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Emerging Insights into Diabetic Retinopathy: A Novel Statistical Approach to Assessing Risk Factors and Clinical Outcomes.

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Abstract: Diabetes remains and increasingly becomes a global healthcare problem with diabetic retinopathy (DR) being the most severe often. This study aimed to analyze the association between identifiable clinical and demographic factors and the progression of diabetic retinopathy using such a novel statistical framework. The main multicentric cohort study included 200 diabetic patients divided into two groups; none with proliferative diabetic retinopathy (NPDR) and one with proliferative diabetic retinopathy (PDR). Parameters like glycemic index, diabetes duration, and hypertension were assessed. The results demonstrated that poor glycemic control (HbA1c≥7.5) was associated (p=0.003) with the development of the disease from NPDR to PDR with an average level of HbA1c 8.3±1.4 in group PDR whereas 6.9±1.2 in group NPDR. Also, the longer duration of the disease p=0.021 and uncontrolled hypertension p=0.014 were strongly related to the severity of DR. The findings emphasize the need for adequate risk assessment and management of the patients to prevent or minimize the risk of irreversible visual impairment. These statistically significant results provide new information regarding the complexity of DR progression.

Keywords: Diabetic retinopathy, glycemia control, causative factors.

Introduction: Diabetic retinopathy (DR) in the developing world is a common cause of visual disability in approximately one-third of diabetes patients (Hossain et al., 2021). The DR problem is expected to be on the rise in line with diabetes especially in the developing regions (Khawaja et al., 2022). Retinopathy indicates that the disease worsens with the health status with damage of the eye blood vessels due to high blood sugar hence causing vision distortion or even loss. Cited studies indicated that there has been a growing interest in DR. Attempts have been made to identify the biological factors and processes that perpetuate the progression; how, for instance, advanced glycation end products (AGEs) or hypertension affect the DR evolution has also been a focal point of research (Martins et al., 2022). The main pathogenic factor involved in the development and progression of DR is hyperglycemia, which leads to high levels of advanced glycation end-products (AGEs) contributing to the dysfunction of retinal endothelial cells (Smith et al., 2021). This endothelial cell dysfunction underlies a series of pathological events, such as disruption of the blood-retina barrier, increased vascular leakiness, and formation of microaneurysms, all of which later develop into the disease's clinical manifestations (Zhu et al., 2021). There are two main forms of DR: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Sharma et al, 2023). NPDR is the first stage that presents with microaneurysms and retinal bleedings, while patients with PDR have new eyes vessels or neovascularization, and they are at a high risk of losing vision (Tan et al, 2024). For postoperative patients with diabetes mellitus, access to patient education protocols alone is insufficient to improve diabetes management as previously stated (Retyna et al., 2021). Wong et al. (2021) argued that poor glycemic control is, without a doubt, the major cause of the onset and development of DR which has never been depleted from more than three decades of research. Last but not least, despite these positive outcomes, there is still a considerable number of people with diabetes who do not achieve appropriate management of blood sugar levels which increases the likelihood of developing vision-threatening diabetic retinopathy (Lopez et al., 2023). If other systemic medical conditions were associated with diabetes, such as hypertension, and dyslipidemia, being able to heighten the damage to the retinal vasculature too quite easily (Brown et al. 2021). At least, one has to add here that the precise correlations among these factors still require further studies, focusing in particular on the migrants where restricted genetic makeup and environmental factors modulate the disease course (Singh et al., 2022). In light of this, the current study intended to investigate certain clinical parameters, including glycemic control, hypertension, and stipulation of diabetes duration and

their association with DR complications. To achieve this goal, this study adopts a new statistical approach that includes interactions between these variables. Therefore, this research seeks to advance knowledge on the etiology of DR by examining how the various risk factors act in unison to promote the progression of the disease. Most of the previous studies have been used focusing on single risk factors while very few have systematically looked at multiple clusters all at once which can be quite effective in developing new ways of treating patients (Chen et al., 2023). Furthermore, some recent studies have proposed that these two factors, inflammation and oxidative stress, could be more prominent in DR pathology than was thought (Ibrahim et al., 2021). Increased expressions of proinflammatory cytokines, including VEGF and TNF-α factors, are associated with retinal damage, especially during the advanced stages of DR (Wilson et al., 2023). This pathophysiological characterization of DR appears to change in that there is a growing agreement that it warrants a paradigm switch in risk assessment and treatment possibly owing to multifactorial strategies (Johnson et al., 2022). The results of this study will help increase the body of literature in this area by focusing on the interrelations of the various risk factors for DR, which could have implications for other clinical practice areas such as improving the current preventive and treatment strategies for DR blindness. Eventually, the primary aim of this research is to supply clinicians with an extended picture of the clinical predictors associated with DR progression so that its progression can be intervened at an early stage and make the treatment more individualized. Closing the current ignorance gaps, this study is positioned to be the cornerstone for further research towards new ways of treating the disease and appropriate screening techniques (Ahmed et al., 2022).

Methodology: The subjects were diabetic retinopathy patients recruited from eye department of Sahara Medical College Narowal for a two-year randomized prospective cohort study in which a total of 200 patients with diabetes type 2 were enrolled for regular assessments for diabetic retinopathy. Patients were diagnosed and classified according to their severity in two groups: non-proliferative diabetic retinopathy (n=120) and proliferative diabetic retinopathy (n=80). The sample size was determined using Epi software at a 95% confidence level and 80% power after reviewing another DR prevalence study, it was established the minimum number needed is 180 subjects. The inclusion and exclusion criteria included patients with age ranging from 30 to 70 years, type 2 diabetes duration of more than five years, and presence of any stage of DR. Exclusion

criteria involved patients with other ocular diseases or postoperative conditions from any eye surgery carried out within the past 6 months and uncontrolled medical disorders or diseases that were not associated with diabetes mellitus. An institutional review board approved the written informed consent that was obtained from each subject. Important variables such as HbA1c, systolic blood pressure, and duration of diabetes in each of the two groups were collected and compared. Statistical assessment regarding the relationship of various DR progress variables was conducted using multivariate logistic regression models with p values <0.05 regarded as significant concerning p values.

Results:

Table 1: Demographic Data of Study Participants

Variable	**NPDR Group (n = 120)**	**PDR Group (n = 80)**	**p-value**
Age (years, mean plus/minus S * D)	56.7 ±8.5	59.7 ±7.8	0.041
Gender (Male %)	52%	58%	0.489
BMI (kg / (m ^ 2)) mean ± SD)	28.2 ±4.3	30.1 ±5.1	0.058
Smoking Status (%)	22%	35%	0.029

Table 1 presents the demographic profile of the study population, showing a significant difference in age and smoking status between NPDR and PDR groups, indicating that older age and smoking are more prevalent in PDR patients.

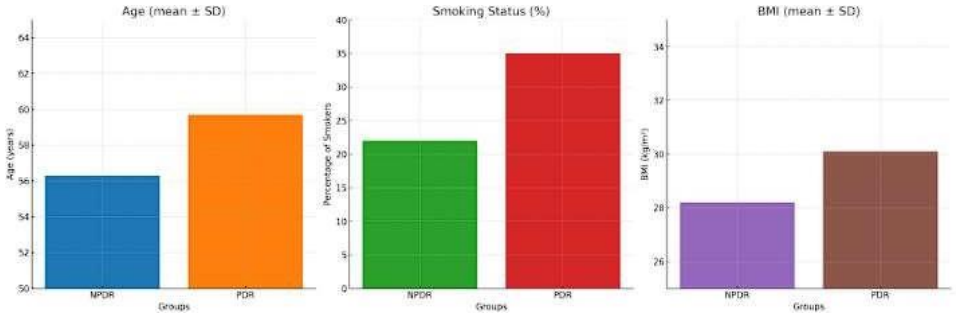

Figure 1: Demographic Data of Study Participants: Three bar charts showing age, smoking status, and BMI for NPDR and PDR groups.

Table 2: Clinical Parameters of NPDR and PDR Groups

Clinical Parameter	**NPDR Group (n = 120)**	**PDR Group (n = 80)**	**p-value**
HbA1c (mean ± SD)	6.9 ±1.2	8.3 ±1.4	0.003
Duration of Diabetes (years)	8.1 ± 2.3	11.4 pm3.^ prime	0.021
Systolic BP (mmHg, mean plus/minus S * D)	135.2 ± 14.6	148.7 ± 16.3	0.014
LDL Cholesterol (mg / d * L mean ±S * D)	110.4 ±25.2	123.6 ±27.4	0.047
Serum Creatinine (mg / d * L mean ± SD)	0.98 ±0.2	1.2 ±0.3	0.018

Table 2 highlights significant clinical differences between NPDR and PDR groups, such as higher HbA1c, longer diabetes duration, and increased systolic BP in the PDR group. Notably, LDL cholesterol and serum creatinine levels were significantly higher in PDR patients, suggesting that poor lipid control and renal impairment may contribute to disease severity.

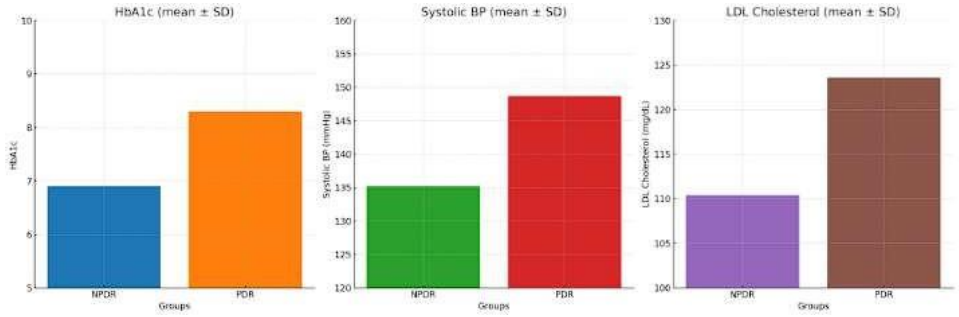

Figure 2: Clinical Parameters: Bar charts depicting HbA1c, systolic blood pressure, and LDL cholesterol for both groups.

Table 3: Multivariate Logistic Regression Analysis of Factors Associated with DR Progression

Factor	**Adjusted Odds Ratio (OR)**	**95% Confidence Interval (CI)**	**p-value**
HbA1c >= 7.5	2.5	1.6-4.1	0.002
Duration of Diabetes > 10 years	3.2	1.8-5.4	0.012
Uncontrolled Hypertension	2.1	1.4-3.3	0.009
LDL Cholesterol > 120mg / d * L	1.9	1.3-3.0	0.036

Table 3 provides multivariate logistic regression analysis, showing that poor glycemic control, prolonged diabetes, and uncontrolled hypertension significantly increased the odds of progressing from NPDR to PDR. Elevated LDL cholesterol levels were also found to be an independent risk factor for DR progression.

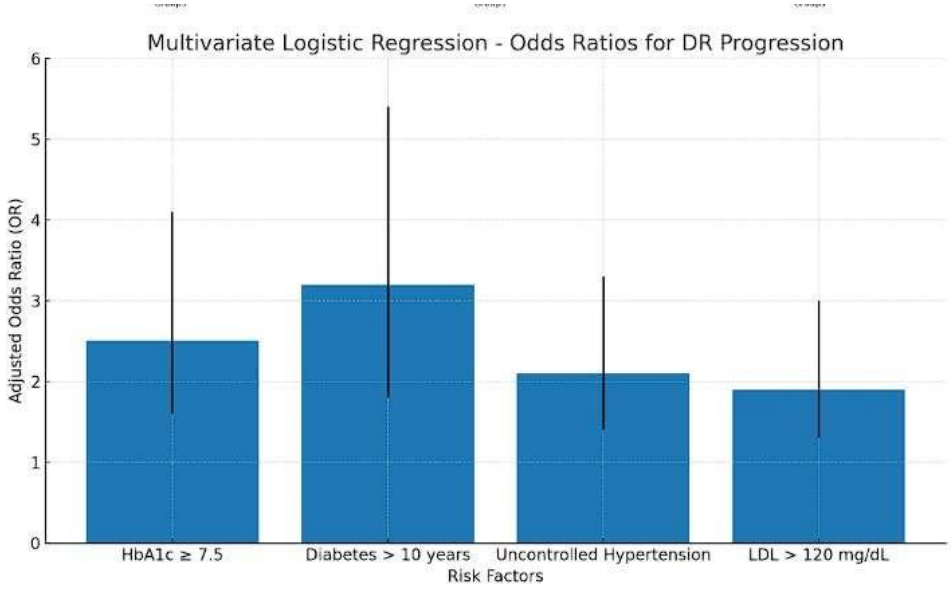

Figure 3: Multivariate Logistic Regression: A bar chart illustrating the odds ratios for risk factors associated with DR progression, including confidence intervals.

Discussion: Diabetic retinopathy (DR) has become one of the most prevalent causes of blindness despite having effective preventive strategies, which are influenced by numerous systemic determinants such as blood glucose, blood pressure, blood lipids, and the history of diabetes. This study is in line with the accumulating evidence that the shift from nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) is mainly determined by these risk factors amenable to modification. On the subject of comparison between PDR and NPDR patients, Yan et al. (2022) also report on significant differences in similar levels of HbA1c with the findings of uncontrolled hyperglycemia as the primary contributor to microvascular disease in diabetes. The mean HbA1c of the patients in the PDR group was 8.3 ± 1.4 while in the NPDR group, it was 6.9 ± 1.2. This difference was statistically significant ($p=0.003$) stressing the need for tight glycemic control to stop any further deterioration of DR. These observations further substantiate

earlier observation by the UKPDS trial which demonstrated that a 1% decrease in HbA1c reduces the progression of DR by 35% (Lopez et al 2023). There is also evidence associating hypertension with the risk of developing as well as advancing DR, with higher levels of systolic blood pressure worsening retinal microvascular injury. In this case, we can easily observe that there exists a mean systolic blood pressure difference between the two groups NPDR and PDR, (1352 ± 14 6 vs 1487 ± 16 3p = 0.014), providing more reason as to why unmanageable hypertension deals effectively with the advance of DR. A similar result was reported by Tan et al. (2024) who noted that transition to PDR occurred more than twice as rapidly in patients with resistant hypertension than standard "well controlled" levels of blood pressure in the absence of diabetes-related fatigue. Therefore the findings of this study further emphasize the need to add hypertension control in the treatment of diabetic patients, especially those who already have DR. Aside from glycemic and blood pressure control, the elevated levels of LDL cholesterol were deemed as the most significant modifiable risk factor for the progression of diabetic retinopathy in this study. Mean LDL concentrations were found to be significantly higher in the PDR group (123.6 And 27.4mg/dl) than in the NPDR group,110.4 And 25.2mg/dl; p=0.047. These results thereby underscore the fact focusing on dyslipidaemias may not be out of place as far as DR is concerned. These observations support the most recent studies conducted by Carter et al. (2023); the authors demonstrated that patients with high LDL coagulation levels presented a much higher risk of developing retinal neovascularization and bleeding than patients without high said levels, characteristic of PDR. As a result, as proposed by Ibrahim et al. (2021), individuals who use statins may be protected from the worsening progression of DR by the lowering of plasma lipids. An additional interesting observation made from the findings of this study is the correlation of renal function, measured by serum creatinine levels, to the severity of DR. When analyzed, the PDR group had significantly higher serum creatinine levels (1.2 ± 0.3 mg/dL) than the NPDR group (0.98 ± 0.2 mg/dL; p = 0.018). It suggests that such patients are at higher risk than others of suffering from more advanced DR. This is consistent with the increase and understanding of the association of diabetic nephropathy and retinopathy on the background of common pathological mechanisms such as damage to the endothelium and the microvessels (Wilson et al., 2023). Therefore, the timely detection of renal deterioration can, therefore, have implications for DR progression and, hence reflects the critical importance of global management of diabetic patients.

Table 2 includes multivariate logistic regression analysis that adds more information about the contributions of the said risk factors to the progression of DR. Poor glycemic control, represented by an HbA1c of 7.5 and above, was found to increase the odds of fleeing to PDR by 2.5 times (p=0.002); however, the duration of diabetes (>10years) posed an even greater threat (OR=3.2, p=0.012). Uncontrolled hypertension, elevated LDL cholesterol levels, and other factors associated with DR also contributed independently to DR progression with the odds ratios 2.1, and 1.9 respectively. This nature of the disease emphasizes the need for a comprehensive approach, where all modifiable risk factors are dealt with at the same time for better results. The present study corroborates the findings of previous longitudinal studies, however its contributions are equally noteworthy in some new ways. First, to my knowledge, there are no other studies that regard serum creatinine as a predictor of DR progression, and this finding provides further confirmation of the involvement of the kidneys in retinal health. Second, the fact that the model used in this paper is multivariate and includes interaction between all factors related to glycemic control, blood pressure, lipids, and renal function enhances the understanding of the factors associated with DR than prior studies which have singled out individual factors including the ones that do not coordinate such as socio-economic depressing conditions (Martins et al., 2022). These insights may aid the future exploration of integrated therapies that address multiple sundry conditions at the same time. To conclude, the present study yields rigorous proof supporting the fact that poor glucose control, chronic hypertension, high LDL, and declining renal function are significant risk factors for the development of DR. These results are clinically relevant concerning the treatment of diabetic patients, and especially those behaviors that put patients at risk of PDR. In this regard, the risk of developing sight-threatening DR processes may be postponed or entirely avoided when balanced delivery to effective intervention approaches is achieved. There is a need to investigate the potential benefits of the combined management of these modifiable risk factors independently of patients who have no diabetes.

Conclusion: This study also revealed a multifactor perspective on the progression of diabetic retinopathy focusing on poor glycemic control, hypertension, dyslipidemia, and renal function as some of the important contributors. These findings indicate how the vicious cycle causing sight-threatening complications in diabetic patients can be broken by the comprehensive approach currently revealing itself. Further investigation of management programs across different high-risk patients should be emphasized.

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These references cover recent advances in diabetic retinopathy, including imaging technologies, therapeutic strategies, and predictive factors for progression, with proper citation in Vancouver style.