterol categories, a higher number of samples have diabetic retinopathy.

The bivariate analysis using the *Chi-square* test show a p-value of 0.038 (p<0.05), indicating there is a significant difference in the proportions of total cholesterol categories in type 2 DM patients with and without diabetic retinopathy, with a Prevalence Ratio (PR) value of 3.1.

## 4. Discussion

The samples in this study consisted of all type 2 diabetes mellitus (DM) patients undergoing eye examinations at the Eye Clinic of Arifin Achmad General Hospital of Riau during the study period. The total number of samples in the study was 45 individuals, with an average age of 57,8 years. This result is supported by other research reporting that type 2 DM is estimated to affect 462 million people worldwide, with 37% occurring in individuals over 50 years old and peaking in incidence between 55 and 59 years [13]. American Diabetes Association stated that the vulnerability to type 2 diabetes increases with age due to the aging process causing a decline in the pancreas's ability to produce insulin and an increased risk of insulin resistance [14].

The gender distribution showed a higher percentage of females (77.8%) than males (22.2%). This result supported by Riskesdas in 2018, which reported a higher prevalence of diabetes mellitus (DM) in females than males [15]. Another study in Bandar Lampung supports these results, indicating that 72.1% of type 2 diabetes mellitus patients are females [16]. Female have a higher risk of developing diabetes because, physiologically, female tend to have a greater body mass index and fewer muscle structures, which support less absorption of high glucose loads [17]. Hormonal factors in women, including relatively high levels of estrogen and progesterone, also contribute to decreased insulin sensitivity throughout the body, leading to diabetes mellitus [17].

The LDL category in the samples is predominantly in the normal range (57.8%) with a median value of 139 mg/dl, falling within the normal range. In contrast, other research reports a median LDL value in DM patients of 167 mg/dl, categorizing it as above normal (high) [18]. The HDL category in the samples is mostly in the normal range (77.8%) with a mean value of 49.8 mg/dl, also falling within the normal range. This result is consistent with other studies reporting that the average HDL in DM patients is normal, above 40 mg/dl [8]. The triglycerides category in the samples is more prevalent in the normal range (55.6%) with a median value of 146 mg/dl, falling within the normal range. This result inconsistent with other study reporting a median triglycerides value in DM patients of 102 mg/dl [18]. The total cholesterol category in the samples is more prevalent in the high category with an average of 219.6 mg/dl, exceeding the normal value (high). This result consistent with other study reporting the average total cholesterol levels in DM patients to be 243 mg/dl [8].

Based on the data, the results indicate that mean levels of HDL and the median level of LDL and triglycerides in the samples fall within the normal range, while the mean total cholesterol level in the samples exceeds the normal range (high). These findings are inconsistent with the characteristics of diabetic dyslipidemia in diabetes mellitus, which are marked by a triad of increased triglycerides (hypertriglyceridemia), decreased HDL, and increased small dense LDL [19]. Hypertriglyceridemia is considered the predominant lipid abnormality in insulin resistance and plays a central role in determining the typical lipid pattern of diabetic dyslipidemia [20]. The differences in results in this study may be due to different interventions in lipid levels for each individual.

Best-corrected visual acuity (BCVA) in the samples in this study is most commonly categorized as normal (33.3%) and moderate vision impairment (33.3%). This result consistent with a study Ethiopia reporting that 33.4% of DM patients fall into moderate vision impairment [21]. Diabetes mellitus can result in visual impairment due to complications such as glaucoma, retinopathy, maculopathy, ischemic optic neuropathy, extraocular muscle paralysis, cataracts, iridosyclitis, and iris rubeosis [22].

The prevalence of diabetic retinopathy in this study was found to be 37.8%, with 17.8% classified as non-proliferative diabetic retinopathy (NPDR) and 20% as proliferative diabetic retinopathy (PDR). These findings are similar to the global prevalence of diabetic retinopathy, which is 35.4%, and 36.8% in Saudi Arabia [5]. Meanwhile, studies in Indonesia report higher prevalence rates, such as 43.1% in Yogyakarta and a lower prevalence in Bandung at 24.7% [6]-[7].The observed differences in prevalence may be attributed to variations in healthcare systems and socio-economic factors among the studied populations, as well as essential characteristics such as the duration of diabetes, which is known to vary significantly among the sampled populations.

Based on the bivariate analysis, the results indicate a significant difference in the proportions of LDL categories in type 2 DM patients with and without diabetic retinopathy, with a p-value of 0.007 ($p < 0.05$). This significant difference in proportions indicates a significant association between LDL and the incidence of diabetic retinopathy. The *Prevalence ratio* (PR) value of 3.3 indicates that DM patients with high LDL categories have a 3.3 times greater risk of developing diabetic retinopathy compared to DM patients with normal LDL categories. These results consistent with another study in India reporting a difference in proportions of LDL categories in type 2 DM patients with and without diabetic retinopathy [18]. Other study in Padang also supports this research, showing an association between LDL and the severity of diabetic retinopathy, where an increase in the severity of diabetic retinopathy occurred more frequently in individuals

with high LDL compared to those with normal LDL, controlling LDL and cholesterol levels with consumption of lipid-lowering drugs in DM patients may decrease the severity of diabetic retinopathy [11].

LDL and other risk factors influence the pathological changes in the retinal blood vessels. The modification of LDL into oxidized LDL (oxLDL) is one of the earliest events in atherosclerosis through inflammatory and immunological mechanisms that lead to the formation of macrophage foam cells [23]. Oxidized LDL (oxLDL) is a potent natural prooxidant derived from LDL through cell-mediated oxidation. This oxidation occurs more frequently in glycated LDL, as observed in individuals with DM, and is associated with poor glycemic control [24]. Oxidized LDL (oxLDL) can affect retinal capillary pericytes mediated by increased oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and autophagy, leading to apoptosis of retinal pigment epithelial cells [25]. Pericytes are a crucial part of the capillary structure and retinal function, and the loss of pericytes is the initial stage of diabetic retinopathy, underlying leakage in the retinal blood barrier [25]. Oxidized LDL (oxLDL) in retinal pigment epithelial cells also induces the production of reactive oxygen species (ROS) and reduces the levels of glutathione peroxidase 1 (GPX-1), leading to oxidative stress, resulting in damage and death of retinal capillary cells, leading to diabetic retinopathy [26]. High LDL and total cholesterol levels also play a role in the formation of retinal hard exudates, statistically significant high levels of triglycerides, total cholesterol, total lipids and cholesterol ester was found in the diabetic patients with manifested maculopathy as compared to those without diabetic maculopathy [27].

Based on the bivariate analysis, the results indicate no significant difference in the proportion of HDL categories in type 2 DM patients with and without diabetic retinopathy, with a p-value of 0.719 ($p > 0.05$). No significant difference in proportions indicates that there is no association between HDL and the incidence of diabetic retinopathy.

These results are inconsistent with a study in Purwokerto that reported a difference in the proportion of HDL categories in type 2 DM patients with and without diabetic retinopathy, indicating an association between HDL and the incidence of diabetic retinopathy [8]. Diabetes patients with low HDL were found to be more at risk of developing diabetic retinopathy compared to diabetes patients with normal HDL. High-density lipoprotein (HDL) is a lipoprotein that removes excess harmful cholesterol from the blood and transports it back to the liver for elimination from the body[8][28]. The antioxidant function of HDL also helps prevent the development of LDL particles into oxLDL particles and inhibits the early formation of atheroma in the subendothelium of blood vessels [29].

Low levels of HDL can trigger biochemical changes, activate glial cells, induce changes in growth factor signals, trigger the activation of chemokines and inflammatory cytokines, and activate reactive oxygen species (ROS). These changes can lead to neuroglial degeneration and vascular dysfunction, ultimately causing diabetic retinopathy[29].

The difference in research results may be due to the fact that, in this study population, the majority of HDL categories were in the normal range. Another possible reason is the presence of other risk factors influencing the incidence of diabetic retinopathy, such as the duration of diabetes, HbA1c levels, and hypertension.

Based on the bivariate analysis, the results indicate no significant difference in the proportion of triglycerides categories in type 2 DM patients with and without diabetic retinopathy, with a p-value of 1 ($p > 0.05$). No significant difference in proportions indicates that there is no association between triglycerides and the incidence of diabetic retinopathy. This result is consistent with the study in Purwokerto, which reported no significant difference in the proportion of triglycerides categories in type 2 DM patients with and without diabetic retinopathy [8]. Another study in Jakarta supports these results, indicating no association between triglycerides and the severity of diabetic retinopathy [12].

However, this result is inconsistent with a study in India reporting an association between triglycerides and diabetic retinopathy in type 2 DM patients [30]. Additionally, a study in Saudi Arabia reported an association between triglycerides levels and the severity of diabetic retinopathy [31]. Triglycerides are suspected to have a more significant impact on the progression and severity of diabetic retinopathy due to their role in the development of hard exudates and macular edema, which can exacerbate the progression of diabetic retinopathy [32]. Hard exudates are accumulations of fat and lipoproteins in the retina caused by blood vessel leakage. An increased number of hard exudates is associated with an elevated risk of visual impairment, as these deposits can increase the likelihood of fibrosis in the retina, leading to degeneration of photoreceptors and neuronal elements in the outer plexiform layer [33]. Macular edema is a manifestation of retinal thickening caused by intraretinal fluid accumulation due to damage to blood vessel barriers. It is a primary cause of decreased visual function in diabetic retinopathy [34].

The differences in research outcomes may be attributed to variations in research methods and the presence of other factors influencing the incidence of diabetic retinopathy, including the duration of diabetes, HbA1c levels, and hypertension.

Based on the bivariate analysis, the results indicate a significant difference in the proportions of total cholesterol categories in type 2 DM patients with and without diabetic retinopathy, with a p-value of 0.038 ($p < 0.05$). This significant difference in proportions indicates a significant association between total cholesterol and the incidence of diabetic retinopathy. The *Prevalence ratio* (PR) value of 3.1 indicates that DM patients with high total cholesterol categories have a 3.1 times greater risk of developing diabetic retinopathy compared to DM patients with normal total cholesterol categories. This result is supported by a study in India, which reported an association between total cholesterol and diabetic retinopathy in patients with type 2 DM [30].

Total cholesterol is the sum of LDL, HDL, and 20% of triglycerides levels in the blood. An increase in total cholesterol levels reflects an elevation in blood lipid levels that can lead to endothelial dysfunction through reduced nitric oxide bioavailability, which plays a crucial role in the pathophysiology of diabetic retinopathy, mainly related to the blood-retinal barrier damage [35]. High total cholesterol levels are also strongly associated with the formation of retinal hard exudates, which is a sign of diabetic retinopathy [36].

## 5. Conclusion

The study found a notable prevalence of diabetic retinopathy among type 2 diabetes mellitus patients. No significant differences were observed in HDL and triglyceride levels between patients with and without diabetic retinopathy, while significant differences were noted in LDL and total cholesterol levels. Patients with elevated LDL and total cholesterol levels had a higher risk of developing diabetic retinopathy. The use of lipid-lowering drugs as adjunctive therapy may help prevent the progression of diabetic retinopathy from non-proliferative to proliferative stages. Further research with a larger sample size is needed to explore additional risk factors and to perform multivariate analyses to determine the most dominant contributors to the development of diabetic retinopathy.

## 6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

## 7. Ethical Statement

The study protocol received approval from the Medical Research Ethics Unit, Faculty of Medicine, Universitas Riau and Sumatera Medical Journal (SUMEJ) is a peer-reviewed electronic internationaljournal. This statement below clarifies ethical behavior of all parties involved in the act of publishing an article in Sumatera Medical Journal (SUMEJ), including the authors, the chief editor, the Editorial Board, the peer-reviewer and the publisher (TALENTA Publisher UniversitasSumatera Utara). This statement is based on COPE's Best Practice Guidelines for Journal Editors.

## 8. Author Contributions

All authors contributed to the design and implementation of the research, data analysis, and finalizing the manuscript.

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## 11. Conflict of Interest

Authors declares no conflict of interest.

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