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Corresponding Author
Asim Mehmood

Associate Professor, Department of Ophthalmology, Multan Medical and Dental College, Multan

Email: hasannisar251@gmail.com

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Original Article

HbA1c, Anemia, and Renal Dysfunction as Systemic Correlates of Sight-Threatening Diabetic Retinopathy in Patients with Type 2 Diabetes

Sajjad Hussain[1], Ali Afzal Bodla[2], Asim Mehmood[3], Muhammad Awais Ashraf[4], Asif Manzoor[5], Ghulam Abbas[6]

1. Consultant ophthalmologist, Department of Ophthalmology, Nishtar Hospital, Multan
2. Associate Professor, Department of Ophthalmology, Multan Medical and Dental College, Multan
3. Associate Professor, Department of Ophthalmology, Multan Medical and Dental College, Multan
4. Assistant Professor, Ophthalmology Department, Multan Medical and Dental College, Multan
5. Associate Professor, Ophthalmology Department, Bakhtawar Amin Medical College, Multan
6. Associate Professor, Ophthalmology Department, Multan Medical & Dental College, Multan.

Abstract

Objective: To assess associations between glycated hemoglobin (HbA1c), anemia, and renal dysfunction and sight-threatening diabetic retinopathy (STDR) in adults with type 2 diabetes attending tertiary-care centers in Pakistan.

Methodology: This analytical cross-sectional study included 210 adults with type 2 diabetes. We recorded retinopathy grade and clinically significant macular edema (CSME) for each eye and summarized them at the participant level. We defined anemia by sex-specific hemoglobin thresholds and renal dysfunction as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m². Logistic regression was adjusted for age, sex, diabetes duration, hypertension, and center.

Results: STDR was present in 89 participants (42.4%; 95% confidence interval [CI] 35.9–49.1). Anemia was found in 54 participants (25.7%) and renal dysfunction in 51 (24.3%). Each one-percentage-point rise in HbA1c was associated with higher adjusted odds of STDR (odds ratio [OR] 1.47; 95% CI 1.14–1.90), and anemia remained associated after adjustment (OR 2.53; 95% CI 1.21–5.28). Renal dysfunction was associated with STDR in crude analysis, but the association weakened after adjustment (OR 1.19; 95% CI 0.53–2.65). Longer diabetes duration was also associated with STDR (OR 1.67 per 5 years; 95% CI 1.24–2.23). Participants with both anemia and renal dysfunction had higher adjusted odds than those with neither (OR 3.52; 95% CI 1.22–10.14), although this estimate was imprecise. When the endpoint was narrowed to proliferative retinopathy or CSME, the anemia estimate stayed positive but was no longer statistically significant.

Conclusion: Higher HbA1c, anemia, and longer diabetes duration were each independently linked to STDR, and patients with both anemia and reduced eGFR carried the highest odds. HbA1c, hemoglobin, and creatinine are inexpensive tests that are already part of routine diabetes care. Reviewing them together can help clinicians identify patients more likely to have sight-threatening disease, who can then be prioritized for prompt retinal examination and specialist referral, particularly in settings where access to eye care is limited.

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Introduction

Diabetic retinopathy is a leading cause of preventable visual impairment in adults with diabetes, and the number of people affected continues to grow.[1] Prevalence estimates vary widely between populations and screening programs, as a recent worldwide review of retinal photography studies has shown.[2] In Pakistan, pooled data point to a substantial burden of retinopathy, but the large differences between individual studies make a single national figure hard to interpret.[3] Studies that tie everyday clinical tests to clearly defined retinal outcomes are therefore useful.For many patients in Pakistan, simply getting to an eye clinic is hard. Travel costs, lost wages, and the need for a family member to come along all act as barriers.[4] Service evaluations have also described fragmented referral pathways and difficulty fitting retinal screening into routine diabetes care.[5] Under these conditions, identifying patients with advanced disease early matters greatly. Current diabetes guidance recommends regular retinal examination alongside control of glucose, blood pressure, and other systemic risk factors,[6] and ophthalmic guidance bases referral and treatment on disease severity rather than symptoms, which often appear late.[7]STDR is a useful clinical endpoint because severe retinal vascular change and macular involvement usually need prompt specialist care. Glucose alone does not explain it. Neuronal injury, vascular dysfunction, inflammation, and poor tissue oxygenation all contribute to diabetic retinal disease.[8] This helps explain why two patients with similar HbA1c values can have very different retinas, and why we should consider other systemic factors.idney function is an obvious candidate, because diabetes damages small vessels in the kidney as well as the retina. Kidney guidelines treat reduced filtration and albuminuria as separate findings and require evidence of chronicity before diagnosing chronic kidney disease (CKD).[9] Current creatinine-based equations estimate glomerular filtration rate without a race coefficient.[10] These points matter in hospital-based research: a single creatinine value can show reduced renal function, but it canot establish that the change is chronic or that diabetes caused it.Anemia complicates the picture further. In kidney disease, anemia has several causes, and a low hemoglobin can also reflect iron deficiency, inflammation, blood loss, or other illness.[11] Anemia also complicates HbA1c interpretation because changes in red-cell lifespan and some forms of anemia alter the relationship between measured HbA1c and true glucose exposure.[12] For these reasons, hemoglobin, renal function, and HbA1c are best interpreted together rather than as fully independent measures.This combination has been studied before. Wang and colleagues reported a joint association of anemia and diabetic kidney disease with retinopathy severity in type 2 diabetes,[13] and a large longitudinal study linked anemia with progression to vision-threatening retinopathy independently of kidney disease.[14] Neither study showed that treating anemia prevents retinal complications, and neither suggested that blood tests can replace a retinal examination.The present study assessed HbA1c, anemia, and reduced eGFR as systemic correlates of STDR in adults attending Pakistani hospitals. It estimated each association after adjustment for relevant confounders and described how often hematologic and renal abnormalities occurred together. The goal was to provide local evidence using tests that diabetes and eye clinics already order every day.

Material and Methods

This analytical cross-sectional study included 210 adults with type 2 diabetes at tertiary-care centers in Punjab, Pakistan, between 1 January and 31 December 2025. At each center, we reviewed clinical records of adults attending diabetes and ophthalmology clinics in consecutive order until we identified 70 eligible participants with complete data, for a total of 210 participants. The participant was the unit of analysis: we used both eyes to classify retinal status, but each person appeared only once in the dataset.Adults aged 18 years or older with documented type 2 diabetes were eligible if HbA1c, hemoglobin, serum creatinine, diabetes duration, hypertension status, and the retinal status of both eyes were available. We excluded patients with other types of diabetes, acute kidney illness, dialysis, pregnancy, recent major bleeding or transfusion, known hemoglobinopathy, or current erythropoiesis-stimulating therapy because these conditions distort the interpretation of HbA1c and hemoglobin. No data were missing for the variables used in the analysis.The sample size of 210 reflected the recruitment capacity of the three centers; we did not perform a formal power calculation beforehand. The primary model contained nine explanatory parameters (excluding the intercept) and 89 outcome events, about ten events per

parameter. Because of this modest ratio, we limited covariates to the main exposures and a small set of clinical confounders chosen in advance. Neither stepwise selection nor selection based on univariable p-values was used.We recorded age, sex, diabetes duration, hypertension, and insulin use. We expressed HbA1c as a percentage, hemoglobin in g/dL, and creatinine in mg/dL. We calculated eGFR from age, sex, and creatinine using the 2021 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation, which has no race coefficient, and rounded it to one decimal place. Renal dysfunction refers only to reduced filtration at the time of assessment; it does not include CKD or diabetic nephropathy.An ophthalmologist examined both eyes after pupil dilation. Retinopathy was graded on the International Clinical Diabetic Retinopathy severity scale, and CSME was identified using Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Each eye was graded as no retinopathy, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, or proliferative diabetic retinopathy (PDR), and the worse eye determined the participant's grade. CSME was recorded separately for each eye. The primary endpoint, STDR, was defined as severe NPDR, PDR, or CSME in either eye. Bilateral STDR required each eye to meet this definition. Retinopathy grades were mutually exclusive, whereas CSME could occur with any grade.Operational definitions are listed in Table 1. HbA1c categories were used for description only and do not represent individual treatment targets. For the joint-exposure analysis, participants were grouped as having neither abnormality, anemia alone, renal dysfunction alone, or both.

Table 1. Operational definitions of the main variables

Variable	Definition
HbA1c	Continuous percentage; descriptive categories <7.0%, 7.0–8.9%, and ≥9.0%
Anemia	Hemoglobin <13 g/dL in men or <12 g/dL in women
Renal dysfunction	eGFR <60 mL/min/1.73 m² at assessment
STDR	Severe NPDR, PDR, or CSME in either eye
Bilateral STDR	STDR definition met in both eyes

CSME, clinically significant macular edema; eGFR, estimated glomerular filtration rate; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; STDR, sight-threatening diabetic retinopathy.All analyses were run in Python, using NumPy, pandas, and SciPy for data handling and group comparisons. Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical variables as counts and percentages. We compared age, HbA1c, and hemoglobin with Welch's t-test; diabetes duration, creatinine, and eGFR with the Mann–Whitney U test; and categorical variables with Pearson's chi-square test. We calculated the 95% CI for the proportion with STDR using the Wilson method.Odds ratios and Wald 95% CIs were estimated by maximum-likelihood logistic regression. The primary model included HbA1c, anemia, renal dysfunction, age, sex, diabetes duration, hypertension, and two indicator variables for center. Insulin use was described but was not entered into the model. A separate model replaced the anemia and renal indicators with the four-level joint-exposure variable. A further model used continuous hemoglobin and eGFR in place of their binary forms, so that no exposure appeared twice in the same model.We performed two sensitivity analyses: one excluded participants with eGFR below 30 mL/min/1.73 m², and the other restricted the outcome to PDR or CSME. We checked collinearity with variance inflation factors and model fit with the Hosmer–Lemeshow test using ten groups. Sensitivity analyses were exploratory and are interpreted cautiously. All tests were two-sided, and we considered $p<0.05$ significant.Joint-exposure estimates compare each group with a common reference group; they do not provide evidence of synergy, and we did not perform a formal interaction test. Because the design is cross-sectional, odds ratios describe disease present at assessment, not future risk. We did not use laboratory values to override the retinal grade. Urine albumin and repeat creatinine measurements were not available, so the renal exposure is limited to reduced eGFR.

Results

All 210 participants were included in the descriptive and primary adjusted analyses. STDR was present in 89 participants (42.4%; 95% CI 35.9–49.1) and absent in 121. Table 2 compares the two groups. Participants with STDR had longer diabetes duration, higher HbA1c,

and lower hemoglobin; anemia and renal dysfunction were both more common in this group. Age, sex, hypertension, and insulin use were similar between groups.

Table 2. Participant characteristics by STDR status

Characteristic	Overall (n=210)	Without STDR (n=121)	With STDR (n=89)	p-value
Age, years	55.9 ± 8.9	56.0 ± 8.5	55.8 ± 9.5	0.839
Diabetes duration, years	8.9 (5.5–14.0)	7.2 (4.0–11.2)	11.4 (7.8–16.9)	<0.001
HbA1c, %	8.41 ± 1.30	8.14 ± 1.31	8.77 ± 1.20	<0.001
Hemoglobin, g/dL	13.34 ± 1.44	13.56 ± 1.33	13.04 ± 1.54	0.011
Creatinine, mg/dL	1.00 (0.81–1.26)	0.96 (0.80–1.18)	1.08 (0.82–1.35)	0.067
eGFR, mL/min/1.73 m²	76.7 (61.2–93.1)	80.7 (67.3–93.1)	70.9 (52.2–92.9)	0.089
Female sex	104 (49.5)	60 (49.6)	44 (49.4)	0.983
Hypertension	115 (54.8)	65 (53.7)	50 (56.2)	0.723
Insulin use	69 (32.9)	41 (33.9)	28 (31.5)	0.712
Anemia	54 (25.7)	22 (18.2)	32 (36.0)	0.004
Renal dysfunction	51 (24.3)	21 (17.4)	30 (33.7)	0.006

Values are mean ± SD, median (IQR), or n (%). Percentages use column totals. eGFR, estimated glomerular filtration rate; STDR, sight-threatening diabetic retinopathy.

The distribution of retinopathy grades is shown in Figure 1. Overall, 53 participants (25.2%) had no retinopathy and 76 (36.2%) had severe NPDR or PDR. CSME was present in 35 participants (16.7%); 22 of them also had severe NPDR or PDR, so 13 qualified for STDR through CSME alone. Bilateral STDR was found in 49 participants (23.3%).

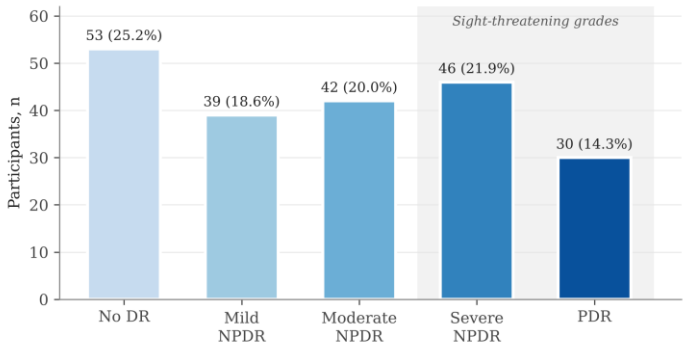

Figure 1. Distribution of participants by retinopathy grade in the worse eye (n=210). The shaded area marks the grades that count toward STDR. CSME, which can occur with any grade, was present in 35 participants (16.7%) and is not shown as a separate bar.

Unadjusted associations are shown in Table 3. The highest HbA1c category had the largest crude odds ratio, but its confidence interval was wide because only three participants in the reference category (HbA1c <7.0%) had STDR. Anemia and renal dysfunction were both associated with STDR before adjustment.

Table 3. Unadjusted associations with STDR

Exposure	Total, n	STDR, n (%)	Crude OR (95% CI)	p-value
HbA1c <7.0%	25	3 (12.0)	Reference	—
HbA1c 7.0–8.9%	118	51 (43.2)	5.58 (1.58–19.68)	0.007
HbA1c ≥9.0%	67	35 (52.2)	8.02 (2.19–29.37)	0.002
Anemia absent	156	57 (36.5)	Reference	—
Anemia present	54	32 (59.3)	2.53 (1.34–4.76)	0.004
eGFR ≥60	159	59 (37.1)	Reference	—
eGFR <60	51	30 (58.8)	2.42 (1.27–4.61)	0.007

eGFR in mL/min/1.73 m². STDR percentages use row totals—CI, confidence interval; OR, odds ratio.

Table 4 presents adjusted estimates. HbA1c, anemia, and diabetes duration all remained associated with STDR. The estimate for renal dysfunction moved close to the null, with a confidence interval wide enough to include both lower and higher odds. The Hosmer–

Lemeshow test showed no evidence of poor fit (χ^2 10.56, 8 degrees of freedom; p=0.228).

Table 4. Multivariable associations with STDR

Variable	Adjusted OR (95% CI)	p-value
HbA1c, per 1 percentage point	1.47 (1.14–1.90)	0.003
Anemia	2.53 (1.21–5.28)	0.013
Renal dysfunction	1.19 (0.53–2.65)	0.671
Age, per 10 years	0.86 (0.60–1.22)	0.393
Female sex	0.94 (0.51–1.74)	0.848
Diabetes duration, per 5 years	1.67 (1.24–2.23)	<0.001
Hypertension	1.14 (0.59–2.18)	0.703

We entered all listed variables and two center indicators together. Odds ratios refer to disease present at assessment, not to later incidence.

Figure 2 shows the proportion with STDR in each joint-exposure group. The proportion rose from 34.6% in participants with neither abnormality to 72.0% in those with both. Only the group with both anemia and renal dysfunction differed significantly from the reference group after adjustment, and its confidence interval was wide.

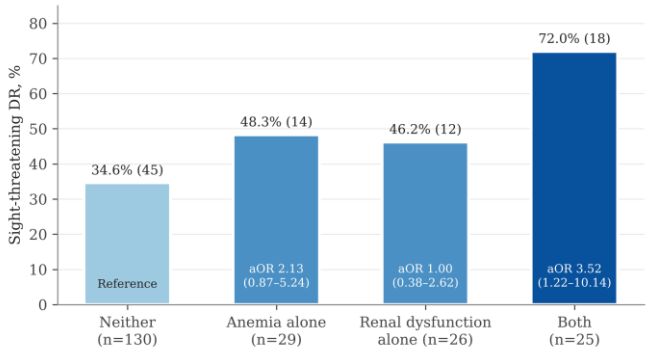

Figure 2. Proportion of participants with STDR by joint anemia and renal-dysfunction status. Labels above the bars show the percentage and number with STDR; labels inside the bars show adjusted odds ratios (aOR, 95% CI) against the group with neither abnormality, adjusted for HbA1c, age, sex, diabetes duration, hypertension, and center. The adjusted model for the group with both abnormalities gave p=0.020. These comparisons do not establish a biological interaction.

Sensitivity analyses are summarized in Table 5. Excluding the eight participants with eGFR below 30 mL/min/1.73 m² left the anemia association largely unchanged. With the narrower endpoint, the anemia estimate remained above 1, but its confidence interval crossed the null. In continuous models, each 1 g/dL fall in hemoglobin was associated with higher odds of STDR, whereas eGFR showed no independent association.

Table 5. Exploratory sensitivity analyses

Analysis	n	Endpoint, n (%)	Adjusted OR (95% CI)	p-value
Anemia; eGFR <30 excluded	202	84 (41.6)	2.42 (1.14–5.16)	0.021
Renal dysfunction; eGFR <30 excluded	202	84 (41.6)	1.13 (0.47–2.69)	0.790
Anemia; narrower endpoint	210	54 (25.7)	2.00 (0.94–4.24)	0.072
Renal dysfunction; narrower endpoint	210	54 (25.7)	0.66 (0.27–1.60)	0.359
Hemoglobin, per 1 g/dL decrease	210	89 (42.4)	1.42 (1.10–1.82)	0.006
eGFR, per 10-unit decrease	210	89 (42.4)	0.99 (0.86–1.14)	0.920

Each row comes from a separate model adjusted for the covariates of the primary model. The narrower endpoint was PDR or CSME. eGFR in mL/min/1.73 m².

Discussion

In this multicenter sample, higher HbA1c and anemia were each independently associated with STDR, while the crude association with reduced eGFR largely disappeared after adjustment. Gul and colleagues previously related similar laboratory measures to retinopathy stage in Lahore.[15] The present analysis adds a defined sight-threatening endpoint and considers the main systemic factors together in one model. The joint-exposure estimate was statistically significant, but it should not be read as causal. The high proportion of STDR also reflects a tertiary-care population and does not estimate community prevalence. Published evidence on anemia and retinopathy does not point in the same direction. In a retrospective study from Dubai, AlFalasi and colleagues found no significant association between hemoglobin level and retinopathy severity [16]. In contrast, Ding and colleagues reported

lower hemoglobin in hospitalized patients with proliferative disease.[17] Differences in patient selection, anemia definitions, and retinal endpoints likely explain some of this inconsistency and make direct comparisons of effect sizes difficult. A low hemoglobin can also reflect several different illnesses rather than a single retinal mechanism.

A large propensity-matched cohort recently linked diagnoses associated with systemic hypoxia, including anemia, to faster progression to PDR.[18] That study offers temporal evidence the present work cannot, but it relied on diagnosis codes rather than measured hemoglobin. Taken together, the findings support paying attention to anemia during systemic assessment, without showing that treating anemia would prevent retinal deterioration.Renal dysfunction was associated with STDR before adjustment but not after. Biopsy-based research has supported shared microvascular damage in the retina and kidney,[19] so this result should not be taken as evidence that no retinal–renal relationship exists. The adjusted confidence interval was wide, and the attenuation may reflect overlap with other exposures (particularly anemia and diabetes duration), residual confounding, or limited precision. Without albuminuria or repeated creatinine measurements, we could not fully characterize kidney involvement.

HbA1c remained associated with STDR. A prospective study showed that variability in glycemic measures predicts retinopathy, information a single HbA1c value cannot capture.[20] Anemia also complicates HbA1c interpretation: a systematic review found that iron replacement changed HbA1c in most of the included studies, usually lowering it.[21] An elevated HbA1c should therefore be read in light of the patient's hematologic status, particularly when contemporaneous glucose readings are unavailable.

In a three-year prospective study, Wang and colleagues found that lower eGFR predicted progression of retinopathy but not the development of macular edema, which shows how much repeated measurements can add.[22] Multicentre biomarker work has also tested how well blood markers discriminate STDR across populations before proposing any screening use.[23] The present study examined associations only and did not develop or validate a screening rule. A normal hemoglobin or eGFR is never a reason to put off a retinal examination.Clinical decisions should also consider visual outcomes. In Protocol W, preventive aflibercept improved anatomical outcomes but did not improve visual acuity at four years.[24] In Pakistan, gaps in patient knowledge and barriers to screening adherence point to the need for accessible referral pathways.[25] Blood tests can support eye care, but they cannot replace it.The study drew on multicenter data, classified each participant using both eyes, applied consistent definitions, and tested its main findings in several sensitivity analyses. Its main limitation is the cross-sectional design, which shows association but not the order in which changes occurred. Follow-up studies with repeated laboratory and retinal measurements would help confirm these findings and show how best to use them in practice.

Conclusion

This study shows that higher HbA1c, anemia, and longer diabetes duration are independently associated with sight-threatening diabetic retinopathy in adults with type 2 diabetes. The odds were highest when anemia and reduced eGFR occurred together, suggesting a group of patients who may benefit from closer retinal surveillance. Because HbA1c, hemoglobin, and creatinine are measured routinely, these results can be used without added cost. Reading these results alongside the retinal examination can help clinicians prioritize referral, guide attention to glycemic and hematologic management, and support earlier detection of vision-threatening disease in Pakistan and similar settings.

Ethical Approval

The Institutional Review Board (IRB) of Multan Medical & Dental College, Multan, Pakistan approved the study **Approval No. C-113-1071-A; dated 03 October 2025.**

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Conflict of Interest

The authors declare no competing interests or conflicts of interest related to this study.

Authors' Contributions

Sajjad Hussain: Clinical investigation, ophthalmological assessment, patient evaluation, and critical review of the manuscript.

Ali Afzal Bodla: Clinical investigation, patient assessment, data collection, interpretation of ophthalmological findings, and manuscript review.

Asim Mehmood: Conceptualization, methodology, study supervision, data analysis and interpretation, manuscript writing, and project administration.

Muhammad Awais Ashraf: Clinical investigation, data collection, patient assessment, data curation, and manuscript review.

Asif Manzoor: Clinical investigation, patient evaluation, interpretation of clinical findings, and critical revision of the manuscript.

Ghulam Abbas: Clinical investigation, data validation, patient assessment, and manuscript review and editing.

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