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Research Article

Diabetes-Onset Age, Retinal Disease Severity, and the Risk of Severe Visual Loss: A Patient-Clustered Analysis

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ABSTRACT
Background: Diabetic retinopathy represents a neurovascular consequence of chronic metabolic dysregulation. The original Diabetic Retinopathy Study (DRS) demonstrated preservation of sight with retinal photocoagulation, but the relation of diabetes-onset age and baseline ocular risk to treatment-associated preservation of vision warrants paired-eye reassessment.
Objective: To quantify the association of baseline retinal risk with severe visual loss and explore whether age at diabetes diagnosis modifies the association between laser photocoagulation and visual outcomes.
Methods: We reanalyzed 394 eyes from 197 patients in the publicly distributed DRS retinopathy dataset. Each participant had one eye randomly allocated to laser treatment and the fellow eye designated as control. Severe visual loss was defined as visual acuity below 5/200 at two consecutive visits. Kaplan-Meier curves and Cox models with patient-clustered robust standard errors assessed laser allocation, age at diagnosis (<20 versus ≥20 years), and the baseline retinal risk score. Treatment-by-onset-age interaction was exploratory. A patient-stratified Cox model was used for sensitivity analysis.
Results: Severe visual loss was recorded in 54/197 treated eyes (27.4%) and 101/197 control eyes (51.3%). The adjusted treated-versus-control hazard ratio (HR) was 0.46 (95% confidence interval [CI], 0.34–0.61). Each one-point higher baseline retinal risk score was associated with an HR of 1.16 (95% CI, 1.03–1.30). In the interaction model, the laser-associated HR was 0.27 (95% CI, 0.17–0.44) for onset at age ≥20 years and 0.66 (95% CI, 0.46–0.96) for onset before age 20; interaction ratio 2.44 (95% CI, 1.33–4.48; P=0.004). A patient-stratified sensitivity model supported a similar interaction direction (P=0.022).
Conclusions: In this historical paired-eye trial subset, greater baseline retinal severity predicted severe visual loss, while the magnitude of the laser-associated reduction in risk differed by age at diabetes diagnosis. This post hoc effect-modification finding is hypothesis-generating and should not be generalized to modern retinal treatment without external validation.

Keywords: Diabetic Retinopathy, Physiology, Retinal Ischemia, Neurovascular Unit,Photocoagulation; Severe Visual Loss, Survival Analysis, Secondary Data.

INTRODUCTION
Diabetic retinopathy is a microvascular and neurovascular manifestation of sustained metabolic stress. Alterations in retinal endothelial integrity, neuroglial homeostasis, inflammatory signaling, and vascular autoregulation link systemic glucose dysregulation to impaired retinal function and structural injury [1–4]. Retinal ischemia can amplify vascular endothelial growth factor signaling, promote pathologic neovascularization, and ultimately threaten

central vision through vitreous hemorrhage or tractional complications [1–3].

Age at diagnosis of diabetes can reflect distinct clinical trajectories, including different lengths of metabolic exposure, potential variation in vascular susceptibility, and historical patterns of glycemic management. However, the age threshold used by the original DRS dataset (<20 years) should not be considered a validated substitute for diabetes type, disease duration, or glycemic burden [1,4–6]. Ocular severity is also important: the eye-specific DRS risk score, determined before treatment, captured clinically meaningful differences in the risk of future vision loss [7,8].

The DRS established retinal photocoagulation as an effective way to reduce severe visual loss in eyes at high risk of complications from proliferative diabetic retinopathy [7]. Later ETDRS and modern treatment trials confirmed the importance of sight-preserving intervention, while contemporary anti-vascular endothelial growth factor regimens broadened the therapeutic landscape [9,10]. Despite major changes in retinal care, the DRS is uniquely useful for a methodological analysis because each patient contributed two eyes with one eye assigned to intervention, allowing patient-level influences to be controlled analytically [11,12].

The aim of this secondary investigation was to assess whether onset-age strata and pre-treatment retinal risk are associated with severe visual loss in the DRS subset. The primary analysis estimated the marginal and risk-adjusted association between randomized eye treatment assignment and severe visual loss; exploratory analyses evaluated effect modification by age at diagnosis and by eye-specific retinal risk. We also examined results from models conditioned on patient identity.

MATERIALS AND METHODS

Data provenance and design

The source was the open retinopathy dataset distributed with the R survival package and mirrored in the openly readable Rdatasets repository [12]. The dataset is a 50% random sample of patients with high-risk diabetic retinopathy from the historical DRS analyzed by Huster and colleagues [11]. It contains 197 de-identified patient identifiers and 394 eye-level records, two per patient. One eye was randomly assigned to laser treatment and the other remained untreated. No new clinical examinations, contact with participants, or extraction of identifiable private data was undertaken.

The publicly posted source codebook defines patient identifier, laser type (argon or xenon), side of eye assigned treatment, age at diagnosis of diabetes, a juvenile/adult indicator, eye-specific treatment allocation, time, severe visual loss outcome, and baseline ocular risk score. The historical dataset has neither contemporary measures of glycemic control nor additional systemic characteristics. All 394 observations were retained because the analysis variables were complete [12].

Outcomes and physiological variables

The endpoint was severe loss of visual acuity, recorded when acuity fell below 5/200 on two consecutive follow-up visits. Event=1 indicated the event and event=0 indicated right censoring from dropout, death, or end of observation. The public dataset measures follow-up in months after subtracting an approximately 6.5-month obligatory ascertainment lag for the repeated-visit endpoint. The same time shift was added back only when displaying the curves by months since initial treatment; Cox hazard ratios are invariant to a common shift of the time origin [11,12].

Age at diagnosis was coded as later onset (≥20 years) or earlier onset (<20 years), following the source data definition. This grouping is descriptive rather than a biological diagnosis of type 1 or type 2 diabetes. The eye-specific retinal risk score ranged from 6 to 12 in the available data and was treated as a continuous predictor per one-point increment. This DRS-specific scale was not equated with contemporary international disease severity categories [8].

Statistical analysis

Descriptive results were expressed as counts, percentages, means, or medians. Kaplan-Meier estimates summarized freedom from severe visual loss by treatment allocation and onset-age group [13]. The primary Cox proportional hazards regression included eye treatment status, age-at-diagnosis category, centered baseline retinal risk score (score minus 10), and the recorded laser technique, with Breslow handling of tied events [14,15]. Sandwiched standard errors were clustered by patient to account for correlation between the two eyes [11,16].

Two exploratory interactions were fitted in separate models: treatment × onset-age

category and treatment × centered baseline risk. Treatment effects within onset strata were derived from the linear combination of the main treatment and treatment-by-onset terms; confidence intervals were calculated from the fitted covariance matrix. The main sensitivity model stratified the Cox baseline hazard by patient identifier, making the treatment contrast conditional on paired patient identity. A second patient-stratified model evaluated the onset-age interaction. All estimates are two-sided with 95% CIs, and a P value below 0.05 was described as statistical evidence rather than definitive proof of an effect. The interaction analyses were not preregistered, and multiplicity adjustments were not performed.

An executable Python analysis and de-identified eye-level data file are supplied separately. Computations used pandas, NumPy, SciPy, and statsmodels PHReg with patient-level clustering. Variables and sample totals were checked against the published source dataset description, including number of patients, age at diagnosis, eye-level event counts, mean follow-up, and risk score distributions. The analytic reporting was structured with reference to STROBE guidance [17].

Ethics

This study analyzed publicly accessible, de-identified data previously collected by the Diabetic Retinopathy Study investigators. No new participants were recruited, no identifiable patient information was accessed, and no new consent was obtained for this secondary analysis.

RESULTS

Cohort profile and events

The 197 patients contributed exactly 197 treated eyes and 197 untreated fellow eyes. The mean age at diabetes diagnosis was 20.8 years (standard deviation 14.8), with median 16 years and a range of 1–58 years. One hundred fourteen patients (57.9%) met the earlier-onset definition. Baseline retinal risk averaged 9.70 points per eye (standard deviation 1.48), and the distribution of risk scores was similar between allocations (treated mean 9.64; untreated mean 9.75). The recorded assigned technique was xenon for 100 patients (50.8%) and argon for 97 (49.2%).

Severe visual loss occurred in 155 of 394 eyes, 54 among treated eyes and 101 among untreated eyes. The observed event proportions were 27.4% and 51.3%, respectively; these proportions are not censoring-adjusted cumulative incidence estimates. The median recorded eye-level follow-up time on the adjusted dataset scale was 38.8 months. Eighty patients had no event in either eye, 63 had an event only in the control eye, 16 only in the treated eye, and 38 in both eyes. Detailed group summaries are presented in Table 1.

Table 1. Cohort and eye-level characteristics

Characteristic	Overall	Onset ≥20 years	Onset <20 years
Patients, n	197	83	114
Eyes, n	394	166	228
Age at diabetes diagnosis, mean (SD), y	20.8 (14.8)	35.3 (11.2)	10.2 (4.7)
Treated eyes, n	197	83	114
Control eyes, n	197	83	114
Treated-eye events, n (%)	54 (27.4)	18 (21.7)	36 (31.6)
Control-eye events, n (%)	101 (51.3)	50 (60.2)	51 (44.7)
Treatment technique, n patients	100 xenon; 97 argon	—	—
Risk score, all eyes, mean (SD)	9.70 (1.48)	—	—

Abbreviations: SD, standard deviation. Event percentages use the respective treated or control eye denominator. Group-specific ages use the corresponding onset-age thresholds. Em dashes indicate values not summarized by subgroup.

Treatment assignment and baseline retinal risk

The unadjusted marginal patient-clustered Cox model estimated an HR of 0.46 (95% CI, 0.34–0.61; P<0.001) for laser-treated relative to untreated eyes. The adjusted HR was similar at 0.46 (95% CI, 0.34–0.61; P<0.001), independent of the source-defined baseline risk, age-at-diagnosis category, and laser type.

Higher eye-specific baseline risk scores predicted a greater hazard of severe visual loss (HR per one point, 1.16; 95% CI, 1.03–1.30; P=0.013). The main-effect model did not find strong evidence of an independent difference by onset age or recorded laser technique (Table 2).

Table 2. Patient-clustered Cox proportional hazards models

Predictor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted P
Laser treated versus control	0.46 (0.34–0.61)	0.46 (0.34–0.61)	<0.001
Diagnosis age <20 vs ≥20 y	—	0.92 (0.65–1.30)	0.647
DRS retinal risk, 1-point increase	—	1.16 (1.03–1.30)	0.013
Argon versus xenon category	—	1.20 (0.85–1.69)	0.309

HR, hazard ratio; CI, confidence interval; DRS, Diabetic Retinopathy Study. Adjusted model accounts for treatment allocation, onset-age category, centered baseline DRS retinal risk, and recorded laser technique, with patient-clustered sandwich standard errors. Laser type is a patient-level technical characteristic, not an eye-level comparison of two laser types.

Effect modification by age at diabetes diagnosis

Among the 83 patients diagnosed at age ≥20 years, severe visual loss occurred in 18 treated eyes (21.7%) and 50 control eyes (60.2%). Among the 114 patients diagnosed before age 20, events occurred in 36 treated eyes (31.6%) and 51 control eyes (44.7%). In the age-interaction Cox model, the laser-associated HR was 0.27 (95% CI, 0.17–0.44) for later onset, compared with 0.66 (95% CI, 0.46–0.96) for earlier onset. The ratio of those treatment HRs was 2.44 (95% CI, 1.33–4.48; P=0.004), consistent with a smaller relative association for treatment in the younger-diagnosis group on the multiplicative hazard scale (Table 3, Figures 1 and 2).

Table 3. Exploratory interaction and sensitivity analyses

Estimate	HR or ratio (95% CI)	P
Treated/control, diagnosis at age ≥20 y	0.27 (0.17–0.44)	<0.001
Treated/control, diagnosis before age 20 y	0.66 (0.46–0.96)	0.028
Treatment × earlier-onset interaction	2.44 (1.33–4.48)	0.004
Patient-stratified treated/control effect	0.39 (0.26–0.58)	<0.001
Patient-stratified onset interaction	2.69 (1.15–6.28)	0.022
Treatment × DRS risk-score interaction	0.93 (0.76–1.15)	0.502

Subgroup laser effects derive from one clustered Cox model with an interaction term and are adjusted for baseline retinal risk and recorded laser technique. The interaction ratio measures the ratio of the two treatment hazard ratios. Stratified models condition on patient identity, and 80 event-free patient strata do not contribute to the conditional partial likelihood. Exploratory findings were not multiplicity-adjusted.

Figure 1. Kaplan-Meier estimates of avoiding severe visual loss, presented by age at diabetes diagnosis and treated/control eye assignment. The time axis displays the documented 6.5-month shift back from the source time-to-event field; individual curves are descriptive and do not incorporate patient-clustered confidence bands.

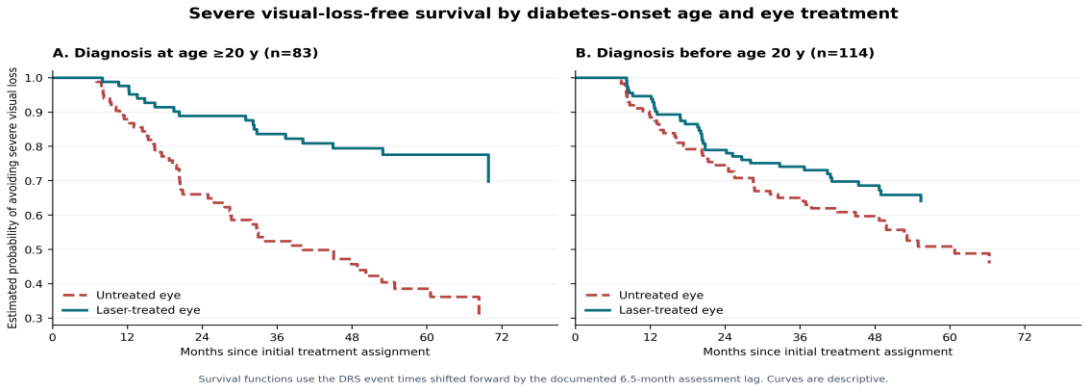
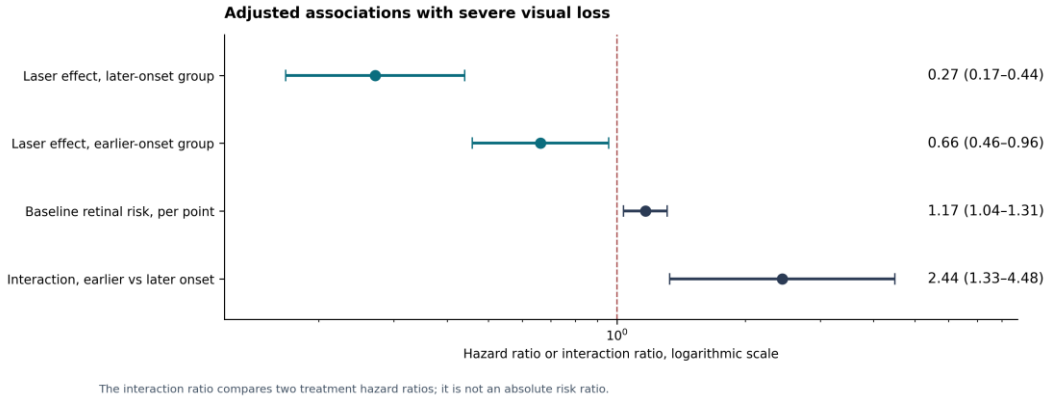


Figure 2. Adjusted patient-clustered hazard ratios and interaction ratio with 95% confidence intervals.

The lower treatment hazard ratio in the later-onset stratum indicates a greater relative association with visual preservation in this historical dataset. The interaction is exploratory and is not a treatment recommendation.



At 60 months from treatment assignment, the descriptively estimated cumulative severe-vision-loss risks were 61.4% in control and 22.4% in treated eyes for later-onset patients, compared with 49.2% and 35.9%, respectively, in earlier-onset patients. These Kaplan-Meier estimates incorporate the published ascertainment lag in the mapping to calendar time, but between-eye comparisons of curves are descriptive and do not themselves provide patient-clustered uncertainty estimates. The absolute contrast should not be interpreted as a contemporary population treatment effect.

Sensitivity analyses

A patient-stratified Cox model using within-patient risk sets estimated an HR of 0.39 (95% CI, 0.26–0.58; P<0.001) for treated versus control eyes after accounting for baseline retinal risk score. Eighty patient strata contributed no events and therefore no partial-likelihood information. In a stratified treatment-by-onset-age model, the interaction ratio remained elevated (2.69; 95% CI, 1.15–6.28; P=0.022). Exploratory testing for treatment-by-baseline-risk interaction did not show evidence of a difference in relative treatment effect per unit of retinal risk (interaction HR 0.93; 95% CI, 0.76–1.15; P=0.502). This lack of evidence should not be interpreted as proof of homogeneous treatment effects at all risk scores.

DISCUSSION

In this reanalysis of the historical DRS, retinal severity at baseline had a measurable association with severe vision loss, and photocoagulation was associated with a substantially lower time-to-event hazard after adjustment for the paired-eye design. The largest additional finding was evidence that age at diabetes diagnosis modified the treatment hazard ratio. Specifically, the relative separation between treated and untreated eyes was more pronounced in the later-onset diagnosis category. This finding was visible in subgroup event patterns, retained in an adjusted marginal interaction model, and preserved in a patient-stratified

sensitivity analysis. Importantly, it was not a prospectively specified primary question of the original trial.

From a physiology perspective, the retina is an exceptionally metabolically active neural tissue reliant on integrated vascular autoregulation, endothelial barrier function, glial support, and oxygen delivery. Dysregulated glucose metabolism damages this neurovascular system through oxidative stress, inflammation, impaired neurovascular coupling, and proangiogenic responses to hypoxia [1–3]. Panretinal photocoagulation was developed to reduce the ischemic stimulus for pathologic neovascularization, lowering the likelihood of late vitreoretinal complications but also sacrificing some peripheral retinal tissue [7,9,10]. Thus, severity-dependent visual prognosis is biologically plausible, and the observed hazard increase per risk-score point is coherent with established retinal pathophysiology.

By contrast, the apparent role of age at diagnosis requires considerably more caution. In the source data, earlier-onset diagnosis was based solely on age under 20 years. It does not identify diabetes type, duration at enrollment, developmental biology, HbA1c exposure, vascular comorbidities, treatment adherence, or retinal morphology. Differences in visual prognosis and in laser-associated hazards could arise through any combination of these variables. It would be inappropriate to claim that younger age at diagnosis itself causes weaker retinal responsiveness to photocoagulation. Moreover, an interaction on a relative hazard scale does not directly establish an interaction on the absolute risk scale.

Our findings are aligned with the established treatment effect reported by the original DRS, which found that photocoagulation substantially reduced severe visual loss [7]. The ETDRS subsequently clarified which stages of retinopathy warrant immediate or deferred treatment [9]. Later evidence has reinforced that glycemic control and blood pressure contribute to retinal microvascular prognosis [5,6], while global analyses have documented a substantial burden of vision-threatening retinopathy [4]. The present reanalysis does not update clinical effectiveness estimates for current practice, because historical scatter-photocoagulation techniques differ from today's algorithms, which may involve contemporary laser parameters, anti-VEGF agents, or combined therapy [10].

Several design features strengthen internal interpretability. One treated eye and one control eye originated from the same participant, so patient-level characteristics were inherently matched at allocation. We used robust patient-clustered uncertainty estimation rather than treating 394 eyes as 394 independent people, as recommended for correlated time-to-event data [11,15,16]. The patient-stratified models were directionally consistent, although only the 117 pairs with at least one eye-level event contributed partial-likelihood information in those conditional models. Furthermore, the source includes actual event or censoring times, which permits survival analysis rather than a simple analysis of binary endpoints.

Limitations are substantial. The dataset is a 50% subsample from an older high-risk trial and cannot represent the spectrum of people with diabetes today. No measures of diabetes duration, sex, glycated hemoglobin, blood pressure, kidney disease, anti-VEGF use, or other systemic exposures were supplied, and age at diagnosis is an imperfect physiological proxy. The baseline DRS risk scale is specific to that study and cannot be substituted for the current International Clinical Diabetic Retinopathy Severity Scale [8]. Laser technique was recorded but its allocation across individuals was not randomized in the same manner as treated-eye assignment. Interval ascertainment and the source-defined 6.5-month offset complicate clinical interpretation of nominal follow-up time. Finally, the age interaction was post hoc, multiple interactions were explored, and statistical significance in this reanalysis does not constitute external replication.

For future investigation, the most relevant next step would be an independent contemporary dataset containing systemic metabolic physiology, including duration of diabetes, longitudinal HbA1c, blood pressure, insulin use, lipid indices, and ocular severity measures, to examine whether onset age retains predictive value beyond cumulative metabolic exposure. A randomized treatment comparison, or a carefully constructed contemporary prospective cohort with reliable treatment and event timing, would be required before making individual therapeutic decisions from the apparent subgroup differences.

CONCLUSION

In 197 individuals represented by 394 eyes in public historical DRS data, higher baseline retinal disease risk independently predicted severe visual loss, while laser allocation was associated with a lower hazard of this endpoint. An exploratory interaction suggested different treatment-associated hazard ratios by age at diabetes diagnosis. The physiological relevance lies in retinal microvascular injury and heterogeneity of disease course, but the effect-modification result should be regarded as preliminary and not used to change contemporary treatment decisions.

Declarations

Ethics approval and consent to participate: This secondary analysis used publicly accessible, de-identified records and involved no new recruitment, patient contact, or access to identifiable patient information.

Consent for publication: Not applicable.

Availability of data and materials: The public source dataset is available in the R survival package and the Rdatasets repository at https://raw.githubusercontent.com/vincentarelbundock/Rdatasets/master/csv/survival/retinopathy.csv. The supplementary submission bundle includes a reformatted copy of the analyzed records and executable Python code. No restricted-access database was used.

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Competing interests: The authors declare no competing interests.

Author contributions: AY and MI conceived the research question and developed the study design. AF and MJ participated in dataset preparation, data curation, and verification of study variables. SA and JK contributed to statistical analysis, validation, and interpretation of the results. MAS contributed ophthalmological interpretation and review of the clinical significance of the findings. NI and ZK contributed physiological interpretation, literature synthesis, and critical revision of the manuscript. SHB contributed to the initial manuscript draft, reference verification, and subsequent revisions. All authors critically reviewed the manuscript, approved the final version, and agree to be accountable for their contributions.

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